EUROPEAN HEMATOLOGY ASSOCIATION

Scientific Working Group
QUALITY OF LIFE AND SYMPTOMS

GUIDELINES PATIENT-REPORTED OUTCOMES IN HEMATOLOGY

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Dear Readers,

The European Hematology Association Scientific Working Group (EHA SWG) "Quality of Life and Symptoms" is proud to offer you the first edition of the patient-reported outcome assessment Guidelines *Patient-Reported Outcomes in Hematology*.
Patient-reported outcomes (PRO) is one of the important outcomes of treatment of hematological disorders. Responding to the patient's voice by means of PROs is a good way to improve the quality of care in hematology. PROs are of value in hematology, both in clinical practice and in clinical trials.

This edition covers issues related to PRO assessment in hematological studies. During the last decade PROs have been increasingly included in clinical trials and postmarketing research in hematology. Incorporation of PROs in clinical trials in hematology provides data from the patients' perspective regarding treatment efficacy, and facilitates better identification of treatment benefits and risks to patients. However, there have been no standards for PRO assessment within the international hematological community. To address this problem, a three-year project was launched by the EHA SWG "Quality of Life and Symptoms" to develop the Guidelines for PRO assessment in patients with hematological disorders. Clinicians and researchers from 17 countries worked together, in close collaboration with the representatives of Patients' Organizations, to complete the book of Guidelines titled *Patient-Reported Outcomes in Hematology*. Preparation of this book has involved extensive work. A number of brain storming sessions were held initially to discuss the contents of the key chapters of the Guidelines. This was followed by intensive and rigorous work within the subgroups responsible for preparation of the Guidelines chapters.

The contributors to these Guidelines have very generously shared their time and scientific expertise to make it possible to offer you this educational tool. We extend our most heartfelt thanks to them.

Very special mention must be made of Carolyn Cooper, responsible for the final editing process, who was so accommodating of late arrivals and so meticulous in her work.

We also express our gratitude to Sanofi, Roche, Amgen, Bristol-Myers Squibb, and Celgene for their support of this project through unrestricted educational grants and with exemplary respect for the scientific autonomy of the editors and authors.

This volume focuses on the application of PROs in hematology in clinical studies. The next, but no less important step, is to develop the Guidelines for implementing PROs in clinical practice in hematology. We welcome your comments and suggestions in this regard.

Sincerely

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On behalf of the members of the EHA SWG "Quality of Life and Symptoms" as well as the contributors to the PRO assessment Guidelines *Patient-Reported Outcomes in Hematology*, we would like to use this opportunity to honor the valuable contributions of Professor Andrei Novik to the activities of the Group and to the successful completion of the development and production of the above Guidelines. His hard work, dedication, expertise, and time are greatly appreciated by all of us.

Andrei Novik contributed substantially to the creation of the EHA SWG "Quality of Life and Symptoms", which was formed in 2006 within the European Hematology Association. He inspired a number of important Group initiatives during his chairmanship which began in 2009. During his leadership, Andrei was successful at uniting hematologists, specialists in PRO research, and representatives of Patient Organizations in Europe to develop a number of projects undertaken by the EHA SWG "Quality of Life and Symptoms". Being a physician, a scientist, and a patient himself, he had a deep understanding of the genuine patient needs and made serious efforts to improve the many aspects of their lives.

The most significant project of the EHA SWG "Quality of Life and Symptoms", initiated by Andrei, was the development and production of the Guidelines on patient-reported outcomes in hematology. His successful project has now come to fruition with the publication of *Patient-Reported Outcomes in Hematology*.

To our great regret, Andrei Novik passed away recently. Ulrich Jager, the President of the EHA, commented that it was a great loss for European Hematology and the EHA in particular. After Andrei's death, Ms. Anita Waldmann, the President of Myeloma Euronet, wrote, "I was very impressed by his expertise as a scientist, combined with his honest empathy for patients. Andrei Novik has taken the patient's needs very seriously and made the differences between personalized, individual, and targeted treatments understandable. I felt honored to have the chance to go a short time with him along his pathway".

Unfortunately, Andrei Novik passed away before the Guidelines were published, but he managed to do everything to ensure the success of this important initiative of the international hematological community.

His commitment and dedication to the EHA SWG "Quality of Life and Symptoms" along with his outstanding work are invaluable. The members of the EHA SWG "Quality of Life and Symptoms" will strive to continue the initiatives of Andrei Novik. However, he will be sorely missed.

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INTRODUCTION

A fundamental component of optimal patient care for those with any chronic disorder, including patients with hematological diseases, is patient-centeredness. Recent Institute of Medicine (IOM) reports provide recommendations for the redesign of 21st century health care and include a call for patient-centered care. This must encompass improved physician-patient communication along with compassion and empathy, as well as responsiveness to the needs, values, and expressed preferences of the individual patient. The key aspect of patient-centered care is the patient's active and central role in managing their disease, including the self-monitoring of patient-reported outcomes (PROs).

PRO is an important aspect of patient care. Responding to the patient's voice by means of PROs is a good way to improve the quality of care that hematological patients receive. The past decade has been characterized by increased attention to PRO assessment from the hematological community.

Effective management of hematological disorders may be achieved if PRO results are taken into consideration. Evaluation of PROs may contribute to personalized treatment in the area of hematology. PROs are of particular importance when adverse effects and symptoms must be proactively managed and when both treatment risks and benefits need to be weighed.

PRO data add to the body of knowledge concerning traditional clinical treatment outcomes for those with hematological diseases by providing the patient's view of the disease and treatment-related burden, which is now highly valued by stakeholders. In addition to traditional clinical end-points, PROs can provide valuable information to improve decision-making. PRO measurements allow patients to directly express how they perceive their present and past health condition. This provides health care providers with valuable tools on how to direct patient care. Patients' preferences are increasingly being considered in decision-making regarding treatment options, so that currently, no option should be forced on patients without providing information about its potential harm and benefits. Implementation of PROs in clinical practice will be of value to help physicians and patients make more informed treatment decisions and may contribute to raising the standards of survivorship care for hematological patients. The use of PRO measures will help physicians identify unmet patient needs and will provide a basis for better capturing benefits and risks of the treatment for different hematological disorders. As a result, it might facilitate patient-physician communication and ensure that doctors are patient-centered.

Assessment of PROs in clinical trials has generated group-level (aggregate) data that provide clinicians and their patients with valuable information to substantiate the

possible quality of life (QoL) consequences of various treatments. This information, combined with other efficacy information, promotes shared and informed decision making. The absence of PRO data makes it difficult to base the risks and benefits of treatment on outcomes other than survival.

Using PROs as an outcome measure in a clinical trial is, in essence, the only way of obtaining evidence-based data from a patient's perspective on treatment effects. The US Food and Drug Administration recently published a document aimed at providing the medical community with its view on PRO instruments as effective end-points in clinical trials, as well as providing guidance for medical product developers on using PRO data. Accurate and robust methodology is a key issue in patient-centered outcomes research in the field of hematology.

Clinicians and researchers working together, in close collaboration with Patients Organizations, could likely facilitate progress in the field and ensure patient-centered care for those with hematological disorders. In conclusion, PROs are of value in hematology, both in clinical practice and in clinical trials.

This volume focuses on the application of PROs in hematology in clinical studies. The first two Chapters cover the conceptual and methodological issues of measuring PROs. Chapter 3 describes state-of-the art of studies with a PRO component in patients with different hematological disorders, summarizes PRO instruments available, and gives some practical considerations for PRO measurement. Chapter 4 focuses on studies with a PRO component for patients undergoing bone marrow transplantation/hematopoietic stem cell transplantation. Chapter 5 deals with PRO assessment in long-term blood cancer survivors. Chapter 6 describes PROs in patients receiving anticoagulants. Finally, Chapter 7 is devoted to PROs in children/adolescents with hematological malignancies.

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CHAPTER 1

Patient-reported outcomes in patients with hematological disorders: conceptual issues

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Patient-reported outcomes: overview

Patient-reported outcome (PRO) is an umbrella term encompassing a number of patient self-reported parameters related to a patient's health status and perception of treatment side effects (*Doward LC, et al, 2004; Efficace F, et al, 2007; Osoba D, 2007; Doward LC, et al, 2010*). As defined by the US Food and Drug Administration (FDA), PRO is "a measurement based on a report that comes directly from the patient about the status of a patient's condition without amendment or interpretation of the patient's response by a clinician or anyone else" (*US Food and Drug Administration: Guidance for Industry. Patient-Reported Outcome Measures, 2009; Speight J, et al, 2010*). PRO assessments introduce the patient's perspective into the clinical process via standardized self-report instruments that are scored by the patient, not a clinician or a researcher. The use of a PRO instrument is thus advised when measuring a concept that is best known to the patient or best measured from the patient's perspective (*Reflection paper on the regulatory guidance, 2004; US Food and Drug Administration: Guidance for Industry. Patient-Reported Outcome Measures, 2009*). As stated by the FDA, some "treatment effects are known only to the patient", and such information can be lost when the patient's perspective "is filtered through a clinician's evaluation of the patient's response to clinical interview questions" (*US Food and Drug Administration: Guidance for Industry. Patient-Reported Outcome Measures, 2009*). PROs include quality of life (QoL), symptoms, satisfaction with and adherence to treatments and any other treatment or outcome evaluation obtained directly from patients (*Levine MN, 2002; Patrick DL, et al, 2007; US Food and Drug Administration: Guidance for Industry. Patient-Reported Outcome Measures, 2009; Bottomley A, et al, 2009*).

Proxy reports from caregivers, health professionals, or parents and guardians (necessary in some conditions such as advanced cancer and cognitive impairment) cannot be considered PROs and should be considered as a separate category of outcomes.

PROs directly measure treatment benefit beyond and above survival, as well as disease and physiologic markers and are often the outcomes of greatest importance to patients. The PRO provides information unavailable from other sources. These data reflect how the patient interprets their experience and conditions not observable by others which are distinct from proxy measures. Patient reports can provide insight into health status, current functional capacity as compared with past performance, the intensity of symptoms or side effects of treatment, impressions of how symptoms affect capability to function, the ability to comply with treatment recommendations or the rationale for nonadherence, and striking descriptions of the difficulties imposed on personal and family life (e.g. inability to work) (*Rothman ML, et al, 2007*).

In summary, the value of the patient's perspective and its rationale for inclusion may be structured around four key points (*Acquadro C, et al, 2003*):

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1. A unique indicator for assessing disease impact. The patient's report of symptoms, side effects, and other health-related data gathered during history taking are important entries in the multifactorial database, which is the foundation for accurate medical diagnosis and treatment.
2. Essential for evaluating treatment efficacy. In clinical trials, as in practice, patient report is the sole source of data on the frequency and severity of symptoms and side effects, and the impact of treatment on functioning and well-being.
3. Useful for interpreting clinical outcomes. PRO data from clinical trials contribute to the comprehensive evaluation of the benefits of a new treatment.
4. A key element in treatment decision making. A number of specialty groups and organizations recommend the use of PROs in clinical trials and have published guidelines for selecting outcome measures specific to the unique characteristics and evaluation needs of the underlying disease.

QoL and symptoms are PROs that are most frequently used in clinical trials and are of major importance in clinical practice.

Quality of life is a complex multidomain construct that represents a patient's overall perception of the impact of an illness and its treatment on the patient's functioning and well-being (*Osoba D, 1994; Schumacher M, et al, 1991; Bowling A, 1996; Gorodokin G, Novik A, 2005*). QoL is the integral characteristics of physical, psychological, and social functioning of a patient based upon his/her perception. Its theoretical framework is largely based on a multidimentional perspective of health as physical, psychological and social functioning and well-being, along the lines of the World Health Organization (WHO) (1947, 1948) definition of health: a "state of complete physical, mental and social well-being and not merely the absence of disease and infirmity". There are three fundamental components of the QoL concept: multidimensionality, subjectivity, and variability (*World Health Organization, 1976*).

- Multidimensionality of QoL. A QoL measure captures, at minimum, physical, psychological (including emotional and cognitive), and social functioning. QoL can be measured accurately both in an individual, and in a group.
- Subjectivity of QoL. QoL is considered to be subjective. However, it is not "subjective" in the usual sense of the term, but in that it derives from a human subject of research or clinical practice. Subjectivity should never be confused with lack of validity. The measurement science behind QoL assessment can ensure the collection of reproducible, substantive data that can be analyzed with as much confidence as most clinical outcomes, such as a blood chemistry value.
- Variability of QoL. Another important feature of QoL is its variability over time. QoL of a patient may change at different time-points of treatment and at follow-up, and these changes may be captured by means of standardized self-reported instruments.

Symptoms comprise an important category of PROs (*Trotti A, 2007; Spivak JL, et al, 2009*). A symptom is any subjective evidence of a disease, health condition, or treatment-

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related effect that can be noticed and recognized only by the patient. Examples of symptoms are pain, fatigue, loss of appetite, etc. Reports from patients may also include the signs reported in diaries. A sign is any objective evidence of a disease, health condition, or treatment-related effect which is usually observed and interpreted by a clinician and may or may not be noticed and reported by a patient. Patients may or may not be aware of signs that are observed by a health professional. Examples are lymph node enlargement, weight loss, icterus, etc.

QoL and symptoms are assessed by PRO instruments (*Fitzpatrick R, et al, 1998; Staquet MJ, et al, 1998; Fayers P, et al, 2007*). At present PRO data are collected via standardized questionnaires. In order to obtain reliable and valid data using PRO instruments, it is strongly recommended to follow the robust methodology of QoL and symptom measurement. Methodological issues of PRO measurement are described in Chapter 2.

Patient-reported outcomes in hematology

In hematology PROs serve a number of important purposes both in clinical trials and in clinical practice. QoL assessment allows the description of the overall well-being of the patient population. It helps in the understanding of the nature and the extent of functional and psycho-social impairment patients encounter during therapy, after treatment completion, and at follow-up. Furthermore, information on QoL has been shown to be of prognostic value in the treatment outcome of specific hematological diseases and may help in guiding treatment selection. Understanding the risk factors for dysfunction can help identify high-risk patients who can be targeted for counseling and psycho-social support.

In patients with hematological disorders the physician-patient partnership is crucial to providing patient-centered care and to reducing suffering due to the disease. One of the ways to improve the physician-patient partnership is to implement PRO assessment in routine practice, and to ensure that clinicians use this information in their decision making process. Furthermore, accurate evaluation of symptom severity is critical for optimal care of patients with hematological disorders and ultimately for alleviating symptom burden and improving the QoL in this patient population.

In clinical trials PRO data are used to measure treatment benefit or risk. In hematology, PROs are sometimes used as primary outcomes in clinical trials, particularly when no surrogate measure of direct benefit is available to capture the patient's well-being. More often, PROs complement primary outcomes such as survival, disease indicators, clinician ratings and physiologic or laboratory-based measures. In situations in which multiple treatment options exist with similar survival outcome or if a new therapeutic strategy needs to be evaluated, the inclusion of QoL as an end-point can provide additional data and help in clinical decision making. In some settings, in particular palliative, PRO assessment may be the sole indicator of treatment assignment or change.

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At present, in hematology, PROs are primarily used in phase III and IV studies. There are also examples of phase II studies where measuring the patient's view is of value. Using PRO as an outcome measure in a clinical trial is the only way of obtaining evidence-based data from the patient's perspective on the effect of treatment. PROs should be included in all patient studies. To note, in a number of international recommendations for various hematological diseases, namely, for hemophilia (*World Federation of Hemophilia, 2005*), immune thrombocytopenia (*Rodeghiero F, et al, 2008*), myelodysplastic syndromes (*Tefferi A, et al, 2006*), chronic lymphocytic leukemia (*Hallek M, et al, 2008*), acute leukemia (*Appelbaum FR, et al, 2007*), non-Hodgkin's lymphoma (*Mauch PM, et al, 2004*), Hodgkin's lymphoma (*Hoppe R, et al, 2007; Engert A, Horning SJ, 2011*) and multiple myeloma (*Morgan GP, et al, 2006*), the importance of PRO issues is stated and advocacy for more research in the field is given.

Proper methodology is mandatory for the valid evaluation of PRO in hematology, since PRO data may influence regulatory and clinical decisions. Measuring PROs in clinical trials should follow the same rigorous procedures as when measuring any traditional clinical end-point.

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CHAPTER 2

Patient-reported outcomes in patients with hematological disorders: methodological issues

Introduction

Patient-reported outcomes (PROs) are valuable outcome measures in hematology. They may be used to evaluate treatment toxicity, overall treatment effectiveness, and quality of patient's well-being at short-term and long-term after treatment from a patient's perspective. In hematological clinical trials, in addition to traditional clinical end-points, PROs can provide unique and important information about the effect of treatment from a patient's view. Although presently it is more common to measure PROs in phase III and IV clinical trials, there is an increasing need in hematology to also consider measuring PROs in earlier phase studies.

A clear and robust methodology for measuring PROs in hematological patients is of great importance. PROs are scientific measures that can evaluate change in outcomes. They must be handled like any other effectiveness end-point in clinical trials. Methods for selecting, developing, validating, measuring, and reporting PROs are similar to those for other clinical effectiveness measures (*Acquadro C, et al, 2003; Patrick DL, et al, 2007*).

Planning clinical trials with a patient-reported outcome component

Assessing PROs in clinical trials requires careful consideration of a number of methodological issues. PROs should be an integral part of the main protocol of the study. The description of all relevant aspects of the PRO measurement should be incorporated in the main study protocol. The use of separate protocols or add-on studies to measure PROs implies that the PRO measurements are optional and might lead to misplacing the materials and/or forgetting to carry out the PRO assessments.

Information and instructions about PRO measurements should be included under each of the conventional protocol headings (*Staquet MJ, et al, 1998*). The standard components of any protocol which includes PROs are:

- Introduction and background
- Objectives
- Eligibility criteria
- Study design
- Instrument description
- Sample size
- Monitoring, ending rules, evaluation, analysis, and testing of psychometric properties of instrument in targeted sample
- Consent form
- Cover sheet for monitoring compliance
- Instructions for administration.

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Details about the characteristics of the PRO instrument, the instrument itself, and detailed instructions for data collection should be included in one or more appendices to the main protocol.

When planning clinical trials with a PRO component the following key issues need to be considered:

- Developing an end-point model
- Choosing an appropriate PRO instrument(s)
- Timing for administering PRO instruments
- Planning and monitoring data collection
- Handling missing data
- Using proper approaches to analyze and interpret PRO data.

Formulating a rationale for PRO assessment in a particular trial and specifying what this type of outcome would add to the primary end-point of the study, is the first and very important step when planning the study. PRO may be either a primary or a secondary end-point in a study. At minimum, an end-point model describes measurable concepts of a specific disease state, including the spectrum of both prominent symptoms and expected clinical course. Additional treatment-specific concepts relevant to the patient population may be incorporated into the model (*Patrick DL, et al, 2007*). PRO end-points are placed in this model within the hierarchy of all end-points. In this way, hypothesized relationships among all measures – including PRO and non-PRO measurements – that could serve as end-points in terms of overall goals of therapy can be included. Articulation of an end-point model ties together disease natural history, treatment goals, and the instrument(s) intended to demonstrate treatment benefit.

The key step in designing the study with a PRO component is the choice of the instrument. Characteristics of quality of life (QoL) and symptom assessment questionnaires as well as guidance for their selection to be used in a particular study are presented in this Chapter below.

The timing for administering PRO instrument in relation to interventions and the illness trajectory is very important (*Staquet MJ, et al, 1998*). A base-line administration, before randomization and treatment initiation, should be mandatory in all trials with a PRO component. The base-line administration is required not only to be able to make inter-group comparison for changes in QoL or symptom scores before and after treatment, but also to check whether patients entered in the arms of a trial are balanced with respect to PRO characteristics. If base-line characteristics are balanced and if the attrition of patients over time is equal in the groups being compared, then a simple comparison of mean scores between various groups may be sufficient. However, if PRO characteristics are not balanced at base-line, then a comparison between groups will require calculation and comparison of the changes in mean scores between the groups from base-line to the time-points of interest and careful interpretation of the results. Base-line measurement is absolutely essential in phase II studies, since the comparisons will be between pre-

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treatment, during treatment, and after treatment. The timing of measurements during the trial will be dependent on the questions being asked and the nature of the trial. In addition, the timing of PRO assessments should be linked to physician visits or treatment dates. It is preferable to have the measurements completed at the same point in time relative to these events that is before the physician's interview and examination, and before the scheduled treatment. If the assessments are completed just before these events, then the answers are not influenced by the information given by the physician, by the administration of a treatment, or by early side-effects of the treatment.

As with all data collected within a clinical study, PRO data should be captured in a way that assures their quality and integrity and minimizes missing information. The individual designated to coordinate PRO data collection at the study site should be thoroughly familiar with the study protocol and the instrument(s) prior to giving them to the patient. Specific quality control procedures which are essential for the individual responsible for PRO data collection should be described in the protocol instructions.

Finally, interpreting PRO data is of paramount importance. Interpreting PRO data is one of the most complicated issues in PRO measurement. Approaches to interpret PRO information in a way compelling to hematologists are described in this Chapter. In addition, accurate reporting of data is crucial when evaluating PRO in clinical trials, in order to provide the scientific community and health care providers with a clear and transparent message about the impact of a given treatment on the patient's health status (*Efficace F, et al, 2009*).

Thus, all aspects of PRO measurement should be taken into account at the stage of protocol development and integrated into the protocol of the study. Of equal importance is attention to the practical aspects of feasibility and data collection. Difficulties with data collection and compliance have been considered barriers to successful implementation of PROs in clinical trials (*Fayers P, et al, 2005*). Particular emphasis should be given to the mechanisms that will ensure a minimum of missing information. To minimize the number of missing data, it is advisable to follow recommendations published in the literature (*Hurny C, et al, 1992; Fayers PM, et al, 2000; Fairclough DL, 2002; Fayers P, et al, 2005; Efficace F, et al, 2009*).

A clinical trial with a PRO component is likely to be planned within a PRO Consensus Group consisting of clinicians, PRO researchers, patient representatives, and sponsors.

Patient-reported outcome instruments

Standardized, self-administered (by the patient) instruments with appropriate psychometric properties are recommended for measuring PROs in patients with hematological disorders. This approach, based on patients' own judgment, enables their personal feelings and perceptions to be collected, quantified, and subsequently interpreted. An overview of QoL and symptom assessment instruments is listed below.

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Quality of life assessment instruments

Broadly, there are two main types of QoL instruments, known as generic (or general) and disease-specific.

Generic (general) QoL instruments are designed to measure QoL over a wide range of disease states and populations, as well as in healthy subjects. They cover a broad spectrum of daily functioning (i.e. physical, social, psychological), disability and distress that are relevant to an individual's QoL (*Guyatt GH, et al, 1989*). The major drawback of generic QoL questionnaires is that problems which are specifically common in the group of patients under study may go undetected, despite their importance.

Disease-specific QoL instruments are designed for use with a specific population or disease state, and focus on areas of particular concern to the target group. A sound responsiveness to small, but clinically important changes makes a disease-specific instrument particularly useful when measuring the effects of medical interventions on a patient's QoL. In particular, the use of disease-specific QoL questionnaires is important for longitudinal trials within a specific disease group (*Jaeschke R, et al, 1991*).

QoL indices and profiles. Another classification of QoL instruments is based on the consideration as to whether the instrument yields an overall single-index score, or profile scores for the various components of QoL. Profiles yield an individual score for each of the areas (domains) of QoL that are assessed by the instrument. One of the major advantages of profiles is the descriptive benefits of having scores for different aspects of QoL, so that specific effects cannot be missed. In fact, this should be considered as the most important attribute of QoL instruments when used either in research applications or in routine clinical assessments.

QoL indices, on the other hand, are somewhat limited in their scope in situations where measures of, or changes in, specific areas of daily living form an important part of the decision-making process. QoL or health indices are also referred to as utility measures and are favored by health economists in assessing the relative monetary value of health care interventions, including drug treatments. The main uses of such scales are in policy decision-making processes and resource allocation. The main advantage of using QoL/health indices is their suitability for use in cost-utility analysis to determine the cost per unit gain in QoL. This class of instruments may be of limited value as therapeutic outcome measures, and their scores may be difficult to interpret in a clinical context.

There are a number of instruments which incorporate both a QoL profile and a QoL index. Examples include the EuroQol-5D, the SF-36, and the FACIT instruments.

Symptom assessment instruments

For symptom assessment there are symptom-based instruments. Currently, a number of symptom assessment tools are available for use with hematological patients. Single symptom can be assessed using visual analogue scales or numerical rating scales. Also

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symptom assessment questionnaires can be applied in order to assess such symptoms as pain, fatigue, depression, anxiety, and other symptoms.
Frequently patients experience a set of symptoms produced by either the disease itself, or the disease treatment. At present, there are questionnaires for multiple symptom assessment.
When choosing a PRO instrument for a study, it is important to have information as to whether the questionnaire has robust psychometric properties. Psychometric properties for which an instrument should be evaluated include reliability, validity, and responsiveness (i.e. sensitivity to clinically significant changes over time) (*Standards for Educational and Psychological Testings, 1999*). The validation process is well defined. Current PRO instruments benefit from the experience accumulated over the past 50 years in this field. Empiric validation supports their status as scientific measures. PRO measures have been primarily developed and validated based on psychometric theory although other approaches are used, e.g. utility.

Psychometric properties of a patient-reported outcome instrument

PRO measures are scientifically valid insofar as: 1. the outcomes can be conceptually defined; 2. they can be put into operation through questionnaires; and 3. the questionnaires can be demonstrated to be reliable, valid, and responsive (*Lohr KN, et al, 1996*).
Reliability. There should be a high degree of reproducibility (ratio of information to random error) of a score between one administration of an instrument and another within a short space of time (test-retest). Reliability is a measure of the consistency and stability of the instrument. "Test-retest" reliability is especially important for a self-administered instrument. In addition, "internal consistency" is a reliability test where items in an instrument are divided into two equivalent parts and correlation between the scores for each part is calculated.
Validity. The instrument must measure what it purports to measure. Validity testing addresses the relevance and appropriateness of an instrument's score in reflecting the health status of the population being studied. There are three basic types of validity frequently described for health status indicators: criterion, content, and construct (*Deyo RA, 1984; Kaplan RM, et al, 1976; Jette AM, 1980*). Criterion validity is the extent to which the scores of a PRO instrument are related to a known gold standard measure of the same concept. For most PROs, criterion validity cannot be measured because there is no gold standard. Content validity is evidence from qualitative research demonstrating that the instrument measures the concept of interest, including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties will not replace or rectify problems with content validity. Construct validity is the evidence that relationships among items, domains, and concepts conform to a priori hypotheses concerning logical relationships that should exist with other measures or characteristics

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of patients and patient groups (*US Food and Drug Administration: Guidance for Industry. Patient-Reported Outcome Measures, 2009*).

Responsiveness. Responsiveness or sensitivity is the extent to which PRO measure can detect true differences within the construct being measured. To evaluate treatment efficacy, it is essential, prior to its use within a clinical study, for a PRO instrument to have demonstrated an ability to detect small but meaningful changes over time. PRO measures must be capable of accurately detecting changes or differences of a magnitude that are considered important (*Guyatt GH, et al, 1990*). These changes could be due to underlying disease, drug treatment, or surgical intervention. To be used in clinical practice, the instrument must be sensitive to small but clinically important changes if it is to yield information useful for clinical decision making.

Should an instrument not meet minimum recognized standards for measurement as defined by the literature (*Bowling A, 1996; Staquet MJ, et al, 1998*), the data from its use are likely to be questionable because of a perceived bias.

Generic quality of life instruments used in hematology

The most common generic QoL instruments used in hematological settings for adults and children are presented in Tables 1 and 2.

Short Form - 36 Health Survey Questionnaire

The Short Form - 36 Health Survey Questionnaire (SF-36) was developed at the RAND Corporation in the USA for the Health Insurance Study Experiment/Medical Outcomes Study (HIS/MOS) to measure generic health concepts relevant across age, disease, and treatment groups (*Ware JJ, et al, 1993*). The SF-36 includes one multi-item scale measuring each of eight health concepts: physical functioning; role limitations due to physical health problems; bodily pain; general health; vitality (energy/fatigue); social functioning; role limitations due to emotional problems; and mental health (psychological distress and psychological well-being). The eight scales contain between

Table 1. Generic QoL instruments used in hematology-adults

Title	Abbreviation	Authors, years	Translations
Short Form-36 Health Survey Questionnaire	SF-36	Ware JJ, Sherbourne CD, 1992	139 languages
Nottingham Health Profile	NHP	Erdman RAM, et al, 1993	21 languages
Sickness Impact Profile	SIP	Bergner M, et al, 1976	23 languages
EuroQol-5D	EQ-5D	EuroQol Group, 1990	59 languages
World Health Organization Quality of Life-100	WHOQOL-100	The WHOQOL Group, 1994	43 languages

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Table 2. Generic QoL instruments used in hematology-children

Title	Abbreviation	Authors, years	Translations
Pediatric Quality of Life Inventory™	PedsQL™	Varni JW, et al, 1999	73 languages
Revidierter KINDer Lebensqualitätsfragebogen	KINDL®	Ravens-Sieberer U, Bullinger M, 1998	15 languages
Child Health Questionnaire	CHQ	Landgraf JM, et al, 1999	72 languages
TNO AZL Children's Quality Of Life Questionnaire	TACQOL	Verrips GH, et al, 1998	5 languages
KIDSCREEN	KIDSCREEN	Ravens-Sieberer U, et al. & the European KIDSCREEN Group, 2005	19 languages
Infant Toddler Quality of Life Questionnaire	ITQOL	Abetz L, 1994	–
EuroQol-5D Youth version	EQ-5D-Y	Wille N, et al, 2010	9 languages

two to ten items each, and a single-item measure of reported health is not used to score any of the eight multi-item scales. The SF-36 was constructed to achieve minimum standards of precision necessary for group comparisons in eight conceptual areas (*Ware JJ, Sherbourne CD, 1992*). It was also constructed to yield a profile of scores that would be useful in understanding population differences in physical and mental health status, the health burden of chronic disease and other medical conditions, and the effect of treatments on general health status. Translation of this instrument is available in 35 European languages.

Strengths: the SF-36 provides a comprehensive, psychometrically sound, and efficient way to measure health from a patient's point of view by scoring standardized responses to standardized questions. Population norms are available in many countries. The SF-36 is the most frequently used generic QoL questionnaire in hematology.

Weaknesses: the social functioning scale is too narrow in scope to cover social well-being. Both role limitations scales have crude response categories and particular subgroups, the frail elderly and those with complex health conditions, require finer response categories for scales such as physical functioning and bodily pain.

Nottingham Health Profile

The Nottingham Health Profile (NHP) is a generic self-administered questionnaire consisting of two parts (*Erdman RAM, et al, 1993*). The first part has 38 statements

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divided into six *a priori* areas of health concern: energy, pain, emotional reactions, sleep, social isolation and physical mobility. The respondent answers "yes" if the statement adequately reflects their current status or feeling or "no" otherwise. Part II contains questions on seven areas of daily life: employment, jobs around the home, social life, personal relationships at home, sex life, hobbies and holidays. Its content is designed to assess the number of aspects of daily life which are being affected by perceived health problems.

Strengths: before the development of the SF-36, the NHP was one of the most widely-used health status measures in Europe. It was an innovative measure at the time of its development, capturing the patient's perception of their health status. Its psychometric aspects are favorable.

Weaknesses: its system of weighting and scoring has been criticized, particularly in people whose disabilities limit their roles. The norms are considered of limited value as standards, because there are no smooth trends in health status across expected groups.

Sickness Impact Profile

The Sickness Impact Profile (SIP) is a generic measure used to evaluate the impact of disease on both physical and emotional functioning (*Bergner M, et al, 1976*). It consists of 136 items that describe activities associated with everyday life. Each item is written in the first person and in the present tense. Respondents are asked to mark those items that describe them on that day and are related to their health. Self-administration requires considerable research staff involvement in presenting instructions and answering questions. The SIP is scored according to the number and type of items that are marked. Each item is assigned a numeric scale value that reflects its degree of dysfunction. An individual's total score is computed by summing the scale values for the items that the patient endorses, dividing by the total possible score (if all items were endorsed) and multiplying by 100. Scoring is also possible at the level of categories and dimensions. There is a short version of the SIP, containing 68 items.

Strengths: the SIP is valid, reliable, and responsive. Because it has been used so extensively, published scores are available for healthy population and several diseases or conditions. The SIP has been widely translated.

Weaknesses: its main disadvantage is that it is time-consuming to complete and score. This may limit its usefulness in clinical practice and in studies where patients are required to complete several questionnaires.

EuroQol - 5D

The EuroQol - 5D (EQ-5D) is designed as an international, standardized, generic instrument for describing and evaluating QoL (*EuroQol Group, 1990*). Of particular

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importance is the instrument's capacity to generate cross-national comparisons of health state valuations. The EQ-5D consists of three parts:

- Part 1. Descriptive: Page 2 provides a simple method for obtaining an accurate self description of current QoL. QoL is classified according to five dimensions: mobility, self-care, usual activities, pain, and mood. Each dimension comprises three levels, generating a total of 243 theoretically possible health states. The levels reflect increasing degrees of difficulty. At the bottom of page 2, patients are asked to indicate their health state today compared with their general level of health over the past 12 months. Page 3 offers a simple method for a self-rating of current QoL on a "thermometer" which has endpoints of 100 at the top and 0 at the bottom. Respondents are asked to indicate their own health point today by drawing a line across the thermometer.
- Part 2. Valuation: Pages 4–7. These pages provide a technique for evaluating health states other than the state which the respondent is currently assessing. Respondents are asked to rate 13 "common core" composite health states plus "unconscious". They are also asked to rate "dead".
- Part 3. Demographic information: Pages 8 and 9 of the EQ-5D contain a series of questions designed to elicit background information. The questionnaire provides a simple descriptive profile and an overall numeric estimate of QoL which can be used for both clinical and economic evaluations of health care. Translations of this instrument are available in many languages with more in progress.

Strengths: simplicity. This instrument is applicable over a wide range of health conditions and treatments. It provides a simple, descriptive profile and an overall numeric estimate of QoL which can be used for both clinical and economic evaluations of health care. It has the capacity to generate cross-national comparisons and has been widely used in clinical trials.

Weaknesses: more valuation and application work is needed. In addition, this questionnaire is culture specific with a focus on concepts common to "western" cultures only.

World Health Organization Quality of Life - 100

The World Health Organization Quality of Life - 100 (WHOQOL-100) is the generic instrument developed under the WHOQOL project (*The WHOQOL Group, 1994*). The project was initiated to develop a concept and definition of QoL that is acceptable across diverse cultures and languages of the world and that could lead to the development of an instrument that allowed QoL to be measured in a scientific and meaningful manner in health care settings. The WHOQOL-100 contains six domains (physical, psychological, level of independence, social relationships, environment, spirituality/religion/personal beliefs), each consisting of one to eight facets. An overall QoL facet is also included. Each facet contains four questions. The questions are rated on five-point response scales, which can be for intensity, capacity, frequency, or evaluation. The exact descriptors used

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in the response scales have been derived in each version, using a pilot with linear analogue methodology to ensure metric quality of the scale in different languages. A set of 32 importance questions can also be used to gather data on the respondents' evaluation of importance of various facets for their QoL.

The WHOQOL-BREF is an abbreviated version of the WHOQOL-100 (*Murphy B, 2000; World Health Organization. WHOQoL Study Protocol, 1993*) which contains a total of 26 questions and has less burden on a patient as compared with the WHOQOL-100. The WHOQOL-BREF is grouped into four domains of QoL (physical health, psychological health, social relationships, and environment) and two items which measure overall QoL and general health.

Strengths: the WHOQOL-100 has been developed simultaneously in a large number of centers in all the regions of the world. It consists of domains that are comprehensive in coverage. It is an appropriate instrument for cross-cultural comparison of QoL.

Weaknesses: the WHOQOL-100 is long and may pose problems of excessive respondent burden if used along with other instruments and in repeat measurement design.

There are a number of generic pediatric QoL questionnaires which are used in children with hematological disorders.

Pediatric Quality of Life Inventory™

The Pediatric Quality of Life Inventory™ (PedsQL™) 4.0 Measurement Model is a modular approach to measuring QoL in healthy children and adolescents, as well as those with acute and chronic health conditions (*Varni JW, et al, 1999*). The PedsQL™ Measurement Model integrates seamlessly both generic core scales and disease-specific modules into one measurement system. It is child self-administered and parent proxy-administered: child self-report – ages 5–18, parent proxy-report – ages 2–18. The PedsQL™ 4.0 Generic Core Scales are multidimensional and include 23 items. The 23-item PedsQL™ Generic Core Scales were designed to measure the core dimensions of health as delineated by the WHO, as well as role (school) functioning. The scales include physical, emotional, social, and school functioning. Disease-specific modules are available for asthma, diabetes, cancer, cardiac diseases, rheumatology/arthritis, etc. The PedsQL™ 4.0 Measurement Model represents a significant advancement in pediatric QoL measurement, combining the reliability, validity, responsiveness, and practicality not typically found together in one pediatric QoL instrument. Translations in 39 European languages are available.

Strengths: this instrument is short and easy to complete. The PedsQL™ is the most frequently used generic QoL questionnaire in pediatric hematology and has been validated in many countries.

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Weaknesses: disadvantages of this measurement model are the lack of instruments for assessing infant health and that some domains specific to child maltreatment may be missing.

Revidierter KINDer Lebensqualitätsfragebogen

The Revidierter KINDer Lebensqualitätsfragebogen (KINDL®) is a generic instrument for self-administered QoL assessment in healthy and ill children aged 8–16 (*Ravens-Sieberer U, Bullinger M, 1998*). Developed in 1994, it is one of the first self-report instruments for QoL assessment in healthy and ill children. The instrument contains 40 items for the assessment of four dimensions of QoL: psychological well-being, physical state, social relationships and functional capacity in every-day life. Parent form is available.

Strengths: it is a widely used generic QoL tool for children and adolescents.

Weaknesses: the KINDL does not differentiate well between healthy and ill children. More valuation and application work is needed.

Child Health Questionnaire

The Child Health Questionnaire (CHQ) is developed to measure general physical and psychological health and well-being of children aged 5 and older (*Landgraf JM, et al, 1999*). It is self-administered by parents and children 10 years of age and older. The instrument consists of 14 concept health profiles and 2 component summary scores (physical/psychosocial). There are three parent-completed versions for children as young as age 5 (PF98 items, PF50 items, and PF28 items) and one version for children aged 10 and older to complete (CF87 items). The CHQ-PF50 is a paper-and-pencil measure completed by parents of children ages 5-12 (*Raat H, et al, 2002*). The instrument includes a broad spectrum of child and family-focused health areas divided into 12 concepts (Physical Functioning - 6 items; Role/Social Limitations-Physical - 2 items; General Health Perceptions - 5 items; Bodily Pain/Discomfort - 2 items; Family Activities - 6 items; Role/Social Limitations-Emotional/Behavioral (counts as 2 concepts) - 3 items; Parent Impact Time - 3 items; Parent Impact Emotion - 3 items; Self-Esteem - 6 items; Mental Health-5 items; Behavior - 5 items; Family Cohesion - 1 item; Change in Health - 1 item). Individual profile scores for each of the concepts can be computed. It is also possible to derive two summary scores (Physical and Psychosocial). Individual items require participants to respond on a Likert-type scale with higher scores indicating better or more positive health status. The CHQ-CF87 is a questionnaire with a similar structure and approach for the assessment of QoL in older children aged 10-16 (*Landgraf JM, et al, 1996; Raat H, et al, 2002*). This is a self-report form that has 87 items divided into over 10 multi-item scales and two single item scales.

Parents and children respond to items based on the past four weeks. Scores for each subscale are converted to a 0–100 scale with higher scores reflecting better functioning.

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The CHQ is a comprehensive measure of physical and psychosocial health.

Strengths: the CHQ has been tested in children with a variety of chronic conditions. The PF50 and PF28 scales have been translated in to more than 60 languages and the CF87 scale has been translated into more than 20 languages.

Weaknesses: the ceiling effects found for four subscales and the test-retest reliability problems found for five subscales limits its use for testing effects of interventions.

TNO AZL Children's Quality Of Life Questionnaire

The TNO AZL Children's Quality Of Life Questionnaire (TACQOL) is a generic instrument, and is appropriate for healthy children aged 6–15, as well as in children suffering from various conditions (*Verrips GH, et al, 1998*). The TACQOL measures QoL, defined as the child's health status plus affective responses to problems in health status. The instrument taps into 7 domains of QoL: pain and symptoms; motor functioning; autonomy; social functioning; cognitive functioning; positive moods; negative moods. Each domain is represented by 8 items. The TACQOL explicitly takes into account the child's subjective emotional response to problems in health status.

Strengths: the TACQOL is constructed as a combination of health status problems and the affective response to those problems that might be important in severe chronic diseases.

Weaknesses: the TACQOL is rather long and may pose problems of excessive respondent burden if used along with other instruments and in repeat measurement design.

KIDSCREEN

The KIDSCREEN instruments are a family of generic QoL measures that have been designed and normed for children and adolescents aged 8–18 (*Ravens-Sieberer U, et al, 2005; The European KIDSCREEN Group, 2005*). It was developed simultaneously in several European countries taking children's concepts of health and well-being into consideration. The KIDSCREEN can be used as a screening, monitoring and evaluation tool in representative national and European health surveys. Three KIDSCREEN instruments are available in child and adolescent as well as parent/proxy versions: KIDSCREEN-52 (long version) covering ten QoL dimensions, KIDSCREEN-27 (short version) covering five QoL dimensions and the KIDSCREEN-10 Index as a global QoL score. Scores can be calculated for each dimension. T-values and percentages will be available for several countries stratified by age and gender.

Strengths: the KIDSCREEN was developed simultaneously in several European countries. It has been developed as a standardized instrument which can be applied with equal relevance in healthy children and adolescents as well as in different pediatric populations.

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Weaknesses: The KIDSCREEN-52 is quite long. Potential limitation of the KIDSCREEN-27 is that the self-perception dimension is less well represented. This should be taken into account when deciding which KIDSCREEN version to use.

Infant Toddler Quality of Life Questionnaire

The Infant Toddler Quality of Life Questionnaire (ITQOL) was developed for use in infants and toddlers from at least 2 months of age up to 5 years (*Abetz L, 1994*). The Infant Toddler Quality of Life Questionnaire adopts the World Health Organization's definition of health, as a state of complete physical, mental and social well being and not merely the absence of disease, and incorporates the results of a review of child health literature and developmental guidelines used by pediatricians, and the feed-back of parents during pilot testing. Next to physical and psychosocial aspects of child health, it covers the impact of child health problems or handicaps on family life. It should be completed by the parents. The 47-item short-form and the 97-item full-length versions measure the same concepts, just with fewer items. For each concept, item responses are scored, summed, and transformed to a scale from 0 (worst health) to 100 (best health). Completion times can vary depending on a complex host of issues such as setting, context, age, cognitive functioning, language, layout, etc. Time frames for response options vary. For example, some scales ask about the past 4 weeks, the global health items asks about health "in general" and the global change items asks about health, as compared to one year ago. There are some skip patterns as the Behavior Scales and the Change in Health items which are not appropriate for infants less than 12 months of age. Response options for both lengths of the ITQOL scales are 5 levels, with the exception of Parent-Time Limitations which is 4 levels.

Strengths: this measure demonstrated acceptable reliability and construct validity in a sample of children who were healthy and another that had morbid conditions requiring neonatal intensive care (*Klassen AF, et al, 2003; De Wee EM, et al, 2011*).

Weaknesses: in its present form, the main disadvantage of the ITQOL is its length.

EuroQol - 5D Youth version

The EuroQol - 5D Youth version (EQ-5D-Y) is an EQ-5D-3L self completed version for children and adolescents aged 7–12 (*Wille N, et al, 2010*). The EQ-5D-Y was developed from the EQ-5D by adapting the original questionnaire to the requirements of measuring QoL in children and adolescents. As in the adult version, it consists of a descriptive system that comprises five items referring to mobility (walking about), self-care (looking after myself), usual activities (doing usual activities), pain and discomfort (having pain or discomfort), and anxiety and depression (feeling worried, sad or unhappy). Each item has three levels of problems reported (no problems, some problems, a lot of problems). The

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EQ-5D-Y also includes an easily understandable modification of the vertical, graduated visual analogue scale (VAS) of EQ-5D, where the respondent rates his or her overall health status on a scale from 0-100 with 0 representing the worst and 100 the best health state he or she can imagine. All items refer to the health state today.

Strengths: simplicity and shortness. It has the same advantages as EQ-5D.

Weaknesses: tested mainly in healthy population.

The examples of QoL indices used in hematological settings are the Health Utility Index and Quality of Well-Being Scale.

Health Utilities Index Marks 2 and 3

The Health Utilities Index Marks 2 and 3 (HUI2, 3) is a Multiattribute Health Status Classification System which includes a set of well-defined, generic, multiattribute health-system classification schemes that are compatible with multiattribute preference functions, allowing the computation of a single summary QoL score (*Torrance GW, et al, 1996*). The health status classification and QoL scoring systems are generic in terms of applying to all people age 5 years and older in both clinical and general populations. Clinical applications include pediatric and adult patients (*Feeny DF, et al, 1992; Horsman J, et al, 2003*). The HUIs use 10 attributes to assess health status: sensation, vision, hearing, speech, ambulation/mobility, dexterity, emotion, cognition, self-care, pain, and fertility.

Strengths: the HUI provides comprehensive, reliable, responsive and valid measures of health status and QoL for subjects in clinical studies. Utility scores of overall QoL for patients are also used in cost-utility and cost-effectiveness analyses. Population norm data are available from numerous large general population surveys. The widespread use of HUI facilitates the interpretation of results and permits comparisons of disease and treatment outcomes, and comparisons of long-term sequelae at the local, national and international levels.

Weaknesses: the focus of the HUIs is on capacity, rather than performance. Social interaction is not assessed directly in the HUIs. HUI may not adequately cover specific disease concerns.

Quality of Well-Being Scale

The Quality of Well-Being Scale (QWB) is intended to be a standardized measure, meant to cover the quality of well-being of healthy subjects and various kinds of disease groups (*Patrick DL, et al, 1973*). It is part of a resource allocation model, and its purpose is to measure variations in the well-being of populations. For each of the 43 function levels a "preference weight" has been established empirically, ranging from 1 (complete well-being) to 0 (death). The appropriate preference weight is assigned to the respondent's function level, and the resulting score is known as the Quality of Well-Being score. The

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QWB Scale consists of three ordinal scales on dimensions of daily activity. Combinations of each of the three scales of mobility, physical and social activity are taken to define 43 function levels. Questions are based on performance, not capacity. Four aspects of function are covered, mobility/confinement, physical activity, social activity (e.g. work, housekeeping) and self-care. The physical activity scale has four categories and the others have five. This instrument provides a basis for calculating quality adjusted life years (QALYs) and is used in cost utility analysis (*Pliskin J, et al, 1980*).

Strengths: the QWB Scale is a well-established measure that is based on a clear conceptual background. Its advantage is that it is able to produce utility data for health economic evaluations.

Weaknesses: this instrument is complex to score and must be administered by trained interviewers. Another major criticism has been the exclusion of psychological or emotional functioning from the scale, although the symptom list does include psychological symptoms. In addition, it describes a patient's state at only one point in time.

Disease-specific quality of life and symptom assessment instruments used in hematology

Disease-specific QoL instruments in hematology are specifically designed for a certain hematological patient population. This can be a very select patient group (e.g. multiple myeloma patients, hemophilia patients), a broader group of patients (e.g. blood cancer patients), or a group of patients that received a certain treatment (e.g. bone marrow transplant patients). Disease-specific QoL instruments, which are used in patients with different hematological disorders, are described in relevant Chapters.

Of particular note are the instruments which are used in patients with hematological malignancies, the so called "QoL questionnaires generic for neoplasms". QoL questionnaires generic for neoplasms, which are used in patients with hematological malignancies, are presented in Table 3.

The descriptions of the EORTC QLQ-C30 and the FACT-G are presented in Chapter 3.1. The Functional Living Index - Cancer and Impact of Cancer Questionnaire are described in Chapter 3.2 and in Chapter 5, respectively.

The EORTC QLQ-C30 and the FACT-G are the most widely used in patients with hematological malignancies. Translations of EORTC QLQ-C30 to 30 European languages, and of FACT-G in 26 European languages are available. These questionnaires also have modules for different hematological disorders.

The following disease-specific modules developed by the EORTC Quality of Life Group are available:

- EORTC QLQ-Leu – leukemia (see description in Chapter 3.1);
- EORTC QLQ-MY20 – multiple myeloma (see description in Chapter 3.3);
- EORTC H8 LQ – Hodgkin's lymphoma.

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The PRO instruments for use in hematology within the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System are listed in Table 4.

Table 3. QoL questionnaires generic for neoplasms used in patients with hematological malignancies

Title	Abbreviation	Authors, years	Translations
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire	EORTC QLQ-C30	EORTC Quality of Life Group, 1988	83 languages
Functional Assessment of Cancer Therapy - General	FACT-G	Cella D, et al, 1993	54 languages
Functional Living Index - Cancer	FLIC	Schipper H, 1984	22 languages
Impact of Cancer Questionnaire	IOC	Zebrack BJ, et al, 2006	–

Table 4. Modules within the Functional Assessment of Chronic Illness Therapy Measurement System for use in hematology

Disease-specific measures
FACT-Leu – leukemia FACT-Lym – non-Hodgkin's lymphoma FACT-MM – multiple myeloma FACT-Th – thrombocytopenia
Treatment-specific measures
FACT-BMT – patients undergoing bone marrow transplantation FACT-BRM – patients receiving biologic response modifiers
Symptom-specific measures
FACIT-F – patients with fatigue FACT-An – patients with anemia/fatigue
Cancer-specific symptom indices
FACT/NCCN Lymphoma Symptom Index (FLymSI) – non-Hodgkin's lymphoma

Among symptom assessment tools, it is important to point out questionnaires which measure pain, fatigue, psychological issues, and other symptoms and can be used in patients with hematological neoplasms.
Commonly used questionnaires to measure pain are presented in Table 5.

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Table 5. Pain assessment instruments used in patients with hematological malignancies

Title	Abbreviation	Authors, years	Translations
Brief Pain Inventory	BPI	Cleeland CS, 1994	44 languages
McGill Pain Questionnaire	MPQ	Melzack R, 1971	22 languages
Memorial Pain Assessment Card	MPAC	Fishman B, Foley K, 1994	3 languages

The tools presented in the Table were originally developed for cancer patients. Currently, they are used in patients with hematological malignancies. Descriptions of these instruments are presented in Chapter 3.3.

The questionnaires used for fatigue assessment in patients with hematological malignancies are presented in Table 6.

The instruments listed in Table 6 are described in Chapter 3.6 and in Chapter 4.

To measure multiple symptoms in patients with hematological malignancies, multiple symptom assessment tools developed for cancer patients are being used. The following

Table 6. Fatigue assessment instruments used in patients with hematological malignancies

Title	Abbreviation	Authors, years	Translations
Piper Fatigue Scale	PFS	Piper BF, et al, 1989	8 languages
Multidimensional Fatigue Inventory	MFI	Smets EM, et al, 1995	11 languages
Functional Assessment of Chronic Illness Therapy-Fatigue	FACIT-F	Cella D, 1997	52 languages
Functional Assessment of Cancer Therapy- Anemia	FACT-An	Cella D, 1997	38 languages
Fatigue Symptom Inventory	FSI	Hann DM, et al, 1998	5 languages
Schwartz Cancer Fatigue Scale	SCFS	Schwartz A, 1998; Schwartz A, et al, 1999	5 languages
Brief Fatigue Inventory	BFI	Mendoza TR, et al, 1999	30 languages
Cancer Fatigue Scale	CFS	Okuyama T, et al, 2000	5 languages
EORTC-Fatigue Module	EORTC QLQ-FA13	EORTC Quality of Life Group	Currently in phase IV evaluation

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tools can be utilized: the M.D. Anderson Symptom Inventory (see description in Chapter 3.2), the Edmonton Symptom Assessment System (see description in Chapter 3.1), and the Memorial Symptom Assessment Scale (see description in Chapter 3.1).
For the evaluation of physical and psychological symptoms in patients with hematological malignancies, the Rotterdam Symptom Checklist (RSCL) can also be used (see description in Chapter 5).
The questionnaires which can be used to measure psychological problems in patients with hematological disorders are presented in Table 7.

Table 7. Instruments to assess psychological distress used in patients with hematological disorders

Title	Abbreviation	Authors, years	Translations
Profile of Mood States	POMS	McNair DM, et al, 1971	21 languages
Hospital Anxiety and Depression Scale	HAD	Zigmond AS, Snaith RP, 1983	79 languages
Psychological Distress Inventory	PDI	Morasso G, Costantini M, 1996	2 languages
Brief Symptom Inventory	BSI	Derogatis LR, et al, 1983	3 languages

Profile of Mood States

The Profile of Mood States (POMS) is a psychological functioning instrument for self-administered QoL assessment (*McNair DM et al, 1971*). The POMS is a 65-item instrument designed to assess transient mood across 6 subscales: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Fatigue-Inertia, Vigour-Activity, and Confusion-Bewilderment. A seventh score, Total Mood Disturbance, is calculated by subtracting the score on the one positively scored subscale, Vigour-Activity, from the sum of the other five subscales. A number of short forms have been developed for use with cancer patients. These include an 11-item version that assesses only total mood disturbance and a 14-item version that excludes items reflecting somatic content and is summarized in a Negative Affect Scale and a Positive Affect Scale, and a 37-item version that retains all 6 subscales and has been extensively validated in cancer patients. The POMS asks people to report how they feel right now.

Strengths: the POMS assessment provides a rapid, economical method of assessing transient, fluctuating active mood states.

Weaknesses: the information about psychometric properties of the short forms of the tool is limited.

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Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HAD) is a questionnaire commonly used to assess levels of anxiety and depression (*Zigmond AS, 1983*). The HADS includes statements that the patient rates based on their experience over the past week. The 14 statements on the scale are equally divided between either generalized anxiety or depression. The latter is largely composed of reflections of the state of anhedonia (i.e. the inability to enjoy oneself or take pleasure in everyday things enjoyed normally). Even-numbered questions relate to depression and odd-numbered questions relate to anxiety. Each question has 4 possible responses. Responses are scored on a scale from 0–3. Thus, the maximum score for each area (i.e. depression and anxiety) is 21. A score of 11 or higher indicates the probable presence of a mood disorder. A score of 8–10 is suggestive of the presence a mood disorder. The two subscales, anxiety and depression, have been found to be independent measures. In its current form the HADS is now divided into four ranges: normal (0–7), mild (8–10), moderate (11–15), and severe (16–21). It takes 2–5 minutes to complete the scale.

Strengths: the HADS has been found to perform well in assessing the symptom severity and caseness of anxiety disorders and depression in somatic, psychiatric, and primary care patients, as well as in the general population. It is sensitive to changes both during the course of the disease and in response to psychotherapeutic and psychopharmacological intervention. Additionally, HADS scores can be used to predict psychosocial and possibly physical outcomes as well.

Weaknesses: comprehensive documentation of the scale's psychometric properties is lacking.

Psychological Distress Inventory

The Psychological Distress Inventory (PDI) is a 13-item self-administered questionnaire developed to measure psychological distress in cancer patients (*Morasso G, Costantini M, 1996*). It is used during the assessment of emotional and interpersonal dysfunction in people with cancer at any stage of the disease, including those who are terminally ill, specifically with regard to adjustment. The recall period for the PDI is the past week.

Strengths: it is a reliable and valid tool for measuring psychological distress in cancer patients and for detecting psychiatric disorders through a screening procedure.

Weaknesses: while an English translation exists, validation to date has been on the Italian version only.

The Brief Symptom Inventory is described in Chapter 4.

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Choosing patient-reported outcome instruments

Standardized questionnaires with established psychometric properties which might be used for patients with hematological disorders are available today. However, choosing PRO instrument(s) is a complex process.

When choosing an appropriate PRO instrument for a specific purpose the following characteristics of a questionnaire should be considered:

- Applicability. The content and emphasis of the measure must be appropriate for the purpose being considered and also acceptable to the patients who are required to complete the questionnaire.
- Practicality. The respondent and professional burden involved in collecting and processing of data must be minimal, and it must be feasible to use the results in a clinical situation.
- Specificity. A PRO measure must be capable of identifying populations correctly (a specific range of scores would be expected for healthy individuals, which would be different from the scores for a sick population).
- Comprehensiveness. The instrument must be comprehensive in its coverage.

A final selection criterion for a questionnaire is the availability of a PRO instrument in the appropriate language, or the appropriate cultural adaptation. The most frequently used PRO instruments are translated and validated in a number of different languages.

Disease stage and treatment type are of importance when choosing a PRO instrument(s) for patients with hematological disorders. One of the major strengths of generic QoL questionnaires is their standardized format, which allows comparisons to be made between results from different studies across different diseases and populations. Furthermore, the wide range of applicability of generic instruments makes them particularly useful in surveys to assess the health of large groups of patients from the general population, thus providing base-line values (norms). Naturally, this permits comparisons to be made between the population as a whole and a specific hematological patient group, thereby facilitating the interpretation of results from clinical studies in the context of society in general. The use of generic QoL questionnaires allows the stratification of patients according to grades of QoL impairment before treatment and to measure QoL treatment response. Depending on the end-point model, non-disease-specific generic instruments do require supplementation with disease-specific instruments or symptom questionnaires which capture disease-specific and treatment-specific issues.

Symptom measurement is of much importance in hematological patients who experience multiple symptoms due to the disease or its treatment. Adequate symptom assessment is a prerequisite of effective symptom management. In accordance with the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (*Basch E, et al, 2009*) symptom assessment tools might be used if the

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following issues are under investigation:

- Targeted symptom reduction
- Drug safety evaluation
- Toxicity identification.

Recently a new series of symptom tools, the Comprehensive Symptom Profile (CSP), has been developed to provide comprehensive symptom assessment in patients with certain hematological disorders (*Novik A, et al, 2010a; Novik A, et al, 2010b; Novik A, et al, 2010c*). The instruments of this series are comprehensive and specific to a certain hematological entity. They allow determination of the symptom profile and the evaluation of symptom severity before and during treatment, as well as during follow-up. The use of the instruments in this series makes it possible to capture disease-specific and treatment-specific issues at different time-points of treatment.

In future clinical trials the standardized approach to capture PRO will be to combine QoL questionnaire(s) with symptom assessment instruments.

Using PRO data calls for more than just instrument selection. A well-defined measurement strategy should be devised with careful attention paid to identification of appropriate domains to be measured, instrument(s) to utilize, and, if necessary, revalidation requirements. The FDA requirements for use of PRO data in labeling claims should be no more or less stringent than those used for other clinical end-points (*Snyder CF, 2007*).

The choice of PRO instrument(s) and measurement strategy for clinical studies should be discussed within the PRO Consensus group, consisting of a multidisciplinary team of experts.

Interpreting patient-reported outcome data

Methods to analyze and interpret PRO data are available in the literature on this topic (*Staquet MJ, et al, 1998; Sloan J, et al, 2003; Ferreira-Gonzalez I, et al, 2007; Montori VM, et al, 2007; Osoba D, 2011*). However, interpreting PRO data is one of the most complicated issues in PRO measurement.

Interpretability means the degree to which one can assign easily understood meaning to an instrument's quantitative score in a particular application (*Patrick DL, et al, 2007*). Interpretation may vary with the clinical trial population and protocol and thus is not considered a property of the PRO instrument *per se* even though accumulated evidence with individual measures may suggest a particular meaning of a score change. One of the major concerns of clinicians regarding use of PRO instruments is uncertainty in translating a score into a meaningful treatment benefit for patients.

PRO information should add to the hematologist's understanding of the way in which the individual patient is likely to be affected by their disease, by the treatment provided, or by the health care in general. The purpose of including PROs in clinical trials is to

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understand the patient's perspective on what is gained or lost from the treatment. This information should help in clinical decision making, i.e. in deciding whether or not to modify specific elements of treatment such as medications, consultant care, patient education, or support services. To facilitate this process, it is necessary to make PROs in clinical trials more interpretable to clinicians. The interpretation of PRO study results hinges on the translation of changes in these scores into clinically meaningful terms (*Johnston BC, et al, 2010; Turner D, et al, 2010*).

Recently, several steps to making PRO data from clinical trials useful to clinicians have been considered (*Guyatt G, Schünemann H, 2007; Guyatt G, et al, 2008a; Guyatt G, et al, 2008b*):

- Establish the minimal important difference (MID)
- Report mean differences, ideally in change, and in relation to the MID
- Choose intuitive thresholds
- Determine the proportion of patients who meet these thresholds
- Use these data to determine the proportion of patients who have achieved important benefit from treatment, and the associated number needed to treat (NNT).

Thus, interpretation of PRO data within clinical trials should provide information relevant to the individual patient. After all, a major objective of PRO is to individualize therapies and to account for different values. However, a significant change in mean PRO scores does not imply that all patients, even most patients, can be expected to show a positive response to therapy. Confusion between population and individual patient perspective is exacerbated by an emphasis on the reporting of clinical trial results in terms of mean difference of the change from baseline between treated and control groups. The mean or median change reported for a group of patients may have little relevance to expected changes for a single patient. To avoid this problem, a separate analysis in the groups with different base-line QoL impairment should be undertaken. Evaluation of treatment outcomes in the patient groups stratified by the QoL impairment grades allows more precise and profound information to be obtained about new products and new treatment strategies. In addition, individual QoL treatment response should be evaluated and the proportion of patients according to the grades of QoL treatment response presented.

Sometimes difficulties in interpreting PRO data are due to discrepancies between self-reported QoL and clinical and physiological markers. In essence, QoL of a patient during and after treatment reflects the level of his/her adaptation to new internal and external factors. The response shift model of QoL may contribute to discrepancies between self-reported QoL and objective impairments. This model suggests that perceptions of QoL are the result of changes in health (*catalysts*, such as a transplant) and/or initiating behavioral processes (*mechanisms*, such as seeking social support) which lead to changes in internal standards, values or conceptualizations of QoL (*response shifts*). Furthermore, the characteristics of an individual (*antecedents*) will influence this process. The model suggests that these concepts are linked through "a dynamic feedback loop" that has the

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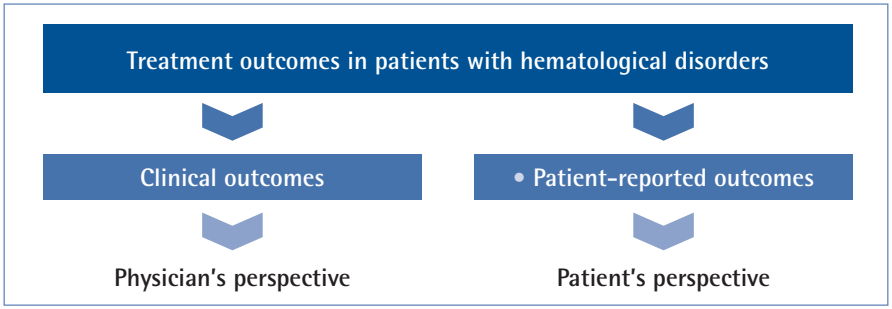
aim of maintaining or improving an individual's perception of their QoL (*Sprangers MA, Schwartz C, 1999; Sprangers MA, et al, 2010*). Patients may, therefore, engage in "recalibration shifts", in which their standards of what constitutes "good" QoL changes due to their experience of illness and treatment, or they may be engaging in response shifts resulting from changing values. Thus, during their illness and treatment, although low scores may be reported consistently on some subscales, the domains of QoL that these scores reflect may become less important and have little impact on perceptions of QoL overall. Finally, patients may simply have reconceptualized the meaning of QoL. Theoretically driven research is needed to better understand the processes underlying patient perceptions of QoL and to clarify if patients are indeed engaging in response shifts. Finally, integration of PROs is essential to evaluate the effect of treatment. Personalized treatment in patients with hematological disorders should be based on detailed information concerning the disease and the patient. A dichotomous model to evaluate treatment outcomes in patients with hematological diseases is presented on the Figure 1. The concept of clinical outcomes (clinician-reported) is the physician's perspective of treatment efficacy, and is considered to be the objective component in this model. PROs are the patient's perspective, and are the subjective component. Clinical outcomes are evaluated in terms of clinical response; PROs in terms of QoL and symptom response.

Figure 1. The dichotomous model for evaluating treatment outcomes in patients with hematological diseases



In addition, for comprehensive evaluation of benefits of new products in the frame of clinical trials, clinical and biological parameters are necessary, but not sufficient. PRO measurements at baseline and during the intervention are recommended to gain full information about patient symptoms, functioning, and satisfaction.

Finally, appropriate approaches to capture PROs in hematological patients are worthwhile. These approaches should be scientifically sound, feasible, and policy relevant. The involvement of a PRO Consensus Group for the planning of a clinical trial with a PRO component is highly recommended.

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CHAPTER 3

Quality of life and symptom assessment in hematological patients

3.1

Leukemias

State of the art

There are four main types of leukemia: chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), and acute myeloid leukemia (AML).

CLL is the most common leukemia in the Western world, occurring predominantly in older patients (>65 years of age). Many patients with CLL will never need treatment, though even in this group some impairment in QoL has been reported (*Shanafelt TD, et al, 2007*). For patients with disease progression, before the initiation of treatment, quality of life (QoL) is substantially impaired compared with population norms, particularly with respect to fatigue, sleep disturbance, role functioning, and global QoL (*Else M, et al, 2008*). The median life expectancy in CLL is approximately six years from the time of treatment (*Catovsky D, et al, 2007*). Long-term QoL is therefore a major issue for patients at all stages of the disease and its treatment. Published data on QoL in CLL include some non-randomized studies, mostly focusing on a single time-point and including both those treated and untreated for this disease (*Bertero C, et al, 1997; Holzner B, et al, 2001; Holzner B, et al, 2004; Levin TT, et al, 2007; Shanafelt TD, et al, 2007*). The results of four large randomized clinical trials (RCT) with QoL as a secondary end-point are now available (*Eichhorst BF, et al, 2007; Else M, et al, 2012; Eichhorst BF, et al, 2009; Robak T, et al, 2010*). In the study by Eichhorst and colleagues comparing fludarabine versus fludarabine plus cyclophosphamide as first line therapy in younger patients with CLL, it was shown that the beneficial clinical effects of fludarabine plus cyclophosphamide were not obtained at the expense of detrimental effects on patients' QoL (*Eichhorst BF, et al, 2007*). In the LRF CLL4 trial, conducted by Catovsky and colleagues, previously untreated patients of any age were randomized to receive chlorambucil, fludarabine or fludarabine plus cyclophosphamide (*Catovsky D, et al, 2007*). QoL in this trial was investigated over a 5-year period (*Else M, et al, 2012*). While on treatment, some transient QoL impairment was seen in patients receiving fludarabine, particularly fludarabine plus cyclophosphamide, as compared with chlorambucil. Thereafter, QoL appeared broadly similar between treatment groups. Sustained remissions, which were most frequent in the fludarabine plus cyclophosphamide group, were associated with long-term QoL benefits, thus supporting the use of primary treatment regimens likely to achieve and sustain remission in otherwise medically fit patients of all ages, including those aged >70 years. A possible survival benefit has been seen when fludarabine plus cyclophosphamide is combined with rituximab (*Robak T, et al, 2010*), and this is now the treatment of choice in CLL. No substantial difference in QoL was seen in trials comparing fludarabine plus cyclophosphamide with fludarabine plus cyclophosphamide plus rituximab (*Eichhorst B, et al, 2009; Robak T, et al, 2010*).

Patient-reported outcome (PRO) issues in CML have been studied in patients receiving different treatment modalities. Until recently, the only treatment choices for CML were

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stem cell transplantation, which is limited to a small proportion of patients, or hydroxyurea-based or interferon alfa-based regimens. Treatment with interferon alfa has a significant adverse impact on QoL and is associated with a broad spectrum of symptoms (*Valentine AD, 1998; Trask P, et al, 2000; Homewood J, et al, 2003*).

Hydroxyurea-based treatment is well tolerated and has few side effects, as compared with interferon alfa, but is of limited efficacy, with no effect on disease progression or survival. At present, targeted therapies are available for CML treatment. QoL and symptoms during imatinib treatment for chronic phase CML patients compared with interferon alfa-based regimen have been studied (*O'Brien SG, et al, 2003; Hahn EA, et al, 2003; Efficace F, et al, 2011a*). Research has shown that imatinib provides a clear advantage in terms of QoL over interferon-based treatments. Recently, a systematic review was undertaken on all studies with CML patients published from 1980-2010 and including a PRO evaluation (*Efficace F, et al, 2011b*). Out of 619 articles scrutinized, 15 met eligibility criteria. None of these studies was published before 1995. Six dealt mainly with interferon-based therapies, 7 with bone marrow transplantation, and only 2 evaluated PROs in the context of targeted therapies. As a result, no disease-specific, validated PRO instrument for these patients was found. The main finding is that imatinib provides a clear advantage in terms of QoL over interferon-based treatments. Thus, there is lack of data concerning PROs in patients treated with current targeted therapies. Documenting QoL and the side effects of CML treatments from the patients' perspective, is needed to evaluate overall treatment effectiveness and net clinical benefit of newer therapeutic strategies.

Intensification of treatment for AML in adult patients has resulted in a substantial improvement in long-term prognosis. Therefore, the assessment of QoL of patients undergoing treatment is of growing interest. Patients with AML may receive aggressive therapies (e.g. chemotherapy and bone marrow transplantation) that are thought to significantly affect QoL. Therefore, it is crucial to assess the QoL impact on AML patients undergoing treatments. A large survey of the literature between 1990–2002 showed that AML and its associated treatments have a substantial negative impact on a patient's QoL (*Redaelli A, et al, 2004*). The most negative QoL burden is apparent soon after the diagnosis of the disease and during the course of therapy at the end of inpatient treatment (*Schumacher A, et al, 1998*). Long-term survivors appear to recover QoL almost completely with respect to physical, and emotional well being, but incur continued sexual dysfunction and reduced psychological functioning (*Persson L, et al, 2001*). At the same time, long lasting impacts occur, and these have been associated with more aggressive treatment. In particular, bone marrow transplantation (BMT) is associated with long-term reductions in QoL. Problems of decreased QoL faced by AML survivors who received allogeneic transplantation in their first remission, compared to survivors who received other post-remission treatments have been highlighted (*Messerer D, et al, 2008*). To note, AML is a hematological disease which is the most prevalent in elderly

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subjects, with the median age of incidence being over 65 (*Brincker H, 1985*). The treatment of elderly patients with AML is still a matter of debate, as intensive chemotherapy leads to unsatisfactory results in this subset, with dismal complete remission, disease-free survival, and overall survival rates lower, as compared with those in younger patients. In addition, many elderly AML patients are unfit for intensive chemotherapy and are generally managed with palliative approaches (*Burnett AK, et al, 2007*). Evaluation of QoL changes and their association with therapy and survival in elderly patients with AML may be a potential factor for treatment decisions. It was recently shown that in elderly AML patients QoL at diagnosis may be considered a prognostic factor for overall survival and, thus, as a potential variable that may be integrated in the process of decision-making for treatment allocation (*Oliva E, et al, 2011*).

ALL accounts for about 20% of adult leukemias. Treatment results in adult ALL have lagged behind the improvements achieved in the pediatric population. At present, intensified approaches to treat adult patients with ALL are being implemented to improve treatment outcomes in this patient population. The results seem to be superior to those reported with conventional adult protocols. However, there is limited data on the impact of such intensified approaches and resulting toxicities on the QoL of these survivors. Identifying important factors affecting the QoL may permit attempts at early interventions and may help to further modify treatment regimens and mitigate these adverse effects on QoL. Thus, studies evaluating PROs during ALL treatment and of long term survivors of adult ALL are needed.

CML, AML and especially ALL occur in children as well as adults. In children, side-effects from treatments for leukemia may have a greater short-term impact on QoL than those for other cancers, which presumably has implications for heightened distress and reduced QoL in children's families. Although prognosis for children is relatively good, impacts on both physical and psychosocial QoL may persist into adulthood. Therefore, QoL and symptom assessment is of importance for children with leukemia, both in the long-term as well as the short-term. PRO issues in pediatric patients are considered in Chapter 7.

Thus, documenting QoL and the side effects of leukemia treatments from the patients' perspective is needed to evaluate overall treatment effectiveness and net clinical benefits/risks of newer therapeutic strategies in this patient population. In the era of risk-adapted therapy, information about the impact of the leukemia and its treatments on patient's QoL in the long-term, as well as the short-term is of special value.

Patient-reported outcome instruments

For QoL measurement in leukemia patients, both generic QoL questionnaires and cancer-specific QoL questionnaires are used. Among generic tools, the SF-36 (see description in

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Chapter 2) and the EuroQoL-5D (see description in Chapter 2) are in use; among the cancer-specific instruments are the EORTC QLQ-C30 and the FACT-G.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire (EORTC QLQ-C30) is a QoL questionnaire developed by the European Organization for Research and Treatment of Cancer Quality of Life Study Group for the measurement of QoL in cancer patients in clinical trials (*Aaronson NK, et al, 1993*). It consists of 30 items, five function scales (physical, emotional, social, role, and cognitive); and three symptom scales (fatigue, nausea/vomiting, and pain). A number of single items are also included (dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The two last items assess global health and overall QoL. Most items are responded to on a 4-point scale ranging from 1 (not at all) to 4 (very much), asking to what extent the patient experienced the symptom during the last week. The two items assessing global health and overall quality of life are responded to in seven categories ranging from 1 (very poor) to 7 (excellent). The EORTC QLQ-C30 is available in 30 European languages.

Strengths: it is simple to score and easy to use. About 10 to 15 minutes is required for its completion. It has been widely used in clinical trials.

Weaknesses: an additional questionnaire or the EORTC QLQ module is needed to cover disease or condition specific issues.

Functional Assessment of Cancer Therapy - General

The Functional Assessment of Cancer Therapy - General (FACT-G) is the cancer core questionnaire from the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System (*Cella D, et al, 1993*). The latest version 4 consists of a total of 27 Likert-type items formulated into separate subscales: physical (7 items), emotional (6 items), social/family (7 items), and functional (7 items) well-being. Subjects are asked to respond to each item with a score of 0–4, where 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. A higher score indicates a better level of QoL. This questionnaire has demonstrated high coefficients for reliability and validity. The FACT-G is available in 26 European languages.

Strengths: this assessment instrument is simple to score and easy to use. About 15 minutes is required for its completion. It is widely used in clinical trials.

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Weaknesses: an additional questionnaire or the FACIT module is needed to cover disease or condition specific issues.

Both questionnaires have been extensively used in international cancer clinical trials. The FACT-G and the EORTC QLQ-C30 questionnaires have four subscales in common, although it should be noted that the labels of the corresponding subscales do not match precisely: physical functioning (EORTC QLQ-C30) versus physical well-being (FACT-G), social functioning versus social/family well-being, emotional functioning versus emotional well-being, role functioning versus functional well-being. A study comparing the four scales showed that the physical subscales of both questionnaires were measuring the same domain. For the emotional and the role/functional domains, correlations of corresponding QLQ-C30 and FACT-G subscales were only moderately high, whereas the correlation for the social subscales was low. Thus, it can be concluded that it is important to choose the questionnaire that is most suitable for the research question, although both questionnaires assess QoL in blood cancer patients.
Currently there are also leukemia-specific QoL questionnaires – the FACT-Leu from the FACIT set, and two modules from the EORTC QLQ set – the EORTC QLQ-CLL16 and the MRC/EORTC Leukemia Module (QLQ-LEU).

Functional Assessment of Cancer Therapy - Leukemia

The Functional Assessment of Cancer Therapy - Leukemia (FACT-Leu) is developed as a module to FACIT's core measure, the FACT-G, to meet the need for a disease-specific QoL questionnaire for patients with leukemia (*Webster K, et al, 2002*). Originally it included 27 items to assess 17 physical symptoms (fevers, bleeding, general pain, stomach pain, chills, night sweats, bruising, lymph node swelling, weakness, tiredness, weight loss, appetite, shortness of breath, functional ability, diarrhea, concentration, and mouth sores) and 10 emotional/social concerns (frustration with activity limitation, discouraged by illness, future planning, uncertainty, worry about illness, emotional lability, isolation, infertility concern, family worry, and worry about infections). These items are rated on a scale of 0–4 (higher scores reflect better QoL). The final version consists of 44 items, 27 items from the FACT-G and 17 items specific to leukemia. They are combined into the Physical Well-being (PWB), Social/Family Well-being (SFWB), Emotional Well-being (EWB), Functional Well-being (FWB), Leukemia Subscale (LeuS), Treatment Outcome Index (TOI), FACT-G Total, and FACT-Leu Total scores.

Strengths: it is easy to interpret, as total scores are available.

Weaknesses: information about psychometric properties of the instrument is limited. It is not specific to certain types of leukemia.

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European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Chronic Lymphocytic Leukemia Module

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Chronic Lymphocytic Leukemia Module (EORTC QLQ-CLL16) is a 16-item questionnaire designed to supplement the EORTC QLQ-C30 in assessing patients with chronic lymphocytic leukemia (EORTC Quality of Life Projects). It assesses fatigue (2 items), treatment side effects (3 items), disease symptoms (5 symptoms), and infection (4 items), and includes two single item scales on social activities and future health worries. The items are measured on a four-point scale where 1 = not at all and 4 = very much. These scores are transformed to give a rating from 0–100, where 0 = no symptoms or problems and 100 = severe symptoms or problems.

Strengths: the instrument is specific to CLL.

Weaknesses: information about psychometric properties of the instrument is limited.

MRC/EORTC-QLQ-LEU

The MRC/EORTC-QLQ-LEU module has been developed to supplement the EORTC QLQ-C30 when assessing long-term QoL in leukemia patients (*Watson M, et al, 1996*). The MRC/EORTC-QLQ-LEU is a 32-item scale that measures symptoms related to chronic graft-versus-host disease, symptoms related to infection, sensory loss, and functional status. Based on data from 388 AML patients undergoing BMT and other treatments, the QLQ-LEU underwent factor analysis; the resulting 3 factors demonstrated Cronbach's alphas ranging from 0.58–0.79. The QLQ-LEU distinguished patients undergoing allograft from those undergoing autograft or chemotherapy. In another study (*Redaelli A, et al, 2003*), 15 items from the module assessing fever, infection, weight loss, vision, taste and smell changes, hearing, sores in mouth, swallowing, dental problems, dizziness, itching, blood in urine, skin changes, and hair loss showed good internal consistency. The leukemia module can be recommended for use alongside generic QoL instruments as a measure of long-term QoL in leukemia trials.

Strengths: this instrument has shown good sensitivity and specificity between treatment arms. It is particularly useful in evaluating the long-term effects of treatment in relation to chronic graft-versus-host disease and infection susceptibility.

Weaknesses: information about the psychometric properties of the instrument is limited.

The FACT-BMT (see description in Chapter 4) offers an alternative to the EORTC QLQ-LEU for assessing QoL in patients undergoing bone marrow transplantation.

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For leukemia patients treated with biologic response modifiers, the FACT-BRM may be applied.

Functional Assessment of Cancer Therapy - Biologic Response Modifiers

The Functional Assessment of Cancer Therapy - Biologic Response Modifiers (FACT-BRM) is part of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system. It is a valid 40-question instrument for the assessment of quality of life in patients treated with biologic response modifiers (*Bacik J, et al, 2004; Mazumdar M, et al, 2006*). Patients use a five-point scale (0 = not at all, 4 = very much) to rate their physical, functional, social and family, and emotional well-being, as well as treatment-specific QoL concerns.

Strengths: a minimal clinically important difference on the FACT-BRM has been identified to be 5–8 points in patients with chronic phase CML undergoing treatment with biologic response modifiers.

Weaknesses: information about the psychometric properties of the instrument is limited.

The Life Ingredient Profile may be also used in leukemia patients to reflect the patient's estimation of the symptoms of disease, as well as the side effects of treatment and is designed for comparing different regimens of chemotherapy.

Life Ingredient Profile

The Life Ingredient Profile (LIP) is a 4-part instrument administered at different times during the course of the patient's disease (*Stalfelt AM, et al, 1993*). LIP 1 consists of 22 questions and is administered at diagnosis to evaluate the patient's physical and mental state, as well as leisure activities at baseline. LIP 2 is a 21-question follow-up component aimed at tracking the physical and mental strain that the disease imposes. LIP 3 consists of 8 questions and is used in conjunction with LIP 2 to evaluate the patient's ability to enjoy activities despite the disease. Finally, LIP 4 is used as a comparison to LIP 1 to show long-term changes to the patient's QoL.

Strengths: the LIP has shown good validity, reliability and sensitivity to change in patients with acute leukemia. It is easy to administer, and the structured interviews take only 10–20 min. The questionnaire appears to assess important dimensions of QoL without being a burden on the patient or the nursing staff.

Weaknesses: the questionnaire was not designed specially for leukemia patients.

It is also worth mentioning that, in certain conditions, visual analogue scales (VAS) may be used to assess cancer related issues in hematological patients, and leukemia patients

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in particular. A VAS consists of a dual-polarity line (usually 10 cm long) representing the extremes of an individual's QoL. Patients are asked to assess their global QoL at a particular point in time or over the time-scale of, for example, the previous week, and mark the line accordingly. The higher the score marked, the better the QoL. A VAS may be highly recommended for the clinical setting for follow-up of patients under treatment. Cancer specific variants of the VAS have been developed (*McCormack HM, et al, 1988*): the Linear Analogue Scale Assessment (LASA) can be used to measure energy level, ability to do daily activities, and overall QoL. Sensitivity of LASA to hemoglobin levels has been demonstrated (*Demetri GD, et al, 1998*). Along with that, QOL-E has been successfully used with elderly patients with AML (see description in Chapter 3.4).

To assess fatigue in leukemia patients, instruments for fatigue assessment in cancer patients can be used (see the descriptions in Chapter 3.6).

For symptom assessment in leukemia patients, the M.D. Anderson Symptom Inventory, the Memorial Symptom Assessment Scale, and the Edmonton Symptom Assessment System can be used. A description of the MDASI is presented in Chapter 3.2.

Memorial Symptom Assessment Scale

The Memorial Symptom Assessment Scale (MSAS) is a patient-rated instrument that was developed to provide multidimensional information about a diverse group of common symptoms (*Portenoy RK, et al, 1994*). It questions patients about their experiences with 32 symptoms commonly associated with cancer along three dimensions: (a) severity; (b) frequency with which it occurs; and (c) distress it produces. Each symptom is scored on a scale of 0–4 ranging from no symptoms to very much. The scoring of the MSAS yields several validated subscale scores.

A 10-item MSAS Global Distress Index is considered to be a measure of overall symptom distress. The Global Distress Index is the average of the frequency of 4 prevalent psychological symptoms (feeling sad, worrying, feeling irritable, and feeling nervous) and the distress associated with 6 prevalent physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, and dry mouth). The Physical Symptom Subscale score is the average of the frequency, severity, and distress associated with 12 prevalent physical symptoms: lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness. The Psychological Symptom Subscale score is the average of the frequency, severity, and distress associated with 6 prevalent psychological symptoms: worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating. The Total MSAS score is the average of the symptom scores of all 32 symptoms in the MSAS instrument. Each symptom score is an average of its dimensions. On the short form, there is only one dimension for each symptom, distress for physical symptoms, and frequency for psychological symptoms. There are forms of the tool for adults, adolescents, and children.

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Strengths: the MSAS is a reliable and valid instrument for the assessment of symptom prevalence, characteristics, and distress. The validity and reliability of the instrument have been established among ethnically diverse populations (*Chang VT, et al, 2000*).

Weaknesses: there is limited use in terminally ill patients and limited assessment of overall QoL.

Edmonton Symptom Assessment System

The Edmonton Symptom Assessment System (ESAS) is designed to assist in the assessment of nine common symptoms experienced by cancer patients: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well being, and shortness of breath (*Bruera E, et al, 1991*). The above symptoms are assessed with the help of VAS (0–100 mm) which may be completed either by the patient alone, by the patient with a nurse's assistance, or by the nurses or relatives. One blank scale is available for patients to use to assess any other problem as needed. The severity of each symptom at the time of assessment is rated from 0–10 on a numerical scale; with 0 meaning that the symptom is absent and 10 that it is the worst possible severity.

Strengths: the ESAS provides a clinical profile of symptom severity over time. It is a simple and useful method for regular assessment of symptom distress in the palliative care setting.

Weaknesses: the instrument is not a complete assessment in itself. For good symptom management to be attained, the ESAS must be used as one part of a holistic clinical assessment.

Practical considerations for patient-reported outcome assessment

Measurement of QoL in leukemia patients at diagnosis may provide useful information regarding patients' preferences and prognosis, while follow-up measurements may indicate acceptance, adaptation, and the adverse effects of disease and therapy. In order to identify benefits and risks of leukemia treatment, it is important to evaluate both QoL profile changes during treatment and the specific configuration of symptoms usually associated with a particular leukemia type and its current treatments. For this purpose the use of a proper questionnaire/questionnaires is the key issue.

The choice of a PRO measure is crucial when planning a study with a PRO component. It depends on the study goal, the type of leukemia, and treatment modality. In general, in leukemia patients, as in patients with other neoplasms, different types of QoL instruments can be used (Table 1).

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Table 1. QoL instruments that can be used with leukemia patients

Generic QoL instrument
Examples: SF-36, EuroQoL-5D
Cancer-specific QoL instrument
Examples: EORTC QLQ-C30, FACT-G, Life Ingredient Profile
Disease-specific QoL instrument
Examples: FACT-Leu, EORTC QLQ-CLL16
Treatment-specific QoL instrument
Examples: FACT-BMT, FACT-BRM

If a study aims to evaluate the efficacy of leukemia treatment, a questionnaire should be chosen to better monitor disease-specific symptoms and the treatment of specific side effects. In this situation the leukemia specific QoL questionnaires and symptom assessment tools could be recommended.

The leukemia treatment modality may influence the choice of a questionnaire. In particular, allogeneic BMT is an established treatment modality for acute leukemia patients with an unfavorable prognosis. To evaluate PROs in patients undergoing transplantation, BMT-specific questionnaires covering the side effects of this treatment regimen should be used.

Disease prognosis in leukemia varies greatly depending on the diagnosis of the sub-group, but for those patients surviving beyond the first year after diagnosis, there can be sequelae which are important to document and take into account when treatment decisions are being made. As long term leukemia survivors become more numerous, addressing the issues of long-term follow-up for these patients is worthwhile. In these studies, as a supplement to generic QoL questionnaires, instruments which could capture disease-specific symptoms, long-term treatment specific side effects, and QoL dimensions, not covered by generic tools which are pertinent to the target group, (e.g. sexual functioning, infertility), may be recommended. As symptoms in leukemia persist long term, patient-reported symptom assessment tools may be useful in these settings as well.

To evaluate the long-term sequelae of leukemia treatments, cross sectional studies are being conducted. The design of these studies, aimed at evaluating treatment efficacy, is longitudinal. The important study time-point is at base-line. Other time-points preferably should coincide with the terms of evaluation of clinical response.

Since leukemia patients vary in age, PRO instruments are likely to be chosen with an emphasis on the target age group. It is obvious that many leukemia patients are elderly. In general, questionnaire items of QoL instruments tend to be phrased, predominantly in

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relation to physical function, in a way relevant to young or middle-aged groups and thus, may inadvertently discriminate against older persons.

In old-age specific QoL questionnaires assessment of QoL incorporates issues of importance to individual older people, thus, representing the QoL status of older patient groups with greater validity. Since old-age specific QoL tools are available for leukemia patients, they should be chosen when planning studies in an older patient population. In addition, the number of questionnaires and the number of study time-points should be taken into consideration (with the tendency of minimization) if the population under study is elderly.

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CHAPTER 3

Quality of life and symptom assessment in hematological patients

3.2

Lymphomas

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State of the art

A large number of studies in Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) patients with a patient-reported outcome (PRO) component have been conducted during the last years. Quality of life (QoL) issues are becoming more important for patients with both HL and NHL. Currently, more than 90% of patients with early stage HL are typically cured and, with the introduction of modern intensified chemotherapy regimens, most of the patients in advanced stage HL have hopes of being cured. However, treatment is accompanied by significant acute and long-term complications. Modifications of treatment schedules have resulted in overall better survival and reduced acute and late toxicity. Information about QoL of patients during and after treatment is needed to further enhance the effectiveness of treatments and to lower acute and late side effects. Such information may be used to modify the treatment schedule in order to optimize cure rates and reduce the probability of late sequelae (*Kaasa S, et al, 1998*). Furthermore, information on morbidity may help clinicians inform patients and establish rehabilitation programs. During the last decades there have been numerous reports in the literature on PROs in long-term HL survivors (*Flechtner H, et al, 1998; Joly F, et al, 1996; Loge JH, et al, 2000; Ballova V, et al, 2005; Roper K, et al, 2009; Brandt J, et al, 2010; Arden-Close E, et al, 2010*). NHL patients appear heterogeneous in terms of histology, immunophenotype, genotype, association with viruses, clinical presentation, and treatment response. NHL affects different patient populations and varies in disease presentation and clinical course. In addition, treatment intent, management approaches, treatment toxicity, responses to therapy, and overall prognosis may differ. As such, aspects of PROs can differ, depending on the subtype of NHL and clinical situation under consideration. In indolent NHL, which is generally considered to be incurable, QoL data can be of considerable value, especially in the absence of clear survival differences among the various treatment strategies. For aggressive NHL, the incorporation of QoL as one of the end-points in clinical trials evaluating novel, more intensive, and potentially more toxic regimens as curative treatments, may provide further insights into the important tradeoffs of alternative regimens. In addition, information about QoL in NHL patients may be used to determine management approaches, as well as to evaluate treatment toxicity, responses to therapy, and overall prognosis. Furthermore, since more patients with NHL may be cured, information about QoL of long-term survivors of NHL is becoming important (*Leak A, et al, 2011*).

A review of relevant literature shows that the number of publications on QoL and symptom assessment in HL and NHL patients is increasing. There are separate chapters dealing with QoL issues in comprehensive textbooks on the biology, diagnosis, staging, and treatment of all forms of NHL (*Ng AK, et al, 2004)* and HL *(Flechtner H, et al, 2007; Flechtner H, et al, 2011*). At the same time, currently, few randomised and non-randomised clinical trials in lymphoma patients with a PRO component have been performed. It may

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be partly explained by the lack of information about the appropriate PRO instruments for lymphoma patients and by insufficient approaches to interpreting PRO data.
There has been an increasing interest in studying PROs in pediatric lymphoma patients. Most studies have focused on survivors and found significant impairment in QoL (*Calaminus G, et al, 2000; von der Weid NX, 2008*). Only a few studies have been conducted with pediatric lymphoma patients during the acute phase of the disease, (i.e. during ongoing treatment). More information about PRO issues in childhood lymphoma is presented in Chapter 7.
Thus, PRO data in Hodgkin's and non-Hodgkin's lymphomas serve a number of important purposes:

- Evaluating end-points of treatment outcome
- Defining treatment toxicity
- Predicting outcome or prognosis
- Evaluating quality of survival
- Addressing the need for rehabilitation.

Patient-reported outcome instruments

There are a number of PRO instruments available to assess QoL and symptoms in lymphoma patients. They can be classified as:

- Generic QoL questionnaires
- QoL questionnaires generic for neoplasms
- Disease-specific QoL questionnaires
- Symptom assessment tools.

The most frequently used generic QoL questionnaire in lymphoma patients is the SF-36 (see description in Chapter 2). The EQ-5D has been used to assess QoL in lymphoma survivors (see description in Chapter 2). Among QoL questionnaires generic for neoplasms the FACT-G (see description in Chapter 3.1) and the EORTC QLQ-C30 (see description in Chapter 3.1) are worth mentioning. Functional Living Index - Cancer and Impact of Cancer Scale (see description in Chapter 5) have also been used with lymphoma patients.

Functional Living Index: Cancer

The Functional Living Index: Cancer (FLIC) was developed to measure QoL in cancer trials as an adjunct to the usual clinical outcomes (*Schipper H, et al, 1984*). It is a 22-item linear analogue scale assessing physical/occupational function, psychological state, sociability and somatic discomfort of people with cancer. The overall score is obtained by the summation of scores for each question. A higher score indicates a better QoL. The instrument has been validated on a large population of patients over a three-year period.

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Strengths: the Index may provide additional patient functional information on which to analyze the outcome of clinical trials.

Weaknesses: there is limited information about validation studies.

There is a disease-specific QoL questionnaire for lymphoma patients called the FACT-Lymphoma.

Functional Assessment of Cancer Therapy - Lymphoma

The Functional Assessment of Cancer Therapy - Lymphoma (FACT-LYM) is a lymphoma-specific subscale for the Functional Assessment of Cancer Therapy (FACT) questionnaire (*Eremenco S, et al, 2004; Webster K, et al, 2005*). It consists of 15 specific items which are used together with the core 27-item questionnaire FACT-G. The patient is asked to respond to each item with a score of 0–4, where 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. A higher score indicates a worse level of QoL. There are translations of the FACT-LYM in 19 European languages.

Strengths: it is the only lymphoma-specific QoL tool used in clinical trials.

Weaknesses: information about the psychometric properties of the instrument is limited.

Symptom assessment in lymphoma patients includes single symptom and multiple symptom assessment. For single symptom assessment, verbal rating scales, numeric scales, visual analogue scales as well as symptom assessment questionnaires are used.
Because fatigue is the most disturbing symptom in lymphoma patients, and it can persist long term, evaluation of fatigue severity during treatment and at long-term follow-up may be highly recommended (*Loge JH, et al, 1999; Rüffer JU, et al, 2003; Oldervoll LM, et al, 2007*). For patients with lymphoma, fatigue may be assessed using fatigue assessment questionnaires developed for cancer patients. Information about fatigue assessment tools is presented in Chapter 2.
The most popular tools to measure fatigue in lymphoma patients are the Brief Fatigue Inventory and the Multidimensional Fatigue Inventory. The description of fatigue assessment questionnaires is presented in Chapter 3.6.
Taking into account that lymphoma patients commonly experience multiple symptoms, questionnaires for evaluating a number of symptoms may be recommended. Among symptom the assessment tools used with lymphoma patients, the M.D. Anderson Symptom Inventory is the most widely used.

M.D. Anderson Symptom Inventory

The M.D. Anderson Symptom Inventory (MDASI) is a multisymptom patient-reported

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outcome measure for clinical and research use (*Cleeland C, et al, 2000*). The MDASI's 13 core items include symptoms found to have the highest frequency and/or severity in patients with different cancers and treatment types. The MDASI uses a 0–10 numerical rating scale to assess the severity of symptoms and interference. The MDASI includes items that report the "sensory" dimension of symptoms (intensity, or severity) and the "reactive" dimension of symptoms (interference with daily function). Subdimensions of symptom interference include an affective subdimension (REM: relations with others, enjoyment of life, and mood) and an activity subdimension (WAW: walking, general activity, and work). Severity is assessed for the 13 core MDASI symptom items (pain, fatigue, nausea, disturbed sleep, distress (emotional), shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling) and for the six interference items (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life). The MDASI can be administered in a number of formats, including traditional "paper and pencil" format (either self-administration or research-staff interview) and electronic formats such as telephone-based interactive voice response systems, PC tablets, and Web-based applications. Translations in 14 European languages are available.

Strengths: the MDASI has several advantages over other symptom-assessment scales in that it applies broadly across cancer types and treatments, is easy for patients to complete, includes items related to symptom interference with daily life, and it is easily translated into other languages.

Weaknesses: severity of multiple symptoms and the impact of symptoms on daily functioning are assessed only during the last 24 hours.

Another symptom assessment tool which is worth mentioning is the Comprehensive Symptom Profile - Lymphoma.

Comprehensive Symptom Profile - Lymphoma

The Comprehensive Symptom Profile - Lymphoma (CSP-Lym) is the disease-specific symptom assessment tool in malignant lymphoma patients (*Novik A, et al, 2010; Kalyadina S, et al, 2010*). It aims to provide comprehensive assessment of the severity of 41 symptoms specific for lymphoma patients. It consists of numerical analogue scales, scored from 0 (no symptom) to 10 (most expressed symptom). It is a bilingual tool developed simultaneously in English and in Russian. At present, the CSP-Lym is available only in English and in Russian.

Strengths: the CSP-Lym might be useful in capturing the risks/benefits of lymphoma treatment, and identifying comprehensive symptom profile changes at different time-points of treatment of lymphoma patients.

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Weaknesses: the tool is available in only two languages.

Practical considerations for patient-reported outcome assessment

In studies aimed at evaluating the effects of lymphoma treatment, the timing of administering PRO instruments is of importance. If a study intends to determine the effects of acute toxicity from therapy, the measurements should be taken when acute toxicity would be expected to be the greatest, for example, during the week after chemotherapy or at the end of a course of radiation therapy. In a study focused on measuring the efficacy of lymphoma treatment, measurements should be taken when acute toxicity has subsided, such as on the last day of a three-week cycle of chemotherapy or a few weeks after the end of a course of radiation therapy.

When interpreting treatment outcomes in patients with malignant lymphomas the information about QoL response should be presented and analyzed along with clinical response (survival, overall response rate, time to progression etc.) (*Novik A, et al, 2011*). In the studies designed to compare lymphoma treatment regimens, prospective studies with longitudinal design are being conducted. QoL may be considered as either a primary or a secondary outcome. Taking into account that heterogeneity of population of new lymphoma patients in terms of QoL has been shown (*Novik A, et al, 2003*), separate analysis in the groups with different base-line QoL impairment might be of value to differentiate treatment outcomes. In long-term survivorship studies and rehabilitation studies QoL may be considered as an independent variable. The design of such studies is cross-sectional, and comparisons are often made with a normative population. In survivorship studies, special analysis of the distribution of lymphoma survivors according to the grades of QoL impairment, as compared to the population norms with careful description of symptom profile is of importance to obtain comprehensive information about the needs of this patient population.

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CHAPTER 3

Quality of life and symptom assessment in hematological patients

3.3

Multiple myeloma

State of the art

New treatment approaches are changing the traditional paradigm for multiple myeloma (MM) management. At present MM is steadily becoming more treatable and manageable. Partial or complete response with first-line therapy is now highly attainable. The availability of high-dose therapy and novel therapies, such as thalidomide, lenalidomide, and bortezomib, has increased the average anticipated survival from 2–3 years to 5–7 years (*Morgan GP, et al, 2006; Blade J, Rosinol L, 2009*). However, long-term follow-up still reflects a pattern of ongoing relapse, even from long-standing complete response or partial complete response. Thus, cure, defined as permanent eradication of the myeloma clone, is rarely if ever achieved. The focus of attention has thus shifted to obtaining the most durable remissions with the highest quality of life (QoL). Thus, durable remission and QoL are considered as primary goals of MM treatment (*Durie BG, 2005; Smith A, et al, 2006*). In connection with this, QoL is an important end-point in the studies aimed at assessing the efficacy of MM treatment.

Furthermore, MM is characterized by a considerable worsening of QoL, with reduced physical and role functioning, fatigue, and pain, as the major problems (*Wisloff F, 1996a; Wisloff F, 1996b; Gulbrandsen N, et al, 2001*). In addition, the treatment of MM is toxic in itself and has a negative impact on patient QoL. It may be accompanied by multiple side effects. Of special note is the importance of evaluating treatment side effects, taking into account the patient's perspective. Results of the Myeloma Euronet International Survey in 2009 titled "Myeloma Treatment Side Effects and Unmet Patient Needs" showed that physician opinion and patient opinion about treatment side effects and patient problems, differ to a large extent (*Gencer D, et al, 2011*). In all, 314 healthcare professionals from 43 countries (76% from European countries) and 260 myeloma patients, and patient relatives/caregivers from 21 countries (96% from European countries) participated in the survey. This survey was designed to find out about, and compare, the opinions of healthcare professionals (physicians and nurses) and patients and patient relatives/caregivers regarding myeloma treatment side effects and potential unmet patient needs. According to physicians and nurses, neuropathy has the most negative impact on a myeloma patient's overall well-being, whereas patients and patient relatives and caregivers stated that fatigue, malaise, weakness, dizziness, somnolence, sedation, and insomnia were the treatment side effects with the most negative impact on a patient's overall well-being. These were also the most frequently experienced treatment side effects, according to patients and patient relatives/caregivers. In addition, more than one-third of the physicians, almost one-quarter of the nurses, almost half of the patients, and more than half of the patient relatives/caregivers reported that they were either "not too satisfied" or "not satisfied at all" with the psycho-social support offered. Thus, the results of this survey as well as other data available, demonstrate the importance of accurate symptom assessment in patients with MM.

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In summary, it is important to assess QoL and symptoms along with a follow-up of the biological course of the disease, to provide adequate care for MM patients (*Wisloff F, Gulbrandsen N, 2000; Lee S, et al, 2003*). In relation to this, it is necessary to carry out monitoring of QoL and symptoms from the onset of the disease through the whole period of treatment and survival time.
To note, the prognostic significance of QoL scores for survival in MM has been shown (*Wisloff F, 1997; Turesson I, et al, 1999*).
In recent years, many randomized and non-randomized clinical trials in MM patients with a patient-reported outcome (PRO) component have been performed. In the registry and the database of the U.S. National Institutes of Health developed together with FDA information about more than 100 clinical trials with PRO component is available. Among them there are studies of Phases I-IV. The PRO component represents an important tool for evaluating the value of effective therapies when weighed against the potential toxic effects of MM treatment from a patient's perspective.

Patient-reported outcome instruments

To assess QoL in patients with MM generic questionnaires, disease specific questionnaires, and questionnaires generic for neoplasms are used. The most widely used generic questionnaire is the SF-36 (see description in Chapter 2). The QoL questionnaires generic for neoplasms are the FACT-G (see description in Chapter 3.1) and the EORTC QLQ-C30 (see description in Chapter 3.1).
As for disease specific questionnaires, the EORTC QLQ-Multiple Myeloma Module is worth mentioning.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Multiple Myeloma Module

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Multiple Myeloma Module (EORTC-QLQ-MY20) was developed to receive additional information on QoL in patients with MM (*Stead ML, et al, 1999*). The questionnaire includes 20 disease-specific items, consisting of 3 multi-item scales and 1 single-item scale. Its reliability and validity have been demonstrated (*Cocks K, et al, 2007*). The instrument is available in 22 European languages.

Strengths: it is developed for use as an adjunct to the core module EORTC QLQ-C30 in MM patients varying in disease stage and treatment modality (i.e. surgery, chemotherapy, radiotherapy, and hormonal treatment).

Weaknesses: the focus is on the frequency of symptoms which MM patients may experience, not on their severity.

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To assess symptoms in patients with MM, different tools are used. To measure the severity of single symptoms, visual analogue scales and numerical rating scales are utilized.
There are several questionnaires which are used to assess pain in MM patients. The Brief Pain Inventory is widely used in this patient population.

Brief Pain Inventory

The Brief Pain Inventory (BPI) was developed to provide information on the intensity of pain, along with the degree to which the pain interferes with everyday functioning (*Cleeland CS, et al, 1994*). Generally, the BPI is used to assess a varied set of factors:

- Severity of pain
- Impact of pain on daily function
- Location of pain
- Pain medications
- Amount of pain relief in a specific period of time (e.g. past 24 hours, past week, etc.).

There are two basic forms of the BPI assessment tool: the short form (9 items) and the long form (32 items).
The BPI assesses the intensity of physical pain using a numerical rating scale (1 to 10) and the percent of pain relief. Since pain can vary to a considerable measure over a day, the BPI asks the patients to rate their pain at the time of responding to the questionnaire. In addition, the questionnaire also asks the respondent to specify the pain at its worst, least, and average over the previous week. The main points covered in the BPI short form include: occurrence of pain, areas of pain, rating of the pain at its worst in the last 24 hours, rating of the pain at its least in the last 24 hours, specifying the average pain level, specifying the current level of pain, specifications of the treatments or medications being currently taken, percentage of pain relief from medications in the past 24 hours, and specifying how much has the pain interfered in the following areas of life in the last 24 hours:

- General activity
- Mood
- Walking ability
- Normal work
- Relation with other people
- Sleep
- Enjoyment of life.

Strengths: the questionnaire is widely used internationally. Although it was developed for assessing cancer pain, the BPI has been validated in nonmalignant chronic pain patients (*Tan G, et al, 2004*). Moreover, the tool is brief, user-friendly and simple to administer.

Weaknesses: as with other self-reports, it is subject to distortion by the respondent.

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The McGill Pain Questionnaire-Short Form and the Memorial Pain Assessment Card have been also used to assess pain in myeloma patients.

McGill Pain Questionnaire - Short Form

The McGill Pain Questionnaire - Short Form (MPQ-SF) is a multidimensional pain assessment scale (*Melzack R, 1987*). The MPQ-SF consists of 17 items and has three components: a pain rating index, a visual analogue scale, and present pain intensity. The pain rating index consists of 15 descriptors (11 sensory and 4 affective) that are rated on an intensity scale (0 = none, 1 = mild, 2 = moderate, or 3 = severe). The present pain intensity is measured on a 0–5 scale of overall pain intensity. The questionnaire is available in 22 languages.

Strengths: it is a useful tool in situations in which the standard MPQ takes too long to administer, yet qualitative information is desired. The validity and reliability of the MPQ-SF have been well established among cross-cultural populations (*Lazaro C, et al, 1994*).

Weaknesses: information about its use with multiple myeloma patients is limited.

Memorial Pain Assessment Card

The Memorial Pain Assessment Card (MPAC) is a simple instrument designed to provide rapid evaluation of pain intensity, pain relief, and psychological distress (*Fishman B, et al, 1987*). It has 4 sections: three visual analogue scales which measure pain intensity, relief and mood, and a section with descriptive words (moderate, mild, strong, week, severe, excruciating, just noticeable, and no pain). The visual analogue scales each have a line with the words "worst" at one end and "best" at the other. The card is 8.5 x 11 inches and is folded in the middle so that each of the 4 sections can quickly be shown to the patient. The patient is asked to mark the place on scale that corresponds to their judgment of the pain. Experienced patients can complete it in less than 20 seconds. Designed initially for use in the assessment of very ill patients suffering from pain of malignant origin, the MPAC is now used in a variety of pain settings.

Strengths: the instrument is very quick to administer. Its ease of use makes it ideally suited in clinical situations such as acute pain management, where frequent repeated assessments are desirable.

Weaknesses: information about the psychometric properties of the tool is limited.

To assess fatigue in MM patients the Brief Fatigue Inventory (see description in Chapter 3.6), and the Multidimensional Fatigue Inventory (see description in Chapter 3.6) are currently in use.

The M.D. Anderson Symptom Inventory (see description in Chapter 3.2) is used to measure

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multiple symptoms in MM patients. The Comprehensive Symptom Profile - Multiple Myeloma is a new multiple symptom assessment tool developed to assess symptoms in MM patients.

Comprehensive Symptom Profile - Multiple Myeloma

The Comprehensive Symptom Profile - Multiple Myeloma (CSP-MM) is a disease-specific symptom assessment tool in myeloma patients (*Novik A, et al, 2010*). It aims to provide a comprehensive assessment of the severity of 51 symptoms specific to myeloma patients. It consists of numerical analogue scales, scored from 0 (no symptom) to 10 (most expressed symptom). It is a bilingual tool developed in English and in Russian. At present the CSP-MM is available in English and in Russian.

Strengths: the CSP-MM might be useful for capturing the risks/benefits of myeloma treatment, identifying side effects of therapy, and registering symptom changes at different time-points of therapy.

Weaknesses: the questionnaire might be too long for use in a clinical setting.

Practical considerations for patient-reported outcome assessment

In a recent critical review of randomized controlled trials in MM with a PRO component it was concluded that the quality and methodology of collecting QoL data must be further improved and the results rendered more comprehensible to clinicians (*Kvam AN, et al, 2009; Kvam AN, et al, 2010a; Kvam AN, et al, 2010b; Kvam AN, et al, 2011*).
Response categorization in terms of clinician-reported outcomes for MM treatment is clear, namely, complete response, very good partial response, partial response, etc. In connection with this, PROs should be also interpreted in a manner understandable to clinicians. The following response categorization may be used: QoL improvement, QoL stabilization, or QoL worsening. Furthermore, comparison with a reference population eases the interpretation of QoL scores and prevents the overestimation of symptoms and the underestimation of subjective treatment response (*Gulbrandsen N, et al, 2004*). In addition, patients with MM, who are homogeneous with respect to their biological characteristics, are heterogeneous in terms of QoL impairment. Evaluation of treatment outcomes in the patient groups stratified by QoL impairment grades allows the collection of more precise and profound information about new products and new treatment strategies.
When choosing QoL or symptom assessment tools for use with MM patients, several issues should be considered. Among them the most important are patient age and

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treatment regimen. Due to the fact that the population of MM patients tends to be quite old, there should not be too many questionnaires in the study, and their format should be appropriate for the elderly. If the patients included in the study undergo bone marrow/hematopoietic stem cell transplantation (BMT/HSCT), treatment specific questionnaires might be added as well (see Chapter 4). The timing for administering PRO instruments should be taken into account when planning a study with a PRO component. The time-points are dependent if the study is intended to determine the toxicity of myeloma treatment, or its efficacy. If the study aims to evaluate the toxicity of treatment, the administration of PRO instruments should be taken when the toxicity would be expected to be the greatest. In studies designed to measure treatment efficacy, time-points depend on the phase of myeloma treatment which the patient is undergoing, and should be taken when acute toxicity has subsided. Preferably, time-points of PRO assessment should coincide with those evaluating clinical response.
Information about study design in long-term MM survivors is presented in Chapter 5.

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CHAPTER 3

Quality of life and symptom assessment in hematological patients

3.4

Myelodysplastic syndromes

State of the art

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid neoplasms characterized by symptomatic cytopenias, and a variable risk to evolve into acute myeloid leukemia (*Vardiman JW, et al, 2009*). MDS primarily affect elderly patients with a median age of onset of about 70. During the course of the disease, approximately 90% of patients experience anemia, which adversely affects their quality of life (QoL) and clinical outcome (*Oliva EN, et al, 2002; Jansen AJG, et al, 2003*).

For the majority of cases, supportive care, mainly packed red blood cell transfusions (pRBCs), remains the main treatment option. Patients with a better prognosis have a longer survival. Thus, transfusion-dependence may last for several years. In this particular patient population, transfusion-dependence has an independent effect on QoL, which has not been shown in the oncological setting. It may be due to the chronic, but progressive, nature of the disease and to the relatively long duration of severe anemia. Furthermore, in low-risk patients, fatigue is not prevalent at diagnosis, again distinguishing symptoms of anemia of MDS from those associated with cancer-related anemia (*Oliva E, et al, 2008*). There is no consensus as to the optimal transfusion regimen to improve QoL in transfusion-dependent MDS. In one study, a cut-off value for Hb of 10.7 g/dL distinguished patients with both cardiac remodeling and poor physical QoL, suggesting this value to be considered for the treatment of anemia in MDS (*Oliva EN, et al, 2005*).

For MDS patients with low-risk disease, treatment of anemia includes erythropoiesis -stimulating agents (ESAs). With adequate doses, erythroid responses are obtained in up to 70% of cases (*Hellström-Lindberg E, 2005; Ria R, et al, 2009; Santini V, et al, 2010*). Response to ESAs has been shown to be associated with improvements in QoL (*Spiriti MA, et al, 2005; Stasi R, et al, 2005; Balleari E, et al, 2006; Oliva EN, et al, 2010*).

Recently, the effects of the immunomodulatory drug, lenalidomide, on QoL in patients with low and intermediate risk MDS with del5q chromosome abnormality and moderate-severe anemia have been determined. Patients obtaining an erythroid response to lenalidomide experience improvements in anemia-related QoL, measured as a >7 point increase in the FACT-An score in one randomized trial (*Fenaux P, et al, 2011*), and a >10 point difference in physical, functional and social scores according to the MDS-specific questionnaire in another single-arm study (QoL-E questionnaire) (*Oliva EN, et al, 2009*).

Iron-chelating agents are indicated mainly in low-intermediate risk patients with a relevant transfusional load, which has been associated with a more severe prognosis (*Malcovati L, et al, 2007*). QoL changes associated with treatment have not yet been reported.

QoL may also deteriorate as a result of limitations due to thrombocytopenia and/or neutropenia as a concurrent cytopenia or be treatment-induced. Though not a prevalent condition, life-threatening thrombocytopenia (platelets <20 Gi/L with or without

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bleeding) remains a significant complication. The only treatment available for severe thrombocytopenia consists of platelet transfusions, mainly in the presence of bleeding, which carry therapeutic limitations, such as a short therapeutic effect (1–5 days), and the development of refractoriness to platelet transfusions. Severe neutropenia may be complicated by infections, which may require hospitalization and be life-threatening.
In patients with a higher risk of having their disease evolve into acute myeloid leukemia or end in death, the primary end-point of treatment is survival. Though allogeneic bone marrow transplantation is the only curative treatment (with elevated treatment-related mortality), only a minority of patients are candidates, due to advanced age, the prevalence of co-morbidities and the availability of a compatible donor. In the last decade, hypomethylating agents, mainly azacytidine, have been placed in first-line therapy for intermediate-high risk patients in which transplant is not indicated (*Santini V, et al, 2011*). It has been shown that these drugs prolong survival and promote improvement in QoL (*Kornblith AB, et al, 2002; Lübbert M, et al, 2011*).

Patient-reported outcome instruments

QoL in MDS may be assessed by generic or by specific instruments. The most frequently used instruments have been the EORTC QLQ-30, the FACT-G and the modules from the Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System. However, only one MDS disease-specific QoL instrument, the QoL-E, has been reported in the literature (*Oliva EN, et al, 2001; Pinchon DJ, et al, 2009*).
The EORTC QLQ-C30 is a QoL questionnaire developed by the European Organization for Research and Treatment of Cancer Quality of Life Study Group for the measurement of QoL in cancer patients in clinical trials (*Aaronson NK, et al, 1993*). See Chapter 3.1 for further details.
The FACT-G is the cancer core questionnaire from the FACIT system (*Cella D, et al, 1993*). See Chapter 3.1 for further details.
To evaluate fatigue in patients with MDS, modules of the FACT-G may be used. These include the Functional Assessment of Chronic Illness Therapy - Fatigue and the Functional Assessment of Cancer Therapy - Anemia.

Functional Assessment of Chronic Illness Therapy - Fatigue

The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) subscale is a questionnaire module developed within the FACIT system (*Yellen SB, et al, 1997*). It consists of 13 items dealing with fatigue (fatigue, weakness, listlessness, tiredness, energy, ability to perform daily activities, limitation of social activities, and need of sleep during the day).
The response format corresponds to the that of the FACT-G questionnaire.

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Strengths: this instrument is simple to score and easy to use. It has been widely used in clinical trials and may be used for comparative measures. It is available in several languages.

Weaknesses: fatigue is not prevalent in MDS. Thus, the scale may not be totally relevant.

Functional Assessment of Cancer Therapy - Anemia

The Functional Assessment of Cancer Therapy - Anemia (FACT-An) is a 55-item questionnaire to assess outcomes in cancer patients with anemia/fatigue (*Yellen SB, et al, 1997; Cella D, 1997*). It consists of the FACT-G, and a 21-item Anemia subscale, the FACT-An subscale. This, in turn, is composed of the FACT-F subscale and 7 additional items covering other anemia related symptoms (walking difficulties, dizziness, headache, shortness of breath, chest pain, lack of interest in sex, and lack of motivation for normal activities).

The scale correlates with hemologlobin levels in patients undergoing cancer treatment and has been used to evaluate QoL changes in patients undergoing treatment for anemia of MDS (*Casadevall N, et al, 2004; Spiriti MA, et al, 2005; Balleari E, et al, 2006; Fenaux P, et al, 2011*).

Strengths: this assessment tool is simple to score and easy to administer. It has been widely used in clinical trials and may be utilized for comparative measures. It is available in several languages.

Weaknesses: the scale has been created exclusively for assessing anemia-related QoL in cancer patients with cancer-related or treatment-induced anemia (*Oliva EN, et al, 2002*).

The QoL-E is the only disease-specific QoL instrument available in patients with MDS.

QOL-E v.2

QoL-E v.2 is a specific MDS QoL questionnaire (*Oliva EN, et al, 2001*). It consists of 2 single items concerning general perception of well-being and 26 items addressing physical, functional, social, and sexual domains, fatigue, and a disease-specific component. Each item is re-scaled so that better health corresponds with higher numerical values. Raw scores are transformed to standardized scores which are then generated for each domain as the unweighted mean of the standardized scores of all items in that domain (scores range from 0–100). The MDS-specific domain comprises items concerning disturbances related to dyspnoea, transfusion-dependence, treatment, and dependence on hospital and staff.

The questionnaire has been used to measure QoL changes in multi-center clinical trials (*Oliva EN, et al, 2009; Oliva EN, et al, 2010*). The subscales correlate with transfusion-dependence and hemoglobin levels in MDS patients.

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Originally in Italian, the instrument has been translated in English, Bulgarian, and German.

Strengths: this instrument is the only disease-specific tool for MDS patients. It is simple to score and easy to use; it can be completed in approximately 12 minutes.

Weaknesses: the questionnaire needs to be translated into additional languages.

Practical considerations for patient-reported outcome assessment

In clinical practice, disease-specific questionnaires are warranted to detect single-item information on the individual patient's QoL. Within clinical trials, whether using a general or disease-specific instrument, assessment should not be limited to changes in summary scores, but should allow for the evaluation of changes in selected informative items relative to the disease and its treatment.

The choice of the questionnaire may depend on the predicted clinical outcomes. If the end-points are the changes in anemia and anemia-related symptoms, the FACT-An may be sufficient. If the effects on QoL related to transfusion-dependence and all aspects of MDS is the issue, the QOL-E may provide further information on the disturbance related to transfusion-dependence and dependence on family and hospital staff regarding trial-related visits (*Oliva EN, et al, 2010*). Furthermore, a more generic instrument, such as the EORTC QLQ-C30, may be used (alone or in combination with a disease-specific instrument) to evaluate symptoms related to the study drug (side effects, such as nausea, constipation, diarrhea, etc.).

The specific effects on QoL of severe thrombocytopenia and neutropenia in MDS have not yet been described and need further exploration. In addition, the identification of an ideal transfusion trigger in MDS based on QoL requires further validation (*Nilsson-Ehle H, et al, 2011*). The increasing number of therapeutic trials within the palliative setting of MDS should focus on meaningful patient-reported outcome (PRO) changes as a primary end-point in the study design, together with changes in transfusion requirement, Hb levels, bleeding, infections, cardiac remodeling, and/or iron overload.

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CHAPTER 3

Quality of life and symptom assessment in hematological patients

3.5

Bleeding disorders

3.5.1 Hemophilia

State of the art

In the last three decades, hemophilia has moved from the status of a neglected and often fatal hereditary disorder to that of a fully-defined group of molecular-pathological entities for which safe and effective treatment is available. The treatment of hemophilia is based on the replacement of the missing clotting factor when bleeding occurs (on-demand treatment) or is made on a regular and continuous way regularly and continuously (prophylactic treatment). Hemophilia is likely to be the first widespread severe genetic condition to be cured by gene therapy in the third millennium (*Mannucci PM, 2003*).

Hemophilia is characterized by spontaneous and post-traumatic bleeding. Its complications in joints and muscles lead almost inevitably to pain, severe joint damage, disability, and a dramatic impairment of quality of life (QoL) (*Barr RD, et al, 2002; Riley RR, et al, 2011*). The importance to assess the patient's perspective via patient-reported outcome (PRO) in hemophilia patients has been highlighted (*Beeton K, 2002; Gringeri A, et al, 2006; Remor E, 2011a*).

In the Guidelines for the Management of Hemophilia by the World Federation of Hemophilia (*World Federation of Hemophilia, 2005*) QoL is considered one of the outcomes of treatment which should be monitored every 6–12 months. According to these Guidelines, patients should be evaluated once every 6-12 months for the following:

- Musculoskeletal status: measure clinical scores annually, and radiological scores, as indicated
- Use of clotting factor concentrates
- Inhibitor development: perform screening tests for inhibitors
- Transfusion-related infections (if appropriate): evaluate for human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV)
- Infections commonly, and other infections if indicated
- Quality of life.

To note, PROs have been increasingly used as outcomes in hemophilia treatment (*Fischer K, et al, 2003; Gringeri A, et al, 2006; Bullinger M, et al, 2009; von Mackensen S, Gringer A, 2010; Remor E, 2011b*). Within the hemophilia literature, one of the first studies addressing QoL issues in hemophilia patients dates back to 1990 (*Rosendaal FR, et al, 1990*). At present, there are a number of observational studies focusing on the impact of the disease and treatment on different functioning aspects of patients with hemophilia (*Rosendaal FR, et al, 1990; Miners A, et al, 1999; Molho P, et al, 2000; de-Joode E, et al, 2001; Solovieva S, 2001; Royal S, et al, 2002*). As for treatment related studies, most of them are not randomized.

There are also studies regarding relevant health-economic data which are related to QoL

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outcomes and are aimed at evaluating the cost-benefit ratio in hemophilia care (*Szucs T, et al, 1996; Szucs T, et al, 1998; Schramm W, Berger K, 2002; Naraine V, et al, 2002*). Compared to studies in adults, research with a PRO component in children with hemophilia is rare (*Globe D, et al, 2009*). It is obvious that the availability of safer products and early prophylaxis have greately improved the management of hemophilic children with a consequent dramatic impact not only on symptoms and survival of these patients, but also on their QoL. In summary, PROs should be included in all clinical evaluations of treatment options of hemophilia, both in adults and children, from product-licensing studies to gene-therapy trials, as one of the main outcomes. Finally, PRO instruments should be part of the medical armamentarium for the global assessment and care of patients with hemophilia.

Patient-reported outcome instruments

Until recently, the most widely used instruments to assess QoL in hemophilia research have been generic measures, such as the SF-36 (see description in Chapter 2) and EuroQoL-5D (see description in Chapter 2) questionnaires for adults, and the Child Health Questionnaire for children (see description in Chapter 2).
However, in the past few years, in order to improve the assessment of QoL in people with hemophilia, several disease-specific questionnaires have been developed. These are new recent measures for adults - the A36Hemofilia-QoL, the HaemoQoL-A, the Haem-A-QoL, the QUAL HEMO and the Hemolatin-QoL, and for children - the Haemo-QoL, the Canadian Hemophilia Outcomes - Kids Life Assessment Tool, and the QUAL HEMO. They were specially developed and validated for adequate assessment of QoL in people living with hemophilia. A review of studies assessing QoL with hemophilia-specific measures has been recently published (*Remor E, 2011a*).

Adult patient-reported outcome instruments

A36Hemofilia-QoL

The A36Hemofilia-QoL is a hemophilia-specific QoL questionnaire which was developed to assess QoL in adults with hemophilia (*Arranz P, et al, 2004*). It is a self-report modular instrument that assesses nine relevant QoL domains for patients with hemophilia (e.g. physical health, daily activities, joint damage, pain, treatment satisfaction, treatment difficulties, emotional functioning, mental health, relationships and social activity). Psychometric examination of the questionnaire involved the assessment of data quality, scaling assumptions, reliability (internal consistency and test-retest), validity (concurrent; external clinical criterion) and sensitivity. The 36-item version questionnaire has acceptable internal consistency, test-retest reliability, and has shown some evidence of validity as well (*Remor E, et al, 2005*).

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Strengths: this questionnaire shows excellent concurrent validity (with the SF-36 Health Survey and the EQ-5D, EQ-5D VAS), external clinical criterion validity (hemophilia clinical status), and sensitivity (health status changes) (*Remor E, et al, 2005; Remor E, 2006*).

Weaknesses: although the A36Hemofilia-QoL is now available in several languages (Czech, Danish, English, Iranian, Norwegian, Polish, Sesotho, Spanish, Swedish, and Tagalog), and is currently being used in research, published psychometric testing has only been conducted on the original Spanish version.

Haemo-QoL-A

The Haemo-QoL-A is a validated instrument with confirmed internal consistency, reliability, and reproducibility that is used to measure QoL in adults with hemophilia (*Rentz A, et al, 2008*). During the development of the tool, data were collected from 221 patients, aged 18–82, in the United States, Canada, Germany, and Spain with an instrument that utilized a six-point Likert-type scale. Questionnaire items were derived from the clinical literature, clinical input, and patient and health care professional focus groups in North America and Europe. Cultural adaptations ensured the consistency of meaning in three languages and four cultures. The final instrument, based on the results of this study, contains 41 questions comprising the six subscales (Physical Functioning, Role Functioning, Worry, Consequences of Bleeding, Emotional Impact and Treatment Concerns), along with four independent items.

Strengths: the Haemo-QoL-A can be used in international clinical trials, as well as in the clinical setting to assess outcomes from regimens such as primary prophylaxis or immune tolerance induction. It can also be used to assess the quality of care rendered in a particular hemophilia population, at a particular institution, or in a particular country.

Weaknesses: validation data are available for only four language versions: English, German, Spanish and Canadian French.

Haemophilia Quality of Life Questionnaire for Adults

The Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) is a specifically designed measure to capture aspects of QoL for adult patients with hemophilia (*Mackensen S, et al, 2004*). Item generation was derived from patient-based focus groups and expert groups organized with physicians and nurses in Italy. It consists of 46 items pertaining to 10 dimensions (physical health, feelings, view of yourself, sport and leisure, work and school, dealing with hemophilia, treatment, future, family planning, partnership and sexuality) and a total score. The Haem-A-QoL was validated in Italian adult patients. The psychometric characteristics showed quite good reliability values, and high convergent and discriminant validity. The Haem-A-QoL has been linguistically validated in 42 different languages.

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Strengths: the instrument is notable because it features shared variables (Haem-A-QoL Core Instrument) with the Haemophilia Quality of Life Questionnaire for children (Haemo-QoL), allowing for comparison of QoL between adults and children.

Weaknesses: validation studies of different language versions are under development.

Haemophilia Quality of Life Questionnaire

The Haemophilia Quality of Life Questionnaire (QUAL HEMO) was designed to document QoL throughout the lifetimes of hemophiliac patients (*Trudeau E, et al, 2003*). The QUAL HEMO is available for 3 age groups: adults, children and adolescents. The adult version includes 53 items; the adolescent version for patients aged 13–17 consists of 77 items. The version for children includes separate child and parent forms. The child version (ages 2–12) consists of 9 items, and the parent version has 35 items. All versions are self-administered. The parent version is completed by the parent from their observation of the child. Originally the instrument was developed in French.

Strengths: the instrument is suitable for a wide range of age groups.

Weaknesses: the translations of the questionnaire have not undergone a full linguistic validation process and require further work to be suitable for use in studies.

Hemolatin-QoL

The Hemolatin-QoL is a disease-specific instrument for assessing QoL in adults living with hemophilia (*Remor E, 2005*). It has been developed in a multinational Latin-American working group, in cooperation with hemophilia treatment centers and national hemophilia organizations in eight Latin-American countries (Argentina, Brazil, Colombia, Cuba, Guatemala, Panama, Uruguay and Venezuela). An international qualitative study with patients was initially performed to develop items for the instrument. To address the content and face validity, the preliminary version of the instrument was sent to Latin-American hemophilia experts and patients with a standardized evaluation form to assess the comprehensiveness, relevance to hemophilia, and suggestions to delete or rephrase the items. The results were used to develop a 47-item questionnaire (*Remor E, 2009*). Additional information is available on the instrument website: *www.hemolatin-qol.info*.

Strengths: the Hemolatin-QoL is a high quality disease-specific bilingual questionnaire developed on an international basis using patient-centered methods. It is available in Latin-American Spanish and Brazilian Portuguese.

Weaknesses: psychometric testing is under development.

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Pediatric patient-reported outcome instruments

Haemo-QoL

The Haemo-QoL is a self-report questionnaire for children (*von Mackensen S, et al, 2004*). It has three versions for different age groups: version I - for children 4–7 (21 items), version II - for children 8–12 (64 items) and version III - for children 13–16 (77 items), as well as a version for parent report. The versions consist of 9–11 subscales, depending on the age group. The psychometric structure of the questionnaire showed acceptable psychometric properties for the three age group versions and for the accompanying parent forms. The Haemo-QoL full version is now available for children of three age groups and their parents and is ready for use in clinical research. A short version (8 items), with the associated psychometric study, of the Haemo-QoL is also available for use in research (*Pollack E, et al, 2006*).

Strengths: the three age-group versions of the Haemo-QoL have shown acceptable internal consistency and retest reliability, as well as possessing sufficient discriminant and convergent validity.

Weaknesses: in young children, when compared to older children, the results of psychometric testing (involving the examination of reliability and validity) were less satisfactory.

Canadian Hemophilia Outcomes - Kids Life Assessment Tool

The Canadian Hemophilia Outcomes - Kids Life Assessment Tool (CHO-KLAT) is a 35-item disease-specific measure of QoL that was developed using child-centered methods (*Young NL, et al, 2004*). It is a promising disease-specific measure of QoL that reflects children's unique perspectives. This child-centered focus distinguishes the CHO-KLAT from alternative measures of QoL. Experiences during the development of this questionnaire, showed that children are able to play an important role in the development of QoL measures and their use. Specifically, children generated unique items and suggested important wording modifications that were not identified by other sources. Their input contributed to the CHO-KLAT's strong psychometric properties (*Young NL, et al, 2006*).

Strengths: the CHO-KLAT is a reliable and valid measure of QoL for boys with hemophilia.

Weaknesses: currently there are a limited number of language versions available (*Young NL, et al, 2011*).

Practical considerations for patient-reported outcome assessment

When selecting a QoL measure, research and instrument-related aspects have to be taken into account (*von Mackensen S, Gringeri A, 2010; Remor E, 2011*). If the study is

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cross-sectional and focuses on well-being and functioning of patients with hemophilia, a generic measure is an appropriate one. It makes it possible to compare QoL of hemophilia patients with those who are healthy or with population norms. For longitudinal studies aimed at identifying treatment outcomes, hemophilia-specific questionnaires are necessary. The use of hemophilia-specific questionnaires is feasible if the study aims to investigate symptom burden and impairments related to the disease. Considering the high costs of hemophilia treatment, health economic studies with a PRO component are of importance and should utilize appropriate assessment tools. In addition, the questionnaire must be matched to the study population age group (i.e. pediatric or adult).

When analyzing PROs in hemophiliacs, it is important to differentiate patients depending on clinical characteristics and treatment history. The following clinical markers should be taken into account: the number of hemarthroses in the prior year, the total number of bleeding episodes in the prior year, the number of damaged joints, the presence of HIV infection, the presence of HCV infection, the presence of chronic pain (not related to bleeding), and the presence of inhibitors. The negative impact of the presence of inhibitors on the QoL has been shown for children, adolescents and adults. When inhibitors are present in adolescents and adults, the QoL domains that are most affected, controlling for age effect, are poor mobility, low self-care, difficulty with daily activities, pain/discomfort, anxiety/depression (mood) in comparison to those without inhibitors (*Remor E, et al, 2002*). For children and adolescents with inhibitors the evidence includes low self-esteem, family attitude (over-protection), poor relationship with friends, difficulties with school activity, increase in the frequency of bleeding events, poor physical health, emotional distress related to the disease (mood), limited sports activity, and poor perceived health (*Remor E, et al, 2005*).

Thus, modern management of hemophilia has greatly influenced not only the survival of patients, their clinical symptoms, and orthopedic outcome, but also PROs in this patient population. PROs have become essential to optimize treatments and allocate resources in a cost-intensive chronic disease such as hemophilia where traditional outcome measures such as mortality are no longer significantly influenced by diverse treatment options.

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CHAPTER 3

Quality of life and symptom assessment in hematological patients

3.5

Bleeding disorders

3.5.2 Von Willebrand disease

State of the art

Among the inherited bleeding disorders (IBD), von Willebrand disease (VWD) is the most common (*Rodeghiero F, et al, 1987*). In population-based studies, the prevalence of VWD is very high (0.81%), but the clinical relevance of many of these cases is uncertain. If only patients referred for clinical manifestations of bleeding are considered, the actual prevalence is 66 to 100 cases per million of the general population (*Mannucci PM, Federici AB, 2006*). The disease is due to quantitative or qualitative defects of the von Willebrand factor (VWF).

Treatment of VWD consists of replacing the VWF and coagulation factor VIII (FVIII) in the case of bleeding, after trauma or prior to invasive procedures. This can be achieved by desmopressin, which induces secretion of autologous VWF and FVIII into the plasma, or by administering the deficient factors using plasma concentrates containing VWF and FVIII (*Sadler JE, 2000; Mannucci PM, 2004*).

Patients with VWD frequently have bleeding episodes, varying from gum bleeds and epistaxis to heavy intestinal bleeding, and menorrhagia in women (*James AH, 2007; Kouides PA, 2006; Kadir RA, et al, 2006*). The bleeding patterns of VWD, especially of severe VWD, may adversely affect short- and long-term quality of life (QoL). Surprisingly, very little has been known about how this disorder affects QoL. A few studies have been conducted with a small number of patients (*Barr RD, et al, 2003; Solovieva S, 2001; Eastaugh SR, 2000*). The only large study on QoL issues in patients with VWD is a nationwide study in over 500 adult patients performed in the Netherlands (*de Wee EM, et al, 2011*). In accordance with the data available, QoL is lower in VWD patients compared with the general population and is strongly associated with bleeding phenotype. In addition, differences in morbidity burden between males and females with VWD have been shown. The magnitude of the morbidity burden revealed for females with VWD is surprising. Women with VWD assessed their own health status as being compromised to an extent similar to that reported by HIV-positive severe hemophilias and even greater than that experienced by adult survivors of brain tumors (*Kouides PA, 2006*). This supports the results of the study undertaken to determine "willingness to pay" in which the average "perceived self-report of health status" of patients with VWD was recorded as 4 on Likert scale of 1 (excellent) to 5 (poor) (*Eastaugh SR, 2000*).

Currently, information about QoL in children and adolescents with VWD is very limited (*Chi C, et al, 2010; de Wee EM, et al, 2011*). It is known that QoL is lower in VWD children than in reference populations, in particular in school children; physical, emotional and social functioning is affected. The negative impact of VWD is sensitive to type of VWD and bleeding phenotype.

The most common and major problem for patients with inherited bleeding disorders, especially with VWD, is menorrhagia (*Shankar M, et al, 2008*). During menstruation and

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ovulation women with inherited bleeding disorders face monthly hemostatic challenges accompanied by significant bleeding and pain leading to limitation in conducting daily activities and changes in social functioning with an adverse effect on QoL (*Kadir RA, et al, 2010*). The reported prevalence of menorrhagia ranges from 32–100% in women with VWD (*James AH, 2005*), 5–98% in women with platelet dysfunction (*Lopez JA, et al, 1998; George JN, et al, 1990*) and 35–70% in women with rare factor deficiencies (*Burrows RF, et al, 2000; Lak M, et al, 1999; Shetty S, et al, 2000*). In a German survey of women with VWD, common bleeding symptoms reported were as follows: menorrhagia (58.2%), hematoma (13%), dental bleeding (12.5%), epistaxis (8.7%) and gastrointestinal bleeding (5.4%) (*Scharrer I, 2004*).

Menorrhagia is also a frequent complaint in adolescent girls. Compared with the adult menorrhagia population, there have been far fewer studies about the prevalence of bleeding disorders and their impact on QoL, as well as the efficacy of different treatment strategies used with this population (*Jayasinghe Y, 2005; Kouides P, et al, 2009*). In 2008, Pawar with coworkers studied QoL in adolescents with menorrhagia (*Pawar A, et al, 2008*). Their survey revealed that a pictorial blood assessment chart score of >100 was associated with a poorer QoL, adversely affected social activities and travel plans, and resulted in greater school absenteeism. Instituting effective treatment for VWD-induced menorrhagia may alleviate many of these unwanted complications.

Thus, the importance of measuring patient-reported outcomes (PROs) in patients with inherited bleeding disorders, especially with VWD, is obvious. To note, at present the prospective study on regular replacement therapy as prophylaxis in severe forms of VWD initiated by the Von Willebrand Disease Prophylaxis Network (VWD PN) Study Group is underway (*Berntorp E, et al, 2010*). The objectives of this study are to provide guidelines for dosing, and address issues of cost-effectiveness and QoL. Clinical studies with a PRO component in patients with bleeding disorders are worthwhile to provide an insight to the effects of different treatment options and to identify optimal treatment strategies for delivering appropriate care.

Patient-reported outcome instruments

Until recently only generic QoL questionnaires were used to measure QoL in patients with VWD. In adults they are the SF-36 (see description in Chapter 2), the Sickness Impact Profile (see description in Chapter 2) and the Health Utility Index 2 and 3 (see description in Chapter 2); in children – the Infant Toddler QOL Questionnaire (0-5 years) (see description in Chapter 2), the Child Health Questionnaire (see description in Chapter 2). At present the disease-specific QoL questionnaire, the VWD-QOL, to measure QoL in patients with VWD is available.

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VWD-QOL

The VWD-QOL, developed to assess QoL in patients with VWD, was originally developed in Italy (*von Mackensen S, et al, 2007*). The VWD-QOL consists of 16 domains including a specific domain for women concerning "menstruation". Different age group versions are available for children aged 4–7 and 8–16. Two respective proxy versions for their parents are available, as well as a version for adult patients. The questionnaire is currently being validated in Germany in the Wil-QOL study. Additional translations are available in Danish, English, Finnish, Norwegian, Portuguese, Russian and Swedish, which are included in the international Wilcome study. Currently a French translation is under development, which will be included in the French Quality of Life Study in Patients with VWD (WISH-QOL).

Strengths: specific attention is paid to the bleeding disorder and its symptoms.

Weaknesses: information about psychometric properties of the tool is lacking.

For the assessment of menorrhagia there are specific patient-administered questionnaires which are the Ruta Menorrhagia Severity Scale and the Menorrhagia Impact Questionnaire.

Ruta Menorrhagia Severity Scale

The Ruta Menorrhagia Severity Scale (RMSS) was developed in Scotland and validated by literature reviews, clinical consultation, and patient endorsement both empirically and subjectively (*Ruta DA, et al, 1995*). This multi-attribute utility scale is also a menorrhagia-specific QoL questionnaire consisting of 15 items which describe the following domains: practical difficulties, social life, psychological health, physical health and well-being, work and daily routine, family life and relationships, and can be summed up to a total score ranging from 0 (worst affected) to 100 (unaffected) (*Shaw RW, et al, 1998*).

Strengths: this questionnaire has shown good psychometric characteristics in terms of reliability and validity.

Weaknesses: this instrument is considered to be narrowly focused, focusing mainly on symptoms, and the lack of a psychological item/domain is a disadvantage.

Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire (MIQ) was developed and validated in the USA in women with menorrhagia and age-matched controls with normal menstrual periods (*Bushnell DM, et al, 2010*). It is an important instrument for assessing treatments for

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heavy and abnormal menstrual bleeding. Women are asked to rate the extent to which their menstrual bleeding limited their work outside and inside the home, their physical, social, and leisure activities, and perceived mean blood loss reduction. A scale of 1 to 5 is used (with 1 being "not at all" and 5 being "extremely" limiting).

Strengths: the MIQ has proved to be a useful instrument to demonstrate progress of pharmacological treatment of menorrhagia and able to differentiate the degree of change that women with menorrhagia perceived as clinically meaningful. The psychometric properties of the MIQ were fully validated.

Weaknesses: there is yet very little data on the use of this questionnaire in clinical trials.

Practical considerations for patient-reported outcome assessment

So far only limited studies have been performed on large cohorts of patients with VWD (*de Wee EM, 2010; de Wee EM, 2011*). These studies show that QoL is strongly dependent upon the type and severity of VWD in an individual.

Study design and questionnaire choice depend on study goals and the focus population. If a study aims to identify the impact of the disease on different aspects of patient functioning, cross-sectional design with reference population comparison may be recommended. In this situation, generic QoL questionnaires are relevant. If PRO is considered to be a measure of treatment efficacy, longitudinal studies with several time-points of PRO assessment including base-line, should be designed. Disease-specific QoL questionnaires are the most informative tools in this case. If a study is conducted on the pediatric population, QoL the questionnaire/questionnaires selected should be age appropriate.

Adolescents are a special population of VWD patients. Such important factors in this population, as time lost from school, limitations in school activities, and travel plans should be taken into account when choosing an appropriate QoL questionnaire.

When interpreting PRO data it is worthwhile to provide analysis along with clinical information. Such variables, as bleeding phenotype and VWD type, along with age, gender, etc. should be adjusted in the analysis for QoL data. Hospitalizations and administration of blood products may be also considered as important variables to be taken into account when interpreting PRO data.

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CHAPTER 3

Quality of life and symptom assessment in hematological patients

3.5

Bleeding disorders

3.5.3 Immune thrombocytopenia

State of the art

Immune (or idiopathic) thrombocytopenia (ITP) is a chronic autoimmune disorder characterized by antibody-mediated platelet destruction and suboptimal platelet production (*Cines DB, Blanchette VS, 2002*). Its diagnosis and treatment has recently been subject to thorough reviews in guideline and consensus documents (*Provan D, et al, 2010; Neunert CE, et al, 2011*). In this chapter patient-reported outcomes (PROs) in patients with ITP will be considered separately in adults and in children.

Patient-reported outcomes in adult immune thrombocytopenia

Adult ITP is a rare blood disorder. The estimated annual incidence of adult ITP ranges from 0.6 to 6.6 cases per 100,000 adults (*Vianelli N, et al, 2001; Neunert CE, et al, 2008; Snyder CF, et al, 2008; Abrahamson PE, et al, 2009*). Unlike the disease course in children, ITP in adults typically has an insidious onset and a chronic course. The signs and symptoms are generally considered to be restricted to bleeding that occurs when the platelet count is <30 x 10^9/L (*George JN, et al, 1996; Cines DB, Blanchette VS, 2002; Stasi R, Provan D, 2004*). Bleeding symptoms may range from mild bruising and mucosal bleeding to severe hemorrhage (*Cines DB, Blanchette VS, 2002*) although the latter is unusual.

A wide range of therapeutic regimens are currently in use, including observation alone, as some patients, in particular children, recover within 4-12 months regardless of treatment (*Imbach P, et al, 2006; Granger JD, et al, 2011*). It must be remembered that for the majority of patients the condition is a mild one and up to 40% require no treatment at all. When treatment is required initial regimens are usually based on steroids, intravenous immunoglobulin or anti-D, either alone or in combination, for first line treatment (*Imbach P, et al, 1981*). A treatment regimen for persistent or refractory ITP may not be necessary in the absence of significant bleeding but when required is focused on decreasing the rate of platelet destruction by immunosuppression, which reduces autoantibody production, or splenectomy, which removes the presumed site of destruction. The risks of these treatments are substantial, often perceived by patients as being worse than the symptoms of ITP. A very recent treatment option are thrombopoietin-receptor agonists which stimulate platelet production (*Newland AC, 2007; Newland AC, 2008; Imbach P, Crowther M, 2011*). Treatment is often successful in the short-term and with few side-effects but their place in treatment is still being. Most current therapies do not provide a durable response and many are associated with substantial side effects that limit their long-term usefulness (*Stasi R, Provan D, 2004; Cines DB, McMillan R, 2005; Matzdorff A, Arnold G, 2007; Provan D, et al, 2010*). The only treatment option

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thought to offer a cure is splenectomy but ultimately only 60% of those treated will show a long-term response and the patient who has been splenectomized and requires further immune suppressive therapy is at a major risk of infection.

Given that many patients with very low platelet counts (<20 x 10^9/L) do not bleed, using a platelet count as the sole outcome measure in clinical trials is inadequate (*Rodeghiero F, 2009*). Symptom experience and QoL might be more valuable outcomes, as they capture the impact of disease and treatment on their daily lives directly from the patients' perspective.

A number of descriptive qualitative surveys have indicated that the symptoms experienced by patients and the treatment of ITP have a significant effect on their QoL. In 2007 the ITP Support Association conducted a survey of its membership and 790 patients primarily in the UK (696 adults and 94 children with primary ITP) with the following results:

- Absence from work (or school) due to fatigue occurred in many participants (12.5%); there was no correlation with disease severity (p = 0.301);
- Delays in surgical procedures and a lack of access to travel insurance were reported by nearly one third of people (31.3% and 30.2%);
- Activity restriction was evident (adults 9.5%, children 23.3%);
- Social engagement was affected as particularly womens' bruising led to a suspicion of physical violence (7.1%) and many women try to conceal their bruises (13.5%).

The above survey was published as a poster at the Annual Meeting of the American Society of Hematology in 2008 and as correspondence to the British Society of Hematology in 2010 (*Sarpatwari A, et al, 2008; Sarpatwari A, et al, 2010*).

A similar survey conducted in 2009 by a group of Dutch hematologists and the Dutch ITP Patient Organization (ITP Patiëntenvereniging Nederland), which included 235 adults and 48 children with ITP (n = 283) (73.9% female, average age - 42) confirmed that the majority of patients experienced symptoms that interfered with their daily life. In addition, they reported concerns related to the disease and its treatment. Side effects during ITP treatment were mentioned by 62% of the patients. About half complained about fatigue in ITP, although this symptom is not always recognized by ITP specialists.

A follow-up study to the findings of the ITP Support Association 2007 Lifestyle Survey, investigated fatigue using validated qualitative questionnaires (Fatigue Impact Scale, The Epworth Sleepiness Scale and the Orthostatic Grading Scale) among 585 patients in the UK and 93 patients in the US (*Newton JL, et al, 2011*). The prevalence of fatigue reported by the UK (39%) and the US (22%) patients was significantly greater than expected when compared with normal subjects (p <0.0001 and p <0.0001, respectively). In a univariate analysis of the combined UK and US patients, fatigue was associated with: a platelet count of less than 100,000/L; treatment with steroids; bleeding symptoms; presence of other medical conditions; daytime sleepiness; and orthostatic symptoms. This internationally important data from two cohorts confirm that fatigue is

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a common and debilitating symptom among patients with ITP.
Both disease symptoms and side effects of treatment (e.g. visible bleeding and side effects of medications) can have a negative impact on a patient's QoL, including social well-being (e.g. lifestyle adjustments for intravenous therapies, physician visits and/or hospitalizations) and psychological effects (e.g. fear of bleeding, fear of infection after splenectomy, negative body image due to bruising and corticosteroid therapy-associated weight gain (*George GN, et al, 2009*). Patients with ITP also report QoL levels that are comparable to other chronic conditions such as arthritis and diabetes, but much lower than the general population (*Zhou Z, et al, 2007; McMillan R, et al, 2008; Snyder CF, et al, 2008*).
Management decisions for adult patients with chronic ITP should not be based solely on disease severity as determined by the platelet count, but should take PROs, including bleeding symptoms, tolerance to treatment, lifestyle and patient preference into consideration as well (*Cines DB, Bussel JB, 2005; Bussel JB, 2006; George JN, 2006*).
QoL and symptom assessment in patients with ITP may be a useful tool for guiding decisions about when to start treatment, which type of therapy to recommend, and also for judging the benefit and risks of treatments. QoL is currently incorporated as a key outcome in clinical trials as part of the approval process of new drugs (*US Department of Health and Human Services FDA Center for Drug Evaluation and Research; US Department of Health and Human Services FDA Center for Biologics Evaluation and Research; US Department of Health and Human Services FDA Center for Devices and Radiological Health, 2006*).

Patient-reported outcome instruments in adult immune thrombocytopenia

The most commonly used generic QoL instruments used in adults with ITP include the SF-36 (see description in Chapter 2) and the EuroQol EQ-5D (see description in Chapter 2).
The only currently published disease-specific measure for adults with ITP is the ITP-Patient Administered Questionnaire.

ITP - Patient Administered Questionnaire

The ITP - Patient Administered Questionnaire (ITP-PAQ) is the first disease-specific QoL questionnaire developed for use in adults with chronic ITP (*Mathias SD, et al, 2007; Mathias SD, et al, 2009*). It assesses multiple facets of disease-specific issues, including symptoms, fatigue, bother, fear, social activity and overall QoL. It consists of 44 items grouped into 10 scales: Physical symptoms (6 items), Bother-Physical Health (3), Fatigue/Sleep (4), Activity (2), Fear (5), Psychological Health (5), Work (4), Social Activity (4), Women's Reproductive Health (6) and Overall Quality of Life (5). Each scale is scored from 0–100, with higher scores representing better QoL. It was found to be valid with moderate correlation to the SF-36 and was able to differentiate ITP patients on treatment

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from those off treatment (*McMillan R, et al, 2008*). So far, the ITP-PAQ has been used in two placebo-controlled randomized trials of romiplostim and has shown significant improvement in Symptoms, Bother-Physical Health, Activity, Fear, Social Activity and Women's Reproductive Health in the active treatment arm (*George JN, et al, 2009*). The ITP-PAQ can be used to describe the burden of illness as well as an outcome measure to assess the efficacy or effectiveness of ITP treatments.

Strengths: this is the only disease-specific tool available for adults. It has solid psychometric properties and has a proven track record with significant findings in clinical trials.

Weaknesses: not all the concepts identified in the qualitative ITP patient surveys are included in the ITP-PAQ.

Patient-reported outcomes in childhood immune thrombocytopenia

In children, ITP is one of the most common hematological disorders, with an incidence of 4–5 cases per 100,000 children per year (*Lilleyman JS, 1999; Zeller B, 2000; Imbach P, et al, 2002*). Although the sudden onset of bruising or bleeding is alarming to parents and primary physicians, affected children generally have a good prognosis.

Numerous controversies, however, have ensued during the past several decades regarding management of childhood ITP. These have included: the need for a bone marrow aspirate to confirm diagnosis, the need for hospitalization for observation and initiation of treatment, and the requirement for drug therapy aimed at raising the platelet count to prevent hemorrhage. The latter controversy primarily stems from concerns about severe or life-threatening hemorrhage and whether drug treatment with corticosteroids, intravenous immunoglobulin, or anti-D immunoglobulin can prevent severe hemorrhage in affected patients.

There are a number of challenges in childhood ITP at different time-points over the course of the disease which might have a negative impact on their QoL (*Neunert C, et al, 2008; Kuhne T, et al, 2011*). Waiting for the diagnosis or treatment response might be accompanied by confusion and anxiety, often enhanced by parents or adolescents surfing the internet for additional information. After diagnosis, the consequences of diagnosis, treatment, side effects, complications, and frequent laboratory checks might be accompanied by absence from school and limited social contacts. A disruption of the emotional and social equilibrium, or a need to redefine values, objectives and expectations might take place. Overprotection from the parents might also negatively affect a child's QoL.

In common with adult studies, the most frequently reported outcome in prior studies of childhood ITP is platelet count (*Blanchette V, et al, 1994; Lilleyman JS, 2004; Beck CE, et al, 2005; Tarantino MD, et al, 2006*). This is often viewed as a surrogate marker of

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hemorrhagic risk, for minor bleeding as well as hemorrhage in critical sites, such as the central nervous system. It has recently been recognized, however, that other outcomes in ITP (*Buchanan GR, Adix L, 2006*) are important, including QoL (*Barnard D, et al, 2003; Klaassen RJ, et al, 2007; Neunert CE, et al, 2009*), adverse effects of treatment (*Buchanan GR, et al, 2004*) and the cost of therapy (*Adams JR, et al, 2002; O'Brien SH, et al, 2007*).
The Intercontinental Childhood ITP Study Group (ICIS) was established in 1997 to facilitate development of prospective registries aimed at better understanding the presentation, management, and outcome of ITP (*Kuhne T, et al, 2001; Kuhne T, et al, 2003; Imbach P, et al, 2003; Imbach P, et al, 2006a; Imbach P, et al, 2006b*), emphasizing the importance of incorporating PROs in this registry.
Children, like adults, report QoL concerns related both with the disease itself and the treatment of ITP (*Sarpatwari A, et al, 2008; Sarpatwari A, et al, 2010*). In terms of PROs, activity restriction and fatigue are issues that appear to affect children the most.

Patient-reported outcome instruments in childhood immune thrombocytopenia

Very few studies on QoL have been done in children with ITP. The most commonly used generic pediatric QoL instruments used in children with ITP include the PedsQL (see description in Chapter 2) and the KINDL (see description in Chapter 2).
There are currently two disease-specific QoL tools developed for children with ITP: the Kids' ITP Tools and the Idiopathic Thrombocytopenic Purpura - Quality of Life questionnaire.

Kids' ITP Tools

The Kids' ITP Tools (KIT) was developed in North America specifically for children (aged 2–18) with ITP and their parents (*Barnard D, et al, 2003*). It consists of three questionnaires. One is for the child (child self-report), where the child is asked to focus on what they thought about and did over the past week. Another is for the parent to complete on behalf of the child (parent proxy report). In this questionnaire, the parent is asked to focus on what their child would have answered about the past week. The third one is for the parent complete about themselves (parent impact report) to capture their experience over a short period of time. All of these questionnaires consist of 26 questions with the total score ranging from 0–100. There are no subscales. Data supporting the validity, reliability and responsiveness of KIT has been published (*Klaassen RJ, et al, 2007*). The KIT has been translated into 24 languages in 21 countries.

Strengths: it is a valid and reliable disease-specific tool for children; translations in different languages are available.

Weaknesses: limited information about psychometric properties of different language versions of the tool is available.

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Idiopathic Thrombocytopenic Purpura - Quality of Life questionnaire

The Idiopathic Thrombocytopenic Purpura - Quality of Life questionnaire (ITP-QoL) was adapted from the Haemo-QoL, a hemophilia disease-specific QoL tool, through interviews with European children with ITP (*von Mackensen S, et al, 2006*). The development of ITP-QoL included three phases: (a) a preparatory phase; (b) a developmental phase; (c) a pilot testing phase. Since dimensions of Haemo-QoL were considered important for children with ITP, items were adapted, reformulated and additional dimensions were included. Two age-group versions were designed for children (aged 3–7, 8–18) and parents in Italian, German, and Swedish.

No more information about ITP-QoL is available.

Practical considerations for patient-reported outcome assessment

Incorporating PRO assessment into all future clinical trials of patients with ITP is recommended since severe morbidity is rare and the platelet count only partly explains the burden of this disease. PROs should be included, in addition to platelet count and a bleeding severity score, as they all provide unique information about what is happening to the patient. Ideally, both generic and disease-specific QoL tools are of use. A generic QoL tool provides a well validated and clearly understood reference point, whereas the disease-specific tools better delineate the disease-specific issues and are more sensitive to changes in health outcome. Currently, disease-specific QoL instruments are available both for adults and children with ITP. Because there are a number of challenges in ITP at different time-points over the course of the disease, in longitudinal studies the timing for administering PRO instruments should be chosen in relationship to the intervention and the course of illness trajectory.

Analysis and interpretation of PRO data in patients with ITP should be done with respect to clinical data. The most important data are disease severity and type. Age, disease duration, etc. are of importance as well. In ITP patients QoL treatment response should be interpreted along with the platelet response.

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CHAPTER 3

Quality of life and symptom assessment in hematological patients

3.6

Anemia of chronic disease

State of the art

Anemia of chronic disease (ACD) is a multifactorial anemia with chronic immunity driven underlying disease, namely malignancy, inflammation, infection, or rheumatic diseases (*Weiss G, 2002; Means RT, 2003; Weiss G, Goodnough LT, 2005*). ACD is the second most prevalent after anemia that is caused by iron deficiency. The most frequent conditions associated with anemia of chronic disease are listed in Table 1 (*Weiss G, Goodbough LT, 2005*). The prevalence of ACD in these specific diseases depends on the stage of the disease as well as on patients' age, treatment associated factors and nutritional status.
Advances in the understanding of the pathophysiology of ACD, including the pathways leading to iron retention in macrophages and thus an iron limited erythropoiesis, impaired proliferation of erythroid progenitor cells, and a blunted erythropoietin response to anemia, are the basis for the development of new diagnostic and therapeutic concepts. When possible, treatment of the underlying disease is the therapeutic approach of choice for ACD (*Weiss G, 2002; Means RT Jr, 2003; Maury CP, et al, 2003*). Improvement in hemoglobin levels has been demonstrated, for example, in patients with rheumatoid disease who were receiving therapy with anti-TNF antibodies. In cases where treatment of the underlying disease is not feasible or does not result in a sufficient increase of

Table 1. Underlying causes of anemia of chronic disease

Associated diseases	Estimated prevalence %
Infections (acute and chronic) Viral infections, including human immunodeficiency virus infection Bacterial Parasitic Fungal	**18–95**
Cancer Hematologic Solid tumor	**30–77**
Autoimmune Rheumatoid arthritis Systemic lupus erythematosus and connective-tissue diseases Vasculitis Sarcoidosis Inflammatory bowel disease	**8–71**
Chronic rejection after solid-organ transplantation	8–70
Chronic kidney disease and inflammation	23–50

Weiss G, Goodbough LT, 2005

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hemoglobin levels, alternative strategies are necessary. At present, they include blood transfusions, iron supplementation, and erythropoietic agents. Before using these agents a careful diagnosis has to be carried out to differentiate between absolute and functional iron deficiency and to rule out other factors which may impact on the response to therapy (e.g. folate or vitamin B12 deficiencies, renal impairment, hemolysis).

Blood transfusions are widely used as a rapid and effective therapeutic intervention. Transfusions are particularly helpful in the context of either severe anemia (in which the hemoglobin is less than 8.0 g per deciliter) or life-threatening anemia (in which the hemoglobin is less than 6.5 g per deciliter), particularly when the condition is aggravated by complications that involve bleeding.

Current data suggest that patients with ACD and absolute iron deficiency should receive supplemental iron therapy (*Winn RJ, 2000; Rizzo JD, et al, 2002; Auerbach M, et al, 2004; Nurko S, 2006*). Erythropoietic agents for patients with ACD are currently approved for use by patients with cancer who are undergoing chemotherapy (in many countries), patients with chronic kidney disease, and patients with HIV infection who are undergoing myelosuppressive therapy. The percentage of patients with anemia of chronic disease who respond to therapy with erythropoietic agents is 25% in myelodysplastic syndromes (*Thompson JA, et al, 2000*), 80% in multiple myeloma (*Ludwig H, et al, 1990*), and up to 95% in rheumatoid arthritis (*Moreland LW, et al, 1997*) and chronic kidney disease (*Nurko S, 2006*). In addition, new therapies are approaching which aim to mobilize iron from the reticulo-endothelial system and make it available for erythropoiesis. This can be achieved by pharmacological or antibody mediated inhibition of the master regulator of iron homeostasis hepcidin which has been shown to be effective for the correction of ACD in a rat arthritis model (*Theurl I, et al, 2011*).

However, little information is available on the effect of any of these treatments on the course of the disease underlying ACD, an essential issue which has to be studied urgently in prospective clinical trials in order to avoid negative side effects of anemia correction (e.g. pulmonary embolism, promotion of cancer cell growth or infection).

ACD is known to be accompanied by anemia-related symptoms and impaired quality of life (QoL). Thus, QoL and symptom assessment are important in this patient population. Prospective, controlled studies with patient-reported outcomes (PRO) are needed to evaluate the effect of the management of ACD. PRO is a valuable outcome when measuring the efficacy of future treatment strategies for ACD. The latter may include new approaches to increase the endogenous formation and biological activity of erythropoietin, hepcidin antagonists or ferroportin agonists, and hormones or cytokines that might effectively stimulate erythropoiesis under inflammatory conditions. End-points that correlate with improvements in morbidity and mortality in well-designed, prospective studies must be identified in order to determine the optimal therapeutic regimen for patients with ACD. Among them, patient perspective of treatment benefits is of no less importance than traditional biomedical markers.

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The most information about QoL and symptom assessment is available for patients with cancer related anemia.

Cancer-related anemia

Anemia is a widely prevalent complication among cancer patients. The prevalence of anemia varies according to the cancer type (*Bohlius J, et al, 2009*). It is also affected by the therapeutic procedure and age. Patients with hematological malignancies frequently experience anemia. At the time of diagnosis, 30–40% of patients with non-Hodgkin's lymphoma or Hodgkin's lymphoma and up to 70% of patients with multiple myeloma are anemic. The figures are even higher in those with myelodysplastic syndromes. The extent of anemia is also influenced by the type of cytostatic treatment. About 37–100% experience fatigue during treatment with cyclophosphamide, doxorubicin, vincristine and other cytostatics. Between 45–90% of patients with myeloma or non-Hodgkin's lymphoma need transfusion during treatment.

The functional definition of anemia is an insufficiency of red blood cells to maintain adequate tissue oxygenation. The resulting tissue hypoxia manifests itself in a number of related symptoms. Table 2 shows the effects of anemia in cancer patients (*Brandberg Y, 2000*). Furthermore, there is a strong association between anemia and fatigue (*Cella D, et al, 1998; Holzner B, et al, 2002*). Anemia affects patients with malignancies by symptoms and the deterioration of QoL.

Fatigue is the most pronounced symptom in patients with cancer-related anemia. According to the guidelines of the National Comprehensive Cancer Network (NCCN), cancer-related fatigue is defined as a persistent subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that significantly interferes with usual functioning. Fatigue and QoL in cancer patients have been related with Hb levels in a longitudinal manner (*Crawford J, et al, 2002; Cella D, et al, 2004*). Anemic cancer patients report more fatigue as compared to non-anemic cancer patients (*Cella D, et al, 2002*). Prevalence estimates of fatigue have ranged from 50–90% of cancer patients overall (*Campos MP, et al, 2011*). Fatigue has been reported as a side effect of chemotherapy in 58–90% of cancer patients (*Groopman JE, et al, 1999*). As many as 75–80% experienced fatigue one month post-diagnosis and 37% had at least two weeks of fatigue after termination of treatment. Five years post chemotherapy therapy, 33% reported still having fatigue (*Cella D, et al, 2002*). The NCCN now suggests that all cancer patients should be screened for cancer-related fatigue at their initial visit, when the diagnosis of advanced disease is made, and at each chemotherapy visit (*Mock V, et al, 2000*).

The effects of anemia on QoL have been evaluated mainly in studies of recombinant human erythropoietin. The number of publications in this area has increased in recent years. Pubmed search 020411 yielded 1,069 results (search terms: anemia, cancer & quality of life). It has been shown that cancer-related anemia has negative impact on all

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Table 2. Effects of anemia in cancer patients

Body system	Symptom
Central nervous system	Fatigue
	Dizziness
	Vertigo
	Depression
	Impaired cognitive functioning
Gastrointestinal system	Anorexia
	Nausea
Cardiorespiratory system	Exertional dyspnoea
	Tachycardia, palpitations
	Cardiac enlargement, eccentric hypertrophy
	Increased pulse pressure, systolic ejection murmur
	Increased risk of cardiac failure
Genitourinary tract	Menstrual problem
	Loss of libido
Vascular system	Low skin temperature
	Pale skin, mucous membranes and conjunctivae
Immune system	Impaired T-cell and macrophage function

Brandberg Y, 2000

QoL domains: physical, mental, and social well-being. Commonly, exercise tolerance is markedly reduced. As a consequence, the demands of every-day life become a burden and social activities are restricted because of a lack of energy. Clinical studies have reported correlations between hemoglobin levels and QoL domains (*Leitgeb C, et al, 1994; Cella D, 1998; Demetri GD, et al, 1998; Thomas ML, 1998*). Nevertheless, one has to keep in mind that the development of anemia and the severity of anemia are primarily a reflection of a more advanced malignant disease.

Many children/adolescents with cancer are anemic, which contributes to the decreased QoL in this population. It has been shown that the amelioration of anemia with recombinant human erythropoietin, results in improved QoL. Thus, PROs are important treatment outcomes for children with cancer-related anemia. Approaches to PRO assessment in children/adolescents are presented in Chapter 7.

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Patient-reported outcome instruments

To evaluate PROs in anemic patients PRO measures should be used. The use of PRO instruments, developed in international collaboration, which have undergone formal translations and that have been tested for reliability and validity, is recommended.
There are several QoL instruments available to assess QoL in anemic cancer patients:

- Generic QoL questionnaires
- QoL questionnaires generic for neoplasms
- Specific QoL questionnaires for the assessment of anemia and fatigue.

A generic questionnaire should be used when the aim of the study is to compare patients' QoL with the QoL of population norms. The SF-36 (see Chapter 2) is an appropriate tool for this purpose.
Two generic QoL questionnaires for neoplasms, FACT-G and EORTC QLQ-C30 (see description in Chapter 3.1) meet modern methodological requirements and are used in blood cancer patients with anemia. There are modules of the FACT-G and the EORTC QLQ-C30 which can be used to assess anemia and fatigue in blood cancer patients.
The description of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and Functional Assessment of Cancer Therapy-Anemia (FACT-An) is presented in Chapter 3.4. Both scales have been shown to differentiate between patients by hemoglobin level, and it has been concluded that these subscales are useful measures of QoL in cancer treatment, adding more focus to the problem of fatigue and anemia (*Bottomley A, 2001; Littlewood TJ, et al, 2001*).

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Fatigue Module

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Fatigue Module (EORTC QLQ-FA13) is currently under development in international collaboration using the guidelines for EORTC questionnaires (*Weis J, 2007*). It has been developed for use in all diagnoses, stages of the disease and treatment settings. It is measuring cancer-related fatigue based on a multidimensional approach including physical, emotional and cognitive aspects of fatigue. One global item is assessing the interference of fatigue with activities of daily living. The development of the module has passed phase I/II based on n=36 expert interviews (physicians, nurses, psychologists) from 8 different European countries. The phase II fatigue module was available in two versions: FA-R15 (reduced version with 15 items) to be used in combination with EORTC QLQ-C30; FA25 (with 25 items) to be used without EORTC QLQ-C30. FA25 includes items of the EORTC QLQ-C30. EORTC QLQ FA-R15 has been pre-tested as a phase III module according to the EORTC Module Development Guidelines. Patient recruitment in pre-testing the module FA-R15 has been finished at the end of November 2007. Data of 318 patients covering various tumor sites and treatment

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settings were evaluated. As collaborators 7 European countries have contributed: France, Germany, Italy, Austria, Sweden, Spain, UK. The final report was submitted in October 2008 and a revised version was accepted in April 2009. As result from phase III EORTC QLQ-FA-R15 was revised into EORTC QLQ-FA13 version as a completed phase III module, which is available for use in clinical trials. Currently the module is in phase IV evaluation.

Among symptom assessment instruments used in blood cancer patients with anemia, fatigue assessment tools are worthwhile. There are unidimentional and multidimentional fatigue scales. The most common unidimentional scales that can be used in research or clinical settings, are 4 or 5-point verbal rating scales, numeric scales, and visual analogue scales (VAS). They typically focus on the important dimension of fatigue severity. VAS-Fatigue is often used in combination with VAS measuring other anemia symptoms.

Multidimensional fatigue assessment tools are the Piper Fatigue Scale (*Piper BF, et al, 1998*), the Lee Fatigue Scale (*Lee K, et al, 1991*), the Brief Fatigue Inventory (*Mendoza TR, et al, 1999*), the Multidimensional Fatigue Inventory (*Smets EM, et al, 1995*), the Cancer Fatigue Scale (*Okuyama T, et al, 2000*), and the Schwartz Cancer Fatigue Scale (*Schwartz A, 1998*). Some of these questionnaires complement the measurement of fatigue severity with information about other characteristics, and others focus on the measurement of the impact of fatigue on different types of functioning. An important advantage of using a multidimensional fatigue questionnaire is that it allows analyses that potentially can clarify the nature of a fatigue syndrome or the type of response that occurs following an intervention. For example, a multidimensional instrument could help determine the extent to which an intervention, such as epoetin alfa, may affect vitality in general, the cognitive component of fatigue, as well as mood or other symptoms.

Information concerning widely used fatigue assessment tools is presented below.

Piper Fatigue Scale - Revised

The Piper Fatigue Scale - Revised (PFS-R) is a multidimensional self-report instrument useful in fatigue assessment (*Wu HS, McSweeney M, 2001; Dittner AJ, et al, 2004*). It originates from a prior longer version of the scale, which was developed from a thorough review of the literature on the conception and measurement of symptoms in general and of fatigue and pain in particular (*Piper BF, et al, 1998*). Although it is frequently used for non-cancer populations, it was originally validated in a sample of breast cancer survivors and is commonly applied in oncological practice as well as research. The scale consists of 22 items supplemented by 5 additional open-ended questions related to the temporal dimension of fatigue, its perceived cause, effect, relief, and additional symptoms not included in the scoring. A principal component factor analysis groups the 22 items into 4 reliable and correlated dimensions: behavioral severity (6 items), relating to the severity and degree of disruption in activity of daily living; affective meaning (5 items), relating to the emotional meaning attributed to fatigue; sensory (5 items),

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relating to the physical symptoms; and cognitivend mood (6 items), relating to mental and mood states. Scaling is based on a 0–10 range (0: none, 1–3: mild, 4–6: moderate, 7–10: severe). To calculate subscale scores, the scores on all items within the particular subscale are added, and this sum is then divided by the number of items within the particular subscale. This gives a mean subscale score for the subject from 0–10 (minimal-maximal fatigue). A total fatigue score can be calculated by adding the four subscale scores and dividing this sum by four. The scale has been validated in France, the Netherlands, and Brazil.

Strengths: with its strong theoretical foundation, the Piper's integrated fatigue model makes the PFS-R unique among existing fatigue measures.

Weaknesses: the dimensional structure of the scale appears not to be constant across cultures; consequently, inspection of its psychometric properties (dimensionality, validity, and reliability) before its usage in a new national context is desirable. Along with that, the scale is fairly long for routine clinical use.

Lee Fatigue Scale

The Lee Fatigue Scale (LFS) or Visual Analogue Scale for Fatigue (VASF) is a fatigue assessment tool that was originally validated in a group of patients with sleep disorders (*Lee K, et al, 1991*). The LFS uses a 100 mm visual analogue scale to evaluate perception (or level) of fatigue. The instrument consists of 18 questions, of which 13 are related to fatigue and 5 are related to energy. Its psychometric properties were assessed in a sample of mixed cancer patients undergoing treatment (*Meek PM, 2000*).

Strengths: the instrument is easy, reliable, and sensitive to time of day changes. Its form of a visual analogue scale affords patients the opportunity to better qualify symptoms, while providing investigators with a more accurate quantification and objectivity. The LFS is useful both for screening and outcome assessments.

Weaknesses: because of a potential overlap with measures of sleep disturbance, it has had very limited use in cancer-related fatigue measurement. This scale requires further assessment of test-retest reliability and convergent, divergent, and discriminator validity.

Schwartz Cancer Fatigue Scale

The Schwartz Cancer Fatigue Scale (SCFS) is a 28-item questionnaire that evaluates the physical, emotional, cognitive, and temporal aspects of cancer-related fatigue (*Schwartz A, 1998*). Patient perceptions of the preceding 2–3 days are assessed by a 5-point Likert scale. The fundamental intent of the SCFS is to simplify the evaluation method while preserving content. The revised version contains only 6 items.

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Strengths: the brief, easy to use scale has shown acceptable reliability and validity.

Weaknesses: there is very little data on the studies using this scale.

Brief Fatigue Inventory

The Brief Fatigue Inventory (BFI) is used to rapidly assess the severity and impact of cancer-related fatigue (*Mendoza T, et al, 1999*). The BFI assesses severity of fatigue and the impact of fatigue on daily functioning in the past 24 hours on the basis of 0–10 numeric rating scales. On the BFI, severe fatigue can be defined as a worst fatigue score of 7 or greater. It can be administered as self-report, interview with research staff, or interactive voice response system. Time required for completion is five minutes. A global fatigue score can be obtained by averaging all the items on the BFI. The 6 inventory items correlate with standard quality-of-life measures. The BFI is a simple technique for the rapid screening of fatigue and for evaluating its impact on the symptoms and daily functioning of cancer patients. The BFI has been translated into 21 European languages.

Strengths: it is easy to administer and score. Using the BFI, cut-points for mild, moderate, and severe fatigue were identified based on their relevance to patient's QoL. Due to the strongest correlation with functional interference, symptoms, depression and QoL, fatigue severity was defined as mild (1–3), moderate (4–7), or severe (8-10). These cut-points might be useful in clinical evaluation of cancer related fatigue.

Weaknesses: the instrument measures the severity of fatigue only over the previous 24 hours.

Multidimensional Fatigue Inventory

The Multidimensional Fatigue Inventory (MFI) is a 20-item self-report instrument designed to measure fatigue (*Smets EM, et al, 1995*). The MFI-20 contains 5 subscales: general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation. Each subscale includes 4 items with 5-point Likert scales. General fatigue includes general statements about fatigue and decreased functioning and was designed to encompass both the physical and psychological aspects of fatigue. Physical fatigue concerns physical sensations related to fatigue. Mental fatigue pertains to cognitive functioning, including difficulty concentrating. Reduced activity refers to the influence of physical and psychological factors on the level of activity. Reduced motivation relates to lack of motivation for starting any activity. Scores on each subscale range from 4–20, with higher scores indicating greater fatigue. The MFI has been used to assess fatigue in patients with a variety of cancers who are receiving chemotherapy or radiotherapy. The tool is available in 13 European languages.

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Strengths: the MFI appears to be a valid and reliable measure of chronically unwell and well populations with a stable multidimensional factorial structure. With the use of this questionnaire it is possible to capture differences in fatigue across time.

Weaknesses: additional research is required to assess the discriminant validity of the MFI scales with regard to depression in cancer patients. Additionally, the instrument's responsiveness to change needs to be assessed.

Cancer Fatigue Scale

The Cancer Fatigue Scale (CFS) is a self-reported, 15-item questionnaire with simple summative scoring (1 = no to 5 = very much) composed of physical (7 items), affective (4 items), and cognitive (4 items) domains (*Okuyama T, et al, 2000*). The scale was designed specifically to reflect the nature of fatigue experienced by cancer patients, by using factor analysis.

Strengths: the CFS is a brief, valid, and feasible measure of fatigue for use with cancer patients. It can be completed in less than 2 minutes.

Weaknesses: there is no psychometric testing available for the English version.

Practical considerations for patient-reported outcome assessment

In clinical trials for anemia patients PROs may be considered as primary or secondary end-points. QoL and anemia-related symptoms may be included in the end-point model. When developing the study design in anemia patients several issues should be noted. Commonly it is a prospective study with longitudinal design with at least 3 time-points. The time-points for PRO and clinical variables assessment should be the same. Base-line PRO assessment should be provided before randomization. Every PRO assessment should be performed before a medical visit.

Interpreting PRO data is the crucial issue. PRO data should be analyzed along with the Hb level. It is worthwhile to provide adjusted analysis for QoL data. Such parameters as age, gender, disease and treatment related indicators, lab indicators, etc. should be considered. QoL and symptom changes in Hb-responders and Hb non-responders should be analyzed separately and compared, controlling for baseline Hb levels. In addition, separate analyses in the groups with different base-line QoL impairment should be conducted.

The target group is of importance when QoL and anemia-related symptoms are the focus of the study. A good illustration is the population of patients with MDS. The palliative

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setting of MDS and an increasing number of therapeutic trials should focus on PRO changes as a primary end-point together with erythroid responses within the study design. The choice of the questionnaires depends on whether the aim of the study is to assess the effects of the study drug only on anemia-related symptoms (FACT-An may be sufficient), or on other aspects of MDS (i.e. QOL-E may provide further information on the disturbance related to transfusion-dependence). Furthermore, a more generic instrument, such as the EORTC QLQ-C30, may be used to evaluate symptoms related to the study drug (side effects such as nausea, constipation, diarrhea, etc.). The identification of an ideal transfusion trigger in MDS is still lacking. For MDS patients resistant to erythropoiesis-stimulating proteins and newer agents, future trials of transfusion strategies should evaluate changes in meaningful PROs over time together with changes in transfusion requirement, Hb levels, cardiac remodeling, and iron overload. Within clinical trials, assessment should not be limited to changes in summary scores, but should allow for evaluation of changes in selected informative items relative to the disease and its treatment (*Oliva EN, et al, 2010*).

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CHAPTER 4

Quality of life and symptom assessment in patients undergoing bone marrow/ hematopoietic stem cell transplantation

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State of the art

During the last 30 years, both the number of bone marrow/hematopoietic stem cell transplants (BMT/HSCT) performed annually, and the number of diseases for which BMT/HSCT is therapeutically indicated have increased. Advances in BMT/HSCT have expanded patient access, a reduction in transplant-related morbidity and mortality and improved long-term outcomes.

There are three groups of factors that may influence the treatment outcomes in patients undergoing BMT/HSCT:

- Disease-related (disease/tumor characteristics, complications, co-morbidities)
- Patient-specific (symptoms, quality of life - QoL)
- Treatment-related (mobilization, type of transplant, conditioning regimen, supportive care).

To assess the treatment outcomes in patients undergoing BMT/HSCT, it is necessary to measure both clinician-reported objective data (disease/tumor, complications, co-morbidities, BMT/HSCT side effects) and patient-reported subjective data (symptoms, QoL, treatment satisfaction).

It is now recognized that the goal of BMT/HSCT is not simply survival, but also the maintenance of a patient's QoL. Information about QoL and symptoms provides a broader understanding of the patient's status after treatment beyond simple disease-free survival. Accurate information about QoL and symptoms is essential in order to allow potential transplant recipients and family members make informed decisions about BMT/HSCT.

Furthermore, although BMT/HSCT has been established as the standard therapy for a number of hematological disorders, it carries an attendant risk of both significant short and long-term morbidity including the potential for reduced QoL.

Most patients report symptoms and diminished overall QoL during the acute phase of BMT/HSCT. The spectrum of symptoms may vary according to the disease, its status and stage at time of transplantation, the type of transplant, the conditioning regimen and other factors. At present, information about the side effects of transplantation is rather physician-oriented and, only to a lesser extent, patient-reported. A better awareness of the likely pattern of symptoms a patient will experience during the transplant allows the team to devise appropriate strategies to deal with these expected symptoms as they occur.

It is worth mentioning that improved transplantation strategies have contributed to increases in overall survival rates of approximately 10% per decade resulting in an increased focus on QoL in long-term survivors. Patients who survive two years after BMT/HSCT now have long-term survival rates exceeding 70%. Therefore, one of the main objectives of recent research has been to evaluate long-term changes in QoL and to identify host- and treatment-related factors that impact on long-term functional recovery. Long-term complications include physical and psychological morbidity due to treatment-related toxicity, infections and graft-versus-host disease (GvHD).

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It is now clearly established that cure or control of the underlying malignancy is not necessarily accompanied by full restoration of health or QoL in long-term survivors. As it has been shown, the burden of nonmalignant late effects after HSCT is high, even with modern treatments and relatively short follow-up (*Khera N, et al, 2012*). These late effects are associated with poor health and functional status, underscoring the need for close follow-up of this group and additional research to address these complications. As self-assessed QoL is the ultimate benchmark of subjective patient health, a proactive approach to addressing QoL is essential in the transplant setting. The vulnerable subgroups identified in recent studies could benefit from more intensive surveillance and a multidisciplinary approach to follow-up, including interventions tailored to the specific needs of each patient. Information about symptom patterns and their change over time are fundamental requirements for symptom treatment in long-term survivors. In summary, data on QoL and symptoms after BMT/HSCT may be helpful in developing rehabilitation programs for this patient population and also in identifying patients who are in need of additional intervention to restore their physical, psychological and emotional well-being.

Data on QoL and symptoms before BMT/HSCT could also be used to create prognostic models for survival.

Thus, information about QoL and symptoms in patients undergoing BMT/HSCT is needed:

- To improve transplantation strategies
- To lower the incidence of acute and long-term side effects
- To predict possible complications
- To evaluate the extent of change in QoL over time and to measure the trajectory of recovery after transplantation
- To develop appropriate rehabilitation programs
- To create prognostic models for treatment outcomes
- To support potential transplant recipients and their family members who are making decisions regarding BMT/HSCT with accurate information about likely QoL and symptoms at different phases of transplantation.

It addition to this, it is essential to carry out monitoring of QoL and symptoms from base-line through all the stages of BMT/HSCT and survival time.

Thus, there has been a growing interest in QoL evaluation in patients undergoing BMT/HSCT. A large number of studies on patient-reported outcomes (PROs) in the BMT/HSCT patient cohort have been carried out in recent years (*Pidala J, et al, 2010; McCabe C, 2011*). A number of reviews are available (*Andrykowski MA, 1994; Whedon M, et al, 1994; Winer EP, et al, 1994; Hjermstad MJ, et al, 1995; Baker F, 1997; Neitzert CS, et al, 1998; Hacker ED, 2003; Pidala J, et al, 2009*).

A summary of QoL and symptom research in patients undergoing BMT/HSCT carried out between 2000 and 2011 is presented in Tables 1 and 2, respectively. Summary details regarding the country, participants, sample size, instruments, design, outcome, measurement and time-frame are presented (*Jarden M, 2011*).

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Table 1. Studies on QoL in patients undergoing BMT/HSCT from 2000 to 2011

Reference	Sample characteristics Sample size	Instruments	Design Outcomes	Measurement Time-frame
Heinonen, et al, 2011, USA	Allogeneic n=109	FACT-BMT POMS MOS SSQ6	Prospective	1 yr 5 yrs
Altmaier, et al, 2006, USA	Allogeneic n=309	FACT (28 items) + BMT (38 items) SF-36 CES-D	Related to conventional allogeniec vs. T-cell depletion	Baseline, day +100 6 mo 1 yr 3 yrs
Jacobs, et al, 2006, USA	Allogeneic and autologous n=122	FACT-Cog EORCT CES-D SF-36 FSI STAI-S (NART (reading test) and Cognitive Performance tests)	Prospective Focus on cognitive functioning	Baseline 6 mo or 12 mo
Broers, et al, 2000, The Netherlands	Allogeneic and autologous n=123	FLB GHQ.12 SCL-90-R HLOC SES QOL (2 items)	Prospective	Pre-HSCT 1 mo 6 mo 1 yr 3 yrs
Heinonen, et al, 2001, Finland	Allogeneic n=109	FACT-BMT POMS MOS SSQ6	Prospective	1 yr 3 yrs
Sherman, et al, 2009, USA	Autologous n=94	FACT-BMT Psychosocial adjustment: Brief Symptom Inventory Impact of Events Scale Satisfaction with Life Scale	Prospective	Pre-transplant (stem cell collection) Post-transplant
Sherman, et al, 2004, USA	Autologous n=213	HADS Psychosocial adjustment: Brief Symptom Inventory Hamilton Depression Rating Scale SF-12 (physical function, pain, energy)	Prospective	Pre-transplant
Kav, et al, 2009, Turkey	Allogeneic n=67	EORTC QLQ-C30 Bush BMT Symptom Inventory for measuring symptom severity and symptom distress	Prospective	At least day +100 (mean 16 mo)
Edman, et al, 2001, Sweden	Allogeneic n=25	SIP (Sickness impact Profile) SFID-BMT(Symptom Frequency, Intensity and Distress scale) SOC (Sense of Coherence scale)	Prospective	2–4 yrs
Van Agthoven, et al, 2001, The Netherlands	Autologous n=91	EuroQoL RSCL Rotterdam Symptom Checklist SF-36	Primary outcome: Cost analysis between PBSCT vs. ABMT Prospective	Post-transplant 3 mo

continue

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Reference	Sample characteristics Sample size	Instruments	Design Outcomes	Measurement Time-frame
Prieto, et al, 2004, Spain	Allogeneic and autologous n=220	Overall physical status Overall emotional status Energy level Systemic symptoms	Tested psychometric properties of 4 PRO QoL instruments devised by the authors	Admission, weekly during hospitalization until discharge
Lee, et al, 2006, USA	Allogeneic n=96 QoI and GvHD	SF12 FACT-BMT TOI (trial outcome index)	Prospective Correlation between FACT-BMT and GvHD No correlation between SF12 and GvHD	Pre-transplant 6 and/or 12 mo
Chiodi, et al, 2000, Italy	Allogeneic n=244	PAIS	Prospective	Pre-transplant 61 mo (mean)
Wettergren, et al, 2008, Sweden	Allogeneic n=22	SEIQoL-DW (Schedule for Evaluation of Individual Quality of Life-Direct Weighting) EORTC QLQ-C30	Prospective	Pre-transplant 1 yr
Frick, et al, 2004, Germany	Autologous n=79	EORTC QLQ-C30 SEIQoL-DW Karnofsky Index	Prospective	Pre-transplant
Hjermstad, et al, 2003, Norway	Allogeneic and autologous n=130	CARES-SF (Cancer rehabilitation and evaluation system short form) EORTC QLQ-C30 (only physical function scale)	Prospective	Pre-transplant 2 mo 6 mo 12 mo
Hjermstad, et al, 2004, Norway	Allogeneic and autologous n=248	EORTC QLQ-C30 HADS Fatigue Questionnaire	Prospective Between group comparison allogeneic vs autologous	9/7 times first year 4–6 mo 12 mo 3 yrs
Schulmeister, et al, 2005, USA	Autologous n=36	FACT-BMT Kvalitative telephone interviews	Descriptive, prospective	Pre-transplant 4–6 weeks 6 mo
Pidala, 2009, QoL and SCT, USA	Allogeneic and autologous	Regarding Clinical evaluation (1990–97) «Include measures of general QoL that are appropriate for both patients and non-patient groups (Medical Outcome Study – Short Form 36, MOS SF-36 (Ware, et al, 1993), measures designed to assess QoL specifically in cancer pt's (e.g. Cancer Rehabilitation Evaluation System-Short Form, CARES-SF (Schag, et al, 1990); EORTC QLQ-C30 (Aaronson, et al, 1993); FACT-G (Cella, 1993), and measures designed to assess QoL specifically in HCT patients (e.g. FACT-BMT (McQuellon, et al, 1997); City of Hope/Stanford Longterm BMT Survivor Index, COH-QoL (Schmidt, et al, 1993). All of the above are well-validated and have been used to assess QoL specifically in HSCT patients»	Review of studies from 1990–97 These studies are not included in Table 1	

Modified from Jarden M, 2011

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Table 2. Studies on symptoms in patients undergoing BMT/HSCT from 2000 to 2011

Study/ country	Participants Sample size	Instruments	Design Outcome	Measurement Time-frame
Anderson, et al, 2007, Cleeland, USA	Autologous n=100	MDASI-BMT (symptom burden) POMS (measure of mood) FACT-BMT (Measure of QoL) ECOG PS The Eastern cooperative oncology Group Performance Status (measure of functional status)	Prospective Assess symptom burden during acute phase autologous transplant Identify predictors of high levels of symptom burden	MDASI-BMT (pre conditioning, day -4, day 0, day of nadir and +day 30 Other assessment measures Baseline +day 30 post-transplantation
Lee, et al, 2002, Dana Farber, USA	Allogeneic n=107 (active cGvHD)	30 item self developed symptom scale (7 subscales to capture the cGvHD specific symptom burden) SF36 FACT-BMT	Prospective, correlational and longitudinal To validate a scale to measure symptoms of cGvHD	Enrollment 3 mo 6 mo
Larson, et al, 1993, Comparison of Perceived Symptoms, San Francisco, USA	Allogeneic and autologous n=30	Karnofsky perfomance status (KPS) (measure of functional status) POMS (Measure of mood) Symptom Distress Scale (SDS) (distress)	Prospective, correlational, and longitudinal	Day 1 Day 7–10 Day 20–23 Day 30–34
Hacker, et al, 2006, Fatigue and Physical activity in patients undergoing HSCT, Chicago, USA	Allogeneic and autologous n=20	Fatigue (measured 3x/daily) Actiwatch score – electronic Physical activity (wrist actigraph) EORTC QLQ-C30 (+ fatigue subscale) measure fatigue using a four-point Likert scale (measure health status perceptions) Quality of Life Index (QLI) (a measure of life satisfaction)	Descriptive, exploratory study used a prospective, repeated-measures design to assess changes in fatigue, physical activity, health status perceptions and QoL	Assessment over 5 days before and after conditioning (total 10 days) Baseline data +day 4–5
Larsen, et al, 2007, Factors associated with poor general health after SCT, Sweden	Allogeneic and autologous n=41	SIP (Sickness Impact Profile) measure for FS SWED-QUAL (Swedish health related QoL profile) – used only one question regarding GH SFID-SCT (Symptom frequency, intensity, and distress for SCT) – to measure and differentiate between symptom occurrence, intensity and distress All3 scales used in SCT in Sweden	Descriptive – correlational functional status (FS), general health (GH) and symptom distress symptom FS&GH	5 time points: Baseline Discharge 3 mo 6 mo 12 mo
So og Tai, 2005, Hong Kong	Allogeneic and autologous n=157	Revised Piper Fatigue Scale (RPFS-CV – Chinese version) Fatigue Relief Scale (FRS-CV – Chinese version)	A descriptive, cross sectional design Explore the intensity of fatigue post HSCT and fatigue relieving strategies frequently used and their effectiveness	Patients were discharged – test time is not stated

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Study/ country	Participants Sample size	Instruments	Design Outcome	Measurement Time-frame
Campagnaro, et al, 2008, MD Anderson, USA	Autologous (multiple myeloma) n=64	MDASI	A prospective evaluation of symptom burden Baseline symptom burden was the most important predictor for symptom burden after transplant	4 time points: Baseline Day 0 Nadir Day 30
Bevans, et al, 2008, The symptom experience in the first 100 days following allo-HSCT, NIH, USA	Allogeneic n=76	SDS Symptom Distress Scale (11 symptoms) to capture symptom occurrence and symptom distress, and to provide data for symptom cluster analysis SF-36 (only the physical component and mental component summary scores served as measures of QoL)	This study was a part of a prospective, longitudinal study of QoL – correlational QoL (health related quality of life study Moderate/severe symptom distress = reported poorer QoL	4 time points: Baseline Day 0 Day 30 Day 100
ORAL Fall-Dickson, et al, 2010 Oral symptom intensity, health, related quality of life, and correlative salivary cytokines in adult survivors of HSCT with oral chronic GvHD NIH, USA	Allogeneic with oral cGvDH n=42	Oral Mucositis Rating Scale (OMRS) – oral pain and perceived intensity of oral dryness via a visual analogue scale and numeric rating scale FACT-G	Prospective Subjects with moderate to severe oral dryness tended to report the poorest overall QoL	
ORAL Epstein, et al, 2002 Quality of life, taste, olfactory and oral function following high dose chemo and allo-HSCT, Vancouver, Canada	Allogeneic and autologous n=50	EORTC QLQ-C30 with an added oral symptom and function scale and assessment of taste and smell was administered to a consecutive series of patients	Prospective The purpose to study QoL, oral function, taste, and smell	Day 90–100

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Study/ country	Participants Sample size	Instruments	Design Outcome	Measurement Time-frame
ORAL McGuire, et al, 2002 The 20 item oral mucositis index: reliability and validity in bone marrow and SCT patients, PA, USA	Allogeneic and autologous n=133	OMI Oral Mucositis Index (20 items)	Evaluation of reliability and validity of OMI (adapted from the 34 item OMI) Internal consistency, test-retest, and inter rater reliability and construct validity	
ORAL Sonis, et al, 2001 Oral mucositis and the clinical and economic outcomes of HSCT, Boston, USA	Allogeneic and autologous n=92 from eight centers	OMAS (Oral Mucositis Assessment Scale)	Pilot study of a new oral mucositis scoring system Examined the relationship between the peak OMAS scores and days with fever, infection, days of TPN, hospitalization days Oral mucositis is associated with significantly worse clinical and economic outcomes	1st day of conditioning and continuing for 28 days 100 days
SLEEP DISTURBANCES Rischer, et al, 2009 Sleep disturbances and emotional distress in the acute course of HSCT, Germany	Allogeneic and autologous n=50	PSQI (Pittsburgh Sleep Quality Index) Sleep diary (to assess sleep quality) EORTC QLQ-C30 (QoL) HADS (German version – anxiety and depression)	Prospective sleep disturbances after HSCT are associated with physical functioning, fatigue and treatment-specific distress	Admission During in-patient treatment Day 100
MUSCULOSKELETAL Syrjala, et al, 2010 Measuring musculoskeletal symptoms in cancer survivors who receive HSCT, Seattle, USA	Allogeneic and autologous n=130	Muscle and Joint Measure (MJM) – primary outcome Correlations with SF-36 Short form-36 (bodily pain, physical function and vitality subscales) FSI Fatigue Symptom Inventory SC90-R Symptom Checklist 90-R depression	Cross-sectional design New measure of muscle and joint symptoms for HSCT	Long-term 5-20 years post HSCT

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Patient-reported outcome instruments

There are a number of PRO instruments available to assess QoL and symptoms in patients undergoing BMT/HSCT and in long-term BMT/HSCT survivors.

Quality of life assessment

Generic and disease-specific QoL questionnaires, as well as treatment-specific QoL measures are currently being used to assess QoL in this population. The two most widely used generic measures are the SF-36 (see description in Chapter 2) and the Sickness Impact Profile (see description in Chapter 2). Among disease/cancer-specific QoL questionnaires, the EORTC QLQ-C30, FACT-G (see description in Chapter 3.1), and FACT-An (see description in Chapter 3.4) have been utilized in different studies.
There are also several treatment-specific QoL questionnaires specially developed to assess QoL in patients undergoing BMT/HSCT. The most commonly used questionnaires are presented in Table 3.

Table 3. Treatment-specific QoL questionnaires for patients undergoing BMT/HSCT

Title	Abbreviation	Authors, years	Translations
Functional Assessment of Cancer Therapy - Bone Marrow Transplantation	FACT-BMT	McQuellon RP, et al, 1997	15 languages
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - High-Dose Chemotherapy	EORTC QLQ-HDC29	Velikova G, et al, 2007	5 languages
Satisfaction with Life Domains Scale - Bone Marrow Transplantation	SLDS-BMT	Baker F, et al, 1992	–
City of Hope Quality of Life Hematopoietic Cell Transplantation	COH-QOL-HCT	Grant M, et al, 1992	–

Functional Assessment of Cancer Therapy - Bone Marrow Transplantation

The Functional Assessment of Cancer Therapy - Bone Marrow Transplantation (FACT-BMT) is a Functional Assessment of Cancer Therapy Scale with a specific module for BMT (*McQellon RP, et al, 1997*). Along with 28 general questions, it includes 12 items specifically designed to test QoL in bone marrow transplant patients. Patients rate all items using a 5-point scale ranging from 0-not at all to 5-very much. They are asked to rate themselves on how they feel today and have felt over the past 7 days. A higher score

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indicates better QoL. The FACT-BMT provides information about overall QoL and the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and transplantation-specific concerns.

Strengths: the questionnaire is able to cover transplantation-specific concerns.

Weaknesses: there are no separate modules for autologous and allogeneic patients despite the different experiences of these types of transplant patients.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – High-Dose Chemotherapy

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – High-Dose Chemotherapy (EORTC QLQ-HDC29) is a supplementary module to the EORTC QLQ-C30. This module assesses QoL during and after high-dose chemotherapy and stem cell transplantation (*Velikova G, et al, 2007*). It can be used in conjunction with EORTC QLQ-C30 to assess treatment-specific aspects of the QoL of patients participating in clinical trials of high-dose chemotherapy with autologous or allogeneic transplants, both during and after treatment. Methodologically it has been developed to measure physical side effects and important emotional and family issues in patients with different malignancies. It consists of a total of 21 items, formulated into separate subscales: gastrointestinal side effects subscale (4 items), worry/anxiety (5 items), impact on family (4 items), body image (2 items), sexuality (2 items) and in-patient issues (3 items). A number of single items are also included (skin problems, fever/chills, urinary frequency, aches or pains in bones, taking regular drugs, finishing things, ability to have children, experience helping to distinguish what is important in life). The questionnaire is available in 5 European languages.

Strengths: the questionnaire is able to cover a wide range of transplantation-specific concerns.

Weaknesses: there are no separate modules for autologous and allogeneic patients despite the different experiences of these types of transplant patients.

Satisfaction with Life Domains Scale - Bone Marrow Transplantation

The Satisfaction with Life Domains Scale - Bone Marrow Transplantation (SLDS-BMT) was developed to assessment of the subjective quality of life of patients receiving aggressive cancer treatment. Eighteen domains are assessed by the SLDS-BMT (*Baker F, et al, 1992*). They include aspects of most areas of life that can be affected by cancer and its treatment. Assessment of satisfaction with factors such as relationships, health, appearance, leisure time, ability to eat, physical strength, and BMT are obtained. Ratings are made on a seven-point scale that has seven faces ranging from extremely happy to extremely unhappy. The items are summed to give an overall score. Higher scores indicate greater satisfaction.

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Strengths: the questionnaire is simple and easy to use for interpreting changes that may occur after transplantation.

Weaknesses: the system of rating is not sensitive enough.

City of Hope Quality of Life Hematopoietic Cell Transplantation

The City of Hope Quality of Life Hematopoietic Cell Transplantation (COH-QOL-HCT) was developed to assess QoL in patients undergoing hematopoietic cell transplantation (*Grant M, et al, 1992*). It contains subscales that assess 4 QoL domains: physical, psychological, social, and spiritual. The physical domain includes 17 subscales related to physical problems such as changes in skin, vision, hearing, appetite, nausea, fatigue, and physical strength. The psychological domain includes 22 subscales on anxiety, depression, fear of recurrence, and satisfaction with life. The social domain contains 12 subscales concerning relationships, family, intimacy, work, and social reintegration. The 7 items of spiritual domain encompass global spirituality, religiosity, and life appreciation. Subscale scores range from 0 (worst) to 10 (best). It has been tested, with test-retest reliability of r = 71 and internal consistency of r = 85. The instrument has been used in several studies and demonstrates discriminant validity between those with and without specific late effects after transplantation.

Strengths: the COH-QOL-HCT instrument was developed specifically for QoL in HSCT patients.

Weaknesses: there are no separate modules for autologous and allogeneic patients despite the different experiences of these types of transplant patients.

Symptom assessment

To assess symptoms in patients undergoing BMT/HSCT, several symptom assessment tools have been developed: M.D. Anderson Symptom Inventory - Bone Marrow Transplantation, Symptom Frequency, Intensity, and Distress Questionnaire for Stem Cell Transplantation, Stem Cell Transplantation - Symptom Assessment Scale and Comprehensive Symptom Profile in Patients Undergoing BMT/HSCT. The M.D. Anderson Symptom Inventory (see description in Chapter 3.2) which is disease/cancer specific symptom assessment tool is also used in patients undergoing BMT/HSCT.

M.D. Anderson Symptom Inventory - Bone Marrow Transplantation

The M.D. Anderson Symptom Inventory - Bone Marrow Transplantation (MDASI-BMT) is an additional module to the M.D. Anderson Symptom Inventory, designed for the assessment of symptoms identified as important to monitor during the post-transplantation period (*Anderson KO, et al, 2007*). It measures the severity of 14 symptoms: pain, weakness, fatigue, nausea, diarrhea, mouth sores, shortness of breath, lack of

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appetite, feeling physically sick, disturbed sleep, difficulty paying attention, sadness, distress and bleeding. Five interference items assessing symptom-related interference in general activity, mood, walking, relations with other people and enjoyment of life are also included. Symptoms are assessed with the help of a 0–10 scale, where ratings of 0–4 are categorized as mild, ratings of 5–6 as moderate, and ratings of 7–10 as severe. A symptom severity score is calculated as the mean intensity of the 14 symptom scores. A symptom interference score is computed as the mean of the 5 interference items.

Strengths: the questionnaire provides information both about symptom severity and symptom interference in everyday life.

Weaknesses: the questionnaire is not able to specify symptoms in patients after autologous versus allogeneic BMT/HSCT.

Symptom Frequency, Intensity, and Distress Questionnaire for SCT

The Symptom Frequency, Intensity, and Distress Questionnaire for SCT (SFID-SCT) was developed to describe symptoms in patients undergoing BMT/HSCT (*Larsen J, et al, 1996*). It consists of 23 symptoms: nausea, vomiting, pain, shivers, fever, breathing difficulties, coughing, tiredness, sore mouth/throat, loss of appetite, diarrhea, constipation, sleeping disturbances, reduced mobility, depression, anxiety, concentration difficulties, memory deficiencies, loss of hair, mouth dryness, changes of taste, skin changes, and changed body image. For each symptom listed above, the respondents are first asked if they perceive the symptom (Yes or No). If they report the symptom they are then asked how distressful they perceive each symptom to be (0 = no distress, 1 = a little distress, 2 = much distress and 3 = very much distress).

Strengths: the SFID-SCT questionnaire is aimed at giving useful information not only about symptom occurrence, but also about symptom intensity and symptoms of distress in patients undergoing BMT/HSCT.

Weaknesses: the questionnaire is not able to specify symptoms in patients after autologous versus allogeneic BMT/HSCT.

Stem Cell Transplantation - Symptom Assessment Scale

The Stem Cell Transplantation - Symptom Assessment Scale (SCT-SAS) is a 24-item symptom assessment questionnaire, developed to assess treatment-related symptoms in patients undergoing HSCT (*Jarden M, et al, 2009*). Individual symptoms are grouped into five symptom clusters: mucositis, cognitive, gastrointestinal, affective, and functional symptom clusters. The scale is designed to give information about symptom occurrence and symptom intensity and is to be completed weekly during hospitalization and at three and six months after HSCT.

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Strengths: the SCT-SAS questionnaire is aimed at giving useful information about symptom occurrence and symptom intensity of both individual symptoms and symptom clusters in patients undergoing allogeneic SCT. The instrument is short and has a simple scoring procedure, and has achieved content validity.

Weaknesses: the tool is only available in Danish.

Comprehensive Symptom Profile - Bone Marrow Transplantation

The Comprehensive Symptom Profile - Bone Marrow Transplantation (CSP-BMT) is the symptom assessment tool within the Comprehensive Symptom Profile series (*Novik A, et al, 2010*). The inventory was developed to provide comprehensive assessment of the severity of 46 symptoms specific for patients during and after BMT/HSCT. It consists of numerical rating scales, scored from 0 (no symptom) to 10 (most expressed symptom). It is a bilingual tool developed simultaneously in English and in Russian. At present, the CSP-BMT is available in English and in Russian.

Strengths: the CSP-BMT is a useful tool to capture risks/benefits of high-dose CT with BMT/HSCT and to identify comprehensive symptom profile changes at different time-points of transplantation.

Weaknesses: the tool is not available in languages other than English and Russian.

Finally, there are also domain-specific questionnaires that are used to evaluate specific issues in patients undergoing BMT/HSCT:

- For fatigue – Brief Fatigue Inventory (see description in Chapter 3.6), and Fatigue Symptom Inventory;
- For psychological problems – Brief Symptom Inventory, Hospital Anxiety and Depression Scale, Profile of Mood States (see description in Chapter 4);
- For oral mucositis – Patient-Reported Oral Mucositis Symptom Scale;
- For sexual functioning – Sexual Function Questionnaire, Derogatis Sexual Functioning Inventory.

Fatigue Symptom Inventory

The Fatigue Symptom Inventory (FSI) is a 14-item self-report measure designed to assess the severity, frequency, and daily pattern of fatigue, as well as its perceived interference with QoL (*Hann DM, et al, 1998*). Severity is measured on separate 11-point scales (0 = not at all fatigued; 10 = as fatigued as I could be) that assess most, least, and average fatigue in the past week as well as current fatigue. Frequency is measured as the number of days in the past week (0–7) that respondents felt fatigued, as well as the amount of each day, on average, that they felt fatigued (0 = none of the day; 10 = the entire day). Perceived interference is measured on separate 11-point scales (0 = no

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interference; 10 = extreme interference) that assess the degree to which fatigue in the past week was judged to interfere with general level of activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life, and mood. These interference ratings can be summed to obtain a total perceived interference score. The final item provides qualitative information about possible diurnal variation in the daily experience of fatigue. The Inventory is available in English, French, German, and Spanish.

Strengths: the questionnaire provides information both about fatigue severity and its interference with everyday life.

Weaknesses: the questionnaire cannot be used to monitor fatigue every day at early post-transplant period as time recall is 1 week.

Brief Symptom Inventory

The Brief Symptom Inventory (BSI) is a 53-item self-report scale used to measure nine primary symptom dimensions (somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism), and three global indices (Global Severity Index (GSI), Positive Symptom Distress Index (PSDI), and Positive Symptom Total (PST)) (*Derogatis LR, et al, 1983*). The BSI is a shortened version of the SCL-90 (Symptom Check List-90), a widely used scale assessing current psychological distress and symptoms in both patient and non-patient populations. The BSI measures the experience of symptoms in the prior seven days up to and including the day the BSI was completed. Answers are on a 5-point scale, from 0 = not at all, to 4 = extremely. The BSI measures current psychological status and distress. The instrument is available in English, Spanish, and French.

Strengths: the BSI is brief and requires only 8–10 minutes to complete, making it well-suited for repeated administration over time to evaluate patient progress. The instrument provides an overview of a patient's symptoms and their intensity at a specific point in time. The BSI is designed to help quantify a patient's severity-of-illness and provides a single composite score for measuring the outcome of a treatment program based on reducing symptom severity.

Weaknesses: the inventory is not transplant-specific.

Patient-Reported Oral Mucositis Symptom Scale

The Patient-Reported Oral Mucositis Symptom Scale (PROMS) scale was designed to assess patient-reported symptoms of transplant-related oral mucositis. (*Kushner JA, et al, 2008*). The PROMS scale consists of a 10-item visual analogue scale (VAS) covering the symptoms frequently reported by patients experiencing chemotherapy-induced oral mucositis. Respondents quantify the severity of symptoms experienced over the previous

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week using a 100-mm scale anchored at either end with various descriptors. The maximum score is 100 for each item and for the overall average. The questionnaire can be completed in 5 to 7 minutes.

Strengths: the instrument has demonstrated high internal reliability, good construct validity, and sensitivity to clinically significant changes. The PROMS scores are based on VAS measurements and are therefore theoretically suitable for parametric testing.

Weaknesses: the tool needs to be validated in other patient populations experiencing oral mucositis.

Sexual Functioning Questionnaire

The Sexual Functioning Questionnaire (SFQ) is a standardized questionnaire which studies sexual impotence problems (*Friedman S, et al, 1982*). It is made up of 62 items (48 of them are meant for both partners while 14 are meant exclusively for the dysfunctional patient). The scoring and the clinical evaluation must be done using the traditional method.

Strengths: the instrument is short and has a simple scoring procedure.

Weaknesses: the questionnaire was not developed specifically for patients undergoing BMT/HSCT.

Derogatis Sexual Function Inventory

The Derogatis Sexual Function Inventory (DSFI) is a standardized self-evaluation questionnaire to address sexual functioning (*Derogatis LR, 1978*). It is made up of 258 items (245 in the original version published in 1975). It produces 9 sexual dimensions (information, experience, sexual drive, attitudes, affectivity, sexual gender and role, sexual fantasies, body image, and sexual satisfaction), a dimension about psychopathological symptoms (anxiety, depression, and somatizations), and a Sexual Functioning Index.

Strengths: it is comprehensive; the answers may be scored as an index.

Weaknesses: due to the high number of items, it requires a considerable amount of time to be completed.

Practical considerations for patient-reported outcome assessment

A number of issues need to be considered when planning a study with PROs in patients undergoing BMT/HSCT. Study design and the choice of instruments will firstly depend

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on the type of transplantation including whether it is allogeneic or autologous.
Typically, studies which look at PROs in BMT/HSCT patients are either prospective longitudinal or cross-sectional. Cross-sectional studies are usually conducted at long-term follow-up after BMT/HSCT. In such studies, comparison of survivors with healthy controls or population norms may be provided. A prospective longitudinal design would be appropriate if the study aims to elucidate the time course of change and to define the trajectory of recovery after BMT/HSCT. In these studies, time-points of QoL and symptom assessment should be chosen with consideration given to the period of transplantation (Table 4). Changes in QoL and symptoms are expected during these periods.
Continuous data acquisition provides a better overall picture of the changes in a patient's life and the healing process (or lack thereof).
In the studies focusing on sexuality issues, a retrospective cross-sectional design may be applied.
A battery of PRO instuments is available for QoL and symptom assessment in patients undergoing BMT/HSCT. At long-term follow-up, generic QoL questionnaires, like the SF-36 or the Sickness Impact Profile, in combination with symptom assessment tools, may be helpful. If patient-reported data are used to assess the treatment outcomes in

Table 4. Periods of transplantation appropriate for PRO assessment

For autologous HSCT	
Before HSCT	–
Pre-transplant	Stem cell mobilization – conditioning
Neutropenic phase	Days 0-15-30
Early phase	Days 15-30 – 3 months
Late phase-1	3–6 months
Late phase-2	6–12 months
Long-term follow-up	More than 1 year
For allogeneic HSCT	
Before HSCT	–
Pre-transplant	Stem cell mobilization – conditioning
Pre-engraftment	Days 0–30
Post-engraftment/early phase	Days 30–100
Late post-engraftment-1/late phase-1	Days 100–180
Late post-engraftment-2/late phase-2	Days 180–360
Long-term follow-up	More than 1 year

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patients undergoing BMT/HSCT, along with clinician-reported data, treatment specific QoL questionnaires, such as the FACT-BMT or the EORTC QLQ-HDC 29, may be recommended. If the QoL treatment response is to be evaluated, generic QoL questionnaires, namely the SF-36, should be used. In studies with an emphasis on treatment toxicity, symptom assessment instruments are of value. They should be administered at the time-points during which side effects are expected to be the most pronounced. To summarize, the harmonization of tools for QoL and symptom assessment should be prioritized to ensure that comparative results can be obtained in studies of patients undergoing BMT/HSCT.

The choice of instruments and study design are of particular concern when a study is focusing on special populations (i.e. adolescents). Details on PRO approaches suitable for use with adolescents are presented in Chapter 7.

We should be cautious when interpreting QoL data in patients undergoing BMT/HSCT. The moderate deficits in self-reported QoL described by existing literature, is somewhat surprising in light of the many objective impairments experienced by this patient population. These findings may result from averaging QoL across subgroups of patients doing well and others doing poorly. Separate analysis of QoL changes after BMT/HSCT in subgroups with different base-line QoL impairment is recommended.

The response shift model of QoL may also contribute to discrepancies between self-reported QoL and objective impairments. This model suggests that perceptions of QoL are the result of changes in health, initiating behavioural processes which lead to changes in internal standards, values, or conceptualizations of QoL. Furthermore, characteristics of an individual will influence this process (*Postulart D, Adang EMM, 1999; Sprangers MA, et al, 1999*). BMT/HSCT patients may therefore engage in recalibration shifts, in which their standards of what constitutes good QoL changes due to their experience with illness and treatment, or they may be engaging in response shifts resulting from changing values (*Beeken RJ, et al, 2011*). Thus, although low scores may be reported consistently on some subscales post-transplant, the domains of QoL that these scores reflect may become less important and have little impact on perceptions of QoL overall. More information about the response shift model is presented in Chapter 2.

When interpreting QoL in long-term survivors it is important to take into account factors that may affect the QoL. The number of predictors of QoL at long-term follow-up after BMT/HSCT have been identified (*Kiss TL, et al, 2002; Dırez-Campelo M, et al, 2004; Bieri S, et al, 2008; Pidala J, et al, 2009; Wong LF, et al, 2010*). They are presented in Table 5.

Research is necessary to further identify risk factors for poor post-BMT/HSCT QoL and to determine the temporal trajectory of post BMT/HSCT QoL.

Continued accumulation of PRO data allows us to define the primary difficulties from the patients' point of view and to address these needs before, during, and after BMT/HSCT.

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Table 5. Predictors of QoL at long-term follow-up after BMT/HSCT

Predictor	Relationship
Type of transplantation (allogeneic or autologous)	Recovery trajectory after allogeneic transplantation is more complicated than after autologous transplantation
Type of donor (syngeneic, HLA-matched related, HLA-matched unrelated, or haplo-identical)	HLA-mismatches increase the risk of post-transplantation complications
GvHD	Acute and chronic GvHD are associated with worse QoL
Conditioning regimen	Reduced intensity condition regimens are associated with better QoL as compared with myeloablative regimens
Disease status before transplant	Patients in first complete remission generally have a better QoL after transplantation compared to those in second or later complete remission prior to transplant
Disease stage at time of transplantation	Advanced disease is associated with poorer QoL
Educational level	Patients with lower education have poorer QoL
Age	Older patients have poorer QoL
Time period after BMT/HSCT	A shorter period is associated with worse QoL
Gender	Female sex is associated with worse QoL
Body mass index	Lower body mass index is associated with worse QoL
Pre-transplantation level of functioning	A worse level of functioning is associated with poorer QoL
Level of interpersonal conflict	Greater interpersonal conflict is associated with poorer QoL
Reduced level of social support	A reduced level of social support is associated with poorer QoL
Symptom severity	More severe symptoms are associated with poorer QoL

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CHAPTER 5

Quality of life and symptom assessment in long-term blood cancer survivors

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State of the art

There is a large and growing population of blood cancer survivors (*Ries LAG, et al, 2009*). A person diagnosed with cancer is a survivor from the moment of diagnosis through the balance of his or her life (*US National Coalition for Cancer Survivorship, 2009*). This includes newly-diagnosed survivors as well as long-term survivors. An expanding literature base documents the impact of cancer on survivors across physical, psychological, emotional, social, and spiritual domains (*Gotay CC, et al, 1998; Aziz NM, 2006a; Aziz NM, 2007b; Alfano CM, et al, 2007; Bloom JR, et al, 2007; Ganz PA, 2008*).

At present it is not uncommon to speak of curing some types of blood cancer; however, cure also encompasses the restoration of health. While cancer can be eradicated, survivors must be restored to health that lasts for decades. Five-year survival is only the beginning, not the end-point of successful treatment. As a result of more effective treatments and approaches for early detection, the long-term survival rates of blood cancer patients has risen dramatically during the past few decades. This has led to a growing interest in the fate of long-term blood cancer survivors. It is obvious that blood cancer has a significant impact on survivors in terms of long-term health and psychosocial sequelae. For example, cancer survivors are at increased risk for developing secondary malignancies and other diseases (e.g. cardiovascular disease, diabetes, and osteoporosis). In addition, it is reported that cancer survivors have an almost two-fold greater likelihood of having at least one functional limitation. A review of the literature on psychological adjustment in individuals diagnosed with cancer yields several broad conclusions (*Zabora J, 2001; Stanton AL, 2006; Adler NE, 2008; Alter CL, 2009; Bishop MM, 2010; Zwahlen D, 2010; Grov EK, 2011*). First, a diagnosis of cancer has the potential to result in marked psychological distress and life disruption. Second, rates of clinically significant psychological disorder in cancer patients are frequently found to exceed those of the general population. Third, for most individuals, distress subsides during the first 24 months after diagnosis, although specific problems can persist. Fourth, many individuals find positive meaning and benefit from their experience with cancer. They report that it prompts enhanced interpersonal relationships, a deeper appreciation for life, increased personal strength, greater spirituality, a significant change in life priorities and goals, and greater attention to health-promoting behaviors. Taken together, studies suggest that persistent psychological and physical problems diminish for a subset of cancer survivors. Thus, with the increasing success of cancer treatment and the cancer survivor's ability to return to previous family, social, and work activities, symptom management and quality of life (QoL) are an essential part of survivorship. The need for research on QoL and symptoms in this growing population was highlighted by the Institute of Medicine (*Hewitt M, et al, 2011*).

Patient-reported outcome (PRO) research has been conducted for different kinds of blood cancer, such as leukemia, lymphoma, and multiple myeloma.

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Hodgkin's lymphoma (HL) is still one of the few adult malignancies that, in most instances, can be cured. At present, more than 90% of patients with early stage HL (Stages I and II) are cured and, with the introduction of modern intensified chemotherapy (CT) regimens, most of the patients in advanced stage HL have a chance of being cured. Radiotherapy and combination CT are effective treatment modalities in HL. However, both modalities are accompanied by significant acute and long-term complications. There are numerous publications on PROs in long-term HL survivors (*Joly F, et al, 1996; Fletcher H, 1998; Mols F, et al, 2006; Roper K, et al, 2009; Brandt J, et al, 2010; Arden-Close E, et al, 2011; Oerlemans S, et al, 2011*). It has been shown that long-term HL survivors face problems that can affect their QoL. They report problems in role physical and cognitive functioning, general health, financial problems, and high levels of fatigue. An increasing proportion of non-Hodgkin's lymphoma (NHL) patients can now expect relatively long-term survival. The overall 5-year average survival rate from 2001–2007 in the United States was 67.3%, ranging from 58% for metastasized disease to 81% for localized disease (*Howlader N, et al, 2011*). Even in cases of relapsed disease, the use of high-dose therapy with autologous hematopoietic stem cell transplantation (HSCT) has increased the number of long-term survivors. Survivors of NHL experience both positive and negative life changes (*Bellizzi KM, 2008*). The issues related to QoL concerns in NHL survivors are described in a recent systematic review (*Oerlemans S, et al, 2011*). However, currently, the majority of information on the long-term physical and psychosocial functioning in survivors of NHL is included in QoL studies on patients who had undergone bone marrow transplantation (BMT)/HSCT.

A review of the English-language literature published worldwide up to 2002, showed that acute myeloid leukemia (AML) and its associated treatments have a substantial negative impact on a patient's QoL in both short and long-term survivors (*Redaelli A, et al, 2004*). However, long-term survivors may recover almost completely with respect to physical, psychological and emotional well-being, but incur continued sexual dysfunction. At the same time, long-term AML survivors after BMT/HSCT may suffer from prolonged physical as well as psychosocial problems (*Hsu C, et al, 2003*). The literature on QoL in long-term chronic lymphocytic leukemia (CLL) survivors is very limited (*Stephens JM, et al, 2005*).

As for multiple myeloma (MM), at present the disease is steadily becoming more treatable and manageable. The availability of new treatment options has increased the average anticipated survival from 2–3 years to 5–7 years. Since research in PROs in long-term MM survivors is scarce, studies are in need to identify QoL concerns in this patient population.

Major QoL concerns of long-term blood cancer survivors are due to late effects from treatment. Many survivors have a risk of developing late effects and experiencing symptoms at long-term follow-up. Cancer-related fatigue is a common side effect during cancer treatment, and research demonstrates that it is a troubling, lingering side

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effect for many long-term survivors. Long-term blood cancer survivors, fatigue is under-reported, under-diagnosed, and under-treated. The National Comprehensive Cancer Network (NCCN) 2011 Practice Guidelines for Cancer-Related Fatigue include a treatment and intervention algorithm for long-term survivors (*National Comprehensive Cancer Network, 2011*). The importance of assessing fatigue in long-term survivors should not be overlooked.

Further studies are needed to reveal substantial deficiencies in the process of readaptation to normal life, to describe more precisely the patient's situation, to find reasons for maladaptation, and to identify patients at high risk. The results obtained will help to better understand the needs of long-term blood cancer survivors, especially of those in groups under-represented in published QoL studies, and to determine follow-up care priorities.

Patient-reported outcome instruments

The most frequently used generic QoL questionnaires are the Sickness Impact Profile (see description in Chapter 2), the Nottingham Health Profile (see description in Chapter 2), and the SF-36 (see description in Chapter 2). With these instruments it is possible to describe QoL in long-term blood cancer patients and to compare QoL of blood cancer patients to the general population in order to see the effect of diagnosis and treatment on patients' lives. These instruments may not possess the necessary sensitivity to issues that are important to blood cancer patients and cannot give a comprehensive overview of a patient's QoL.

PRO tools available to evaluate QoL in long-term cancer survivors are listed in Table 1.

Table 1. PRO instruments for use with long-term cancer survivors

Title	Abbreviation	Authors, years
Quality of Life-Cancer Survivors	QoL-CS	Ferrell BR, et al, 1995
Quality of Life in Adult Cancer Survivors	QLACS	Avis NE, et al, 2005
Impact of Cancer Scale	IOC	Zebrack B, et al, 2006

Quality of Life - Cancer Survivors

The Quality of Life - Cancer Survivors (QoL-CS) scale was developed to measure the specific concerns of long-term cancer survivors (*Ferrell BR, et al, 1995*). The QoL-CS is a 41-item visual analogue scale composed of four multi-item subscales (physical well-being, psychological well-being, social well-being, and spiritual well-being) and two

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sub-components (fears, distress). The analogue scale has 11 points, with 0 representing the worst possible outcome and 10 representing the best possible outcome.

Strengths: strong evidence for the validity and reliability of the QoL-CS has been reported.

Weaknesses: there is limited information about its use in blood cancer survivors.

Quality of Life in Adult Cancer Survivors

The Quality of Life in Adult Cancer Survivors (QLACS) scale was developed to measure QoL in adult cancer survivors (*Avis NE, et al, 2005*). The 47-item instrument consists of five cancer-specific domains that relate specifically to having had cancer and include appearance concerns, financial problems, distress over recurrence, family-related distress, and benefits of cancer, along with 7 generic QoL domains (negative feelings, positive feelings, cognitive problems, sexual problems, physical pain, fatigue, and social avoidance). Each has a separate subscale.

Strengths: the QLACS is a multidimensional measure with good internal consistency and validity and is appropriate for comparisons between cancer and non-cancer populations, as well as long-term follow-up of cancer patients.

Weaknesses: there is limited information about its use in blood cancer survivors.

Impact of Cancer Scale

The full Impact of Cancer (IOC) Scale includes 81 items that present statements regarding specific impacts of cancer to which respondents indicate their level of agreement from 1 (strongly disagree) to 5 (strongly agree) (*Zebrack B, et al, 2006*). The items are organized under 12 headings representing the investigators' theoretical notions of the emerging constructs suggested by the titles: Your Body and Your Health, Cancer Treatment and Health Care, Having Children, Who are You, Talking and Thinking About Cancer, Meaning of Cancer, Memory and Thinking, Finances and Money, Family, Relationships, Socializing and Being with Friends and Life Goals. All items were scored on a five-point Likert-type scale ranging from 1 (not at all) to 5 (very much). Higher scores indicate greater impact. There are five positive impact subscales and five negative impact subscales. In most instances, items were worded such that impact is either inherently and intuitively positive (I eat a healthy diet) or negative (I am afraid to die). In some instances, however, one cannot assume that the impact is positive or negative. For example, the items «I wonder why I got cancer», «People treat me differently after they find out I have had cancer» and «I wonder why I survived and others do not» are not inherently positive or negative.

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A shorter version was recently developed (*Crespi CM, et al, 2008*). This shorter version uses 37 items taken from the longer 81-item questionnaire (*Zebrack B, et al, 2006*). The 37 items form 4 positive subscales: Altruism and Empathy, Health Awareness, Meaning of Cancer, Positive Self-Evaluation and 4 negative subscales: Appearance Concerns, Body Change Concerns, Life Interferences and Worry. These 4 subscales form a Positive and Negative impact scale respectively.

Strengths: psychometric analysis indicated that the IOC instrument measures distinct and relevant constructs for long-term survivors.

Weaknesses: the full questionnaire is quite long and might be a burden for respondents to fill in. For a shorter version with 37 items information about its psychometric properties is worthwhile.

With these instruments it is possible to characterise the impact of the disease and treatment on QoL of long-term cancer patients and to develop appropriate interventions for long-term blood cancer patients.

In some cases disease and treatment-specific QoL tools may be used in long-term blood cancer survivors. The EORTC QLQ-C30, the QoL questionnaire generic for neoplasms, is often used in long-term blood cancer survivors (see description in Chapter 3.1). Disease-specific QoL questionnaires are described in subchapters of Chapter 3.

Treatment specific instruments that are available for use in blood cancer patients are:

- Functional Assessment of Cancer Therapy - Bone Marrow Transplantation (see description in Chapter 4);
- Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity instrument;
- EORTC QoL Module for Chemotherapy-Induced Peripheral Neuropathy module (EORTC QLQ-CIPN20).

Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity

The Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity (FACT/GOG-Ntx) subscale is the FACT-G plus an eleven-item subscale (Ntx subscale) that evaluates symptoms and concerns associated specifically with chemotherapy-induced neuropathy (*Calhoun EA, et al, 2003*). The additional concerns of patients include numbness and tingling in hands and feet, discomfort in hands and feet, joint pain or muscle cramps, weakness, troubles with hearing, ringing or buzzing in ears, troubles with buttoning buttons, difficulty feeling the shape of small objects with one's hands and troubles with walking. The items are described with the help of a 5-point scale, with 0 – not at all and 4 – very much.

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Strengths: the FACT/GOG-Ntx is a reliable and valid instrument for assessing the impact of neuropathy on QoL. The Ntx subscale has demonstrated sensitivity to meaningful clinical distinctions and change over time.

Weaknesses: there is limited information about its use to distinguish between different chemotherapy regimens in blood cancer survivors.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy Module

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Chemotherapy-Induced Peripheral Neuropathy Module (EORTC QLQ-CIPN20) is a 20-item QoL questionnaire, which has been developed to elicit patients' experience of symptoms and functional limitations related to chemotherapy-induced peripheral neuropathy (*Postma TJ, et al, 2005*). The QLQ-CIPN20 has 3 subscales: a sensory, motor, and autonomic subscale. In combination with the more classical, physician-based clinical rating scales, the QLQ-CIPN20 should yield a more complete picture of the nature, frequency, and severity of CIPN in a wide range of oncology patient populations.

Strengths: the questionnaire provides valuable information on CIPN-related symptoms and functional limitations of patients exposed to potentially neurotoxic chemotherapeutic and/or neuroprotective agents.

Weaknesses: information about psychometric properties of the tool is currently limited.

For evaluation of late effects from a patient's perspective, symptom assessment tools may be helpful. Due to the fact that blood cancer patients may experience a number of long-term symptoms after the end of treatment, multiple symptom assessment instruments can be useful. Such instruments as the M.D. Anderson Symptom Inventory (see description in Chapter 3.2), the Rotterdam Symptom Checklist, The Edmonton Symptom Assessment System (see description in Chapter 3.1), and the Memorial Symptom Assessment Scale (see description in Chapter 3.1) can be mentioned.

Rotterdam Symptom Checklist

The Rotterdam Symptom Checklist (RSCL) is a cancer-specific tool used to measure psychological and physical distress in cancer patients participating in clinical research (*de Haes JC, et al, 1990*). It is a 38-item list comprised of physical and psychological symptoms. Patients are asked to indicate the degree to which they have been bothered by the indicated symptoms during the past three days, on a 4-point Likert-type rating

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scale (categories: not at all, a little, quite a bit, very much). Eight items referring to the activities of daily living are added to cover the patient's functional status. Completion of the RSCL takes about 8 minutes.

Strengths: it is easy to administer and covers relevant domains in the cancer patients' experience. It may also be useful in the evaluation of supportive care.

Weaknesses: experience with use of this questionnaire as a screening instrument needs to be studied further.

Fatigue affects patients to a greater degree than other symptoms and it can persist long-term, therefore, it is important to assess fatigue over time. Though specific measures to assess fatigue in long-term survivors have not been developed, scales that measure fatigue during treatment appear to be psychometrically sound in the long-term survivor setting. The most efficient and relevant clinical measure of fatigue continues to be a 10-point scale (i.e. 0-to-10 scale), which is easy to administer and is easily understood by patients (*Minton O, et al, 2009*). Questionnaires which can be used to assess fatigue in long-term blood cancer survivors are presented below:

- Piper Fatigue Scale, PFS (*Piper BF, et al, 1989*);
- Multidimensional Fatigue Inventory, MFI (*Smets EM, et al, 1995*);
- Functional Assessment of Patients with Anemia/Fatigue, FACT-An (*Cella D, 1997*);
- Fatigue Symptom Inventory, FSI (*Hann DM, et al, 1998*);
- Schwartz Cancer Fatigue Scale, SCFS (*Schwartz A, 1998; Schwartz A, et al, 1999*);
- Brief Fatigue Inventory, BFI (*Mendoza TR, et al, 1999*);
- Cancer Fatigue Scale, CFS (*Okuyama T, et al, 2000*);
- EORTC-Fatigue Module, currently in Phase IV Evaluation, sponsored by EORTC and German Fatigue Association.

The description of these instruments is presented in Chapter 3.6.

Practical considerations for patient-reported outcome assessment

To understand whether a patient has been really cured of cancer, it is necessary to ascertain whether his/her health has been restored. It is also important to compare survivors' QoL with the QoL of healthy controls or general population norms. Comparisons should be made with an age- and gender-adjusted reference population. The method for calculation of age- and gender-adjusted expected QoL scores is simple, and can be performed without having access to a complete data file (*Hjermstad MJ, et al, 1998; Gulbrandsen N, et al, 2004*). To describe a specific survivors population in terms of QoL status, information about the proportion of survivors with QoL scores similar to the

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reference population and the proportion of survivors with worse QoL scores is desirable. Study designs that more accurately measure QoL among blood cancer survivors by adjusting for the effects of aging and long-term therapy and the impact of second cancers should be utilized. In particular, longitudinal research comparing survivors to a reference population should be performed in order to better understand the impact of long-term side effects of treatment on QoL and symptoms and to provide adequate follow-up care aimed to alleviate the symptoms present.

To measure QoL concerns in long-term survivors, a combination of generic QoL instruments and symptom assessment instruments might be helpful.

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CHAPTER 6

Quality of life and symptom assessment in patients receiving anticoagulant therapy

State of the art

Arterial and venous thromboembolic events are frequently encountered and cause significant morbidity and mortality. The introduction of anticoagulants more than 50 years ago, resulted in a significant step forward in the therapeutic management of these diseases (*Guyatt GH, et al, 2008; Kleinjan A, Buller HR, 2009*). Anticoagulants currently used for the prevention of venous thrombosis are low molecular weight heparins (LMWH) and fondaparinux. Vitamin K antagonists, LMWH, and fondaparinux are the main drugs for the treatment of symptomatic venous thrombosis. For the prevention of arterial thrombosis anti-platelet drugs and again vitamin K antagonists LMWH and fondaparinux are the current drugs of choice.

Oral anticoagulants (OACs) are effective and commonly used anticoagulant agents for the secondary prevention of venous thromboembolic disease and the prevention of systemic embolism in patients with atrial fibrillation (*Hirsh J, et al, 1998*). At present OACs are indicated in cases such as venous and pulmonary thromboembolism, atrial fibrillation, acute myocardial infarction, the presence of a mechanical cardiac valve prosthesis, congestive cardiac failure, dilated cardiomyopathy, cerebrovascular accident, and other special conditions (*Abray KD, et al, 2007; Prins MH, et al, 2009; Romano ER, et al, 2006*). However, because of patients' monitoring requirements, their inherent limitations in daily life (e.g. diet and activities) and the considerable inter-individual variability in the pharmacodynamic effect, the burden of OACs on patients' daily life is highly significant (*Prins MH, et al, 2009a*). In particular, there are a number of characteristics of current oral anticoagulation therapies that can potentially reduce the quality of life (QoL) in patients after a deep-vein thrombosis (DVT) event (*Beyth RJ, et al, 1995*). Patients often report problems with functioning, low levels of energy, sleep disturbance, pain, and limitations in physical mobility. Thus, to increase the understanding of treatment outcomes in this patient population, the evaluation of outcomes from a patient's perspective is needed.

It is often necessary for anticoagulation to be maintained over a long period of time. The long-term use of OACs can influence the patient's perception of their QoL and health status. This is due to the changes it causes in the patient's life-style, and mainly because patients are submitted to a treatment that brings no symptomatic benefit, but rather presents a well-defined risk. Thus, it is important to realize the difficulties involved while living with oral anticoagulant treatments (*Almeida GQ, et al, 2011*). Among these problems are changes in diet, the use of alcohol, and the performance of physical activity (*Lancaster TR, et al, 1991; Devereaux PJ, et al, 2001; Casais P, et al, 2005*). In addition, there is the burden caused by new tasks related to the use of medication. This includes daily ingestion of the medication and the need for frequent visits to health services for monitoring of the anticoagulation range, and the fear of complications such as bleeding and thrombus formation (*McCahon D, et al, 2010; Corbi ISA, et al, 2011*). All of these

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changes, regardless of the model of care, can potentially cause patient dissatisfaction and reduce their QoL.

It is obvious that anticoagulant treatment, when coupled with its possible side effects such as bleeding, may negatively affect a patient's QoL and treatment satisfaction. This, in turn, is likely to result in a decrease in treatment effectiveness and ultimately, its failure. Patients' satisfaction with treatment depends mainly on their previous experiences with similar treatment, as well as their expectations (*Prins MH, et al, 2009b*). Therefore, when clinical outcomes regarding treatment efficacy and tolerance are rare and are indistinguishable between different treatments, information about patients' QoL and satisfaction with their treatment is highly valuable. In connection with this, evaluation of patient-reported outcomes (PROs), along with an oral anticoagulant therapy control, is necessary for all patients receiving OACs.

Frequent monitoring of the prothrombin time (PT)/International Normalized Ratio (INR) values however, continues to be an important aspect of treatment, which may have physical, psychological, social and financial consequences for both patient and the health care system. This need for frequent monitoring may interfere with a patient's social and working life, in addition to the possible stress caused by the treatment itself and the condition necessitating this treatment (*Gadisseur APA, et al, 2004*). The development of hand-held PT/INR measurement devices, which determine the prothrombin time from capillary whole blood, has led to the development of the self-management of OAC (self-measurement of INR values and self-dosing of coumarin medication) by patients. The potential advantages of patient self-management include improved convenience for patients, with less lifestyle interference, better compliance and more frequent monitoring, as well as improved OAT quality, resulting in less thromboembolic and hemorrhagic complications (*Gardiner C, et al, 2005; Heneghan C, et al, 2006*). Benefits of self-monitoring of the INR on QoL have been shown (*Gadisseur AP, et al, 2003; Kulinna W, 1999; Gadisseur APA, et al, 2004*).

It is worth noting that an increasing number of children are requiring long-term anticoagulant therapy. Currently, the long-term anticoagulant of choice for children is warfarin. However, the use of this narrow therapeutic index medication requires frequent INR monitoring (*Streif W, et al, 1999; Monagle P, et al, 2008*). Anticoagulation in children is well described and best practices have been established (*Monagle P, et al, 2008*). However, there are a number of characteristics of long-term warfarin use that can potentially cause treatment dissatisfaction and reduce QoL for children and their families (*Jones SE, 2011*). The absence of robust evidence regarding the management and clinical outcomes of anticoagulant therapy in children challenges the interpretation of the risks and benefits of long-term anticoagulation therapy for children. Decisions about treatment increase in complexity, in light of the potential burden of treatment on children and families. QoL is a recognized and validated measure of the burden of treatments on children; yet, there is a lack of data about the impact of long-term

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warfarin therapy on QoL for children and families. Thus, evaluation of PROs in a pediatric population receiving anticoagulation would be helpful to identify barriers in care and areas for improvement in order to modify care to provide the best management (improved QoL associated with safety and efficacy) for children requiring anticoagulation therapy.

Patient-reported outcome instruments

Patient-reported outcome instruments for adults

There are two types of instruments for measuring QoL with patients receiving anticoagulation: generic and condition-specific. The most frequently used among the generic QoL tools is the SF-36 (see description in Chapter 2).

A comprehensive literature search identified several condition-specific instruments for patients receiving anticoagulation (*Wild D, et al, 2008*). Results of this literature review showed that psychometric data are available for three measures: the Sawicki Instrument, the Duke Anticoagulation Satisfaction Scale, and the Deep Vein Thrombosis Quality of Life Questionnaire.

Sawicki Instrument

The Sawicki Instrument was developed by Sawicki and his coworkers for QoL assessment in patients receiving oral anticoagulation, and validated in their multicenter study comparing patient self-management with conventional anticoagulant care (*Sawicki PT, 1999*). The questionnaire was created using the clinical impact method in which items are selected from a larger pool of statements based upon the importance given to them by the patients. The resulting questionnaire mirrors the most important concerns of the patients regarding their defined condition or treatment. The instrument consists of 32 items covering 5 treatment-related topics: general treatment satisfaction, self-efficacy, strained social network, daily hassles, and distress. Self-efficacy pertains to the patient's belief in being able to perform self-care activities. In modern clinical health psychology self-efficacy has been shown to predict preventive health behavior and illness behavior. Daily hassles are minor stressful events that add to the burden of having to cope with a chronic medical condition. Patients have to assess the degree to which the different statements are applicable to their individual situation, with a minimum score of 1 (total disagreement) to a maximum score of 6 (total agreement). Groups of individual statements are combined into 5 topics, leading to a mean score from 1-6 for the different topics. Improved QoL was indicated by rising scores for the topics of self-efficacy and general treatment satisfaction, and by diminishing scores for the topics of daily hassles, distress, and strains on the social network.

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Strengths: the use of this questionnaire increases general treatment satisfaction.

Weaknesses: one of the weaknesses of the questionnaire is relatively low Cronbach α values (0.53–0.74) (*Cromheecke ME, 2000*).

Duke Anticoagulation Satisfaction Scale

The Duke Anticoagulation Satisfaction Scale (DASS) is a specific scale to evaluate the QoL of patients under treatment with OACs which addresses the negative and positive impacts of anticoagulation (*Samsa G, et al, 2006*). It is a 25-item scale; each item has 7 possible response categories: not at all, a little, somewhat, moderately, quite a bit, a lot, and very much. The pattern of the questions is arranged to roughly correspond to 3 possible dimensions pertaining to anticoagulation: limitations (e.g. limitations in physical activities due to a fear of bleeding, dietary restrictions); hassles and burdens (e.g. both daily hassles like remembering to take the medicine, as well as occasional hassles like having to wait while visiting a provider for blood testing), and positive psychological impacts (e.g. reassurance because of anticoagulation treatment). The items with the lowest scores show a higher QoL satisfaction. The overall score varies from 25–175. The instrument is divided into 3 domains: limitation (score from 9–63), treatment inconvenience (score from 8–56), and psychological impact (score from 8–56).

Strengths: the DASS is a clinically relevant questionnaire which helps summarize satisfaction with anticoagulation and identify aspects of anticoagulation that may hinder individual patients from maintaining a PT/INR within therapeutic range.

Weaknesses: additional research is needed to show the relationship between QoL issues related to anticoagulation and adherence to treatment regimens.

Deep Venous Thrombosis Quality of Life Questionnaire

The Deep Venous Thrombosis Quality of Life Questionnaire (DVTQOL) is aimed at focusing on early symptoms and problems related to anticoagulation management that patients experience after a recent DVT event (*Hedner E, et al, 2004*). The questionnaire consists of 29 items composed of 6 dimensions depicting problems with: emotional distress; symptoms (e.g., pain, swollen ankles, cramp, bruising); limitation in physical activity; hassle with coagulation monitoring; sleep disturbance; and dietary problems. Responses are arranged on a 7-point Likert-type scale to assess how much or how often the item described the feelings of the patient: degree of distress (not at all, minor, mild, moderate, moderate severe, severe, extremely severe) and frequency of the problem (never, hardly ever, occasionally, sometimes, frequently, most of the time, all of the time). Seven-point scales are supposed to be easier for the patients to learn and understand and changes are

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easier to interpret, as compared to visual analogue scales. Summary scores for each of the 6 domains can be calculated (maximum range between 30-210). The higher the score, the more discomfort, distress, inconvenience and hassle patients feel. Good reliability and validity of the questionnaire have been shown.

Strengths: the DVTQOL is a short and user-friendly instrument that can be used for measuring QoL in patients with a recent DVT event, and are currently on oral anticoagulation treatment.

Weaknesses: its test-retest reliability and responsiveness to change in clinical trials needs to be evaluated.

In order to evaluate the full benefits of anticoagulant treatments, specific patient-reported questionnaires that assess patients' satisfaction with anticoagulant treatment are required. In clinical practice, the measurement of satisfaction with anticoagulation management helps support interventions that increase time in therapeutic range and reduce adverse thromboembolic or bleeding events. The Perception of Anticoagulant Treatment Questionnaire was developed to assess patients' expectations of, and satisfaction with, their anticoagulant treatment.

Perception of Anticoagulant Treatment Questionnaire

The Perception of Anticoagulant Treatment Questionnaire (PACT-Q) is focused on patients' expectations and satisfaction regarding anticoagulant treatment, as well as their opinion about treatment usage convenience (*Prins MH, et al, 2009a*). The original PACT-Q contains 27 items grouped into 4 domains: treatment expectations (7 items), convenience (11 items), burden of disease and treatment (2 items), and anticoagulant treatment satisfaction (7 items). The questionnaire consists of two parts: the first part, the PACT-Q1, is used to measure expectations and the second one, the PACT-Q2, is designed to evaluate convenience, as well as burden and treatment satisfaction, prior to and after anticoagulant treatment, respectively. All the items of the PACT-Q1 and the PACT-Q2 parts are answered on a 5-point Likert-type scale. The questionnaire was simultaneously created in French, American English, and Dutch following a rigorous development process, in which the data collected from the patients were given particular importance. It was further translated and adapted into 11 different country-specific versions following recommended linguistic validation procedures.

Strengths: the good acceptability and psychometric properties of the questionnaire have been demonstrated with patients with various conditions including DVT, pulmonary embolism, and atrial fibrillation. It is brief and easy to administer.

Weaknesses: further quantitative psychometric validation steps are necessary to consolidate its validity and suitability for application in clinical research studies.

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Patient-reported outcome instruments for children

To assess QoL in children requiring anticoagulant therapy, the generic QoL questionnaires, namely the PedsQL™ 4.0 Generic Core Scales and the PedsQL™ 4.0 Family Impact Module (see description in Chapter 2), have been used. The KIDCLOT Pediatric Anticoagulation Quality of Life Inventory is the first and only QoL questionnaire developed to assess QoL in children on long-term anticoagulant therapy.

KIDCLOT Pediatric Anticoagulation Quality of Life Inventory

The KIDCLOT Pediatric Anticoagulation Quality of Life Inventory (KIDCLOT PAC QL©) questionnaire consists of separate versions for children and for parents (*Bruce AA, et al, 2010*). The KIDCLOT PAC Child-Tween QL© Inventory has 37 items with 4 open-ended questions. Item responses are rated on a 4-point scale (always to never). The KIDCLOT PAC Parent-proxy QL© Inventory has 39 items with 2 open-ended questions. Parent-proxy item responses are rated on a 5-point scale (often to never). The content and face validity of the questionnaires was assessed by experts, parents, and patients. The internal consistency, determined by Cronbach's alpha, was high for both the parent-proxy (0.82) and child (0.89) forms. The Pearson correlation was acceptable with > 0.5 for test-retest reliability (Parent Inventory). The Inventory identifies barriers in care and areas for improvement in order to modify care to provide the «best» management (improved QoL associated with safety and efficacy) for children requiring long-term anticoagulation therapy.

Strengths: the KIDCLOT-PAC-QL was developed especially for children receiving long-term anticoagulation therapy.

Weaknesses: the questionnaire specifically addresses children receiving warfarin and needs modification in order to be used in children receiving other anticoagulants.

Practical considerations for patient-reported outcome assessment

There are many factors that may interfere with oral anticoagulant therapy. Research in this field is of utmost importance. It can provide relevant data regarding treatment, acceptance of medication, and improvement of patients' QoL.

Furthermore, concentrated research is currently underway in an effort to develop safer and more effective anticoagulants. Some of these have the advantage of an increased half-life, allowing for once-a-week administration. Others have the potential to be given orally, without laboratory monitoring. For assessing the real value of new drugs in this field, the evaluation of patients' perspectives and satisfaction towards these treatments

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will be necessary. Traditional efficacy end-points alone may not be able to include all the benefits of novel therapies, such as the reduction in treatment burden. PROs are important end-points of anticoagulation therapy.

The choice of a PRO measure is crucial when planning a study with a PRO component in patients requiring anticoagulant treatment. It depends on the study goal, the study population (adults, children or adolescents) and issues related to treatment attributes, such as the route of administration (e.g. subcutaneous versus oral). If the relationship between the concept and the assessment instrument is not clear and coherent, there will be confusing results, as well as difficulty with comparisons and clinical applicability (*Dantas RAS, 2011*).

To evaluate the risks and benefits of long-term anticoagulation therapy, a combination of generic and condition-specific questionnaires is helpful. The use of specific instruments in combination with generic ones can be employed concurrently, and provide inter complementary data about what is being researched, can be employed concurrently, offering inter complementary data (*Childs AL, et al, 2005*). To provide full evaluation of the treatment benefits for the patient, treatment satisfaction questionnaires can be recommended as well.

Of special note is the choice of a PRO measure for children/adolescents receiving anticoagulation. Practical issues for PRO assessment in this patient population are presented in Chapter 7.

It is necessary to make efforts towards a high quality assessment, from the choice of the construct to be researched to the instrument to be used, so that these choices may provide to a trustworthy account of the patient's perception about what is being assessed.

The analysis and interpretation of PROs in patients receiving anticoagulant therapy is a complicated issue. Yet, so far, there does not seem to be a practical, efficient and effective manner to translate what was recorded by the PRO data into clinical practice. At the same time, there are a number of considerations which should be taken into account when analyzing and interpreting the results of studies with a PRO component in patients requiring anticoagulant treatment. When interpreting treatment outcomes in these patients, information about PRO issues should be presented and analyzed along with the PT/INR values. It is important to differentiate patients depending on their clinical characteristics and treatment history. The following clinical markers should be taken into account: duration and indication for the use of anticoagulants, the route of administration of anticoagulants, the mode of INR measurement, etc. Gender, age, lifestyle, and place of living (urban areas vs rural surroundings) are also important.

Broader studies involving patients requiring anticoagulation therapy with a PRO component will be a valuable contribution to providing higher quality care for this patient population and improving their well-being.

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CHAPTER 7

Quality of life and symptom assessment in children/adolescents with hematological malignancies

State of the art

During the past few decades there has been a dramatic improvement in the long-term survival of childhood blood cancer patients (*Imbach P, et al, 2011*). This is related to new treatment approaches, centralization of care, improved supportive care, and the development of large international clinical trials. Traditionally, progress in pediatric oncology has been measured in terms of survival and rates of response to treatment. The five-year survival rate for children with acute lymphocytic leukemia (ALL) is now exceeding 80%; for non-Hodgkin's lymphoma (NHL) it increased between 1975–2002 from 45 to 88% in children younger than 15 and from 47 to 77% for adolescents aged 15–19 (*Smith MA, et al, 2010*). However, the same treatments leading to increased survival rates can also cause potentially debilitating physical deficits, such as endocrine dysfunction, neuropsychological deficits, or secondary malignancies. They can also result in diminished physical, psychological, and social functioning of a child (*Clarke SA, Eiser C, 2004; Erickson JM, et al, 2011*). While survival rates and health status are fairly easy to assess, they often do not appropriately mirror the entire impact of the cancer and its treatment on the individual child, particularly with respect to subjective experiences. Such consequences of disease and treatment can be assessed by measuring patient-reported outcomes (PROs).

Using PROs with pediatric cancer patients can provide validated evidence of health concerns from the point of view of a child. They may also improve the quality of interactions between health professionals, children, and their families. Today, PRO questionnaires are increasingly being used in daily clinical practice, being provided to the physician to facilitate communication with children and families during a consultation. Additionally, PROs can provide service outcome data for the purposes of audit, quality assurance, and comparative performance evaluation.

Measurement of PROs in pediatric cancer patients is being increasingly emphasized in clinical trials. However, compared to the studies in adults, quality of life (QoL) research in children is still relatively uncommon. This outcome is important as it provides a measure of well-being from the perspective of the child or parent. Ultimately, better understanding of PROs in children with cancer may be useful for several reasons.

This knowledge may help parents and children anticipate the expected course of events during treatment. In addition, the measurement of QoL may help families and health care professionals choose among treatment strategies with similar survival rates but with different expected QoL. Furthermore, QoL is considered to be an important variable in the evaluation of new medical treatments in pediatric cancer patients. Another goal, though, may be to identify a group of children with expected poor QoL. They could then be targeted for supportive care interventions to improve their health. Finally, children suffering from hematological malignancies experience a wide spectrum of symptoms during very long and intensive treatment (*Meeske K, et al, 2004; Dupuis LL, et al, 2010*).

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Symptoms may persist long after the treatment is over. Assessment and monitoring of symptoms is important to provide adequate symptom control and supportive care if necessary.

QoL and symptom assessment in children with blood cancer is important at all the stages of treatment: before and during intensive therapy, as well as at follow-up. Yet, treatment takes a long time. It normally requires 1-3 years, followed by check-ups for the next 3-7 years. The child newly diagnosed with cancer is critically ill during the first 2-6 months. After this, his/her life continues similar to that of a healthy child, except that periodic treatment adjustment and check-ups are necessary. Information about QoL and symptom severity trajectory at different stages of treatment is of value to ensure high quality care in this complicated pediatric patient population.

Notably, most QoL studies in pediatric cancer patients have focused on childhood survivors (*Robison LL, et al, 2005; Weintraub N, et al, 2011; Barrera M, et al, 2012*). Only a few studies have been conducted during the acute phase of the disease, (i.e. during ongoing treatment). Taken together, these studies suggest that QoL in children during therapy is significantly lower than in survivors that have completed treatment and in the normal population. QoL during active treatment is important to study. Doing so, it is possible to capture deterioration in child functioning due to the toxicities of therapy and to evaluate the results of disease status (minimal residual disease, remission, risk of relapse, etc.) and often radical changes in normal day-to-day routines for the child and family. Conversely, QoL in survivors would be expected to be primarily influenced by the sequelae of therapy. Both of these perspectives are important, and improvement in QoL during both periods should be a priority.

ALL is the most common malignancy in children. The majority of PRO studies in childhood blood cancer have been performed on this patient population. Today ALL has a greatly improved survival rate of approximately 80% (*Pui CH, Evans WE, 2003; Gatta G, et al, 2005*). Treatment of the central nervous system (CNS) with cranial irradiation and/or chemotherapy has been an important factor contributing to the increased survival rate. However, leukemia treatment has been implicated as being responsible for a diversity of long-term adverse effects (*Pui CH, et al, 2003*). CNS treatment has been suspected of causing long-term neurocognitive deficits, especially when cranial irradiation is used (*Moore BD, 2005; Campbell LK, et al, 2007*). The awareness of the harmful effects of cranial irradiation therapy, especially among young children, has led to the practice of replacing it with CNS-directed chemotherapy. This includes mainly high dosage IV methotrexate and intrathecal methotrexate. The harmful effects of CNS chemotherapy appear to be less than radiation, but are still worrisome (*Kingma A, et al, 2001*). Another major concern is physical, psychosocial and educational deficits after cranial irradiation and CNS-directed chemotherapy, which can occur even years after diagnosis and can seriously impair survivors' performance status and QoL (*Moore BD, 2005; Campbell LK, et al, 2007; Schultz KA, et al, 2007*). These deficits may increase the possibility of mental

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distress and depression. A growing number of studies have documented the substantial impact of childhood cancer treatment which may cause impairments that diminish social functioning, including obtaining or retaining employment (*Pang J, et al, 2008*). The number of ALL survivors among young adults is increasing rapidly, and the need to improve their QoL is becoming an increasingly important and topical issue. Notably, most of the studies have focused on the follow-up of childhood ALL survivors (*Zebrack B, Chesler MA, 2002; Meeske KA, et al, 2005; Pemberger S, et al, 2005; Stam H, et al, 2006; Harila MJ, et al, 2010*) and, to a lesser extent, on children during active treatment. In the recent multicentre prospective cohort study it was demonstrated that children during treatment for ALL experienced a reduced QoL, as compared to healthy children, which is further aggravated by the use of dexamethasone (*de Vries M, et al, 2008*). This is the first study to specifically assess the second year of ALL treatment and to identify an additional negative effect of corticosteroids on QoL, although the effect of other therapeutic agents can not entirely be ruled out. To summarize, it is obvious that most children with ALL experience reduced QoL during and soon after treatment. More attention to treatment-related factors of decreased QoL in pediatric ALL patients may provide health-care providers with specific tools to address these issues. Thus, clinical studies with a PRO component are of value.

Lymphoma (Hodgkin's lymphoma and non-Hodgkin lymphoma) is the third most common childhood malignancy (*Imbach P, et al, 2011*). The incidence of HL in childhood varies by age, such that HL is exceedingly rare in infants, but is the most common childhood cancer in the 15-19 age group. NHL accounts for approximately 7% of cancers in children younger than 20. With increased survival rates, issues concerning the QoL of these children are becoming increasingly relevant. It's worth noting that the 1st International Symposium on Childhood, Adolescent and Young Adult Hodgkin Lymphoma (May 12–14, 2011, Washington D.C.) postulated that the major goal of pediatric HL treatment is to improve survival and QoL for children, adolescents and young adults with HL worldwide. One of the core topics of the symposium was to discuss recent research advances in the field of late effects and QoL issues of long term HL survivors. However, studies with a PRO component in pediatric lymphoma patients are scarce; moreover, they have been conducted on a mixed population of cancer patients.

QoL and symptom assessment in children with hematological malignancies who underwent bone marrow transplantation/hematopoietic stem cell transplantation (BMT/HSCT) is of special interest (*Felder-Puig R, et al, 2006; Perkins JL, et al, 2007; Clarke SA, et al, 2008; Barrera M, et al, 2009; Packman W, et al, 2010*). The number of childhood BMT/HSCT patients has increased in recent years, particularly allogeneic transplants for serious hematological diseases (malignant and non-malignant). This has been facilitated by developments in the use of alternative donors (unrelated or mismatched related) and stem cell sources (peripheral blood stem cells, PBSC, or umbilical cord blood, UCB). The most common indication for allogeneic transplantation in children is leukemia (62%),

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followed by non-malignant conditions, such as thalassemia major, sickle cell disease etc (36%), and other cancers (2%) (*Leiper A, 2002*). Late adverse consequences of BMT/HSCT occur both as a result of the original treatment for the disease for which BMT/HSCT was performed and secondary to the toxicity associated with conditioning regimens. Additional damage is sustained through the toxic effects of antibiotics, antifungals, or immunosuppressive agents used to prevent or treat infections or graft-versus-host disease (GvHD). Chronic GvHD may itself cause late treatment-related toxicity. Cardiac, pulmonary, endocrine, renal, neurological, neuropsychological, and other late effects have been recorded. Published information about late effects typically relates to BMT, but it is anticipated that a similar profile of late effects will be found following PBSC or UCB transplant. Given the toxicity of treatment, questions have been raised about the QoL of children during and after BMT/HSCT. Much of the evidence on QoL after BMT/HSCT comes from survivors who are years post transplantation. Some studies showed that pediatric patients who survived a couple of years were likely to achieve a reasonable adjustment and satisfactory QoL (*Helder DI, et al, 2004*). Other studies suggest that pediatric BMT/HSCT recipients are at risk of developing long-term emotional or social problems (*Pemberger S, et al, 2005; Pang JW, et al, 2008; Schultz KA, et al, 2009; Harila MJ, et al, 2010*). Continued PRO research is necessary because children undergoing treatment on current protocols do not receive the same therapy as those from whom the "evidence" has been obtained and such details may alter the long-term impact of the therapy (*Jenney MEM, Levitt GA, 2002; Engelen V, et al, 2011*). There have been practical changes in the administration of therapy and improvements in treatment protocols, such as the introduction of reduced-intensity conditioning (*Perez-Simon JA, et al, 2005*), which may have led to less adverse side effects and a better QoL.

On the one hand, the measurement of QoL in pediatric oncology has been advocated for a number of years, on the other hand, the emerging paradigm shift toward PROs in clinical trials (*US Food and Drug Administration: Guidance for Industry. Patient-Reported Outcome Measures, 2009*) has provided an opportunity to further emphasize the value and essential need for pediatric patient self-reported PRO measurement in pediatric oncology clinical trials (*Razzouk BI, et al, 2006*). During the past decade, legislative changes have created both voluntary and mandatory guidelines for drug studies in children, resulting in a substantial increase in pediatric clinical trials. Under the Pediatric Exclusivity Provision of the Best Pharmaceuticals for Children Act (BPCA), reauthorized in 2002, companies that conduct drug studies with children, as requested by the FDA, are eligible for an additional 6 months of marketing exclusively for the studied drug. The Pediatric Research Equity Act (PREA), signed in 2003, allows the FDA to require pediatric studies if it is determined that the product is likely to be used by a considerable number of pediatric patients, or if the product would offer an important advantage to pediatric patients over existing treatments. Nevertheless, while the above pediatric initiatives have opened the opportunity for children to be included in clinical trials, pediatric

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patients have not been afforded the right to self-report on matters pertaining to their health and well-being when evaluating the health outcomes of treatments in the majority of pediatric clinical trials to date (*Varni J, et al, 2007*). This fact is in sharp contrast to the recent FDA Guidance for Industry publication, in which the FDA describes how it evaluates PRO instruments as health outcomes in clinical trials (*US Food and Drug Administration: Guidance for Industry. Patient-Reported Outcome Measures, 2009*). In the Guidance for Industry document, the FDA is quite definitive in stating that «some treatment effects are known only to the patient». Thus, what has been an obvious recognition in clinical trials for adult patients, has not received the same level of recognition in clinical trials for pediatric patients (*Clarke SA, Eiser C, 2004; Varni J, et al, 2007*).

Pediatric patient-reported outcomes

Although there is an essential need for pediatric patient self-reported PRO measurements as health outcomes in pediatric cancer, the data on PROs in children with hematological malignancies are limited. It may be partly explained by the fact that there are a number of methodological issues in pediatric PRO research which differ from those in adults.

First, it is well documented in the PRO measurement of children with chronic health conditions, including pediatric cancer, and healthy children that there is imperfect agreement between self-report and proxy-report (*Varni J, et al, 1998; Chang P, Yeh C, 2005; Felder-Puig R, et al, 2006*). Historically, QoL in children has been represented by the parents' view. However, research has shown that children's and parents' ratings are not identical, and that the difference may vary according to the health condition under study. Depending on the condition, parents can tend to either over- or underrate their child's well-being. Such diversion can also exist among dimensions within the same questionnaire (*Ravens-Siberer U, Bullinger M, 1998*). Research to date shows a divergence of parents' and children's ratings, suggesting that parents' ratings do not constitute proxy measures of children's QoL, but that their ratings should be used as an independent source of information (*Eiser C, Morse R, 2001*). Thus, a child-centered approach should be used to assess QoL and symptoms in pediatric patients. It has been shown that children as young as 5 can reliably and validly self-report their QoL and symptoms when an age-appropriate instrument is utilized (*Varni J, et al, 2007*). Parent proxy-report is recommended when pediatric patients are too young, too cognitively impaired, too ill, or too fatigued to complete a questionnaire, but not as substitutes for child self-report when the child is willing and able to provide their perspective.

Second, age specificity must be taken into account when measuring QoL and symptoms in pediatric patients. The age-relatedness of measures is due to the fact that children's concerns and relevant dimensions change dramatically from early childhood to

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adolescence, where aspects of peer relationships, their future, and intimacy become important. Furthermore, the social context of children's lives varies at different stages of development. It is increasingly clear that the social dimension in children is of specific importance and should be subdivided, containing aspects of family, friends and others, and that the self-concept needs to be addressed more specifically. Therefore, depending on the purpose of the assessment, the content may need to be adjusted for different age groups. This is particularly the case when aiming to assess children's activities and social participation.

It is still not well understood how cancer diagnosis and treatment specifically affect adolescents. Adolescence is typically a period of rapid physical, cognitive, and psychosocial change that takes place in the context of shifting relationships and roles within the family. Cancer and associated teen and family stressors may challenge adolescents' QoL through their impact on normative adolescent developmental tasks (e.g. ability to attend school, engage in activities with peers, participate in extracurricular activities, and take on greater responsibilities within their families, in their schools, and in their communities) (*Barrera M, et al, 2006; Schwartz LA, et al, 2009*). As the result, adolescents with cancer have been identified as being at greater risk for QoL worsening than their younger counterparts up to 15 months post-diagnosis. This highlights the importance of examining PROs in adolescents with cancer (*Barrera M, et al, 2006*). To reveal the relative contribution of treatment intensity, family sociodemographic risk, family resources, and other factors contributing to QoL burden in adolescents with cancer, a number of studies have been conducted (*Ward-Smith P, et al, 2007; Wu E, et al, 2007; Carpentier M, Mullins L, 2008; Barakat LP, et al, 2010*).

In addition, there are legal aspects to consider regarding children's/adolescents' right to consent and to report their own health, and when it is appropriate for parents to answer on their behalf without their consent. The United Nations Conventions on the Rights of the Child and the Rights of Persons with Disabilities advocate that children themselves should report their own health outcomes whenever possible. Therefore, children should be shown the same respect for personal autonomy accorded to adults when invited to complete questionnaires about themselves. Children should be approached directly and their explicit informed consent should be sought prior to administering a questionnaire. For infants and children with intellectual deficits who are unable to provide informed consent, or complete questionnaires themselves, a parent/caregiver can be approached as a proxy informant. In addition, children who are competent can decline to consent and not complete questionnaires. In these instances, guidelines recommend that children be asked to agree to participate or to give consent for their parent/caregiver to complete a questionnaire on their behalf (*General Medical Council, 2007*).

In summary, PRO is considered an important variable in the evaluation of treatment in pediatric cancer patients. In the future, standardized QoL and symptom assessment is likely to be routinely incorporated into clinical trials. PRO research can be used to

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optimize treatment and to give important information for decision making if treatment strategies with similar survival rates are compared.

Patient-reported outcome instruments

There are a number of PRO instruments available to assess QoL and symptoms in children with hematological malignancies.

Quality of life assessment

Although papers on the subjective perception of health and illness in children are available, instruments to assess QoL have only recently begun to be developed. Currently, there are several instruments which may be used to assess QoL in children with cancer, both generic and disease-specific. The most widely used in childhood cancer generic and disease-specific QoL questionnaires are presented in Table 1.
Generic QoL questionnaires are described in Chapter 2. A description of cancer-specific child questionnaires is presented below.

Table 1. Generic and disease-specific child QoL questionnaires used in children with cancer

Generic child QoL questionnaires
Pediatric Quality of Life Inventory™ (PedsQL™)
Child Health Questionnaire (CHQ)
Revidierter KINDer Lebensqualitätsfragebogen (KINDL®)
TNO AZL Children's Quality of Life (TACQOL)
Cancer-specific child QoL questionnaires
Pediatric Cancer Quality of Life Inventory-32 (PCQL-32)
Pediatric Oncology Quality of Life Scale (POQOLS)
Pediatric Quality of Life Inventory™ Cancer Module (PedsQL™ Cancer Module)

Pediatric Cancer Quality of Life Inventory-32

The Pediatric Cancer Quality of Life Inventory-32 (PCQL-32) is a standardized patient self-report and parent proxy-report assessment instrument designed to systematically assess pediatric cancer patients' QoL outcomes (*Varni JW, et al, 1998a, Varni JW, et al, 1998b, Varni JW, et al, 1999*). The 32-item PCQL-32 short form was empirically derived from the PCQL long form (84-87 items), which was administered to 291 pediatric cancer patients aged 5-18 and their parents during various stages of treatment. The PCQL-32

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has demonstrated acceptable internal consistency reliability, clinical validity, and construct validity suitable for randomized controlled clinical trials. In its short form, the PCQL-32 is practical for Phase III clinical trials.

Strengths: the questionnaire has been used in children with hematological malignancies. It includes a multidimensional framework, focuses on observable behaviors, and has good psychometric properties and ability to distinguish between stages of illness.

Weaknesses: there are no age-appropriate self-report versions.

Pediatric Oncology Quality of Life Scale

The Pediatric Oncology Quality of Life Scale (POQOLS) is a parent report measure for assessing the QoL of children with cancer. The instrument has a form of a 21-item 7-point Likert-type scale which was developed to measure the frequency of pediatric oncology patients' daily activities over 2 weeks (*Goodwin D, et al, 1994; Boggs SR, Durning P, 1998*). It yields a total score and three factor subscores: Role restriction and Physical Functioning, Emotional Distress, and Response to Current Medical Treatment. Internal consistency measured by coefficient alphas yielded reliability scores for the three factors ranging from 68 to 87. Lower scores indicate better QoL.

Strengths: the results of reliability analyses indicate excellent internal consistency for the measure as a whole and for each of its three factors.

Weaknesses: the instrument does not contain a child response form and is limited to proxy-report.

Pediatric Quality of Life Inventory™ Cancer Module

The Pediatric Quality of Life Inventory™ Cancer Module (PedsQL™ Cancer Module) is a widely used instrument to measure pediatric cancer specific QoL for children and adolescents aged 2 to 18 years (*Varni JW, et al, 1998*). It includes a total of 27 items in eight scales: pain and hurt (2 items), nausea (5 items), procedural anxiety (3 items), treatment anxiety (3 items), worry (3 items), cognitive problems (5 items), perceived physical appearance (3 items), and communication (3 items). It provides nine scores, one for each of the subscales and a total score based on all subscales. The child instrument differs by age group: 5–7, 8–12, and 13–18. The parent's version also differs by child age group: 2–4, 5–7, 8–12, and 13–18. The patients evaluate how often a particular problem occurred in the past month, using a 3-point Likert scale (0 = never, 2 = sometimes, 4 = often) for children 5–7 years and a 5-point Likert scale (0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always) for children 8–18 years and for the parents of all ages. For children aged 5–7, a Face Scale with 3 pictures varying from a smiling face to a sad face is used.

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Strengths: the questionnaire covers wide age range. It has been used in children with hematological malignancies (*Tsuji N, et al, 2011; Ji Y, et al, 2011*).

Weaknesses: information about the psychometric properties of different language versions is lacking.

There are several QoL questionnaires which are recommended for use with adolescent cancer patients (*Clinton-McHarg T, et al, 2010*). Among them are the PedsQL 3.0 Cancer Module, the Pediatric Oncology Quality of Life Scale and the Pediatric Cancer Quality of Life Inventory-32 with appropriate age-forms for adolescents.
There are also questionnaires that have been developed with a focus on adolescent patients. These are the Adolescent Quality of Life Instrument and the Minneapolis-Manchester Quality of Life Instrument.

Adolescent Quality of Life Instrument

The Adolescent Quality of Life Instrument (AQoL) is a 16-item Likert-type survey that assesses QoL in respondents aged 9-20. It was tested in hematology/oncology clinics on patients with leukemia, bone/joint lymphomas, neurological tumors, Hodgkin's lymphoma, and other forms of cancer (*Ward-Smith P, et al, 2007a; Ward-Smith P, et al, 2007b*). The questionnaire includes 16 items grouped into five domains: normal activities, social/family interactions, health status, mood, and meaning of being ill.

Strengths: the tool appears to accurately assess and reflect changes in QoL in cancer patients ongoing treatment as well as in pre- and post treatment periods.

Weaknesses: there is limited information about the psychometric properties of the tool.

Minneapolis-Manchester Quality of Life Instrument - Adolescent Form

The Minneapolis-Manchester Quality of Life Instrument - Adolescent Form (MMQL-Adolescent Form) was developed as a self-report measure of QoL in survivors of childhood cancer. This instrument can be used to assess QoL in patients aged 13–20 (*Bhatia S, et al, 2002; Hutchings HA, et al, 2007; Cantrell MA, et al, 2008*). It consists of 46 items and includes seven domains: physical, psychological, social, and cognitive functioning, body image, outlook on life, and intimate relations. There are other age-appropriate versions of this tool to address the differing developmental needs of younger individuals (8–12 years) and those who are older (21–45 years) survivors of childhood cancer.

Strengths: this instrument addresses the special needs of childhood cancer survivors.

Weaknesses: longitudinal studies are needed to address the sensitivity of this instrument to small changes in QoL.

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Pain assessment

Children with hematological malignancies often experience pain. These children have many potential sources of pain. Pains may arise from the disease process itself (e.g. neuropathic pain or bone pain), be secondary to the treatment (e.g. bone pain from steroids or discomfort from accessing their central line) or incidental (e.g., tooth ache or otitis media). However, because children have difficulty in communicating their pain it can go unrecognized and untreated. It is the child's behavior often, rather than their verbal report, which has to be interpreted to determine if they have pain. Because it can sometimes be difficult for parents and health care professionals to distinguish which behaviors indicate pain and to follow the progress of pain relief treatments, much attention should be paid to the development and use of pain assessment instruments.

Since 1974, a myriad of self-report approaches have emerged for use with children. The approaches include interviews, diaries, projective tests, body maps, pain words, color matching, visual analogue scales, and graphic rating scales. Graphic rating scales include numeric rating scales, word-graphic rating scales, pain thermometers, and facial scales, including photographic and cartoon-face scales (*Tomlinson D, et al, 2010*). Although most self-report approaches were developed for children with pain secondary to diagnostic, monitoring, and surgical procedures, self-report tools with adequate psychometric evidence appear to capture appropriately the pain intensity for children with cancer.

The measurement may be focused on three attributes of pain: intensity, location, and quality. Most tools measure intensity of pain. The earliest tools developed, the Poker Chip Tool and Oucher Scale, which have been used in children with blood cancer, measure intensity only. The Eland Color Tool focuses on both pain intensity and location.

Poker Chip Tool

This tool uses 4 red poker chips to quantify pain (*Hester N, et al, 1990*). The red chips represent pieces of "hurt". One chip is a little bit of hurt while all four chips are the most hurt the child can have. The child is told to select the number of chips that indicate how much pain he/she is experiencing. Some versions have a white chip to represent no pain. The Poker Chip Tool has been successfully used with children aged 3–5.

Strengths: the Poker Chip Tool appears to have the most utility as a very simple clinical assessment tool to identify presence/absence of pain and very gross estimates of pain intensity in young children. Children learn to use this tool rapidly.

Weaknesses: in comparison with other pain assessment scales, the Poker Chip Tool is often the least preferred by children and their parents.

Oucher Scale

The Oucher Scale (Oucher) is a poster-like instrument designed to help children provide self-reports of the intensity of their pain (*Beyer JEI, 1989*). It consists of two scales: a

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0-100 numerical scale for older children and a six-picture photographic scale for younger children. There are currently five versions of the Oucher: (1) White or Caucasian, (2) Black or African American, (3) Hispanic, (4) First Nations (boy and girl), and Asian (boy and girl). Each version has been tested primarily with children in the ethnic group depicted in the photographs. All have been tested scientifically for content and construct validity, except for the First Nations Oucher which has been tested only for content validity. It is recommended that children/parents select the version of the Oucher that they would like to use. The Oucher provides useful information about the pain associated with nursing, dental, and medical treatments and procedures, as well as pain associated with injury and disease. It can also be used to assess the effectiveness of various pain relief measures. The scale can be used with children ages 3-12. To determine if a child has the cognitive ability to use this tool, the child is asked to seriate 6 geometric figures in ascending order of size. For health care professionals, it provides additional information about the child's experience which aids in both the assessment and management of pain. The Oucher eliminates the need to have children accurately verbalize the amount of their pain, and, therefore, eliminates the need for health care providers to interpret the meaning of their words.

Strengths: for children, the Oucher Scale provides an easy-to-use device for the estimation of the intensity of their pain. It helps them communicate their experiences to adults more effectively. The Oucher is the only color photographic pain tool for children with a version for children of several different cultures.

Weaknesses: First Nations Oucher hasn't yet been tested for construct validity.

Eland Color Tool

The Eland Color Tool focuses on both pain intensity and location (*Eland JM, 1977*). This tool involves the child's development of a color scale. After selecting four colors to represent no hurt, little hurt, moderate hurt, and the most hurt, the child chooses the color representing his or her hurt and marks where the pain is on a clothed body map. For example, a 12-year-old boy who used this tool after a lumbar puncture colored a red line along his spinal cord and then made a zigzag line on top of it. He commented that the zigzag line was «because it hurt so bad» (*Hester NO, et al, 1978*).

Strengths: children easily learn how to use this tool.

Weaknesses: in each case it is necessary to indicate the child's use of right and left.

Children who are too young to self-report or who are cognitively impaired require observations of behavior to assess pain.

The Pediatric Pain Profile can help parents and healthcare providers assess pain in nonverbal children.

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Pediatric Pain Profile

The Pediatric Pain Profile (PPP) is a 20-item behavior-rating scale designed to assess pain in children with severe to profound neurological impairment (*Hunt A, et al, 2004; Hunt A, et al, 2007*). The instrument has 20 different types of pain cues. These include vocal cues, changes in posture, different movements the child might make, changes in their facial expression and mood, and changes in the way they sleep or eat. Each of the behaviors in the scale is rated between zero and three for the extent to which it occurs within a given time frame. Because the parents' role in assessing pain in this group of children is so important, the scale has been incorporated into a record that the parent can keep at home. The tool is aimed at making it easier to describe and record pain behaviors, monitor pain and the effectiveness of treatments, and communicate concerns about a child's pain to professionals. It has potential for use both clinically and in intervention research.

Strengths: the PPP is a valid and reliable scale for recording the pain behavior of children with severe disabilities and for monitoring the effectiveness of methods used to relieve the children's pain.

Weaknesses: the health professional needs to know the child before the appearance of pain.

Monitoring coping strategies in children is of great clinical importance as they have been shown to mediate the influence of pain intensity on functional disability and QoL and to influence pain adjustment. To assess coping strategies in children the two most frequently used instruments are:

- Pediatric Pain Coping Inventory;
- Coping Strategies Questionnaire-Child Version.

Pediatric Pain Coping Inventory

The Pediatric Pain Coping Inventory (PPCI)™ was developed as a standardized questionnaire to systematically assess children's pain coping strategies (*Varni JW, et al, 1996*). It is aimed at helping health-care professionals identify the strategies children use to cope with pain. The PPCI consists of 41 items in which the respondent is asked to rate, on a three-point response scale, how frequently coping skills are used in five areas: (a) cognitive self-instruction, (e.g. pretending that I don't have any pain or hurt, tell myself to be brave), (b) seek social support, (e.g. have a parent or friend sit with me, ask someone to tell me that the pain will go away and I'll feel better), (c) strive to rest and be alone, (e.g., sit quietly, ask to stay by myself), (d) cognitive refocusing, (e.g., watch TV/read a book, think about happy things), (e) and problem-solving/self-efficacy, (e.g., tell my parents, know I can ask for something that will make it feel better). Higher scores indicate more frequent use of a particular coping strategy.

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Strengths: the PPCI is a conceptually valid and internally reliable measure for assessing pediatric pain coping strategies.

Weaknesses: the instrument does not determine how changes in coping lead to changes in psychological and physical functioning; future experimental research is required.

Coping Strategies Questionnaire - Child Version

The Coping Strategies Questionnaire - Child Version (CSQ-C) is a version of the Coping Strategies Questionnaire modified for children in order to measure the use of various coping strategies in children, and the extent to which they perceive these strategies as effective in controlling and decreasing pain (*Schanberg LE, et al, 1996*). This 42-item questionnaire is comprised of seven subscales, each representing a different coping strategy and consisting of six items. The subscales assess six cognitive strategies (i.e., diverting attention, reinterpreting pain sensations, calming self-statements, praying or hoping, and catastrophizing) and one behavioral strategy (increasing behavioral activity level). Catastrophizing is the strategy seen as maladaptive, while the others are usually seen as adaptive in most cases. Patients rate each item using a 7-point scale, ranging from 0 (never) to 6 (always), to indicate how often they use that strategy to cope with pain. At the end of the questionnaire, participants make 2 separate ratings of the overall effectiveness of coping strategies. Using a 7-point scale, participants rate how much control they have over pain, ranging from 0 (no control) to 6 (complete control), and how much they are able to decrease pain, ranging from 0 (can't decrease it at all) to 6 (can decrease it completely).

Strengths: it is a reliable measure for assessing variations in pain coping in children.

Weaknesses: information about its use with child blood cancer patients is limited.

Fatigue assessment

Fatigue is a common symptom found in the adult oncology literature, but has less emphasis in publications concerning children with cancer. However, many children with hematological malignancies experience fatigue during and following treatment. Children may describe fatigue as being tired and/or feeling weak. Common causes of fatigue include treatment (surgery, chemotherapy, or radiation), low blood counts, poor nutrition, fever, pain, not getting enough sleep, poor quality of sleep, worry, and trying to do too much. Thus, it is essential to assess fatigue in children both during the whole course of treatment, and at long-term follow-up.

To assess fatigue in children with cancer the PedsQL™ Multidimentional Fatigue Scale may be used.

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Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale™

The 18-item Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale™ (PedsQL™ Multidimensional Fatigue Scale™) was designed to measure fatigue in pediatric patients (*Varni JW, Limbers CA, 2008*). It is comprised of the General Fatigue Scale (6 items), the Sleep/Rest Fatigue Scale (6 items), and the Cognitive Fatigue Scale (6 items). The format, instructions, Likert response scale, and scoring method are identical to the PedsQL 4.0 Generic Core Scales, with higher scores indicating better QoL (fewer problems or symptoms).

Strengths: the instrument may be utilized in the evaluation of fatigue for a broad age range.

Weaknesses: information about its use with child blood cancer patients is limited.

Multiple symptom assessment

Children with hematological malignancies are often very symptomatic and highly distressed by their physical and psychological symptoms. Lack of energy, pain, nausea, and psychological symptoms are frequent complaints of these children, with the most distressing symptoms being difficulty swallowing, mouth sores, pain, and insomnia. Multiple symptoms experienced by these children are due to disease itself and its treatment. In connection with this, comprehensive symptom assessment is worthwhile for this pediatric population. The Memorial Symptom Assessment Scale (MSAS) is now available to assess symptoms in children with cancer. In pediatrics this questionnaire has two modifications: a child version (MSAS 7–12) and an adolescent version (MSAS 10–18).

Memorial Symptom Assessment Scale 7–12

Collins and colleagues revised the Memorial Symptom Assessment Scale (MSAS) for use with children aged 7–12 (*Collins JJ, et al, 2002*). This version of the instrument evaluates only eight symptoms, with a recall period of 48 hours. The MSAS 7–12 is multidimensional and measures the dimensions of frequency, severity and distress, using Likert scales at a reading and comprehension age-equivalent of 7 years. However, the response options for the MSAS 7–12 are simpler than those for the MSAS 10–18. The responses regarding frequency (i.e. a very short time, a medium amount, almost all the time) and severity (i.e. a little, a medium amount, a lot) contain only three options. The distress questions contain four response options (i.e. not at all, a little, a medium amount, very much). It takes 5–8 minutes to complete the questionnaire. Younger children need more assistance and take longer to complete the MSAS 7–12. Data provide evidence of the reliability and validity of MSAS 7–12 and demonstrate that children with cancer as young as age 7 can report clinically relevant and consistent information about their symptom experience (*Collins JJ, et al, 2002*).

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Strengths: the completion rate for MSAS 7–12 is high and the majority of children complete the instrument in a short period of time and with little difficulty. The instrument appears to be age appropriate and may be helpful to older children unable to independently complete MSAS 10–18.

Weaknesses: the tool can't be used in patients younger than age 7.

Memorial Symptom Assessment Scale 10-18

The Memorial Symptom Assessment Scale (MSAS) 10–18 is a 30-item patient-rated instrument adapted from a previously validated adult version (*Collins JJ, et al, 2000*). It provides multidimensional information about the symptoms experienced by children with cancer. The questionnaire assesses symptoms in terms of frequency, severity, and distress, and can be completed, on average, in about 11 minutes. Subscale analyses measure physical, psychological, and global distress.

The first question asks about the presence of a symptom over the past week. If participants respond in the affirmative, then they rate the symptom's frequency, severity, and distress using Likert scales. The MSAS 10–18 has three subscales: the Global Distress Index (GDI), which includes 10 highly prevalent physical and psychological symptoms; the PHYS subscale; and the PSYCH subscale. The MSAS 10–18 is scored by averaging the values reported for symptom frequency (i.e. 1 = almost never to 4 = almost always), severity (i.e. 1 = slight to 4 = very severe), and symptom distress (i.e. 0 = not at all to 4 = very much) to obtain an overall value for each symptom. The 30 overall item scores are then averaged to obtain a total scale score (i.e. 0 to 4). Similar calculations can be made for the 11 items in the PHYS subscale, the 6 items in the PSYCH subscale, and the 10 items in the GDI. Convergent and divergent validity of the MSAS 10–18 was established through comparing the results of the MSAS 10–18 with other symptom assessment instruments.

Strengths: the instrument is well adapted to reading and comprehension age-equivalent of 10 years, and its psychometric properties have been evaluated with a sample of both children and adolescents (*Collins JJ, et al, 2000*).

Weaknesses: comparative studies with younger children using this tool cannot be performed.

The Symptom Checklist-90 - Revised® may be used in children with cancer to measure psychological symptom status.

Symptom Checklist-90 - Revised®

The Symptom Checklist-90 - Revised® (SCL-90R) is a 90-item self-report symptom inventory which is a measure of current psychological symptom status with a time reference of the past 7 days including the present day (*Derogatis LR, 2000*). Scores for

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each of the nine factors (Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism) are the average rating given to the symptoms of that factor. The remaining seven items do not measure any particular factor, but are evaluated qualitatively. There are three global indices: the Global Severity Index (GSI), the Positive Symptom Distress Index (PSDI), and the Positive Symptom Total (PST). The GSI is the average rating given to all 90 items. The PST is the number of symptoms complained of (i.e., the number of items rated higher than zero). The PSDI is the average rating, from 1 to 4, given to those symptoms which are complained of (i.e. not rated "0"). Raw scores for each of the primary symptoms are converted into standardized scores. The progress report graphically displays the patient's progress for up to 5 previous administrations.

Strengths: it takes very little time for the patient to complete the test (about 12–15 minutes).

Weaknesses: the tool can be used only in individuals aged 13 and older with a sixth grade reading level and thus, isn't appropriate for younger children.

Practical considerations for patient-reported outcome assessment

PRO assessment is an important component of pediatric cancer care for patients both under treatment, and at follow-up in a conventional and special (BMT/HSCT) treatment. PRO assessments might be of value for spitex/home care organizations and children hospices.

When choosing PRO instrument in pediatric population a number of requirements should be addressed. Recommendations when choosing a QoL questionnaire in children are presented in Table 2.

Table 2. Recommendations for choosing QoL instruments for use with the pediatric population

Child-centered focus
Availability of self-report and proxy report forms
Age appropriate for the respondents
Inclusion of both positive and negative aspects of the health condition
Short
Concise
Practical

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Ideally, a questionnaire should have both child and parent forms which measure the same constructs with parallel items, in order to make comparisons between self- and proxy-report more meaningful.

Self-report is recommended for children as young as age 5. Parent proxy-report is an option when pediatric patients are too young, too cognitively impaired, too ill, or too fatigued to complete a questionnaire.

When PROs are measured during treatment and short-term follow-up, the best data will be obtained if a combination of generic and disease-specific QoL instruments is used. A symptom assessment questionnaire is of value for monitoring a child's symptom profile before, during, and after treatment. In addition, the use of a symptom assessment questionnaire makes it possible to capture early and late side effects of treatment from a child perspective. To assess PROs in long-term pediatric cancer survivors, generic QoL questionnaires along with symptom assessment instruments are of value. The use of symptom assessment tools might be of help to identify long-term complications.

Children should be shown the same respect for personal autonomy accorded to adults when invited to complete PRO measures. Children should be approached directly, and their explicit informed consent should be sought prior to administering a questionnaire. Some children are unable to consent or give their own responses due to age or intellectual deficits. For infants and children with cognitive limitations, a parent/caregiver can be approached as a proxy informant. Furthermore, some children may only be able to answer if they are provided with assistance to read the question and communicate the response. It is important that the personnel involved in arranging PRO assessment organize the process in such a way to avoid stimulation of patient symptom awareness. The PRO measures administrator is crucial in developing rapport with the respondents, emphasizing the importance of the questionnaire, addressing concerns, and ensuring that the PRO measure is completed accurately and confidentially. At present nurses regularly use some PRO assessment, especially pain assessment. Repetitive assessments should be done and evaluated by the same person, if possible.

The integrating algorithm for selecting pediatric PRO measure is shown in Table 3.

Additionally, there are also a number of important guidelines to keep in mind during PRO assessment in children and adolescents. Depending on the study design and the study population, the type of administration mode may be chosen from the following formats: interviewer-administered, self-administered (self-report by a child/adolescent and proxy-report by a parent/caregiver), and telephone/mailing administered. The computer-administered format, (e.g. electronic system for PROMs data collecting), has been developed for some instruments and includes both child and parent forms. Finally, informed assent/consent issues must be considered.

Therefore, careful planning of a study with the consideration of ethical and legal aspects is of no less importance in pediatric population as in adults. A child-centered approach should be the priority when analyzing and interpreting PRO data.

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Table 3. Considerations for choosing PRO instruments in children/adolescents

Issues to be considered	Variants	Type of instrument
Study purpose	Assessment of a single problem	Single symptom assessment scale and/or single symptom assessment questionnaire
	Assessment of several problems	QoL questionnaire and/or symptom assessment questionnaire
	Comprehensive assessment of health concerns	QoL index/QoL questionnaire(s) and/or multiple symptom assessment questionnaire
Treatment phase of study population	During anti-cancer treatment	Generic QoL questionnaire(s)and/or cancer-specific QoL questionnaire(s) and/or symptom assessment tool(s)
	Follow-up	General QoL instrument(s) and/or symptom assessment tools
Age of respondents	Younger than 5 yrs	Parent proxy-report instrument
	5-7 yrs	Interviewing of a child and filling in the appropriate age form of instrument with faces scale by interviewer and parent/ caregiver proxy-report instrument
	>8 yrs	Child/adolescent self-report instrument and parent/caregiver proxy-report instrument
Health condition (related to ability to answer the questionnaire)	For infants and children/ adolescents with intellectual deficits, for children/adolescents with severe conditions who are not able to answer the questionnaire	Parent/caregiver proxy-report instrument
	Cognitive and physical ability of a child/ adolescent to answer the questionnaire	Child/adolescent self-report instrument and parent proxy-report instrument

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LIST OF ABBREVIATIONS

ACD	anemia of chronic disease
ALL	acute lymphocytic leukemia
AML	acute myeloid leukemia
BMT	bone marrow transplantation
BPCA	Best Pharmaceuticals for Children Act
CLL	chronic lymphocytic leukemia
CML	chronic myeloid leukemia
CNS	central nervous system
CT	chemotherapy
DVT	deep-vein thrombosis
ESA	erythropoiesis-stimulating agent
EWB	emotional well-being
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
FWB	functional well-being
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HL	Hodgkin's lymphoma
HSCT	hematopoietic stem cell transplantation
IBD	inherited bleeding disorder
ICIS	Intercontinental Childhood ITP Study Group
INR	International Normalized Ratio
IOM	Institute of Medicine
ITP	immune thrombocytopenia
IVIG	intravenous immunoglobulin
LMWH	low molecular weight heparins
MDS	myelodysplastic syndromes
MID	minimal important difference
MM	multiple myeloma
MOS	Medical Outcomes Study

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NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin's lymphoma
NNT	number needed to treat
NRS	numerical rating scale
OAC	oral anticoagulant
PBSC	peripheral blood stem cells
pRBC	packed red blood cell transfusion
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PT	prothrombin time
PWB	physical well-being
QoL	quality of life
RCT	randomized clinical trial
RIC	reduced intensity conditioning
SFWB	social/family well-being
UCB	umbilical cord blood
VAS	visual analogue scale
VWD	von Willebrand disease
VWD PN	von Willebrand Disease Prophylaxis Network
VWF	von Willebrand factor
WHO	World Health Organization

LIST OF QUESTIONNAIRES

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Multiple Myeloma Module (EORTC-QLQ-MY20)	Ch. 3.3
EuroQol-5D (EQ-5D)	Ch. 2
EuroQol-5D Youth version (EQ-5D-Y)	Ch. 2
Edmonton Symptom Assessment System (ESAS)	Ch. 2; Ch. 3.1
Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F)	Ch. 2; Ch. 3.4
Functional Assessment of Cancer Therapy - Anemia (FACT-An)	Ch. 2; Ch. 3.4
Functional Assessment of Cancer Therapy - Bone Marrow Transplantation (FACT-BMT)	Ch. 2; Ch. 4
Functional Assessment of Cancer Therapy - Biologic Response Modifiers (FACT-BRM)	Ch. 2; Ch. 3.1
Functional Assessment of Cancer Therapy - General (FACT-G)	Ch. 2; Ch. 3.1
Functional Assessment of Cancer Therapy/Gynecologic Oncology Group - Neurotoxicity (FACT/GOG-Ntx)	Ch. 5
Functional Assessment of Cancer Therapy - Leukemia (FACT-Leu)	Ch. 2; Ch. 3.1
Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)	Ch. 2; Ch. 3.2
Functional Living Index - Cancer (FLIC)	Ch. 2; Ch. 3.2
Fatigue Symptom Inventory (FSI)	Ch. 2; Ch. 4
Hospital Anxiety and Depression Scale (HAD)	Ch. 2
Haemophilia Quality of Life Questionnaire (QUAL HEMO)	Ch. 3.5.1
Haemophilia Quality of Life Questionnaire for Adults (Haemo-A-QoL)	Ch. 3.5.1
Haemo-QoL	Ch. 3.5.1
Haemo-QoL-A	Ch. 3.5.1
Hemolatin-QoL	Ch. 3.5.1
Health Utilities Index Marks 2 and 3 (HUI 2 and 3)	Ch. 2
Impact of Cancer Questionnaire (IOC)	Ch. 2; Ch. 5
ITP-Patient Administered Questionnaire (ITP-PAQ)	Ch. 3.5.3
Idiopathic Thrombocytopenic Purpura - Quality of Life Questionnaire (ITP-QoL)	Ch. 3.5.3
Infant Toddler Quality of Life Questionnaire (ITQOL)	Ch. 2

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KIDCLOT Pediatric Anticoagulation Quality of Life Inventory (KIDCLOT PAC QL©)	Ch. 6
KIDSCREEN	Ch. 2
Kids' ITP Tools (KIT)	Ch. 3.5.3
Lee Fatigue Scale (LFS)	Ch. 3.6
Life Ingredient Profile (LIP)	Ch. 3.1
M.D. Anderson Symptom Inventory (MDASI)	Ch. 2; Ch. 3.2
M.D. Anderson Symptom Inventory - Bone Marrow Transplantation (MDASI-BMT)	Ch. 4
Multidimensional Fatigue Inventory (MFI)	Ch. 2; Ch. 3.6
Menorrhagia Impact Questionnaire (MIQ)	Ch. 3.5.2
Minneapolis-Manchester Quality of Life Instrument - Adolescent Form (MMQL-Adolescent Form)	Ch. 7
Memorial Pain Assessment Card (MPAC)	Ch. 2; Ch. 3.3
McGill Pain Questionnaire (MPQ)	Ch. 2; Ch. 3.3
McGill Pain Questionnaire - Short Form (MPQ-SF)	Ch. 3.3
MRC/EORTC-QLQ-LEU	Ch. 3.1
Memorial Symptom Assessment Scale (MSAS)	Ch. 2; Ch. 3.1
Memorial Symptom Assessment Scale (MSAS) 7-12	Ch. 7
Memorial Symptom Assessment Scale (MSAS) 10-18	Ch. 7
Nottingham Health Profile (NHP)	Ch. 2
Oucher Scale (Oucher)	Ch. 7
Perception of Anticoagulant Treatment Questionnaire (PACT-Q)	Ch. 6
Pediatric Cancer Quality of Life Inventory-32 (PCQL-32)	Ch. 7
Psychological Distress Inventory (PDI)	Ch. 2
Pediatric Quality of Life Inventory™ (PedsQL™)	Ch. 2
Pediatric Quality of Life Inventory™ Multidimensional Fatigue Scale™ (PedsQL™ Multidimensional Fatigue Scale™)	Ch. 7
Pediatric Quality of Life Inventory™ Cancer Module (PedsQL™ Cancer Module)	Ch. 7
Piper Fatigue Scale (PFS)	Ch. 2; Ch. 3.6
Piper Fatigue Scale-Revised (PFS-R)	Ch. 3.6
Poker Chip Tool	Ch. 7
Profile of Mood States (POMS)	Ch. 2
Pediatric Oncology Quality of Life Scale (POQOLS)	Ch. 7
Pediatric Pain Coping Inventory (PPCI)™	Ch. 7

Pediatric Pain Profile (PPP)	Ch. 7
Patient-Reported Oral Mucositis Symptom Scale (PROMS)	Ch. 4
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QOL-E v.2	Ch. 3.4
Quality of Well-Being Scale (QWB)	Ch. 2
Revidierter KINDer Lebensqualitätsfragebogen (KINDL®)	Ch. 2.
Ruta Menorrhagia Severity Scale (RMSS)	Ch. 3.5.2
Rotterdam Symptom Checklist (RSCL)	Ch. 2; Ch. 5
Sawicki Instrument	Ch. 6
Schwartz Cancer Fatigue Scale (SCFS)	Ch. 2; Ch. 3.6
Symptom Checklist-90 - Revised® (SCL-90R)	Ch. 7
Stem Cell Transplantation - Symptom Assessment Scale (SCT-SAS)	Ch. 4
Short Form-36 Health Survey Questionnaire (SF-36)	Ch. 2
Symptom Frequency, Intensity, and Distress Questionnaire for SCT (SFID-SCT)	Ch. 4
Sexual Functioning Questionnaire (SFQ)	Ch. 4
Sickness Impact Profile (SIP)	Ch. 2
Satisfaction with Life Domains Scale - Bone Marrow Transplantation (SLDS-BMT)	Ch. 4
TNO AZL Children's Quality Of Life Questionnaire (TACQOL)	Ch. 2
VWD-QOL	Ch. 3.5.2
World Health Organization Quality of Life - 100 (WHOQOL-100).	Ch. 2









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