APPLICATION OF PERSONALIZED MEASURES IN THE CONTEXT OF CANCER REHABILITATION

Ala' Sami Aburub, B.Sc. (Physical Therapy), M.S.c. (Physical Therapy), M.S.c. (Rehabilitation Science)

School of Physical and Occupational Therapy

Faculty of Medicine

McGill University

Montreal, Quebec, Canada

April, 2016

A thesis submitted to the Faculty of Graduate Studies and Research

in partial fulfillment of the requirements of the degree of

Doctor of Philosophy (Rehabilitation Science)

Happiness does not come from doing easy work but from the afterglow of satisfaction that comes after the achievement of a difficult task that demanded our best." – ***Theodore Isaac Rub***

"All our dreams can come true… if we have the courage to pursue them." – **Walt Disney**

"Nothing stops the man who desires to achieve. Every obstacle is simply a course to develop his achievement muscle. It's a strengthening of his powers of accomplishment. " – ***Eric Butterworth***

Table of Contents

ABSTRACT

Quality of life (QOL) in people with cancer has become an important outcome for both clinical care and research as a way of summarizing across a wide range of physical and emotional sequelae that arise from the disease itself and from its treatment. Individualized measures are ideally suited for assessing the impact of cancer and its treatment, but how their unique information relates to information gathered by more standardized approaches is still lacking.

The Patient Generated Index (PGI) is one of two main individualized measures and is designed to identify personal QOL concerns and summarize their importance in a total score. The validity of the PGI with respect to standard QOL measures has not been fully established for advanced cancer when QOL concerns predominate. The global aim of this thesis is to contribute evidence towards the applicability of the PGI in the context of QOL in cancer.

The thesis comprises four manuscripts. The psychometric properties of individualized measures in the context of cancer was summarized systematically and reported in Manuscript 1. Individualized measures were shown to be feasible and acceptable among people with cancer. Their correlations with standardized measures were low to moderate but, as they provide the opportunity for people to nominate their own concerns, this was not surprising. Individualized measures were found to be sensitive to change. The review pointed out areas that needed further exploration and formed a foundation for the other studies in the thesis.

Three manuscripts reported on quantitative analyses made possible owing to an existing database arising from an observational study on an inception cohort of people with advanced cancer the aim of which was to investigate mechanisms and outcomes of anorexia-cachexia. A total of 192

patients completed five QOL measures at study entry (T1): PGI, generic measures (SF-6D, EQ-5D), and cancer-specific measures of QOL (McGill Quality of Life Questionnaire (MQOL) and Edmonton Symptoms Assessment (ESAS)) and one year later (T2).

Two studies conducted as part of this thesis provided evidence of validity by comparing PGI to the standard measures at the total score and at the item levels (Manuscripts 2 and 3). The results from Manuscript 2 showed that PGI allowed patients to express a wide range of QOL concerns, many that were not assessed by other QOL measures. Patients voiced 114 areas of QOL concerns by the PGI with the top three being fatigue, sleep, and pain. PGI total QOL score was 25 to 30 percentage points lower than those documented by the other measures. Correlations between PGI and other measures were low. The results from Manuscript 3 showed that within one severity rating, agreement ranged from 32.1% to 76.9% within the fatigue domain, 34.2% to 95.2% for pain, and between 84.2% and 94.7% for physical function. Of the 10 items where the PGI had the highest agreement, 7 came from the RAND-36. At the domain level, people nominating an area scored in the more impaired range on standard measures than people who did not. PGI gives comparable information as do standard measures.

A fourth study aimed to estimate the extent to which reconceptualization response shift occurred over time in cancer population and the impact of this response shift on estimated change in QOL (Manuscript 4). A total of 97 people completed the study measures at entry and one year later (T1 and T2) providing an opportunity to investigate the contribution of reconceptualization response shift to change in QOL measures. Four response shift indicators were operationalized: adding new areas, change in number of areas, ratio, and composite.

People with cancer do reconsider what is important to them as they experience health and treatment challenges. No one person had exactly the same profile of areas at the two time points. Some of this is simple measurement error and some is reconceptualization. Two different reconceptualization patterns predominated. Some people (~15%) dropped 2 or more areas that they originally nominated and, as the PGI score improved (on average), by doing this, areas of high impact were dropped indicating a shift away from negative aspects of life. Some people (~35%) added areas and, as the PGI score was lower (on average), these new areas were those that were newly problematic. The observation that the reconceptualization did not affect global rating of QOL suggests a recalibration to maintain as high a QOL as possible in the presence changing health. The high prevalence of reconceptualization found in this study underlines the importance of considering the evaluation of the response shift in studies that aim to evaluate QOL change over time.

ABRÉGÉ

La qualité de vie (QV) chez les personnes atteintes de cancer est devenue un important indicateur de résultat autant au niveau des soins cliniques qu'en recherche. Elle permet de résumer l'étendue des séquelles physiques et émotionnelles résultant de la maladie et de son traitement. Les mesures individualisées sont idéales pour évaluer l'impact du cancer et son traitement. Cependant, la manière dont leur information unique est liée à l'information obtenue par des approches plus standardisé est toujours inconnue.

L'index généré par le patient (Patient Generated Index, PGI) est l'une des deux principales mesures individualisée et est conçue pour identifier les préoccupations personnelles concernant la QV et résumer leur importance dans une note globale. La validité du PGI à l'égard des mesures standardisée de QV n'a pas été établie pour les gens atteint de cancer avancé pour qui les préoccupations de QV sont prédominantes. L'objectif global de cette thèse est de contribuer des preuves utiles envers l'applicabilité du PGI dans le contexte de la QV en cancer.

Cette thèse comprend quatre manuscrits. Les propriétés psychométriques des mesures individualisées dans le contexte du cancer ont été révisées systématiquement et rapportées dans le manuscrit 1. Il a été démontré que les mesures individualisées étaient faisable et acceptables pour les personnes atteintes de cancer. Leurs corrélations avec les mesures standardisées étaient faibles à modérés. Cependant, puisque celles-ci offrent l'opportunité de nommer leurs propres préoccupations, cela n'était pas surprenant. Les mesures individualisées se sont montrée sensible au changement. Cette revue systématique a identifié les domaines qui nécessiteront une exploration plus approfondie et a formé le fondement sur laquelle les autres études de cette thèse se basent.

Trois manuscrits rapportent des analyses quantitatives rendues possible grâce à une banque de données existante provenant d'une étude observationnelle de cohortes selon le mode d'installation avec des personnes atteintes de cancer avancé. Le but de cette étude était d'investiguer les mécanismes et les indicateurs de résultats de l'anorexie-cachexie. Au début de l'étude (T1) et un an plus tard (T2), 192 patients ont complété les cinq mesures de QV: PGI, mesures génériques (SF-6D, EQ-5D) et des mesures de QV spécifiques au cancer (McGill Quality of Life Questionnaire (MQOL) et le Edmonton Symptoms Assessment (ESAS))

Deux études réalisées pour cette thèse ont contribué des preuves de validité en comparant le PGI aux mesures standardisées, tant au niveau du score global qu'au niveau des items (manuscrits 2 et 3). Les résultats du manuscrit 2 ont démontré que le PGI permettait aux patients d'exprimer un large éventail de préoccupations en ce qui a trait à la QV, plusieurs n'étant pas évaluées par d'autres mesures de la QV. À travers le PGI, les patients ont nommé 114 domaines de leur QV les préoccupant. Les trois domaines nommés le plus souvent sont la fatigue, le sommeil et la douleur. La note globale du PGI était de 25% à 30% plus basse que celles des autres mesures. Les corrélations entre le PGI et les autres mesures étaient faibles. Les résultats du manuscrit 3 ont démontré que, à l'intérieur d'un point de sévérité, l'accord entre les items du PGI and des mesures génériques variait de 32.1% à 76.9% pour le domaine de la fatigue, de 34.2% à 95.2% pour la douleur, et de 84.2% à 94.7% pour la fonction physique. Des 10 domaines ayant l'accord le plus élevé avec le PGI, 7 proviennent du RAND-36. Les personnes ayant nommé un domaine attribuaient une valeur plus sévère sur les mesures standardisées de ce domaine que les personnes qui ne l'avaient nommé. Le PGI donne des informations similaires que les mesures standardisées.

Une quatrième étude visait à estimer à quel point le changement de la réponse par reconceptualisation se produit au fil du temps ainsi que l'impact de ce changement de la réponse sur le changement estimé de QV (Manuscrit 4). Au total, 97 personnes ont complété les évaluations et début et à la fin de l'étude un an plus tard (T1 et T2), offrant ainsi l'opportunité d'explorer la contribution de la reconceptualisation au changement dans la QV. Quatre indicateurs de changement de la réponse ont été identifiés : ajout de domaines, changement au nombre de domaines, changement au ratio et au composite.

Les gens atteints du cancer reconsidèrent ce qui est important pour eux lorsqu'ils rencontrent des problèmes de santé et des difficultés avec les traitements. Personne n'avait exactement le même profil aux deux temps d'évaluation. Une partie de cela est simplement dû à une erreur de mesure et un autre est dû à la reconceptualisation. Deux différents patrons de reconceptualisation ont prédominé. Quelques personnes (~15%) ont laissé tombé deux domaines ou plus qui étaient originalement nommés. Puisque la note globale du PGI s'est améliorée (en moyenne) en faisant ceci, des domaines à fort impact furent abandonnées indiquant un éloignement des aspects négatifs de la vie. D'autres personnes (~35%) ont ajouté des domaines. Puisque la note globale du PGI était plus basse (en moyenne) en faisant ceci, ces nouveaux domaines étaient ceux nouvellement problématiques. L'observation que la reconceptualisation n'affectait pas le score global de QV suggère que de la recalibration a eu lieu pour maintenir une QV aussi élevé que possible en présence de changement dans la santé. La prévalence élevée de reconceptualisation détectée dans cette étude démontre l'importance de considérer l'évaluation du changement de la réponse dans les études évaluant la QV au fil du temps.

PREFACE

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my supervisor, Dr. Nancy Mayo, for her guidance, patience, support, encouragement and leadership throughout my studies. I would also like to thank her for her comments and guidance on earlier drafts of the thesis and for being the ideal thesis supervisor.

This thesis would not have been possible without the guidance and help of my supervisor and several individuals who in one way or another contributed and extended their valuable assistance in the preparation and completion of this thesis. I would like to thank my colleagues at the Division of Clinical Epidemiology at McGill University (Carolina Moriello, Lois Finch, Lyne Nadeau and Susan Scott Marie-Eve Letellier, Vanessa Bouchard, Behtash Bakhshi, Alaa Arafah, Sabrina Figueiredo, Stanley Hum, Kedar Mate, Sorayya Askari, Owis Eilayyan, Fadi Al Zoubi). Special thanks to Dr. Nancy Mayo (my supervisor), Dr. Isabelle Gélinas, (Graduate Program Director) and Dr. Laurier Snider (Graduate Program Director) for the financial support provided during my PhD journey. My sincere thanks also goes to Dr. Eva Kehayia for introducing me to Dr. Nancy Mayo.

I also wish to express all my gratitude to my beloved family for their understanding and endless love. Special thanks to Nafisa Intwala for her support and kindness throughout my studies and for making my stay in Montreal, easier, pleasant and comfortable. Many thanks to my little brother Ahmed Abou Sharkh for guiding me on the process of getting my license in Ontario as a physiotherapist.

ORGANIZATION OF THE THESIS

McGill University Regulations for Manuscript-Based Theses

"As an alternative to the traditional thesis style, the research may be presented as a collection of papers of which the student is the author or co-author. These papers must have a cohesive, unitary character making them a report of a single program of research".

"The structure for the manuscript-based thesis must conform to the following":

- "These texts must conform to thesis guidelines with respect to font size, line spacing and margin sizes and must be bound together as an integral part of the thesis.
- The thesis must conform to all other requirements listed under Thesis Components above.
- The thesis must be more than a collection of manuscripts. All components must be integrated into a cohesive unit with a logical progression from one chapter to the next. The thesis must have connecting texts to provide logical bridges between the different chapters, thereby achieving an integration of information. These connecting sections are mandatory. Not including adequate connective texts could compromise the ability of the examiners to evaluate the thesis with subsequent consequences.
- Manuscripts for publication are frequently very concise documents. The thesis is expected to be a more detailed scholarly work than manuscripts for publication in journals. The thesis must include details of methodology, rationale for choice of approach, a detailed defense of conclusions, and explicit description of contribution to knowledge. Where appropriate, additional material including supplementary data must be provided (e.g., in connecting text or appendices) in sufficient detail to allow a clear and

precise judgment to be made of the importance and originality of the research reported in the thesis.

- In the case of multiple-authored articles, the student must be the primary author, although it is expected that co-authors may have had input in revisions. The thesis must include a statement explicitly outlining the contributions of the student and all co-authors. This statement must appear in a section entitled Contributions of Authors in the "Preface" of the thesis. The supervisor, by signing the thesis submission form, attests to the accuracy of these statements and will be asked to reaffirm at the oral defense in the case of a doctoral thesis ".

It is a great privilege that I present this thesis which will be in manuscript format. It consists of 10 chapters describing thoroughly the following points: a literature review, thesis objectives, thesis manuscripts, rationale and preface for each manuscript, and a summary and conclusion. This thesis has followed the guidelines in accordance to the Faculty of Graduate and Postdoctoral Studies at McGill University.

Chapter one is a review of the literature on cancer statistics, impact of cancer on physical and general health, Quality of Life (QOL) models, patient-centered care, personalized measure and the thesis rationale.

Chapter 2 presents the thesis objectives. The global aim of this thesis is to contribute evidence towards the applicability of the Personalized measures (Individualized measures) in particular the Patient Generated Index (PGI) in the context of QOL in cancer.

Chapter 3 consists of the first Manuscript. The specific objective of the study is to summarize the evidence on the psychometric properties of individualized measures in the context of cancer including information on feasibility and application.

Chapter 4 presents the rationale and preface to Manuscript 2. This chapter provides information about the rationale of the second manuscript and its links to the first manuscript

Chapter 5 presents the second Manuscript, entitled “Using a personalized measure (Patient Generated Index (PGI)) to identify what matters to people with cancer”. The specific objective of this study is to identify, for people with advanced cancer, similarities and differences in ratings of global QOL between personalized and standard measures. In this manuscript, PGI is compared to standard QOL measures at the total score level.

Chapter 6 presents the rationale and preface to Manuscript 3 and its links with the second manuscript.

Chapter 7 presents Manuscript 3 entitled "Agreement between personally generated areas of quality of life concern and standard outcome measures in people with advanced cancer". The study objective is to estimate, for people with advanced cancer, the extent to which areas of quality of life concern, spontaneously nominated and non nominated status of fatigue, pain and physical function through the use of a personalized measure (PGI), agree with ratings obtained from standard outcome measures. In this manuscript, PGI is compared to standard QOL measure at the item level.

Chapter 8 presents the rationale and preface to manuscript 4 and its links with the third manuscript. The topic of response shift is introduced here

Chapter 9 contains Manuscript 4. The aim of this study was to estimate the extent to which people with advanced cancer re-conceptualize QOL over time.

Chapter 10 is the last chapter of this thesis and presents a summary and overall Discussion of the findings as well as suggestions for future research.

Each section included in this thesis has its own reference section.

CO-AUTHORS' CONTRIBUTIONS

The data for this study comes from a study of anorexia/cachexia in people with advanced cancer, and the data collection included a comprehensive assessment of factors contributing to overall quality of life . This data source comes from a Terry Fox funded project "Towards an Understanding of the Anorexia Cachexia Syndrome – Linking Molecular Mechanisms with Novel Treatment Options" (PIs: Pelltier, Gagnon: Tremblay, Mayo among others). The data was used to answer the thesis questions. This thesis is presented in manuscript format and consists of four manuscripts, one manuscript already published at the Journal of Supported Care in Cancer, and a second paper has been revised and submitted to the same journal. The other two manuscripts will be submitted for publication in a peer-reviewed journal. The papers will be co-authored with Dr. Nancy Mayo, Dr. Bruno Gagnon and Dr. Ana Maria Rodríguez. The PGI review will be co-authored with Dr. Nancy Mayo. This thesis has followed the guidelines in accordance to the Faculty of Graduate and Postdoctoral Studies at McGill University.

All the steps were carried out by Ala' Aburub to complete this manuscript-based thesis. The first step was to conduct a literature review on the application and the psychometric properties of individualized measures in people with cancer. The second step was to formulate each manuscript question and prepare the introduction and the method sections for each. The third step was preparing the thesis protocol which was approved by my supervisor (Dr. Nancy Mayo) and my committee member (Dr. Sara Ahmed). The fourth step was to write the results and the discussion sections of each manuscript. The final step was to prepare the thesis content and putting all the pieces together to make this manuscript-based thesis.

With the guidance of my supervisor and also the statistician , Ms. Susan Scott , I was successfully able to analyze the results and write the thesis. I was responsible for the originality of the ideas, the scientific quality of the research, preparation of the manuscripts , and the overall text, tables and figures for this thesis. I received valuable direction and constructive comments from Dr. Nancy Mayo on the study design, analyses, interpretation , and the writing of all manuscripts and my thesis.

STATEMENT OF ORIGINALITY

I attest that the manuscripts and the contents presented in this thesis are the products of my own original work and reflect the knowledge, skills and abilities I have acquired during my PhD journey and that all the guidance and feedback received in preparing and completing this thesis have been recognized and acknowledged. I also declare that the materials in this thesis have not previously been submitted for a degree in any university nor published or written by another person except where due acknowledgement is made in the thesis itself.

This thesis presents work carried out to understand the application of personalized measures in the context of cancer rehabilitation. Cancer survivors will experience a wide range of physical and emotional sequelae from cancer and from its treatment which will negatively impact their well being and quality of life (QOL). As a result, QOL in people with cancer has become an important outcome for both clinical care and research.

QOL measures are of three types, full standardized, which can be generic or cancer-specific, and individualized. The Patient Generated Index (PGI) is one of two main individualized or personalized measures and it is designed to identify personal QOL concerns and summarize their importance in a total score.

This thesis present a series of studies to validate the PGI in the context of cancer as its validity with respect to standard QOL measures has not been fully established for advanced cancer when QOL concerns predominate. I had access to a data set on a population of people with advanced cancer which included the PGI. This outcome had not been investigated in this data set and hence I undertook to prepare the data from the PGI for analyses. After conducting a systematic

review of the psychometric properties of individualized measures, I identified several gaps and set about to use the current data to address these gaps. In particular, I compared the total score on the PGI to scores from other quality of life measures available on the data set. Although, I had a model for this work from previous research carried out by the team of Dr. Nancy Mayo (in a sample of people with Multiple Sclerosis), I had access to different types of measures and so conducted original work as well as replicating previous findings from a different population.

I conducted original research validating the PGI at the item level. To my knowledge this has not been done in any population.

Finally, I investigated the phenomenon of response shift using the PGI which is ideal for this purpose. I developed four response shift indicators and investigated each one systematically in this data set. The approach could serve as a model for this type of work in other populations.

AUTHORIZATION

I, hereby, authorize McGill University to provide copies of my thesis to libraries, institutions and other entities requesting a copy. Moreover, I authorize McGill University to duplicate or reproduce this thesis by photocopying or other means, in total or in part, at the request of other institutions or individuals for the purpose of scholarly research.

DEDICATION

This thesis is dedicated to my father, mother, sisters and brothers for their endless support and by instilling the importance of hard work and higher education. To my parents, who molded and solidified my values, drive, and sense of accomplishment. To my parents for always being there for me.

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1: REVIEW OF LITERATURE

1.1 Cancer Statistics

The Canadian population is aging and the risk of cancer and the number of people who will be diagnosed with cancer is expected to increase dramatically [1]. Studies have shown that the number of people diagnosed with cancer has doubled in the last three decades such that, in 2013, 187,600 Canadians were newly diagnosed [2]. By 2035, an estimated, 24 million individuals will receive a cancer diagnosis.[3] In Canada, cancer is the chronic disease with the highest mortality and now one-third of all deaths are due to cancer [2].

Despite the increase in the number of people diagnosed with cancer, the mortality rate has decreased over the past decades for both men and women due to technological advances permitting early diagnosis and offering better treatment options [4, 5]. Thus, the number of people living with the sequelae of cancer is increasing; over 63% of people diagnosed with cancer today will stay be alive in 5 years [2].

1.2. Impact of Cancer on Physical Function and General Health

Cancer survivors face a wide range of physiological, psychological and functional effects from the disease itself and from its treatment including fatigue, pain, sexual dysfunction, cognitive impairment, emotional distress, depression, distress, and anxiety all of which impact negatively on quality of life (QOL) [6-12]. As far back as the 1970s, the impact of cancer on physical function has been noted. In 1978, Lehman et al showed that, in a sample of 805 patients with cancer, more than 1/3 had weakness and fatigue leading to limitations in mobility and self care

[9]. A study conducted by Elliot and colleagues in 2011, showed that cancer survivors with these functional sequelae reported poorer health than those without [13]. Data arising from NHANES, indicates that more than half of cancer survivors have one or more difficulties in physical performance [14].

1.3 Quality of Life (QOL) in Cancer Patients

Rehabilitation is offered to help cancer survivors regain maximal function and health by reducing cancer related impairments and enhancing capacity for physical activity, with the ultimate aim of improving adaptation to the environment, participation in the social and community activities, and OQL [15].

In 1984, the World Health Organization (WHO) defines health as "not merely the absence of disease, but complete physical, psychological, and social well-being" [16]. In 1982, Flanagan identified 15 components of QOL including : Physical and material well-being; Relations with other people; Social; community; and civic activity; Personal development and fulfillment; and Recreation [17]. Most of these components are outside of the capacity of the health care system to manage leading to the concept of health-related QOL (HRQL) [18].

QOL is a unique construct that can only be considered from the person's own perspective and not from the perspective of an observer, a spouse, family member, or health professional. Many definitions of QOL have been proposed as there is a wide variety of individual experiences contributing to QOL [18-20].

QOL has been defined as "The adequacy of people's material circumstances and their feelings about these circumstances" [21], as well as "the ability to enjoy normal life activities" [22]. The

World Health Organization defined quality of life as “the individuals’ perceptions of their position in life, in the context of the cultural and value systems in which they live and in relation to their goals, expectations, standards and concerns” [23]. Using this definition, when there is a gap between patient’s goals, expectations and achievements, QOL is affected.[24].

A cancer diagnosis will alter a person’s goals and expectations and, over time, each individual will develop different coping mechanisms. As a result, QOL will not only differ from one individual to another, it will also differ over time for each individual. In the context of cancer, accurately identifying QOL is important as it will influence treatment options, however, its accurate measurement remains a challenge.

1.4 Quality of life Models

Two frameworks that are linked to QOL predominate in the context of rehabilitation, the World Health Organization’s (WHO) International Classification of Functioning, Disability and Health (ICF) [15] and the Wilson and Cleary model of Health-Related Quality of life (HRQL) [25].

a. International Classification of Functioning, Disability and Health (ICF)

The ICF is a classification system used to describe health and health status from personal, biological, social perspectives [15]. ICF model has been used across a wide spectrum of diseases such as Multiple Sclerosis [26], Stroke [27, 28], Osteoarthritis [29], Rheumatoid Arthritis [30, 31], and Cancer (Breast cancer [32]; and Head and Neck Cancer [33]). ICF encompasses both function (positive component) and disability (negative component). Function is an umbrella term for all the positive components of body functions and structure, activities and participation; disability is an umbrella term for all the negative components, impairments body functions and

structure, activity limitations and participation restrictions [34]. Both are influenced by environmental and personal factors (Figure 1).

Body structures are defined as the anatomical parts of the body such as muscle and limbs. Body functions refer to the physiological functions of body systems such as muscle strength and mobility of joint function. Defects in body structures and/or body functions are referred to as impairments. Both body structure and function are directly impacting the activity. Activity is the ability of a person to perform a specific task, while difficulty of performing a task is known as activity limitations. Activity directly influences participation which is defined as the ability of a person to be involved in a life situation such as carrying out household tasks, while participation restriction is the inability of a person to be involved in a life situation [15]. All ICF components are associated bi-directionally with each other and they, in turn, influence an individual's perception of his/her QOL.

b. Wilson and Cleary Model of Health-Related Quality of Life (HRQOL)

The Wilson and Cleary model was developed to explain the causal relationships among constructs contributing to HRQOL [25]. This model includes 5 components, 4 of which form the construct of HRQOL (biological and physiological variables, symptom status, functional status, and general health perceptions); the fifth component is overall quality of life which is influenced by HRQOL. This model also includes the influences of personal and environmental characteristics on HRQOL components and on QOL.

The biological and physiological component is defined as any functional changes that may occur at the level of cells, organs and systems. Symptoms are defined as a patient's perception of an

abnormal physical, emotional, or cognitive state. Functional status is defined as the ability of a person to perform specific tasks. Many studies have shown that biological and physiological components, symptoms, and function are correlated [35-38], however, variation in function cannot be explained only by variation in the other components.

The first three components of Wilson and Cleary model (biological and physiological components; symptoms status; and function status) correspond to the ICF domains of impairment, activity limitations and participation restrictions [39]. The last two components of this model general health perception and overall QOL. These two components are not covered by ICF.

1.5 Patient-Centered Care and Personalized Measures

The suggested hypothesis for measuring QOL is to narrow the gap between patient expectations and reality [24]. Patient-centered care is one of the health models that has been proposed to narrow this gap. The main concept behind using a patient-centered care model is to enhance the role of the patients in decision making and to improve the communication between patients and health care providers [40-42].

Patient-centered care occurs when the focus is on outcomes that are important to patients [40-42]. These outcomes are survival, symptoms, function, and health related quality of life (HRQOL) [43]. In a typical clinical encounter, these important outcomes are often not asked, and even less so written down making it difficult to use this important information to guide care [44]

The literature often uses the terms QOL and HRQOL synonymously despite considerable conceptual and measurement differences [45]. In this literature review, the terms will be used to

match how they were used in context. In clinical practice, HRQOL measures are most relevant and incorporating these measures into clinical practice is an effective way of identifying what matters to patients [46, 47]. HRQOL measures are of three types*:* generic, disease-specific and personalized measures.

Some of the best known generic HRQOL measures are the EQ-5D [48, 49], SF-36 [50, 51], and the Health Utilities Index (HUI) [52-54], all of which have been used in cancer populations [48, 51, 55-59]. The most widely used cancer-specific HRQOL measures are the Functional Assessment of Chronic Illness Therapy (FACIT) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) [60-62].

True QOL measures are few. Two of the best known are the Quality of Well-being Scale (QWB) and the WHOQOL measure [63-67].

The QWB scale was one of the first measures developed (circa 1970) to summarize a person's current symptoms and disability into a single index representing the "social undesirability" of the problem and express this in terms of quality-adjusted life year (QALY). For disability, performance (does do), rather than capacity (can do), is rated on three dimensions is assessed: mobility, physical activity and social activity. These dimensions have levels yielding 3*3*5 combinations plus death for 46 levels of function. In addition, 26 levels for symptoms and problem are described. Each level of function and level of symptom complex is associated with a specific preference weight. QALY is derived by subtracting from unity, the weight for each level of the dimensions.

QWB is a valid measure and it has been used in a variety of populations including cancer [64-66, 68-74]. QWB is difficult to use in a clinical setting as it is very long to complete. [75]. In addition, it is lacking a dimension for mental health [67], However, it served as a model for the development of other measures and hence broke new ground as far as quantifying well-being [76].

The World Health Organization's WHOQOL group developed the WHOQOL-100 [63] (circa 1998) to assess QOL but the length of the questionnaire makes it impractical for most uses. A shorter measure, WHOQOL-Bref, was derived from the longer and comprises 26 items, two single indicators of general health and global QOL and 24 items covering four domains (physical health, psychological, social relationships and environmental).

The WHOQOL was based on the WHO's definition of QOL: "not merely the absence of disease, but complete physical, psychological, and social well-being" but the definition does not provide a framework for operationalizing a measure of QOL. Flanagan in 1982 identified 15 components of QOL including: material comforts, health and personal safety, relationships, learning, creative expression, opportunity to help and encourage others, participation in public affairs, socializing, and leisure [17]. WHOQOL-Bref includes few from Flanagan's list.

Mayo et al. identified that the content of the WHOQOL-Bref was closely related to domains of function as defined by the WHO's International Classification of Functioning, Disability and Health (ICF) [77]. The content represented body-function and activity/participation (7 items), satisfaction with function (5 items), important environmental factors (5 items), satisfaction with environmental factors (4 items), with 4 items outside of function reflecting perception health, QOL, and self worth[77]. As few items went beyond functioning, the WHOQOL-Bref would not

be responsive to interventions if function was not targeted as the environment and aspects of satisfaction are not easily amenable to change. .

Personalized measures have been less frequently used in cancer but provide a valid alternative for tapping QOL, in addition to generic of cancer-specific HRQOL measures. The two main personalized or individualized measures are the Schedule for the Evaluation of Individual Quality of Life (SEIQOL) and the Patient Generated Index (PGI) [78-82]. As this thesis focuses on the PGI, this measure will be described in detail.

PGI is completed in three steps: (1) identify the five most important areas of their life affected by cancer and a sixth area for all other aspects of life making the PGI closer to a QOL measure; (2 rate how much each area has been affected using a scale from 0-10, where 0 is the worst imaginable and 10 exactly as they would like it to be and how much; (3) distribute an imaginary 12 spending tokens to improve on the selected areas and allocate these tokens to the areas according to their own priority. A global index is calculated by multiplying the ratings for each area in step 2 by the proportion of tokens given to that area in step 3, which are then summed to produce an index from 0 to 100 with higher scores indicating higher QOL. According to Ruta (1994) [82], the final score indicates the extent to which the reality falls short of patient's hopes and expectations for those areas of life for which they would most value an improvement [24, 82].

Similar to a typical clinical profile of health status requiring multiple tests of organ and system function, the assessment of patient centered outcomes involves the administration of multiple measures, the results from which would need to be stored, interpreted, and then re-interpreted over time. Clinicians take a systematic approach to assessing clinical health status, but rarely are

systematic in obtaining information on the different aspects of symptoms, functions and HRQOL that matter to patients [44].

1.6 The Rationale:

The measurement framework of individualized measures would be ideal in the context of cancer care as this technology ascertains patient's values and, with a clear portrait of values, it will be easier to match care. The literature indicates that multi-item questionnaires [83-85] correlate only moderately with individualized measures indicating that standardized measures may not capture what is important to individuals. However, as these standardized measures have items that have been tested for validity and reliability, cross-walking endorsed areas from the PGI to standardized items would reinforce the validity of the PGI as both a clinical and research technology to ascertain what matters to patients.

PGI has been widely used for assessing QOL in different patient populations such as people with systemic sclerosis [86], total knee arthroplasty [87] and urinary incontinence [88]. To date, PGI has not been widely used in people with cancer, only four studies involving people with cancer, with no reported studies of use in people with advanced cancer [80, 89-91] (Table1).

PGI has evidence for validity at the level of the total score, sufficient reliability for group comparisons, but limited evidence as yet for responsiveness [92-94]. No study has yet validated the PGI at the item level in any health condition and at the total score level in people with advanced cancer. Additionally, PGI is simple to use, has low response burden response, and provides a format for facilitating communication between patients, family and health care providers and for guiding intervention to focus on patients' priorities. However, there is a need

for further research on the validity of the PGI in people with advanced cancer to support this as a method to inform personalized cancer care including personalized cancer rehabilitation.

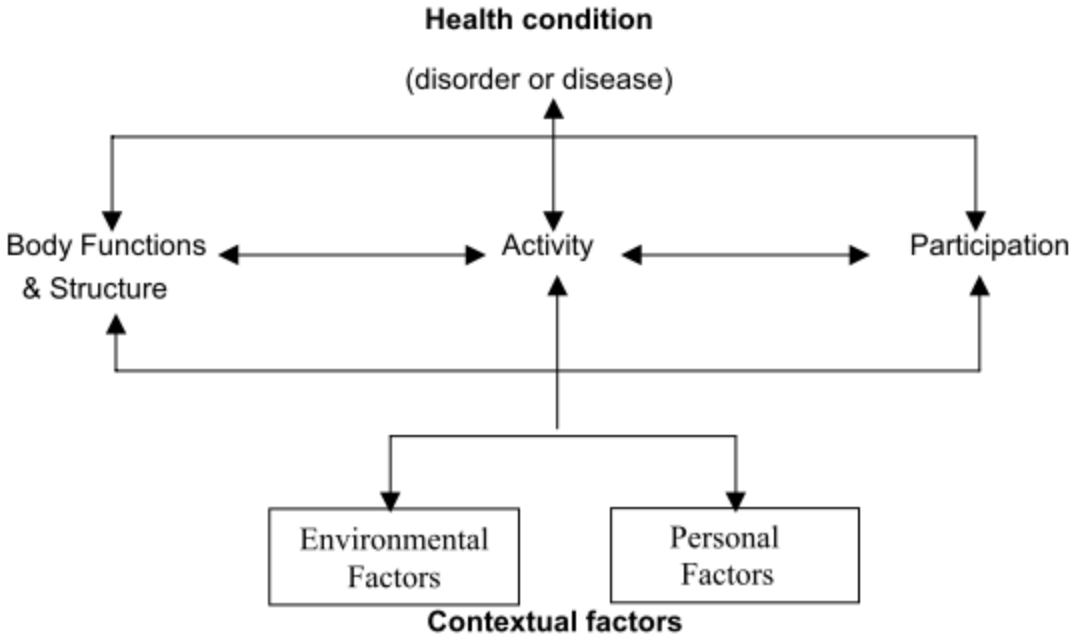


Figure1: "ICF Model (WHO, Geneva 2002)" [34]

Table 1: Studies have used PGI in people with cancer

Study	Sample Size	Type of Cancer	Procedure	Results
Camilleri-Brennan, Ruta et al. 2002	33 (25 male, 8 female)	Rectal Cancer	Validate PGI with SF3-36, Quality-of-Life Questionnaire–Core (LQ-C30), and QLQ-CR-38. Patients completed all instruments before and after surgery.	Postoperative, participants nominated on average 3.2 areas with median of 3 compared to 3.6 areas with median of 4 three months postoperative. PGI has moderate correlation at the global level with both QLQ-C30 and SF-36 (range r=0.53-0.59)
Lewis, Bridge et al. 2002	59	Palliative Care	Validate PGI with McGill Quality of Life Questionnaire. Psychometric analyses were not included.	This study supports the construct validity of PGI
Llewellyn, McGurk et al. 2006	55 (36 male,19 female)	Head and Neck Cancer	Validate PGI with the SF-12 version 2 and EORTC QLQ-C30 QQ-C30	PGI has moderate correlation (r=0.46) with EORTC QLQ-C30 QQ-C30 at the global level and moderate correlation with SF-12 mental (r=0.42) domain and emotional (r=0.48)
Tavernier, Beck et al. 2011	65(17male, 35 female)	Mixed (25 Breast , 6 Lung, 4 Non-Hodgkin lymphoma, 4 Colorectal, 2 Prostate, 2 Head and neck and 9 Others)	Validate PGI with Distress Thermometer (DT) and QLQ-C30 before (T1) and after (T2) radiation, 2 days after T2 (T3) and within 2 days of to past day of radiation (T4)	Patients made on average three changes in the areas nominated in the first step of the PGI between the following time points (pre-treatment to third week, third week to end of treatment, and pretreatment to end of treatment). PGI has low to moderate correlation with global health, fatigue and pain from QOL QLQ-C30

References

1. Canadian Cancer Society, *Canadian Cancer Statistics . http://www.cancer.ca/en/cancer-information/cancer-101/cancer-statistics-at-a-glance/?region=sk; http://www.phac-aspc.gc.ca/cd-mc/cancer/ccs-scc-2012-eng.php.* 2012
2. Statistics Canada, *Canadian Cancer Registry, http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=3207&lang=en&db=imdb&adm=8&dis=2 (2013).* 2013.
3. International, W.C.R.F. *Cancer Worldwide data*. [cited 2015 5/3]; Available from: http://www.wcrf.org/int/cancer-facts-figures/worldwide-data.
4. de Boer, A.G., et al., *Work ability and return-to-work in cancer patients.* Br J Cancer, 2008. **98**(8): p. 1342-7.
5. Hoffman, B., *Cancer survivors at work: a generation of progress.* CA Cancer J Clin, 2005. **55**(5): p. 271-80.
6. Corner, J., *Addressing the needs of cancer survivors: issues and challenges.* Expert Rev Pharmacoecon Outcomes Res, 2008. **8**(5): p. 443-51.
7. Gerber, L.H., *Cancer rehabilitation into the future.* Cancer, 2001. **92**(4 Suppl): p. 975-9.
8. Gotay, C.C., *Assessing cancer-related quality of life across a spectrum of applications.* J Natl Cancer Inst Monogr, 2004(33): p. 126-33.
9. Lehmann, J.F., et al., *Cancer rehabilitation: assessment of need, development, and evaluation of a model of care.* Arch Phys Med Rehabil, 1978. **59**(9): p. 410-9.
10. Paul, K. and R. Buschbacher, *Cancer rehabilitation: increasing awareness and removing barriers.* Am J Phys Med Rehabil, 2011. **90**(5 Suppl 1): p. S1-4.

11. Richardson, A., et al., *Knowledge, ignorance and priorities for research in key areas of cancer survivorship: findings from a scoping review.* Br J Cancer, 2011. **105 Suppl 1**: p. S82-94.

12. Silver, J.K. and L.S. Gilchrist, *Cancer rehabilitation with a focus on evidence-based outpatient physical and occupational therapy interventions.* Am J Phys Med Rehabil, 2011. **90**(5 Suppl 1): p. S5-15.

13. Elliott, J., et al., *The health and well-being of cancer survivors in the UK: findings from a population-based survey.* Br J Cancer, 2011. **105 Suppl 1**: p. S11-20.

14. Ness, K.K., et al., *Physical performance limitations and participation restrictions among cancer survivors: a population-based study.* Ann Epidemiol, 2006. **16**(3): p. 197-205.

15. World Health Organization, *International Classification of Functioning, Disability and Health: ICF,.* Geneva, Switzerland: World Health Organization;, 2001.

16. World Health Organization, *Constitution of the World Health Organization.* Geneva; Report No.: Basic Documents, 1948.

17. Flanagan, J.C., *Measurement of quality of life: current state of the art.* Arch Phys Med Rehabil, 1982. **63**(2): p. 56-9.

18. Ware, J.E., Jr., *Standards for validating health measures: definition and content.* J Chronic Dis, 1987. **40**(6): p. 473-80.

19. Gill, T.M. and A.R. Feinstein, *A critical appraisal of the quality of quality-of-life measurements.* JAMA, 1994. **272**(8): p. 619-26.

20. Wood-Dauphinee, S., *Assessing quality of life in clinical research: from where have we come and where are we going?* J Clin Epidemiol, 1999. **52**(4): p. 355-63.

21. McDowell I , N.C., *Measuring Health: A guide to Rating Scales and Questionnaires.* . 2nd ed. Oxford: Oxford University Press, 1996.

22. Ferrans, C.E., *Quality of life: conceptual issues.* Semin Oncol Nurs, 1990. **6**(4): p. 248-54.

23. World Health Organization, *Programme on Mental Health:.* WHOQOL User Manual. Geneva., 1998.

24. Calman, K.C., *Quality of life in cancer patients--an hypothesis.* J Med Ethics, 1984. **10**(3): p. 124-7.

25. Wilson, I.B. and P.D. Cleary, *Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes.* JAMA, 1995. **273**(1): p. 59-65.

26. Kesselring, J., et al., *Developing the ICF Core Sets for multiple sclerosis to specify functioning.* Mult Scler, 2008. **14**(2): p. 252-4.

27. Geyh, S., et al., *ICF Core Sets for stroke.* J Rehabil Med, 2004(44 Suppl): p. 135-41.

28. Starrost, K., et al., *Interrater reliability of the extended ICF core set for stroke applied by physical therapists.* Phys Ther, 2008. **88**(7): p. 841-51.

29. Dreinhofer, K., et al., *ICF Core Sets for osteoarthritis.* J Rehabil Med, 2004(44 Suppl): p. 75-80.

30. Kirchberger, I., et al., *Validation of the comprehensive international classification of functioning, disability and health core set for rheumatoid arthritis: the perspective of physical therapists.* Phys Ther, 2007. **87**(4): p. 368-84.

31. Uhlig, T., et al., *Reliability of the ICF Core Set for rheumatoid arthritis.* Ann Rheum Dis, 2007. **66**(8): p. 1078-84.

32. Brach, M., et al., *ICF Core Sets for breast cancer.* J Rehabil Med, 2004(44 Suppl): p. 121-7.

33. Tschiesner, U., et al., *Developing core sets for patients with head and neck cancer based on the International Classification of Functioning, Disability and Health (ICF).* Eur Arch Otorhinolaryngol, 2007. **264**(10): p. 1215-22.

34. World Health Organization, *Towards a Common Language for Functioning, Disability and Health ICF.* Geneva, Switzerland., 2002.

35. Cleary, P.D., et al., *Health-related quality of life in persons with acquired immune deficiency syndrome.* Med Care, 1993. **31**(7): p. 569-80.

36. Laupacis, A., C. Wong, and D. Churchill, *The use of generic and specific quality-of-life measures in hemodialysis patients treated with erythropoietin. The Canadian Erythropoietin Study Group.* Control Clin Trials, 1991. **12**(4 Suppl): p. 168S-179S.

37. Meenan, R.F., et al., *Outcome assessment in clinical trials. Evidence for the sensitivity of a health status measure.* Arthritis Rheum, 1984. **27**(12): p. 1344-52.

38. Wachtel, T., et al., *Quality of life in persons with human immunodeficiency virus infection: measurement by the Medical Outcomes Study instrument.* Ann Intern Med, 1992. **116**(2): p. 129-37.

39. Valderas, J.M. and J. Alonso, *Patient reported outcome measures: a model-based classification system for research and clinical practice.* Qual Life Res, 2008. **17**(9): p. 1125-35.

40. Beck, R.S., R. Daughtridge, and P.D. Sloane, *Physician-patient communication in the primary care office: a systematic review.* J Am Board Fam Pract, 2002. **15**(1): p. 25-38.

41. Stewart, M., et al., *The impact of patient-centered care on outcomes.* J Fam Pract, 2000. **49**(9): p. 796-804.

42. Anderson, E.B., *Patient-centeredness: a new approach.* Nephrol News Issues, 2002. **16**(12): p. 80-2.

43. PCORI. *Patient-Centered Outcomes Research Institute*. 2015 [cited 11.2015; Available from: http://www.pcori.org/.

44. Rosenzveig, A., et al., *Toward patient-centered care: a systematic review of how to ask questions that matter to patients.* Medicine (Baltimore), 2014. **93**(22): p. e120.

45. Mayo, N.E., *ISOQOL Dictionary of Quality of Life and Health Outcomes Measurement. First Edition.* 2016.

46. Brundage, M.D., et al., *Communicating patient-reported outcome scores using graphic formats: results from a mixed-methods evaluation.* Qual Life Res, 2015. **24**(10): p. 2457-72.

47. Black, N., et al., *Patient-reported outcomes: pathways to better health, better services, and better societies.* 2015.

48. *EuroQol--a new facility for the measurement of health-related quality of life.* Health Policy, 1990. **16**(3): p. 199-208.

49. Gudex, C., et al., *Health state valuations from the general public using the visual analogue scale.* Qual Life Res, 1996. **5**(6): p. 521-31.

50. Brazier, J., et al., *Deriving a preference-based single index from the UK SF-36 Health Survey.* J Clin Epidemiol, 1998. **51**(11): p. 1115-28.

51. Ware, J.E., Jr., *SF-36 health survey update.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3130-9.

52. Feeny, D., et al., *Multiattribute and single-attribute utility functions for the health utilities index mark 3 system.* Med Care, 2002. **40**(2): p. 113-28.

53. Horsman, J., et al., *The Health Utilities Index (HUI): concepts, measurement properties and applications.* Health Qual Life Outcomes, 2003. **1**: p. 54.

54. Torrance, G.W., et al., *Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2.* Med Care, 1996. **34**(7): p. 702-22.

55. Noel, C.W., et al., *Comparison of Health State Utility Measures in Patients With Head and Neck Cancer.* JAMA Otolaryngol Head Neck Surg, 2015. **141**(8): p. 696-703.

56. Boele, F.W., et al., *Health-related quality of life in stable, long-term survivors of low-grade glioma.* J Clin Oncol, 2015. **33**(9): p. 1023-9.

57. Boyle, F.M., et al., *Health related quality of life of women in TEACH, a randomised placebo controlled adjuvant trial of lapatinib in early stage Human Epidermal Growth Factor Receptor (HER2) overexpressing breast cancer.* Eur J Cancer, 2015. **51**(6): p. 685-96.

58. Ander, M., et al., *Development of health-related quality of life and symptoms of anxiety and depression among persons diagnosed with cancer during adolescence: a 10-year follow-up study.* Psychooncology, 2015.

59. Aaronson, N.K., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst, 1993. **85**(5): p. 365-76.

60. Rodrigues, A.R., et al., *Fatigue in Patients With Advanced Terminal Cancer Correlates With Inflammation, Poor Quality of Life and Sleep, and Anxiety/Depression.* Am J Hosp Palliat Care, 2015.

61. Denkinger, M.D., et al., *Predicting fatigue in older breast cancer patients receiving radiotherapy. A head-to-head comparison of established assessments.* Z Gerontol Geriatr, 2015. **48**(2): p. 128-34.

62. Cella DF, B.A., Leslie WT, Von Roenn J, Tchekmedyian NS., *Quality of life and nutritional well-being: Measurement and relationship. .* Oncol Suppl 1993. **7**: p. 105-111.

63. *Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group.* Psychol Med, 1998. **28**(3): p. 551-8.

64. Orenstein, D.M., et al., *The quality of well-being in cystic fibrosis.* Chest, 1989. **95**(2): p. 344-7.

65. Kaplan, R.M., et al., *Validity of the Quality of Well-Being Scale for persons with human immunodeficiency virus infection. HNRC Group. HIV Neurobehavioral Research Center.* Psychosom Med, 1995. **57**(2): p. 138-47.

66. Kaplan, R.M., et al., *The Quality of Well-being Scale. Applications in AIDS, cystic fibrosis, and arthritis.* Med Care, 1989. **27**(3 Suppl): p. S27-43.

67. Anderson, G.M., *A comment on the Index of Well-Being.* Med Care, 1982. **20**(5): p. 513-5.

68. Groessl, E.J., R.M. Kaplan, and T.A. Cronan, *Quality of well-being in older people with osteoarthritis.* Arthritis Rheum, 2003. **49**(1): p. 23-8.

69. Kaplan, R.M., S.M. Schmidt, and T.A. Cronan, *Quality of well being in patients with fibromyalgia.* J Rheumatol, 2000. **27**(3): p. 785-9.

70. Kaplan, R.M., *Quality of life assessment for cost/utility studies in cancer.* Cancer Treat Rev, 1993. **19 Suppl A**: p. 85-96.

71. Hughes, T.E., et al., *Construct validities of the Quality of Well-Being Scale and the MOS-HIV-34 Health Survey for HIV-infected patients.* Med Decis Making, 1997. **17**(4): p. 439-46.

72. Anderson, J.P., et al., *Interday reliability of function assessment for a health status measure. The Quality of Well-Being scale.* Med Care, 1989. **27**(11): p. 1076-83.

73. Kaplan, R.M., C.J. Atkins, and R. Timms, *Validity of a quality of well-being scale as an outcome measure in chronic obstructive pulmonary disease.* J Chronic Dis, 1984. **37**(2): p. 85-95.

74. Ganiats, T.G., D.K. Browner, and H.C. Dittrich, *Comparison of Quality of Well-Being scale and NYHA functional status classification in patients with atrial fibrillation. New York Heart Association.* Am Heart J, 1998. **135**(5 Pt 1): p. 819-24.

75. Kaplan, R.M., et al., *The Quality of Well-Being Scale: critical similarities and differences with SF-36.* Int J Qual Health Care, 1998. **10**(6): p. 509-20.

76. Newell, I.M.a.C., *Measuring Health: Guide to Rating Scales and Questionnaires. A Guide to Rating Scales and Questionnaires.* 1987.

77. Mayo, N.E., et al., *The extent to which common health-related quality of life indices capture constructs beyond symptoms and function.* Qual Life Res, 2011. **20**(5): p. 621-7.

78. Becker, G., et al., *Measuring individual quality of life in patients receiving radiation therapy: the SEIQoL-Questionnaire.* Qual Life Res, 2014. **23**(7): p. 2025-30.

79. Lindblad, A.K., et al., *Focus on the individual--quality of life assessments in oncology.* Acta Oncol, 2002. **41**(6): p. 507-16.

80. Tavernier, S.S., et al., *Validity of the Patient Generated Index as a quality-of-life measure in radiation oncology.* Oncol Nurs Forum, 2011. **38**(3): p. 319-29.

81. McGee, H.M., et al., *Assessing the quality of life of the individual: the SEIQoL with a healthy and a gastroenterology unit population.* Psychol Med, 1991. **21**(3): p. 749-59.

82. Ruta, D.A., et al., *A new approach to the measurement of quality of life. The Patient-Generated Index.* Med Care, 1994. **32**(11): p. 1109-26.

83. Frick, E., M. Tyroller, and M. Panzer, *Anxiety, depression and quality of life of cancer patients undergoing radiation therapy: a cross-sectional study in a community hospital outpatient centre.* Eur J Cancer Care (Engl), 2007. **16**(2): p. 130-6.

84. Montgomery, C., et al., *Individual quality of life in patients with leukaemia and lymphoma.* Psychooncology, 2002. **11**(3): p. 239-43.

85. Waldron, D., et al., *Quality-of-life measurement in advanced cancer: assessing the individual.* J Clin Oncol, 1999. **17**(11): p. 3603-11.

86. De Achaval, S., et al., *HRQoL domain coverage of the patient generated index in patients with systemic sclerosis: An application of the PROMIS framework.* Arthritis and Rheumatism, 2009. **60**: p. 80.

87. Lopez-Olivo, M.A., et al., *Using the Patient Generated Index (PGI) to measure personalized quality of life (QoL) in patients undergoing total knee arthroplasty (TKA).* Arthritis and Rheumatism, 2010. **62**: p. 178.

88. Ternent, L., et al., *Measuring outcomes of importance to women with stress urinary incontinence.* BJOG, 2009. **116**(5): p. 719-25.

89. Camilleri-Brennan, J., D.A. Ruta, and R.J. Steele, *Patient generated index: new instrument for measuring quality of life in patients with rectal cancer.* World J Surg, 2002. **26**(11): p. 1354-9.

90. Lewis, S., et al., *Quality of life issues identified by palliative care clients using two tools.* Contemp Nurse, 2002. **12**(1): p. 31-41.

91. Llewellyn, C.D., M. McGurk, and J. Weinman, *Head and neck cancer: to what extent can psychological factors explain differences between health-related quality of life and individual quality of life?* Br J Oral Maxillofac Surg, 2006. **44**(5): p. 351-7.

92. Choopan, P.S.W.W.-W.K., *Usefulness of Patient-Generated Index for HIV to Measure Individual Quality of Life: A Study from Thailand.* Value in Health Regional 2014. **3**(null): p. 101-107.

93. Martin, F., et al., *Twelve years' experience with the Patient Generated Index (PGI) of quality of life: a graded structured review.* Qual Life Res, 2007. **16**(4): p. 705-15.

94. Ruta, D.A., A.M. Garratt, and I.T. Russell, *Patient centred assessment of quality of life for patients with four common conditions.* Qual Health Care, 1999. **8**(1): p. 22-9.

CHAPTER 2: THESIS OBJECTIVES

The global aim of this thesis is to contribute evidence towards the applicability of the Patient Generated Index in the context of measuring quality of life in cancer. The specific objectives are to:

1) To summarize the evidence on the psychometric properties of individualized measures in the context of cancer including information on feasibility and application.

2) To estimate extent to which information gathered using the PGI is concordant with information gathered from a battery of standardized measures of cancer quality of life, cross sectionally and over time.

3) To estimate, for people with advanced cancer, how well fatigue, pain, and physical function identified on the PGI (a personalized measure) agree with ratings obtained from standard outcome measures (non-personalized measures).

4) To estimate the extent to which people with advanced cancer re-conceptualize QOL over time.

CHAPTER 3: MANUSCRIPT 1

A Review of the Application, Feasibility and the Psychometric Properties OF the Individualized Measures in Cancer

Ala' S. Aburub Nancy E. Mayo

Abstract

Purpose To identify from the published literature the feasibility and the application of the individualized measures (Patient Generated Index (PGI), Schedule for the Evaluation of Individual Quality of Life (SEIQOL) and the short form of it (the direct weighting SEIQOL-DW)) in the context of cancer and to summarize the evidence on the psychometric properties of these measures.

Methods Ovid Medline, Pub-Med, Embase and CINAHL were searched up to o April 2016. All studies were included if they reported information about the psychometric properties of the individualized measures and included patients diagnosed with any type of cancer at any age. effect size (ES) was calculated to test for the responsiveness.

Results 54 full articles were reviewed. Full text assessment of these articles resulted in 27 eligible studies that were included in our analysis. The majority of the studies (81%) reported data on the SEIQOL-DW, and only 15% on the PGI. Fourteen areas of quality of life (QOL) concerns were identified by patients using the PGI with the top 4 being Family (90%), health (85%), finance (85%), work, (80%). The correlation between the individualized measures and standard measures ranged from 0.45 to 0.49 at the global level and from 0.26 to 0.51 at the symptoms level. The ES of the individualized measures was high (ranged from 0,98-1.0) in the studies that expected high positive change compared to standard QOL measures (ES=0.1)

Conclusion Individualized measures are feasible and acceptable among people with cancer and . could easily be incorporated clinically and used in a research context. Individualized measures are sensitive to change and cover a wide range of patients QOL concerns in comparison to standard measures.

Keywords Individualized Measures, Patient Generated Index , Schedule for the Evaluation of Individual Quality of Life , Cancer , Psychometric Properties

Introduction

The number of people who will be diagnosed with cancer is expected to increase by 79% between 2028 to 2032 compared to 2003 to 2007 [1]. The number of survivors is increasing due to technological advances in early disease detection and treatment, accordingly people with cancer will now live five years or more [2, 3]. On the other hand, people with cancer experience a wide spectrum of functional sequelae including fatigue, pain and decrease in physical function, from the cancer itself and its treatments which impact negatively on quality of life (QOL) [4].

In 1948, the World Health Organization (WHO) defined QOL as “not merely the absence of disease, but complete physical, psychological, and social well-being” [5]. QOL in the context of a serious illness (such as cancer) is defined as "the impact on general health, physical functioning, physical symptoms and toxicity, emotional functioning, cognitive functioning, role functioning, social well-being and functioning, sexual functioning and existential issues" [6]. This definition focuses mainly on the health aspects of quality of life, and would be better referred to as Health Related QOL (HRQOL).

HRQOL is defined as "the functional effect of a medical condition and/or its consequent therapy upon a patient" [7, 8]. Improvement of HRQOL is important in a treatment’s decision making [9, 10] and the outcome evaluation [11, 12], which is the ultimate goal of health care [13]. Many oncology studies have shown that collecting information about HRQOL is important for patient care [14-16]. HRQOL and QOL are constructs that can only be reported on by the person and reflect the person’s perspective on the cancer experience and its treatment [8] and their preferences in terms of defining outcome. Patient-centered care is defined as care that is

"respectful of and responsive to individual patients' preferences, needs and values, and ensures that patients' values guide all clinical designs" [17]. This definition suggests that the patient is the only one who should identify and weight the important QOL areas. Individualized measures have been developed for this purpose. Unlike standard measures of HRQOL such as the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) [18] and the Short From 36-item Health Survey (SF-36) [19]) which have a predetermined set of questions to be answered by all, individualized measures allows a patient to nominate and weight the important areas to his/her QOL. Two individualized measures, Patient Generated Index (PGI) [20] and the Schedule for the Evaluation of Individual Quality of life (SEIQOL) and the short form of it (the direct weighting SEIQOL-DW)) [21, 22] have been used to evaluate HRQOL and QOL in cancer.

Both measures are completed in three steps and administered by semi-structured interviews. In the first step, in both measures, participants are asked to nominate the top five areas that are important to their QOL in general (SEIQOL/SEIQOL-DW) or that are affected by their disease (PGI). In the second step, participants are asked to rate their current status in each area using a visual analogue scale. In the final step , participants are asked to weight each area according to its importance to their overall QOL using a judgmental analysis (SEIQOL-JA) or simple direct weighting technique that uses a pie chart (SEIQOL-DW) or imagining having tokens to spend on each area with more tokens on the areas that they would like to improve more (PGI).The index score for both measures (SEIQOL/SEIQOL-DW and the PGI) is calculated by multiplying the severity rating of each nominated area by the weight chosen for each area and summing across the areas. The resultant index ranges from 0-100, where higher scores indicate a higher QOL [20-22].

Both individualized measures have had some testing of their psychometric properties (validity, reliability and responsiveness) tested in a variety of health conditions, including cancer [23-33]. But a comprehensive summary has not been undertaken. Therefore, the objective of this review was to summarize the evidence on the psychometric properties of individualized measures in the context of cancer including information on feasibility and application.

Methods

Search Strategies

Ovid Medline, Pub-Med, Embase, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) electronic databases were searched for studies published up to April 2016 using the following key words and combination:(Schedule for the Evaluation of the Individual Quality of Life (SEIQoL) **OR** Patient Generated Index (PGI)) **AND** (Malignancy **OR** Cancer **OR** Tumor **OR** Neoplasm). The search was limited to the English language.

Study Selection and Review Criteria

The inclusion criteria were the following 1) studies aimed to test the the psychometric properties of the SEIQoL/SEIQOL-DW and/or PGI 2) studies included patients diagnosed with any type of cancer at any age. Studies were excluded if they were 1) published as an abstract form or conference proceeding and protocol form 2) narrative and systematic reviews 3) published in languages other than English.

Data Abstraction

Each study was classified according to the following; 1) application (authors names(year), sample size (N), mean age, men (%), type of cancer); 2) procedure (type of individualized measures used and the method of administration (semi-structured interviews, telephone interviews, touch screen or other methods); 3) feasibility (time needed to complete (min) the questionnaire and the completion rate (%)); 4) the psychometric properties (content validity, construct validity and responsiveness). The completion rate was calculated as the proportion of number of participants who completed the questionnaire (PGI or SEIQOL/SEIQOL-DW) divided by the number of participants who were asked to complete the questionnaire.

Psychometric Properties and Meta-Analysis

Content Validity

Content validity is the degree to which the measure contains and reflects the most relevant and important aspects of a concept in the context of a given application [34]. Mayo has demonstrated that mapping measures to a standard framework representing the content area supports content validity [35]. The following steps were conducted to test the content validity of the individualized measures; 1) studies were selected if they presented the domains nominated by patients using the individualized measures (PGI and SEIQOL/SEIQOL-DW); 2) Top domains were identified and then were; 3) mapped directly to a standard framework called the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF).

The ICF was developed to describe health and health related states from personal, biological and social perspectives. ICF is a bio-psycho-social model of functioning and disability [36, 37]. Functioning is an umbrella term that covers all positive components of function (body functions and structure, activities, and participation in life situations). While disability is an umbrella term for all negative components of function (impairments of body functions and structure, activity limitations, and participation restrictions) [36, 37]. Functioning is affected by the health condition and modified by environmental and personal factors [36].

Construct Validity

Construct validity is the degree to which an instrument measures the construct of interest in an accurate way [38]. Convergent validity is one of the subtype of construct validity and it refers theoretically to the degree to which the measures of constructs are related to each other are in reality related [39]. To summarize across estimates of convergent validity of the individualized measure, the correlation of the individualized index score and other HRQOL measures were compared using the Schmidt–Hunter method. This method is a weighted mean of the correlation values and it's based on the random effect which weights each study based on its sample size. Following Polgar and Thomas [40], pooled correlation values of 0.1–0.3, 0.4–0.6 and 0.7 or above are considered to represent small, moderate and large associations, respectively.

Responsiveness

Responsiveness is defined as the ability of a measure to precisely detect the change over time when change has occurred [34, 41]. To test the responsiveness of the individualized measures, studies were selected if they presented the total score of the individualized measures at more than

one time point (e.g. before and after treatment), and/or presented the domains nominated by patients over at least two time points. Studies were selected if they clearly stipulated the hypothesis of expecting change over time. Expected change also was inferred by the population included in the study and the type of treatment provided. After identifying the studies , the effect size (ES) was calculated as the difference between the mean baseline score and the last follow-up score on the measure, divided by the standard deviation (SD) of the baseline score and the studies were categorized into expectation of high positive change or expectation of low to moderate change. High positive effect size indicates greater sensitivity to change, with ES of 0.2, 0.5, and 0.8 or above representing small, moderate and large changes, respectively [42, 43]. If the individualized measures have higher ES than standard measures then their ability to detect change overtime is higher.

Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) Checklist Guidelines

COSMIN checklist with 4 point rating scale (Excellent, Good, Fair, Poor) was used to review the psychometric properties of the measures for the studies for which the primary objective was validation [44]. COSMIN checklist consists of 9 boxes (Box A- Box I), each box evaluating one of the psychometric properties of a measure with an item ranged from 4-18 per box to evaluate the methodological quality of the study. For example, there are 14 items for reliability (Box B), 5 items for content validity (Box D) and 18 items for responsiveness (Box I). If a study achieves a poor score in any item then the global rating score of that study is poor.

COSMIN checklist "aims to improve the selection of health measurement instruments". The instructions for rating each of the psychometric properties are available in the COSMIN checklist manual which is available on the COSMIN web site (www.cosmin.nl).

Results

Study Selection

Figure 1 presents the study section process. The literature search yielded 108 studies. After removing 54 duplicate studies, the full texts of the remaining 54 studies were reviewed. and 27 studies met the inclusion criteria [23, 24, 26, 30-33, 45-64] . The sample size in the included studies ranged from 11 to 357 participants.

Application and feasibility of the individualized measures

Table 1 presents information on the clinical application and the feasibility of the individualized measures in cancer from the 27 included studies [23, 24, 26, 30-33, 45-64]. Mean age was reported in 17 studies (65%) which ranged from 24 to71 years; 7 studies (26%) reported median age which ranged from 46 to 67 years; 2 studies reported only age range and 1study did not provide information on age [31].

Multiple cancer types were included in 11 (40%) studies; the rest reported on only one cancer type. For gender, 16 studies (59%) included more men than women and one study did not report gender [31].

The most common measure was the SEIQOL-DW with 20 studies (74%) ; reported data only on the measure, 2 studies (7.4%) used the original SEIQOL [61], and 5 (18.5%) studies used the

PGI. [33]. The majority of the studies (n=24;89%) administered the individualized measures (PGI, SEIQOL/SEIQOL-DW) using the semi-structured interviews method , 2 studies (7.4%) used semi- structured phone interviews, and one study (3.7%) used the touch screen as a method of administration [62]. For the original SEIQoL, the time needed to complete ranged from 24 to 94 minutes and for the SEIQOL-DW, the time ranged from 5 to 32 minutes. Time to complete was not reported for the PGI. The completion rate of the individualized measures ranged from 70% to 100%.

Psychometric properties

Content Validity

Twenty studies (74%) out of 27 asked participants to nominate domains (areas) which are considered important to their QOL [23, 30-33, 45-52, 56-60, 62, 63]. Table 2 lists the top domains (n=14) identified by cancer participants using the individualized measures (PGI, SEIQOL/SEIQOL-DW) along with results of the ICF classification. Family (90%), health (85%), finance (85%), work, (80%) and leisure/hobbies (70%) were the top five domains. Out of the top14 domains identified, nine of them (64%) were mapped to the activity limitation/participation restriction level, two domains (14%) to the impairment body function level, two domains (14%) to the environmental factors level. Only one domain fell outside of the function/disability construct, general health.

Convergent Validity

Figure 2 shows a forest plot of the convergent validity of the individualized measures (SEIQOL-index and/or PGI) against the global score of the EORTC-QLO-C30. The pooled correlation

coefficient for convergent validity of the individualized measures was 0.45 with 95% confidence interval (CI) ranged from 0.33 to 0.56.

Figure 3 shows a forest plot of the convergent validity of the individualized measures (SEIQOL-index and/or PGI) against the mental health subscale of the SF-12. The pooled correlation coefficient for convergent validity of the individualized measures was 0.43 with 95% confidence interval (CI) ranged from 0.42-0.45.

Figure 4 shows a forest plot of the convergent validity of the individualized measures (SEIQOL-index and/or PGI) against the global score of the FACT-G. The pooled correlation coefficient for convergent validity of the individualized measures was 0.51 with 95% confidence interval (CI) ranged from 0.36 to 0.67.

Figure 5 shows a forest plot of the convergent validity of the individualized measures (SEIQOL-index and/or PGI) against the global score of the SEIQOL- VAS (visual analogue scale). The pooled correlation coefficient for convergent validity of the individualized measures was 0.49 with 95% confidence interval (CI) ranged from 0.44 to 0.53.

Table 3 summarized the convergent correlation of the individualized measures (SEIQOL-index and/or PGI) against HRQOL measures using the Schmidt-Hunter meta-analysis method at global score level and symptom level. For example, the pooled correlation coefficient for convergent validity of the individualized measures at the global level were moderate and ranged from 0.45-00.49, while it was low to moderate at the symptom level with range between 0.26-0.51. The highest pooled correlation coefficient for convergent validity of the individualized measures

against the HRQOL measures was for the FACT-G (r= 0.51 with 95% confidence interval (CI) ranging from 0.36 to 0.67)

Responsiveness

Only five studies (18%) presented the total score of the individualized measures over time [23, 32, 50, 55, 57].Table 4 represents the effect size (ES) scores for the individualized measures and the standardized (HRQOL) measures in the included studies. Three studies reported the total score of the SEIQOL-DW [50, 55, 57] and two studies for the PGI [23, 32]. Two studies out of 5 expected high positive change over time [32, 55] and three expected low to moderate positive change over time [23, 50, 57]. For the studies that expected high positive change, one of them recruited patients with rectal cancer. PGI and EORTC measures were administered pre-operative and 3 months postoperative. The other study included patients with mesothelioma (stage I-III), SEIQOL-DW was administered at five different time points ("baseline, at day 1 of cycle 3, and 1, 3 and 6months post-surgery"). For the three studies that expected low to moderate change, one study recruited 56 patients with metastatic cancer who were treated with a palliative intent[50], SEIQOL and FACT-G were administered at 3 time points (baseline, 3 months and 6 month). A second study included patients with malignant blood disorders following stem cell transplantation (SCT), SEIQOL-DW was administered before SCT and one year post SCT [57]. The third study included 86 patients with variety of cancer types, PGI and EORTC were administered before radiation, during week three of radiation, and at the end of the treatment [23].

For the two studies that expected high positive change over time, the ES of the individualized measures ranged from 0.98 to 1.0, indicating high clinical changes from the baseline, while the

ES of the standard QOL measure was 0.1, indicating low clinical change from the baseline. For the three studies that expected low to moderate change, the ES ranged from 0.008 to 0.42, and from 0.1 to 0.6 for the individualized measures and the standard QOL measures, respectively (table 4).

Only 5 studies reported the domains nominated by the patients using individualized measures over time [23, 32, 50, 55, 57]. In these studies, patients were shifting their response from one domain to another over time. These shifting responses were either adding new domains or shifting their priorities from one domain to another over time (table 5).

COSMIN Checklist

A total of 5 studies presented aspects of psychometric validation (Appendix A) [23, 24, 30, 32, 33]. These studies were reviewed according to the guidelines recommended by COSMIN checklist with a 4 point rating scale. The COSMIN checklist has different number of the criteria depending on the psychometric parametric being assessed (http://www.cosmin.nl/COSMIN%20checklist.html).

One study evaluated two aspects, reliability and criterion validity [33]. Of the 8 reliability criteria were applied, 6 achieved a rating of excellent and one of poor. For criterion validity, 4 of the 6 guidelines achieved a rating of excellent. No study achieved rating of excellent on all criteria and according to the COSMIN guidelines; all these studies will receive a global rating of poor. Appendix B shows an example of the criterion validity guidelines according to the COSMIN checklist box with 4 point rating scale.

Discussion

All the studies that used individualized measures in a cancer population were reviewed. The measurement framework of individualized measures would be ideal in the context of cancer care as this technology ascertains patients' values , and with a clear portrait of values, it would be easier to match care. Results from the 27 included studies demonstrated that individualized measures are acceptable to use in a cancer population. The majority of studies used the SEIQOL and only five studies used PGI, one of which was a qualitative [24] The four quantitative studies were covered in a 2014 systematic review by Tang et.al [65] and the two earliest studies were included in the 2007 review by Martin [66]. A recent review has shown that SEIQOL is feasible in a variety of populations including cancer [67]

Family, health, finance, and work were among the top 14 areas identified by cancer patients. This review is the first review that used the ICF framework to map the nominated areas from the individualized measures in the context of cancer. The majority of the identified areas were mapped to activity and participation level with 2 areas to the impairment body function level and two to the environmental factors. Only one area (health) was not mapped to ICF. This indicates that individualized measures cover a wide spectrum of cancer patients concerns. This current review showed that individualized measures had low to moderate correlation with standard HRQOL measures. SEIQOL has higher validity and reliability than PGI, with no study focusing on testing the PGI reliability. In a recent study from our group [68], the PGI was correlated with a different set of generic (EQ-5D^{TM} and SF-6D) and cancer-specific measures McGill Quality of Life, ESAS), the correlations were low ranging from 0.12 to 0.22 .

Compared to the standard HRQOL measures, individualized measures have a higher responsiveness to change and capture different constructs. These results are in line with previous studies [67, 69]. Recent study conducted on 192 people with advanced cancer showed that patients identified 114 areas of QOL concerns using PGI, some of these areas are not assessed by other HRQOL/QOL measures [68].For the 5 included studies, individualized measures were able to detect the change when it occurred. For example, individualized measures had higher effect size (ranged from 0.98-1) for the studies that expected high change over time compared to standard QOL measures (ES=0.1). Individualized measures and standard QOL measures had low to moderate effect size (ranged from 0.008 to 0.42 and from 0.1 to 0.6, respectively) for the studies that expected low to moderate change over time. This indicates that the ability of individualized measures to detect change over time is much better than the standard QOL measures particularly for patients after surgery. In addition, the ability of the individualized measures to detect the effect of treatment is similar to standard QOL measures when there is no change/effect. Overall, individualized measures have higher responsiveness to change than standard QOL measures.

Conclusion

Individualized measures are feasible and acceptable among people with cancer. The top 4 concerns were family, health, finance, and work. Individualized measures are related in an expected way to other cancer-specific and generic HRQOL measures, are sensitive to change ,and cover a wide spectrum of areas that are important to patients' quality of life. Individualized measures could easily be incorporated clinically and used in a research context.

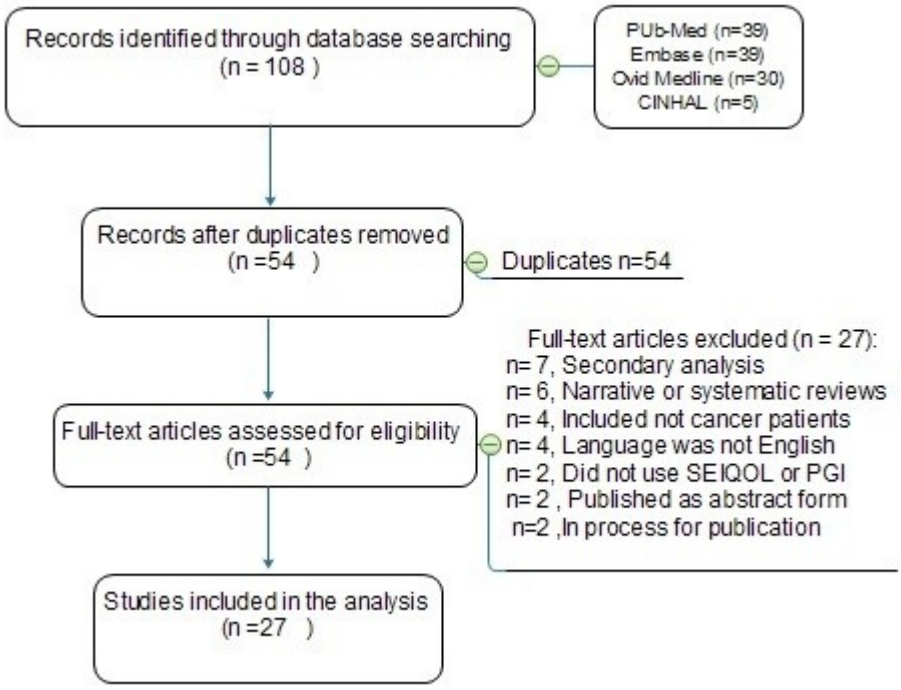


Figure 1 Flow chart of the study selection

Table 1 Clinical application and feasibility of the individualized measures in people with cancer

Author (Year)	N	Mean age	Men (%)	Type of Cancer	Individualized measure used	Time needed to complete (min)	Completion rate (%)	Method of administration
Broadhead, J.K (1998) [30]	15	65.3	100.0	Prostate	SEIQOL	30-90	100%	Semi- structured interview
Campbell, S. and F. Whyte (1999) [31]	15	NR	NR	NR	SEIQOL-DW	5-20	86.7	Semi- structured interview
Waldron, D., et al. (1999) [33]	80	62 (median)	47.5	Mixed type	SEIQOL, SEIQOL-DW	24-94(SEIQOL), 7-40 (SEIQOL-DW)	78%	Semi- structured interview
Montgomery, C., et al. (2002) [45]	51	54	70.6	leukemia and lymphoma	SEIQOL-DW	NR	100%	Standardized interview
Camilleri-Brennan, J., D.A. , et al., (2002) [32]	33	67 (median)	75.8	Rectal	PGI	NR	100% pre-operative, 69% post operative	Semi- structured Interview
Wettergren, L., et al. (2003) [46]	357	46 (median)	47.6	Hodgkin's lymphoma (HL)	SEIQOL-DW (Swedish version)	NR	100%	Semi- structured interview
Frick, E., et al. (2004) [47]	79	10-70 (range)	57.0	Mixed type	SEIQOL-DW	15–25	79%	Semi- structured interview
Levack, P., et al. (2004) [48]	319	median 65	63.6	Malignant cord compression	SEIQOL-DW	NR	70%	Semi- structured interview
Carlson, L.E., et al. (2005) [49]	16	53	37.5	Mixed type	SEIQOL-DW	13.5 (Range 5-30)	100%	Semi- structured interview
Sharpe, L., et al. (2005) [50]	56	46	48.2	Mixed type	SEIQOL-DW	NR	100% at T1, 66% at T2, 50% at T3	Semi- structured interview
Willener, R. and V. Hantikainen (2005) [51]	11	66	100.0	Prostate	SEIQOL-DW	NR	100%	Semi- structured interview
Westerman, M., et al (2006) [52]	31	39-82 (range)	51.6	Small cell lung cancer	SEIQOL-DW	10-30	84%	Semi- structured interview
Llewellyn, C.D., et al., (2006) [26]	55	59	65.5	Head and Neck	PGI	NR	83%	Semi- structured Interview
Frick, E., et al. (2007) [53]	63	60.7	36.5	Mixed Type	SEIQOL-DW	NR	NR	Semi- structured interview
Llewellyn, C., et al., (2007) [54]	82	60	65.9	Head and Neck	PGI	NR	72%	Semi- structured Interview
Ribi, K., et al., (2008) [55]	61	59 (median)	93.4	Malignant pleural mesothelioma	SEIQOL-DW	24 (mean)	93% at baseline and 76% at the endof treatment (months)	Semi- structured interview
Stone, P.C., et al. (2008) [56]	194	71	100.0	Prostate	SEIQOL-DW	20.4 (mean)	93%	Semi- structured interview
Wettergren, L., et al. (2008) [57]	22	50 (median)	59.1	Mixed Type	SEIQOL-DW	NR	100%	Semi- structured interview
Somani, B.K., et al., (2009) [58]	32	69	71.9	Bladder	SEIQOL-DW	16 (Range 8-32)	100%	Semi- structured interview

Sundberg, K.K., et al., (2009) [59]	246	24	52	Mixed type	SEIQOL-DW (Swedish version)	NR	100%	Semi- structured phone interview
Sundberg, K.K., et al., (2010) [60]	246	24	43%	Mixed type (long term survivors of childhood cancer)	SEIQOL-DW	NR	100%	Semi- structured phone interview
Wettergren, L., et al., (2011) [62]	40	58.4	50.0	Gastrointestinal	SEIQOL-DW	6.2 (mean)	80%	Touch screen
Tavernier, S.S., et al., (2011) [23]	86	62.5	40.7	Mixed Type	PGI	NR	90% before radiation and 78% at the end of treatment	Interview and/or self complete
Tavernier, S.S., et al (2011) [24]	16	62	43.8	Mixed Type	PGI	NR	87%	Semi- structured Interview
Stiel, S., et al.(2011) [61]	72	66	42.0	Mixed Type	SEIQOL	NR	93%	Semi- structured Interview
Durner, J.,al., (2013) [63]	64	60 (median)	57.8	Multiple myeloma	SEIQOL-DW	NR	100%	Semi- structured interview
Lucchiari, C., et al., (2015) [64]	73	48.9	65.8	Brain	SEIQOL-DW	NR	100%	Semi- structured interview

Mixed Type : Multiple cancer types

Table 2 The top domains identified by cancer participants using the individualized measures (PGI, SEIQOL and SEIQOL-DW)

Domains	*Studies included n=20*	*%*	*ICF components*
1. Family	18	90.0	Activities and participation
2. Health	17	85.0	---
3. Finance	17	85.0	Environmental factors
4. Work	16	80.0	Activities and participation
5. Leisure and hobbies	14	70.0	Activities and participation
6. Social life	13	65.0	Activities and participation
7. Relationship to partner	13	65.0	Activities and participation
8. Living condition (doing house work)	12	60.0	Activities and participation
9. Physical activity	11	55.0	Activities and participation
10. Spiritual /Religion	11	55.0	Activities and participation
11. Emotional issues	10	50.0	Body function
12. Friends	8	40.0	Environmental factors
13. Marriage	7	35.0	Activities and participation
14. Fatigue/pain	6	30.0	Body function

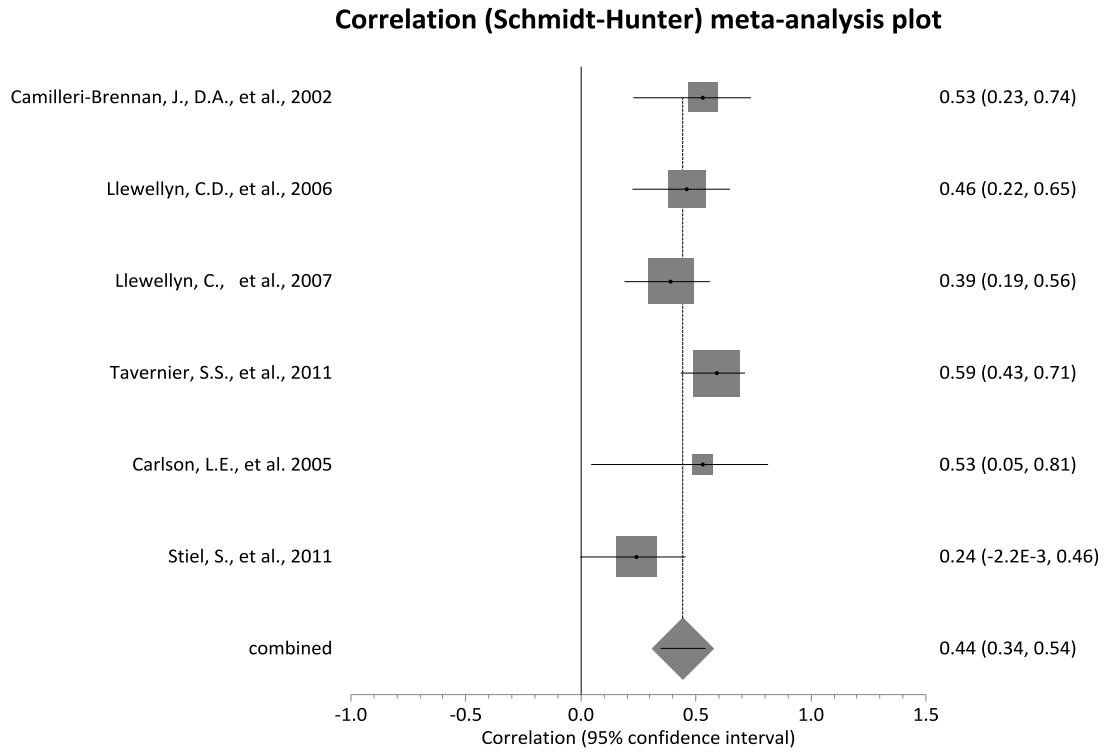


Figure 2 Forest plot with correlation coefficients (r) of the individualized measures against the global score of the EORTC-QLO-C30 using the Schmidt-Hunter meta-analysis method.

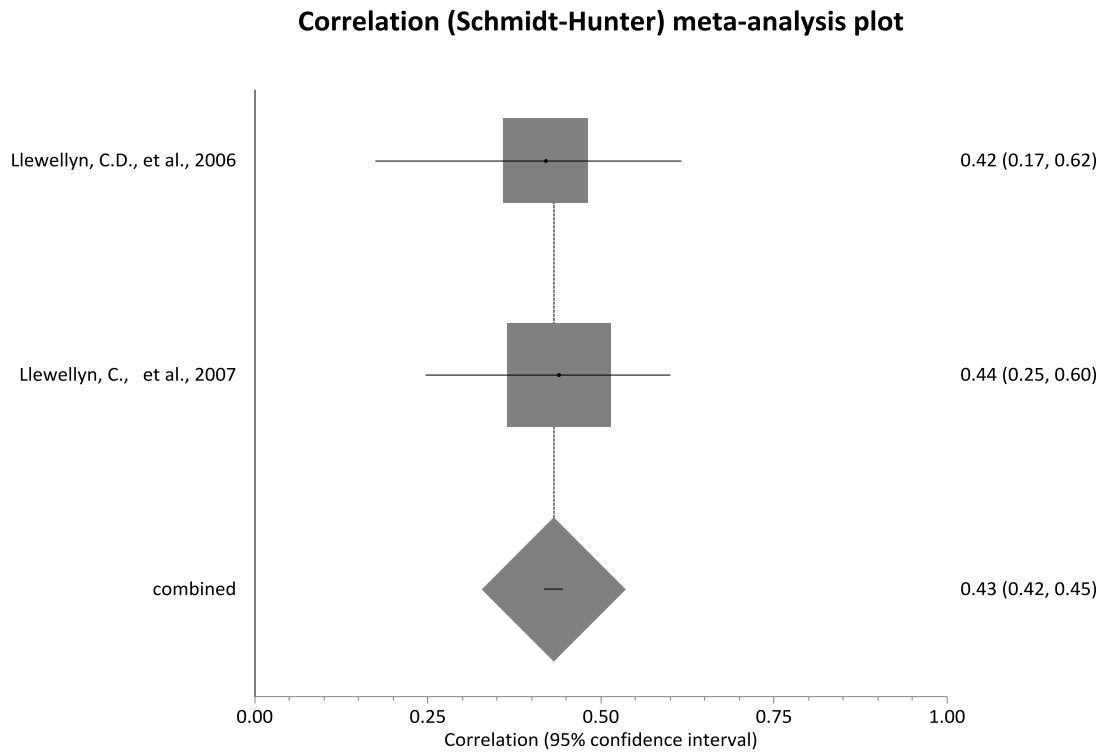


Figure 3 Forest plot with correlation coefficients (r) of the individualized measures against the global score of the mental health subscale of the SF-12 using the Schmidt-Hunter meta-analysis method.

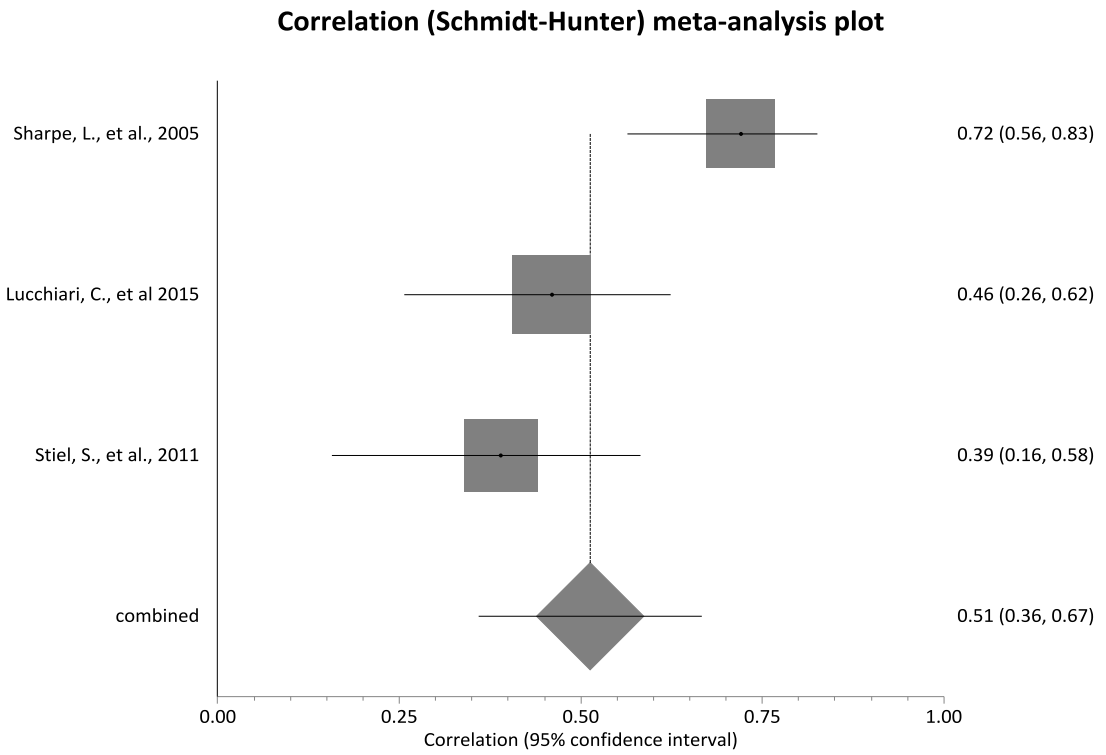


Figure 4 Forest plot with correlation coefficients (r) of the individualized measures against the global score of the global score of the FACT-G using the Schmidt-Hunter meta-analysis method.

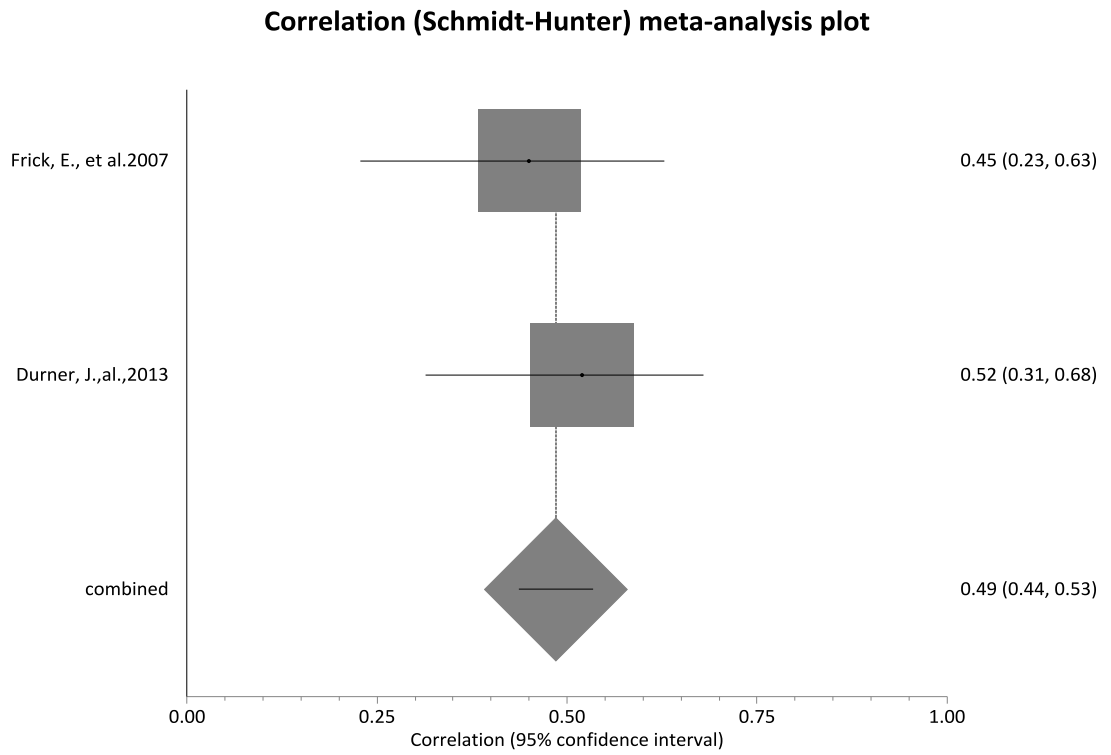


Figure 5 Forest plot with correlation coefficients (r) of the individualized measures against the global score of the global score of the SEIQOL-VAS using the Schmidt-Hunter meta-analysis method.

Table 3 Summary of the convergent correlations of the individualized measures (SEIQOL-index and/or PGI) against the HRQOL measures using the Schmidt-Hunter meta-analysis method.

HRQOL measures	Pooled correlation (r)	95% CI	Individualized measures
Global score			
EORTC	0.45	0.33-0.56	SEIQOL-index and PGI
SEIQOL-VAS	0.49	0.44-0.53	SEIQOL-index
Symptoms			
EORTC			
Pain	0.40	0.37-0.43	PGI
Physical functioning	0.35	0.23-0.48	SEIQOL-index and PGI
Cognitive	0.35	0.28-0.43	SEIQOL-index and PGI
Emotional functioning	0.29	0.19-0.4	SEIQOL-index and PGI
Fatigue	0.28	0.05-0.51	SEIQOL-index and PGI
Social functioning	0.27	0.35 E-3 - 0.53	SEIQOL-index and PGI
Role function	0.26	0.1-0.43	SEIQOL-index and PGI
SF-12			
Mental health	0.43	0.42-0.45	PGI
FACT-G			
Total score	0.51	0.36 -0.67	SEIQOL-index

Table 4 Mean change scores in individualized measures and other HRQOL measures

Author Name, Year	Measure	N time points (N Subjects)	Time Fame (Months)	Baseline score Mean (SD)	Follow up score Mean (SD)	Largest change (difference)	Effect Size
High expected change							
Camilleri-Brennan, J et al. 2002 [32]	PGI	2 (33)	3	4.8 (1.32)	6. 1 (1.87)	1.34	0.98
	EORTC QLQ-C30 Global QOL/Health	2 (33)	3	NR	NR	1.89	0.11
Ribi, K., et al., 2008 [55]	SIEQOL-DW	4 (52)	6	70.9 (18.9)	NR	20	1.0
Low to Moderate expected change							
Sharpe, L., et al., 2005 [50]	SIEQOL-DW	3 (56)	6	65 (23)	74 (20)	9	0.39
	FACT-G	3 (56)	6	84.7 (15.5)	86.8 (17.3)	2.1	0.13
Wettergren, L., et al., 2008 [57]	SEIQQL-DW	2 (52)	12	4.6 (1.2)	5.1 (0.9)	0.5	0.42
Tavernier, S.S., et al., 2011 [23]	PGI Overall	4 (77)	Till end of treatment (radiation)	51.8 (27.2)	55.8 (24.5)	3.95	0.14
	Radiation only	4 (45)	Till end of treatment (radiation)	55.7 (26.4)	56.0 (25.8)	0.23	0.008
	Radiation and chemotherapy	4 (32)	Till end of treatment (radiation)	46.3 (26.4)	55.5 (22.5)	9.1	0.34
	EORTC QLQ-C30 Global QoL/Health	4 (85)	Till end of treatment (radiation)	62.2 (2.21)	63.5 (2.1)	1.32	0.6

Table 5 Domains (Areas) nominated over time by cancer participants using individualized measures

Author	Measure	Results
Camilleri-Brennan, J et al. 2002 [32]	PGI	Postoperative, participants nominated on average 3.2 areas with median of 3 compared to 3.6 areas with median of 4 three months postoperative
Sharpe, L., et al., 2005 [50]	SIEQOL-DW	More than half (53%) of the participants nominated same areas at both baseline and time point 2, and 57% between T2 and T3. Only 43% of the participants nominated different areas
Ribi, K., et al., 2008 [55]	SIEQOL-DW	" SEIQoL scores improved to baseline-level at month 3 after surgery, but worsened again at month 6 (median change: − 16)". "SEIQoL index remained stable during chemotherapy, followed by a clinically significant deterioration 1 month after surgery (Median change -14)"
Wettergren, L., et al., 2008 [57]	SIEQOL-DW	Same number of areas were nominated by 50% of the participants in both assessments (before (baseline) and one year after stem cell transplantation (SCT)). Third of the participants nominated more areas one year after stem cell transplantation compared to before, while 18% of the participants nominated fewer areas one year after the SCT compared to before.
Tavernier, S.S., et al., 2011 [23]	PGI	Patients made on average three changes in the areas nominated in the first step of the PGI between the following time points (pre-treatment to third week, third week to end of treatment, and pretreatment to end of treatment).

Appendix A Rating studies evaluated the psychometric properties of the individualized measures according to COSMIN checklist with 4 point rating scale [44]

Box B. Reliability	**Year**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**				
Study																			
Waldron, D., et al.[33]	1999	E	E	G	E	E	NA	NA	NA	E	E	P	NA	NA	NA				
Box D. Content Validity	**Year**	**1**	**2**	**3**	**4**	**5**													
Study																			
Tavernier, S.S., et al., [24]	2011	E	E	E	F	E													
Box F. Hypothesis	**Year**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**								
Study																			
Camilleri-Brennan, J., D.A. , et al., [32]	2002	E	E	F	E	E	G	G	P	E	E								
Box H. Criterion validity	**Year**	**1**	**2**	**3**	**4**	**5**	**6**	**7**											
Study																			
Broadhead, J.K [30]	1998	E	E	P	P	E	E	NA											
Waldron, D., et al. [33]	1999	E	E	G	P	E	E	NA											
Camilleri-Brennan, J., D.A. , et al., [32]	2002	E	E	F	P	E	E	NA											
Tavernier, S.S., et al., [23]	2011	E	E	G	P	E	E	NA											
Box I. Responsiveness	**Year**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Study																			
Camilleri-Brennan, J., D.A. , et al., [32]	2002	E	E	F	E	E	E	E	E	E	G	E	P	E	E	P	E	E	NA

E: Excellent, G: Good F: Fair P: Poor NA: Not applicable.

Each box contains questions that are listed in oder according to COSMIN checklist. For example questions listed in box B, **1**. Was the percentage of missing items given? **2**. Was there a description of how missing items were handled? **3.** Was the sample size included in the analysis adequate? **4.** Were at least two measurements available? **5.** Were the administrations independent? **6.** Was the time interval stated? **7**. Were patients stable in the interim period on the construct to be measured? **8**. Was the time interval appropriate? **9.** Were the test conditions similar for both measurements? e.g. type of administration, environment, instructions **10.** Were there any important flaws in the design or methods of the study? **11.** for continuous scores: Was an intraclass correlation coefficient (ICC) calculated? **12.** for dichotomous/nominal/ordinal scores: Was kappa calculated? **13.** for ordinal scores: Was a weighted kappa calculated? **14.** for ordinal scores: Was the weighting scheme described? e.g. linear, quadratic

For the rest of the boxes please see the manual on the COSMIN web site (www.cosmin.nl).

Appendix B Example of the criterion validity guidelines according to COSMIN checklist with 4 point rating scale 4 [44]

Box H. Criterion validity				
	Excellent	**Good**	**Fair**	**Poor**
Design requirement				
1. Was the percentage of missing items given?	Percentage of missing items described	Percentage of missing items NOT described		
2. Was there a description of how missing items were handled?	Described how missing items were handled	Not described but it can be deduced how missing items were handled	Not clear how missing items were handled	
3. Was the sample size included in the analysis adequate?	Adequate sample size (≥100)	Good sample size (50-99)	Moderate sample size (30-49)	Small sample size (<30)
4. Can the criterion used or employed be considered as a reasonable 'gold standard'?	Criterion used can be considered an adequate 'gold standard' (evidence provided)	No evidence provided, but assumable that the criterion used can be considered an adequate 'gold standard'	Unclear whether the criterion used can be considered an adequate 'gold standard'	Criterion used can NOT be considered an adequate 'gold standard'
5. Were there any important flaws in the design or methods of the study?	No other important methodological flaws in the design or execution of the study		Other minor methodological flaws in the design or execution of the study	Other important methodological flaws in the design or execution of the study
Statistical methods				
6. for continuous scores: Were correlations, or the area under the receiver operating curve calculated?	Correlations or AUC calculated			Correlations or AUC NOT calculated
7. for dichotomous scores: Were sensitivity and specificity determined?	Sensitivity and specificity calculated			Sensitivity and specificity NOT calculated

References

1. Canadian Cancer Statistics. *Special topic: Predictions of the future burden of cancer in Canada*. 2015; Available from: http://www.cancer.ca/en/cancer-information/cancer-101/canadian-cancer-statistics-publication/?region=qc.
2. de Boer, A.G., et al., *Work ability and return-to-work in cancer patients.* Br J Cancer, 2008. **98**(8): p. 1342-7.
3. Hoffman B, *survivors at work: a generation of progress. CA.* A Cancer Journal for Clinicians 2005. **55**: p. 271–80.
4. Smith, T., et al., *The rationale, design, and implementation of the American Cancer Society's studies of cancer survivors.* Cancer, 2007. **109**(1): p. 1-12.
5. Group, W., *Development of the WHOQOL: Rationale and current status.* International Journal of Mental Health, 1994. **23**(3): p. 24-56.
6. Machhin, P.M.F.a.D., *Qulaity of life, second edition: The assessment, analysis and interpretation of patients reported outcomes.* 2007.
7. Cella, D.F., *Measuring quality of life in palliative care.* Semin Oncol, 1995. **22**(2 Suppl 3): p. 73-81.
8. Schipper H, C., JJ, Olweny CLM *Quality of life studies: definitions and conceptual issues, In Spilker B (ed) Quality of Life and Pharmaco-economics in Clinical Trials.* Lippincott-Raven Publishers:Philadelphia. , 1996: p. PP 11-23.
9. Soni, M.K. and D. Cella, *Quality of life and symptom measures in oncology: an overview.* Am J Manag Care, 2002. **8**(18 Suppl): p. S560-73.
10. Tanaka, T. and C.C. Gotay, *Physicians' and medical students' perspectives on patients' quality of life.* Acad Med, 1998. **73**(9): p. 1003-5.

11. Patrick-Miller, L.J., *Is there a role for the assessment of health-related quality of life in the clinical evaluation of novel cytostatic agents?: Commentary re: P. M. LoRusso, Improvements in quality of life and disease-related symptoms in phase I trials of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 in non-small cell lung cancer and other solid tumors. Clin. Cancer Res., 9: 2040-2048, 2003.* Clin Cancer Res, 2003. **9**(6): p. 1990-4.

12. Sprangers, M.A., *Quality-of-life assessment in oncology. Achievements and challenges.* Acta Oncol, 2002. **41**(3): p. 229-37.

13. Osoba, D., *Outcomes research applied. Paper presented at the ISOHRQL Symposium, Boston.* 2004.

14. Morris, J., D. Perez, and B. McNoe, *The use of quality of life data in clinical practice.* Qual Life Res, 1998. **7**(1): p. 85-91.

15. Taylor, K.M., et al., *Physicians' perspective on quality of life: an exploratory study of oncologists.* Qual Life Res, 1996. **5**(1): p. 5-14.

16. Bezjak, A., et al., *Oncologists' use of quality of life information: results of a survey of Eastern Cooperative Oncology Group physicians.* Qual Life Res, 2001. **10**(1): p. 1-13.

17. Medicine, I.o., *"Crossing the Quality Chasm: A New Health System for the 21st Century.* 2001.

18. Aaronson, N.K., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst, 1993. **85**(5): p. 365-76.

19. Ware, J.E., Jr., *SF-36 health survey update.* Spine (Phila Pa 1976), 2000. **25**(24): p. 3130-9.

20. Ruta, D.A., et al., *A new approach to the measurement of quality of life. The Patient-Generated Index.* Med Care, 1994. **32**(11): p. 1109-26.

21. Hickey, A.M., et al., *A new short form individual quality of life measure (SEIQoL-DW): application in a cohort of individuals with HIV/AIDS.* Bmj, 1996. **313**(7048): p. 29-33.

22. McGee, H.M., et al., *Assessing the quality of life of the individual: the SEIQoL with a healthy and a gastroenterology unit population.* Psychol Med, 1991. **21**(3): p. 749-59.

23. Tavernier, S.S., et al., *Validity of the Patient Generated Index as a quality-of-life measure in radiation oncology.* Oncol Nurs Forum, 2011. **38**(3): p. 319-29.

24. Tavernier, S.S., A.M. Totten, and S.L. Beck, *Assessing content validity of the patient generated index using cognitive interviews.* Qual Health Res, 2011. **21**(12): p. 1729-38.

25. Lewis, S., et al., *Quality of life issues identified by palliative care clients using two tools.* Contemp Nurse, 2002. **12**(1): p. 31-41.

26. Llewellyn, C.D., M. McGurk, and J. Weinman, *Head and neck cancer: to what extent can psychological factors explain differences between health-related quality of life and individual quality of life?* Br J Oral Maxillofac Surg, 2006. **44**(5): p. 351-7.

27. Wettergren, L., M. Bjorkholm, and A. Langius-Eklof, *Validation of an extended version of the SEIQoL-DW in a cohort of Hodgkin lymphoma' survivors.* Qual Life Res, 2005. **14**(10): p. 2329-33.

28. Koch, T., *Life quality vs the 'quality of life': assumptions underlying prospective quality of life instruments in health care planning.* Soc Sci Med, 2000. **51**(3): p. 419-27.

29. Browne, J.P., et al., *Individual quality of life in the healthy elderly.* Qual Life Res, 1994. **3**(4): p. 235-44.

30. Broadhead, J.K., J.W. Robinson, and M.J. Atkinson, *A new quality-of-life measure for oncology: The SEIQoL.* Journal of Psychosocial Oncology, 1998. **16**(1): p. 21-35.

31. Campbell, S. and F. Whyte, *The quality of life of cancer patients participating in phase I clinical trials using SEIQoL-DW.* J Adv Nurs, 1999. **30**(2): p. 335-43.

32. Camilleri-Brennan, J., D.A. Ruta, and R.J. Steele, *Patient generated index: new instrument for measuring quality of life in patients with rectal cancer.* World J Surg, 2002. **26**(11): p. 1354-9.

33. Waldron, D., et al., *Quality-of-life measurement in advanced cancer: assessing the individual.* J Clin Oncol, 1999. **17**(11): p. 3603-11.

34. Mokkink, L.B., et al., *The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes.* J Clin Epidemiol, 2010. **63**(7): p. 737-45.

35. Mayo, N.E., et al., *The extent to which common health-related quality of life indices capture constructs beyond symptoms and function.* Qual Life Res, 2011. **20**(5): p. 621-7.

36. Organization., W.H., *International Classification of Functioning, Disability and Health, 2nd revision edn. Geneva: WHO.* . 2001.

37. Organization., W.H., *International Classification of Functioning, Disability and Health: ICF. World Health Organization.* 2008.

38. Fayers, P.M. and D.J. Hand, *Factor analysis, causal indicators and quality of life.* Qual Life Res, 1997. **6**(2): p. 139-50.

39. Campbell, D.T. and D.W. Fiske, *Convergent and discriminant validation by the multitrait-multimethod matrix.* Psychol Bull, 1959. **56**(2): p. 81-105.

40. Polgar. S and Thomas. SA, *Introduction to research in the health sciences.* Elsevier Health Sciences;, 2013.

41. Husted, J.A., et al., *Methods for assessing responsiveness: a critical review and recommendations.* J Clin Epidemiol, 2000. **53**(5): p. 459-68.

42. Cohen, J., *Statistical Power Analysis for the Behavioral Sciences (second ed.).* . 1988.

43. Cohen, J., *A power primer.* Psychol Bull, 1992. **112**(1): p. 155-9.

44. Terwee, C.B., et al., *Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist.* Qual Life Res, 2012. **21**(4): p. 651-7.

45. Montgomery, C., et al., *Individual quality of life in patients with leukaemia and lymphoma.* Psychooncology, 2002. **11**(3): p. 239-43.

46. Wettergren, L., et al., *Individual quality of life in long-term survivors of Hodgkin's lymphoma - A comparative study.* Quality of Life Research, 2003. **12**(5): p. 545-554.

47. Frick, E., et al., *Individual quality of life of patients undergoing autologous peripheral blood stem cell transplantation.* Psychooncology, 2004. **13**(2): p. 116-24.

48. Levack, P., J. Graham, and J. Kidd, *Listen to the patient: quality of life of patients with recently diagnosed malignant cord compression in relation to their disability.* Palliat Med, 2004. **18**(7): p. 594-601.

49. Carlson, L.E., B.D. Bultz, and D.G. Morris, *Individualized quality of life, standardized quality of life, and distress in patients undergoing a phase I trial of the novel therapeutic Reolysin (reovirus).* Health Qual Life Outcomes, 2005. **3**: p. 7.

50. Sharpe, L., et al., *Changes in quality of life in patients with advanced cancer: evidence of response shift and response restriction.* J Psychosom Res, 2005. **58**(6): p. 497-504.

51. Willener, R. and V. Hantikainen, *Individual quality of life following radical prostatectomy in men with prostate cancer.* Urol Nurs, 2005. **25**(2): p. 88-90, 95-100.

52. Westerman, M., et al., *Problems eliciting cues in SEIQoL-DW: quality of life areas in small-cell lung cancer patients.* Qual Life Res, 2006. **15**(3): p. 441-9.

53. Frick, E., M. Tyroller, and M. Panzer, *Anxiety, depression and quality of life of cancer patients undergoing radiation therapy: A cross-sectional study in a community hospital outpatient centre.* European Journal of Cancer Care, 2007. **16**(2): p. 130-136.

54. Llewellyn, C., M. McGurk, and J. Weinman, *The relationship between the Patient Generated Index (PGI) and measures of HR-QoL following diagnosis with head and neck cancer: are illness and treatment perceptions determinants of judgment-based outcomes?* Br J Health Psychol, 2007. **12**(Pt 3): p. 421-37.

55. Ribi, K., et al., *Individual versus standard quality of life assessment in a phase II clinical trial in mesothelioma patients: feasibility and responsiveness to clinical changes.* Lung Cancer, 2008. **61**(3): p. 398-404.

56. Stone, P.C., et al., *Measuring the individual quality of life of patients with prostate cancer.* Prostate Cancer Prostatic Dis, 2008. **11**(4): p. 390-6.

57. Wettergren, L., et al., *Quality of life before and one year following stem cell transplantation using an individualized and a standardized instrument.* Psychooncology, 2008. **17**(4): p. 338-46.

58. Somani, B.K., et al., *Quality of life and body image for bladder cancer patients undergoing radical cystectomy and urinary diversion--a prospective cohort study with a systematic review of literature.* Urology, 2009. **74**(5): p. 1138-43.

59. Sundberg, K.K., et al., *Positive and negative consequences of childhood cancer influencing the lives of young adults.* Eur J Oncol Nurs, 2009. **13**(3): p. 164-70.

60. Sundberg, K.K., et al., *Long-term survivors of childhood cancer report quality of life and health status in parity with a comparison group.* Pediatr Blood Cancer, 2010. **55**(2): p. 337-43.

61. Stiel, S., et al., *Assessment of quality of life in patients receiving palliative care: comparison of measurement tools and single item on subjective well-being.* J Palliat Med, 2011. **14**(5): p. 599-606.

62. Wettergren, L., et al., *Comparing two versions of the Schedule for Evaluation of Individual Quality of Life in patients with advanced cancer.* Acta Oncol, 2011. **50**(5): p. 648-52.

63. Durner, J., H. Reinecker, and H. Csef, *Individual quality of life in patients with multiple myeloma.* Springerplus, 2013. **2**: p. 397.

64. Lucchiari, C., et al., *Cognitive strategies and quality of life of patients with high-grade glioma.* Support Care Cancer, 2015.

65. Tang, J.A., et al., *The current trend of administering a patient-generated index in the oncological setting: a systematic review.* Oncol Rev, 2014. **8**(1): p. 245.

66. Martin, F., et al., *Twelve years' experience with the Patient Generated Index (PGI) of quality of life: a graded structured review.* Qual Life Res, 2007. **16**(4): p. 705-15.

67. Wettergren, L., et al., *The use, feasibility and psychometric properties of an individualised quality-of-life instrument: a systematic review of the SEIQoL-DW.* Qual Life Res, 2009. **18**(6): p. 737-46.

68. Aburub, A.S., et al., *Using a personalized measure (Patient Generated Index (PGI)) to identify what matters to people with cancer.* Support Care Cancer, 2016. **24**(1): p. 437-45.

69. Patel, K.K., D.L. Veenstra, and D.L. Patrick, *A review of selected patient-generated outcome measures and their application in clinical trials.* Value Health, 2003. **6**(5): p. 595-603.

CHAPTER 4: RATIONALE AND PREFACE TO MANUSCRIPT 2

In the first Manuscript, a systematic review was conducted to summarize the evidence on the psychometric properties, including feasibility and application, of individualized measures in the context of cancer. Four electronic databases were searched for studies published up to April 2016. The full texts of 54 studies were reviewed and only 27 studies were included in the analysis. Twenty studies (74%) of them asked participants to nominate areas important to their QOL. A large number of areas of quality of life (QOL) concern were nominated, with the top four being family, health, finance, and work. The Patient Generated Index (PGI) is not as widely used as the Schedule for the Evaluation of Individual Quality of Life (SEIQOL) in cancer populations with only four studies identified and none with an advanced cancer population. Correlations between individualized measures and other standard measures were moderate at the global score level and low to moderate at the symptoms level. The results of this manuscript indicated that individualized measures are acceptable for use among people with cancer.

The PGI first asks patients to nominate up to five important areas affecting their QOL, to rate each on a scale from 0 to 10 on severity with 10 being “as good as it could be”, and finally to weight each area in terms of priority for improvement, by allocating 12 tokens across the areas. The total score is derived as ((∑severity rating * (tokens/12)) *10). It takes about 5 minutes to administer and its format is suitable for a clinical encounter as well as for research purposes.

Manuscript 1 provided a comprehensive overview of the use and the psychometric properties of individualized measures in people with cancer and served to understand the need and the areas of future research. PGI is designed to both query and document QOL concerns and, thus, could

potentially be a valuable clinical and research tool to evaluate changes in health outcomes in patients undergoing cancer care. However, An gap in evidence remains. The PGI's validity with respect to standard QOL measures has not been fully established in the context of advanced cancer.

The global objective of Manuscript 2 is to contribute evidence to validate the PGI as quality of life measure in people with advanced cancer. The specific objective is to identify similarities and differences in ratings of global quality of life between personalized and standard measures. Manuscript 2 will provides evidence that the PGI would be a good measure for patients and clinicians to use together to identify areas of concern that require attention and monitor changing needs. The paper that follows has been published and the reprint is included.

CHAPTER 5 : MANUSCRIPT 2

Using a Personalized Measure (Patient Generated Index (PGI)) to Identify What Matters to People with Cancer

Ala' S Aburub, B Gagnon, A M Rodríguez, Nancy E. Mayo.

Support Care Cancer
DOI 10.1007/s00520-015-2821-7

ORIGINAL ARTICLE

Using a personalized measure (Patient Generated Index (PGI)) to identify what matters to people with cancer

Ala' S. Aburub[1] · B. Gagnon[2] · A. M. Rodríguez[3] · Nancy E. Mayo[4]

Received: 10 March 2015 / Accepted: 15 June 2015

Abstract
Purposes Patient Generated Index (PGI) is designed to both ask and document quality of life (QOL) concerns. Its validity with respect to standard QOL measures has not been fully established for advanced cancer when QOL concerns predominate. The specific objective of this study is to identify, for people with advanced cancer, similarities and differences in ratings of global QOL between personalized and standard measures.
Methods A total of 192 patients completed five QOL measures at study entry: PGI, generic measures (SF-6D, EQ-5D), and cancer-specific measures of QOL (McGill Quality of Life Questionnaire and Edmonton Symptoms Assessment Scale). Comparisons among total scores were compared using Generalized Estimating Equations (GEE).
Results Patients voiced 114 areas of QOL concerns by the PGI with the top three being fatigue, sleep, and pain (39.2, 22.6, and 21.6 %, respectively). PGI total QOL score was 25 to 30 percentage points lower than those documented by the other measures, particularly when QOL was poor. Correlations between PGI and other measures were low.
Conclusion PGI allowed patients to express a wide range of QOL concerns, many that were not assessed by other QOL measures. If only one QOL measure is to be included, either in a clinical setting or for research, the PGI would satisfy many of the criteria for "best choice." PGI could be considered a cancer-specific QOL measure.
Implications for cancer This study provides evidence that the PGI would be a good measure for patients and clinicians to use together to identify areas of concern that require attention and monitor changing needs.

Keywords Personalized measure · The Patient Generated Index · Quality of life · Generic measure · Cancer-specific measure

✉ Nancy E. Mayo
nancy.mayo@mcgill.ca

B. Gagnon
gagnon.bruno@crchuq.ulaval.ca

A. M. Rodríguez
Ana.rodriguez@mcgill.ca

[1] School of Physical and Occupational Therapy, Division of Clinical Epidemiology, McGill University, Royal Victoria Hospital Site, Ross Pavilion R4.29, 687, Pine Ave W., Montreal, QC H3A 1A1, Canada

[2] Département de Médecine Familiale et de Médecine d'Urgence, Centre de Recherche sur le Cancer, Universite Laval, Centre de recherche du CHU de Québec, 9 rue McMahon, Local 1899-6, Québec, QC G1R 2J6, Canada

[3] School of Rehabilitation Sciences, McGill University, 3654 Prom Sir-William-Osler, Montréal, Québec H3G 1Y5, Canada

[4] Division of Clinical Epidemiology, McGill University Health Center, Ross Pavilion R4.29, Royal Victoria Hospital Site, Montreal, Quebec H3A 1A1, Canada

Introduction

Worldwide, in 2012, there were 14.1 million people living with cancer, 7.4 million in men and 6.7 million in women [1]. By 2035, an estimated, 24 million individuals will be diagnosed with cancer [1]. Technological advances have played a key role in improving survival through early detection and better treatment [2, 3]. As a result, approximately 75 % of people with cancer will now live 5 years or more [2, 3], but still many will experience a wide range of physical and psychological sequelae from the disease process itself and

Published online: 23 June 2015

its treatment [4, 5]. These sequelae matter to patients and impact negatively on their quality of life (QOL).

It remains a challenge in a busy clinical setting to systematically obtain information on the different symptoms, functions, and health aspects of QOL. As a result, these concerns are often not systematically queried nor documented despite the fact that this information is important to guide patient-centered care.

One measurement technology designed specifically to obtain personalized information on areas of concerns to patients is personalized QOL measures [6–10]. The literature indicates that multi-item questionnaires [11–13] correlate only moderately with personalized measures indicating that standardized measures may not capture what is important to individuals. One such measure constructed to capture important concerns of the patient is the Patient Generated Index (PGI).

PGI is a personalized measure designed to both query and document QOL concerns and, thus, could potentially be a valuable clinical and research tool to evaluate changes in health outcomes in patients undergoing cancer care. However, its validity with respect to more standard QOL measures has not been fully established in the context of advanced cancer when QOL concerns predominate. The global objective of this study is to contribute evidence to validate the PGI as quality of life measure in people with advanced cancer. The specific objective is to identify similarities and differences in ratings of global quality of life between personalized and standard measures.

Methods

Subjects

The data for this study comes from a study of anorexia/cachexia in people with advanced cancer, and the data collection included a comprehensive assessment of factors contributing to overall quality of life [14].The target population of this study was people with advanced cancer of any origin. The sample was recruited from two tertiary care university hospitals. This was a cross-sectional study using data from the first assessment post-diagnosis, before start of oncology treatment.

The sample included people with unresectable stage 3A, 3B, or 4 non-small cell lung cancer (NSCLC); stage 3 or 4 upper gastrointestinal (GI) cancer; stage 4 colorectal, hepatobiliary, or head and neck (ENT) cancers; breast and prostate cancers with visceral metastases; all stages of pancreatic cancers; an estimated life expectancy of 3 months or more; and an Eastern Cooperative Oncology Group performance status score of 0 to 3 [15, 16]. People with symptomatic brain metastases were excluded from the study as well as those who were not able to follow the instructions.

Measures

The measurement framework for this study was based on the Wilson-Cleary model [17] of health-related quality of life. In addition to the personalized measure, both generic and cancer-specific QOL measures were used. Measures were chosen based on brevity, comprehensiveness, and inclusion of items on quality of life in addition to symptoms and function.

Personalized measure

The PGI, a personalized measure to identify the impact of specific conditions on QOL [7], has been used and validated in both noncancer populations [7, 18] and a variety of cancer populations [9, 10, 19–21].

PGI is completed in three steps: (1) patients identify the most important five areas of their life affected by cancer; (2) patients rate how much each area has been affected using a scale from 0 to 10, where 0 is the worst imaginable and 10 exactly as they would like it to be and how much; (3) patients now imagine that they have 12 tokens to spend to improve on the selected areas and they allocate these tokens to the areas according to their own priority. A global index is calculated by multiplying the ratings for each area in step 2 by the proportion of tokens given to that area in step 3, which are then summed to produce an index from 0 to 100 with higher scores indicating higher QOL. According to Ruta [7], the final score indicates the extent to which the reality falls short of patient's hopes and expectations for those areas of life for which they would most value an improvement [7, 22].

Generic health-related quality of life measures

Two measures were used: the EQ-5D$_{index}$ from the EuroQoL group [23, 24] and the SF-6D derived from the comprehensive SF-36 Health Survey. The EQ-5D™ is a brief generic measure that provides a descriptive system consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has three levels of response: no problems, some problems, and extreme problems. The EQ-5D™ describes 243 health states each with a unique index value calculated using country-specific weights [25–27] with values for EQ-5D$_{index}$ ranging from −0.6 to 1.0 [25, 28]. The EQ-5D$_{index}$ has been used extensively in population health and cancer research [29–32].

The SF-6D is a generic measure (39, 40) with six multilevel dimensions covered by the SF-36 Health Survey: physical functioning, role limitation ((combined role-physical and role-emotional)), social functioning, bodily pain, and mental health. Each dimension contains four to six levels of function or limitation. Therefore, the SF-6D index classifies 18,000 unique health states. The SF-6D index is calculated using preference weights obtained from a sample of the general

population using the standard gamble and ranges from 0.3 (worst health state) to 1.0 (best health state) [33]. The SF-6D has been widely used and validated in cancer population [34–39].

Cancer-specific quality of life measures

Two single-item and one multi-item measures were used. The single items were: (1) Edmonton Symptoms Assessment Scale (ESAS-Version 1) [40] QOL, with a rating scale from 0 to 10 with 10 being the worst possible QOL, and (2) McGill Quality of Life Questionnaire (MQOL) [15, 41–44], also with a 0 to 10 rating scale with 10 being the best QOL. The multi-item questionnaire was the existential subscale from the MQOL with six items, each rated on 0 to 10, scale with 0 meaning the worst and 10 being the best. The ESAS is a brief cancer-specific measure of symptom severity and it is a valid and reliable tool to help in the assessment of nine symptoms commonly experienced by cancer patients (pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, itching, and shortness of breath) and one item for overall quality of life [45, 46].

McGill QOL questionnaire was developed to measure QOL at all stages of the disease trajectory for people with a life-threatening illness such as cancer [15, 41–44]. There are five MQOL sub-domains: physical symptoms (items 1–3), physical well-being (item 4), psychological symptoms (items 5–8), existential (items 9–14), and support (items 15 and 16). The existential sub-domain captured aspects related to meaning of life considering the last 2 days. Many studies have shown that the total score and the sub-domain scores of the MQOL have a good validity (construct validity) and reliability (internal consistency reliability) for people with cancer and other palliative populations [15, 41–43, 47].

All of the measures used in this study, with the exception of the ESAS and the MQOL, have legitimate total scores [48] based on weighting the dimensions before summing. Therefore, from the ESAS and MQOL, we chose the two single items for QOL and the one sub-domain (existential) of the MQOL.

Procedure

This study was approved by the Institutional Review Board of the Faculty of Medicine of McGill University. People who met the study criteria were approached by a member of their primary oncology and medical team in order to obtain verbal consent. Once consent was granted, study personnel contacted the patients to explain the goals and procedures of the study. All participants gave written informed consent. At the first assessment, patients were interviewed on all study measures by trained research personnel.

Analysis

The first step was to identify the most frequently nominated areas using the PGI measure and to calculate the PGI score. Secondly, scores were calculated for all the measures and comparisons between personalized measure (PGI), generic measures (SF-6D, EQ-$5D_{index}$), and the cancer-specific measures (ESAS-qol, MQOL single items, and MQOL existential) made using generalized estimating equations (GEE) to account for the clustering of the questionnaire scores within person. All measures were transformed to range from 0 to 100 with 100 being the best QOL.

Spearman's correlation coefficient was used to measure the strength of the association between the PGI and the other QOL measures. The regression coefficients from the GEE model were used to calculate the difference between measures and the corresponding 95 % CIs, accounting for the correlation among measures. Also calculated from the regression coefficients were effect sizes (β/SE).

The Bland-Altman plot was used to depict differences between the measures under study here: the PGI and the EQ-$5D_{index}$, and the PGI and the SF-6D. While developed to depict agreement, in this context, the graphic representation permits a visualization of the variability in the magnitude of the latent variable QOL arising from using different measures of the latent construct. The latent construct is represented, on the *x*-axis, by the average of the scores of the two measures. The unique contribution to the latent construct from the different measures is shown on the *y*-axis as the difference between the two measures. If both measures equally represent the latent construct throughout its range, there will be no discernible pattern to the distribution of the difference along the latent construct.

Results

A total of 192 persons completed the PGI at baseline, and their characteristics are shown in Table 1. Table 2 lists the 11 most frequent areas of QOL affected by advanced cancer, at time of diagnosis, as documented using the PGI. Also indicated is whether or not the areas of QOL concern are present in the other study measures: EQ-$5D_{index}$, the SF-6D, the MQOL, and the ESAS. Overall, participants nominated 114 areas of QOL concern, using the PGI.

Participants nominated a wide range of QOL concern affected by cancer with fatigue being the most common, nominated by 39 % of participants, to mobility, nominated by 3.5 %. Fatigue was present as an item in the SF-6D, the MQOL, and the ESAS but not in the EQ-$5D_{index}$. Sleep function, the second most frequent area, was found only in the MQOL. Pain was the only area that was included in all of the measures. In the five top commonly nominated areas, the

Table 1 Demographic and clinical characteristics of the study population

Characteristics	*N* (%)
Age (63.8 ± 12.3)	
<35	4 (2)
36–50	19 (10)
51–64	74 (39)
≥65	95 (49)
Gender	
Women	79 (41)
Men	113 (59)
Cancer type	
Pancreatic	45 (23)
Non-small cell lung carcinoma (NSCLC)	33 (17)
Colorectal	23 (12)
Upper GI	23 (12)
Ear, nose, and throat cancer (ENT)	22 (11)
Breast	17 (9)
Hepatobiliary	15 (8)
Prostate	6 (3)
Urological	3 (1.6)
Retroperitoneal	1.(0.5)
Ovarian	1 (0.5)
Thyroid	1 (0.5)
Unknown	2 (1)

MQOL included all the areas (five areas) important to the people with advanced cancer, followed by the ESAS (four areas), the SF-6D (three areas), and then the EQ-5D$_{index}$ (two areas).

The average rating from the PGI was substantially lower (37 ± 25) than the average QOL ratings from generic measures (EQ-5D$_{index}$ (mean 66 ± 17) and SF-6D (mean 65 ± 14)). The correlations between the PGI and the generic measures were low (0.16 and 0.22 for EQ-5D$_{index}$ and SF-6D, respectively); the correlation between the two generic measures was moderate (0.53). The magnitude of the difference between the PGI and generic measure ranged from −28.5 to −27.5; effect size estimates ranged from −14.3 to −13.4 (see Fig. 1a). The results comparing the PGI with the cancer-specific QOL measures are shown in Fig. 1b. Correlations between the PGI and these measures were also low (range 0.12 to 0.18), and the magnitude of differences were similar for the MQOL single item (−26.7) and the ESAS single item (−26.1) and larger for the MQOL existential single item (−43.3).

Figure 2 represents the relationship between the PGI and the generic measures (EQ-5D$_{index}$ and SF-6D) using the Bland-Altman plot. The *y*-axis represents the difference between the PGI and each measure, EQ-5D$_{index}$ (Fig. 2a) and SF-6D (Fig. 2b). The *x*-axis represents the latent construct of QOL as the average between the two measures. The gray line, which is parallel to the *x*-axis, represents the line of equality (0 differences between measures). The middle red line represents the mean difference between the two measures. The upper and lower red lines represent the corresponding 95 % CI. The black dots represent the score of each participant on both measures. At the left end of the *x*-axis when the participant's QOL was poor, the score from the PGI was lower (except for

Table 2 The most frequent areas identified by cancer participants using PGI compared with items in generic measures and specific disease measure

Measure construct	Proportion of patients reporting problem *N* (%)	SF-6D	EQ-5D	MQOL (existential)	ESAS
PGI areas					
Fatigue	78 (39.2)	Y	*N*	Y	Y
Sleep function	45 (22.6)	N	N	Y	N
Pain	43 (21.6)	Y	Y	Y	Y
Appetite	35 (17.6)	N	N	Y	Y
Emotional function	30 (15.1)	Y	Y	Y	Y
Work	28 (14.1)	Y	Y	N	N
Recreation and leisure	16 (8.0)	Y	N	N	N
Socializing	15 (7.5)	Y	N	Y	N
Eating	14 (7.0)	N	N	N	N
Family relationship	11 (5.5)	N	N	N	N
Mobility	7 (3.5)	N	Y	N	N
Other domains (n = 103)			Self-care	Nausea, vomiting, diarrhea, sweating, past life reflection, physical well-being, support	SOB, drowsiness, itching, nausea

SOB shortness of breath

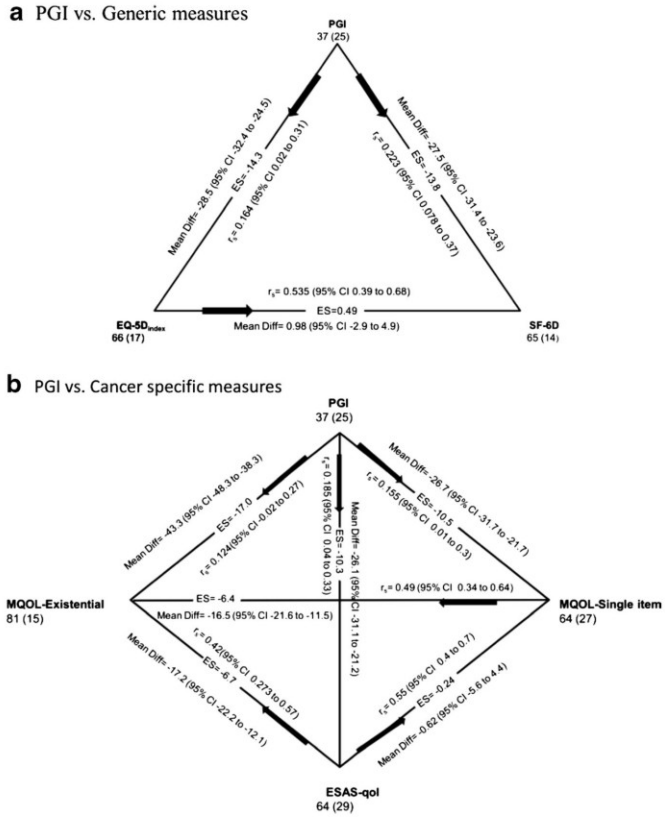


Fig. 1 The mean and standard deviation values for **a** PGI and generic measures with differences, Spearman's correlation, and 95 % CI calculated using generalized estimating equations and **b** PGI and cancer-specific measures

one observation) than the score obtained from the EQ-$5D_{index}$ (Fig. 2a). This was also observed for the middle range (shown in rectangle), where the majority of the observations were below the line of equality. However, at the right end of the *x*-axis, when the participant's QOL was good, there was no discernible pattern to the difference between the two measures. Similar results were found for the comparison between the PGI and SF-6D (Fig. 2b).

Discussion

The PGI identified a total of 114 areas of QOL concern, with the top three, fatigue, sleep disruptions, and pain. Other studies that have used the PGI in cancer samples also found this wide range of areas [9, 19]. Our findings are concordant with the literature on the importance of fatigue, sleep, and pain to QOL, as the most recent systematic reviews endorsed their importance [48–53].

This heterogeneity in QOL contributors is not reflected in standard QOL measures, either generic or cancer specific, as the combined measures used in our study queried only nine areas. All of the measures used in this study except the EQ-$5D_{index}$ included fatigue; sleep was only included in the MQOL. Pain, the third most frequently endorsed area, was the only domain that was included in all of the measures. In contrast, two of the ten top areas identified using the PGI (eating, family relationships; see Table 2) were not represented in any of the standard measures used here. ESAS, a symptom measure, captured all the important symptoms identified by the participants, except sleep disruption.

One of the most frequently used cancer-specific measures is the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) [54]. While we did not include this 30-item measure, its content has been shown to capture 25 domains related to symptoms and function and also includes three questions, one each on health perception, overall QOL rating, and financial impact of cancer [55]. The functional domains on the EORTC

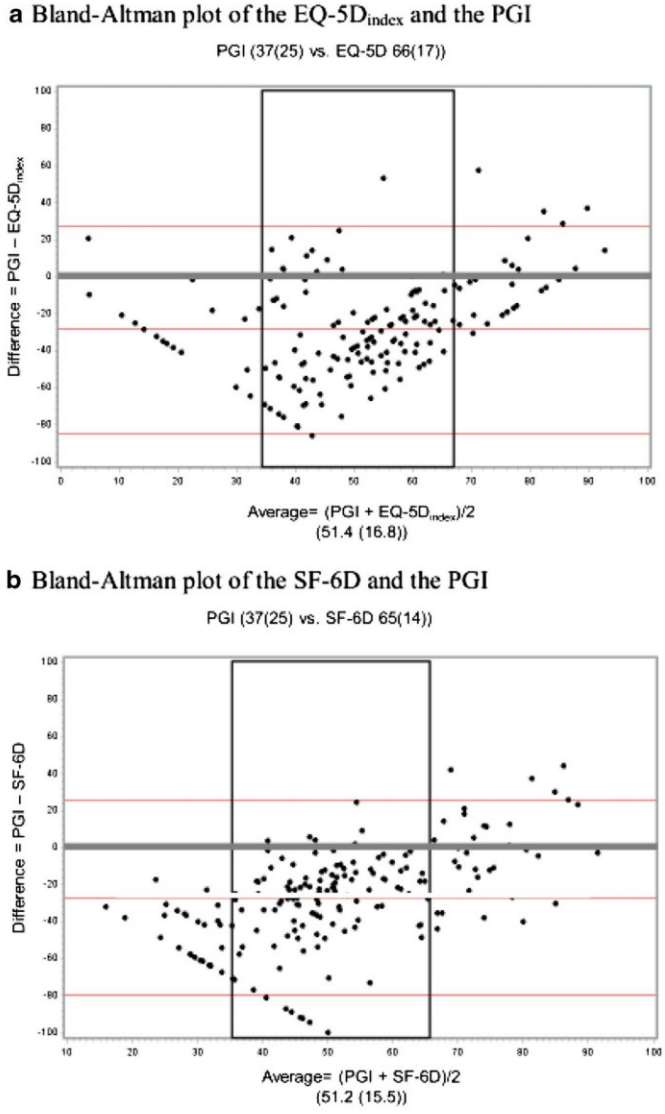


Fig. 2 Relationship between the PGI and the generic measures: **a** Bland-Altman plot of the relationship of the PGI and the EQ-5D$_{index}$ and **b** Bland-Altman plot of the relationship of the PGI and the SF-6D

were all nominated using the PGI and are present as items in the measures chosen for this study (see Table 2). Another widely used measure the Functional Assessment on Cancer Therapy—General Scale (FACIT-G) [56] comprises 27 items that capture 6 emotional impairments and 4 physical impairments (pain, fatigue, nausea, and insomnia); 2 items for work; 1 for role; and the remaining 14 items reflect aspects of QOL, general health, and environmental factors. These areas were all identified in the PGI.

This study found that the PGI consistently produced values for QOL that were lower than standard generic or cancer-specific measures of QOL. One reason for this is the scoring system which not only rates the severity of the impact of nominated areas but also weighs them in terms of their priority for intervention. For example, a person would get a low QOL score if an area has a large negative impact and receives a lot of "tokens," therefore identified as a very important priority. Another reason is that the PGI allows patients to mention

important QOL contributors that may not be captured by other measures. The other measures that use weights to derive total scores ($EQ\text{-}5D_{index}$ and SF-6D) have obtained these from the general population, not from people with cancer [57]. The consequence is that QOL is overestimated if measurement relies only on standard "one-size-fits-all" measures and/or weights. The PGI could be useful in the clinical setting as the combination of weight and priority for each contributor would probably be more effective in orientating interventions to improve overall QOL.

There was a low correlation between the PGI and the other study measures. This finding is supported by earlier studies that found low to moderate correlation between the PGI and EORTC and the PGI and the SF-36 [9, 19]. Also, our finding is in line with a study done in multiple sclerosis using the same methodology [58]. This further supports the importance of exploring the priority attached by the patient to the QOL contributors.

This was a study of a unique sample compromised entirely of people with advanced cancer before any oncological treatment for whom QOL is of primordial concern for making treatment and life decisions. Because a restricted number of QOL measures were included in the study based on the fewest items per questionnaire, in order not over burden the participants, direct comparisons with the well-known 30-item EORTC and the 27-item FACIT could not be performed.

The PGI may be an interesting instrument to evaluate the impact of clinical trials that target QOL. The standard measures tend to yield higher QOL ratings, and hence, comparisons with baseline may be disappointing as there is limited room for improvement with intervention. It would not be unusual for a cancer clinical trial to use the SF-6D or EQ-5D as an outcome [59]. If so, the effect of the intervention in a sample of patients with similar QOL as our study, considering a ½ SD effect size [60], would mean that the SF-6D would need to improve from a mean of 66 to a mean of 75 (and the $EQ\text{-}5D_{index}$, from 65 to 72), whereas the same effect size on PGI would require a change from 37 to 49, a more achievable change. For the cancer-specific measures, the SDs were as high as the PGI but the means were also higher indicating an important change would be difficult to achieve.

Conclusion

PGI is a personalized measure and was developed to identify the impact of a health condition on QOL. This study showed that, in comparison to commonly used generic and cancer-specific QOL measures, the PGI covers the widest spectrum of health concepts as it allows respondents to nominate, weigh, and prioritize any areas that are important to their QOL, not just those presented to them. The PGI has additional advantages in that it is short and easy to administer and yields a value farther away from the ceiling and with a lower standard error in comparison to standard measures. If only one QOL measure is to be included, either in a clinical setting or for research, the PGI would satisfy many of the criteria for "best choice" [61]. When used in a cancer population, the PGI could be considered a cancer-specific QOL measure.

Financial disclosure None.

Funding This study received funding from the Terry Fox Research Institute.

Conflict of interest

The authors declare that they have no competing interests.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statement of informed consent Informed consent was obtained from all individual participants included in the study.

References

1. WCRF International (2015) Cancer worldwide data. [cited 5/3]; Available from: http://www.wcrf.org/int/cancer-facts-figures/worldwide-data
2. de Boer AG et al (2008) Work ability and return-to-work in cancer patients. Br J Cancer 98(8):1342–1347
3. Hoffman B (2005) Cancer survivors at work: a generation of progress. CA Cancer J Clin 55:271–280
4. Lehmann JF et al (1978) Cancer rehabilitation: assessment of need, development, and evaluation of a model of care. Arch Phys Med Rehabil 59(9):410–419
5. Ness KK et al (2006) Physical performance limitations and participation restrictions among cancer survivors: a population-based study. Ann Epidemiol 16(3):197–205
6. O'Boyle CA et al (1992) Individual quality of life in patients undergoing hip replacement. Lancet 339(8801):1088–1091
7. Ruta DA et al (1994) A new approach to the measurement of quality of life. The Patient-Generated Index. Med Care 32(11):1109–1126
8. Broadhead JK, Robinson JW, Atkinson MJ (1998) A new quality-of-life measure for oncology: The SEIQoL. J Psychosoc Oncol 16(1):21–35
9. Tavernier SS et al (2011) Validity of the Patient Generated Index as a quality-of-life measure in radiation oncology. Oncol Nurs Forum 38(3):319–329
10. Tavernier SS, Totten AM, Beck SL (2011) Assessing content validity of the patient generated index using cognitive interviews. Qual Health Res 21(12):1729–1738
11. Frick E, Tyroller M, Panzer M (2007) Anxiety, depression and quality of life of cancer patients undergoing radiation therapy: a

cross-sectional study in a community hospital outpatient centre. Eur J Cancer Care 16(2):130–136
12. Montgomery C et al (2002) Individual quality of life in patients with leukaemia and lymphoma. Psychooncology 11(3):239–243
13. Waldron D et al (1999) Quality-of-life measurement in advanced cancer: assessing the individual. J Clin Oncol 17(11):3603–3611
14. Rodriguez AM, Mayo NE, Gagnon B (2013) Independent contributors to overall quality of life in people with advanced cancer. Br J Cancer 108(9):1790–1800
15. Cohen SR et al (1997) Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain. Palliat Med 11(1):3–20
16. Osoba D, King M (2005) Meaningful differences. In: Fayers PM, Hays RD (eds) Assessing quality of life in clinical trials, 2 edn. Oxford University Press, New York, pp. 243–257 p. 5 A.D. 251
17. Wilson IB, Cleary PD (1995) Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 273(1):59–65
18. Ruta DA, Garratt AM, Russell IT (1999) Patient centred assessment of quality of life for patients with four common conditions. Qual Health Care 8(1):22–29
19. Camilleri-Brennan J, Ruta DA, Steele RJ (2002) Patient generated index: new instrument for measuring quality of life in patients with rectal cancer. World J Surg 26(11):1354–1359
20. Lewis S et al (2002) Quality of life issues identified by palliative care clients using two tools. Contemp Nurse 12(1):31–41
21. Llewellyn CD, McGurk M, Weinman J (2006) Head and neck cancer: to what extent can psychological factors explain differences between health-related quality of life and individual quality of life? Br J Oral Maxillofac Surg 44(5):351–357
22. Calman KC (1984) Quality of life in cancer patients—an hypothesis. J Med Ethics 10(3):124–127
23. EuroQOL Group (1990) EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 16(3):199–208
24. Gudex C et al. (1996) Health state valuations from the general public using the visual analogue scale. Qual Life Res 5(6):521–531
25. Dolan P (1997) Modeling valuations for EuroQol health states. Med Care 35(11):1095–1108
26. Bansback N et al (2012) Canadian valuation of EQ-5D health states: preliminary value set and considerations for future valuation studies. PLoS One 7(2):e31115
27. Oremus M et al (2014) Health utility scores in Alzheimer's disease: differences based on calculation with American and Canadian preference weights. Value Health 17(1):77–83
28. Shaw JW, Johnson JA, Coons SJ (2005) US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 43(3):203–220
29. Lee JA et al (2014) Comparison of health-related quality of life between cancer survivors treated in designated cancer centers and the general public in Korea. Jpn J Clin Oncol 44(2):141–152
30. Shim EJ et al (2011) Comprehensive needs assessment tool in cancer (CNAT): the development and validation. Support Care Cancer 19(12):1957–1968
31. Glick HA et al (1998) Empirical criteria for the selection of quality-of-life instruments for the evaluation of peripheral blood progenitor cell transplantation. Int J Technol Assess Health Care 14(3):419–430
32. Pickard AS et al (2007) Health utilities using the EQ-5D in studies of cancer. PharmacoEconomics 25(5):365–384
33. Brazier J, Roberts J, Deverill M (2002) The estimation of a preference-based measure of health from the SF-36. J Health Econ 21(2):271–292
34. Hever, N.V., et al (2014) Health related quality of life in patients with bladder cancer: a cross-sectional survey and validation study of the Hungarian version of the bladder cancer index. Pathol Oncol Res
35. Gallop K et al (2015) A qualitative evaluation of the validity of published health utilities and generic health utility measures for capturing health-related quality of life (HRQL) impact of differentiated thyroid cancer (DTC) at different treatment phases. Qual Life Res 24(2):325–338
36. Teckle P et al (2013) Mapping the FACT-G cancer-specific quality of life instrument to the EQ-5D and SF-6D. Health Qual Life Outcomes 11:203
37. Lee L et al (2013) Valuing postoperative recovery: validation of the SF-6D health-state utility. J Surg Res 184(1):108–114
38. Barton GR et al (2008) An assessment of the discriminative ability of the EQ-5D index, SF-6D, and EQ VAS, using sociodemographic factors and clinical conditions. Eur J Health Econ 9(3):237–249
39. Hornbrook MC et al (2011) Complications among colorectal cancer survivors: SF-6D preference-weighted quality of life scores. Med Care 49(3):321–326
40. Bruera E et al (1991) The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 7(2):6–9
41. Cohen SR et al (2001) Changes in quality of life following admission to palliative care units. Palliat Med 15(5):363–371
42. Cohen SR, Mount BM (2000) Living with cancer: "good" days and "bad" days—what produces them? Can the McGill quality of life questionnaire distinguish between them? Cancer 89(8):1854–1865
43. Cohen SR et al (1995) The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. Palliat Med 9(3):207–219
44. Cohen SR et al (1996) Existential well-being is an important determinant of quality of life. Evidence from the McGill Quality of Life Questionnaire. Cancer 77(3):576–586
45. Nekolaichuk CL et al (1999) Assessing the reliability of patient, nurse, and family caregiver symptom ratings in hospitalized advanced cancer patients. J Clin Oncol 17(11):3621–3630
46. Chang VT, Hwang SS, Feuerman M (2000) Validation of the Edmonton Symptom Assessment Scale. Cancer 88(9):2164–2171
47. Cohen SR et al (1996) Quality of life in HIV disease as measured by the McGill quality of life questionnaire. AIDS 10(12):1421–1427
48. Glare PA et al (2014) Pain in cancer survivors. J Clin Oncol 32(16): 1739–1747
49. Denlinger CS et al (2014) Survivorship: sleep disorders, version 1.2014. J Natl Compr Cancer Netw 12(5):630–642
50. Dickerson SS et al (2014) Sleep-wake disturbances in cancer patients: narrative review of literature focusing on improving quality of life outcomes. Nat Sci Sleep 6:85–100
51. Moens K, Higginson IJ, Harding R (2014) Are there differences in the prevalence of palliative care-related problems in people living with advanced cancer and eight non-cancer conditions? A systematic review. J Pain Symptom Manag 48(4):660–677
52. Olson K (2014) Sleep-related disturbances among adolescents with cancer: a systematic review. Sleep Med 15(5):496–501
53. Otte JL et al (2015) Systematic review of sleep disorders in cancer patients: can the prevalence of sleep disorders be ascertained? Cancer Med 4(2):183–200
54. Aaronson NK et al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85(5):365–376
55. Letellier, M.E., D. Dawes, and N. Mayo (2014) Content verification of the EORTC QLQ-C30/EORTC QLQ-BR23 with the International Classification of Functioning, Disability and Health. Qual Life Res
56. Cella DF et al (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 11(3):570–579

57. Dolan P (1999) Whose preferences count? Med Decis Mak 19(4): 482–486
58. Kuspinar A, Mayo NE (2013) Do generic utility measures capture what is important to the quality of life of people with multiple sclerosis? Health Qual Life Outcomes 11:71
59. Garratt A et al (2002) Quality of life measurement: bibliographic study of patient assessed health outcome measures. BMJ 324(7351):1417
60. Norman GR, Sloan JA, Wyrwich KW (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 41(5): 582–592
61. McHorney CA, Tarlov AR (1995) Individual-patient monitoring in clinical practice: are available health status surveys adequate? Qual Life Res 4(4):293–307

CHAPTER 6: RATIONALE AND PREFACE TO MANUSCRIPT 3

The global objective of Manuscript 2 was to contribute evidence to validate the PGI as a QOL measure in people with advanced cancer. The specific objective was to identify similarities and differences in ratings of global QOL between personalized and standard measures. A total of 192 People with advanced cancer completed five QOL measures at study entry: PGI, generic measures (SF-6D, EQ-5D), and cancer-specific measures of QOL (McGill Quality of Life Questionnaire and Edmonton Symptoms Assessment Scale).

People with advanced cancer identified 114 areas of QOL that are of concern by the PGI, with the top three being, fatigue, sleep disruptions, and pain. PGI covers a wide range of QOL concerns in comparison to commonly used generic and cancer specific QOL measures. People with advanced cancer consistently scored lower in the PGI than other standard generic or cancer specific QOL measures, particularly when QOL was poor. There also were low correlations between PGI and other measures (generic and cancer specific QOL measures).

The validly of the PGI at the global score was investigated in the previous manuscript. To further support the value of using a measure like the PGI for clinical and research purposes, Manuscript3 addresses the relationship between what patients self-nominate and rate for severity using the PGI and what would be ascertained from items on fully standardized measures. This information would contribute evidence towards the validity of personalized measures in the context of cancer. Manuscript 3 will contribute evidence to validate the PGI at the item and domain level. Items pertaining to fatigue, pain and physical function were selected to evaluate the validity of the PGI at the item level.

Fatigue and pain are the most common symptoms in cancer ranging from 25% to 99% and from 62% to 86% , respectively. The effect of cancer on physical function has been long documented. Thus, the main objective of Manuscript 3 was to estimate how well fatigue, pain, and physical function identified on the PGI (a personalized measure) agree with ratings obtained from standard outcome measures (non-personalized measures).

CHAPTER 7: MANUSCRIPT 3

Agreement between Personally Generated Areas of Quality of Life Concern and Standard Outcome Measures in People with Advanced Cancer

Ala' S Aburub, B Gagnon, A M Rodríguez, Nancy E. Mayo

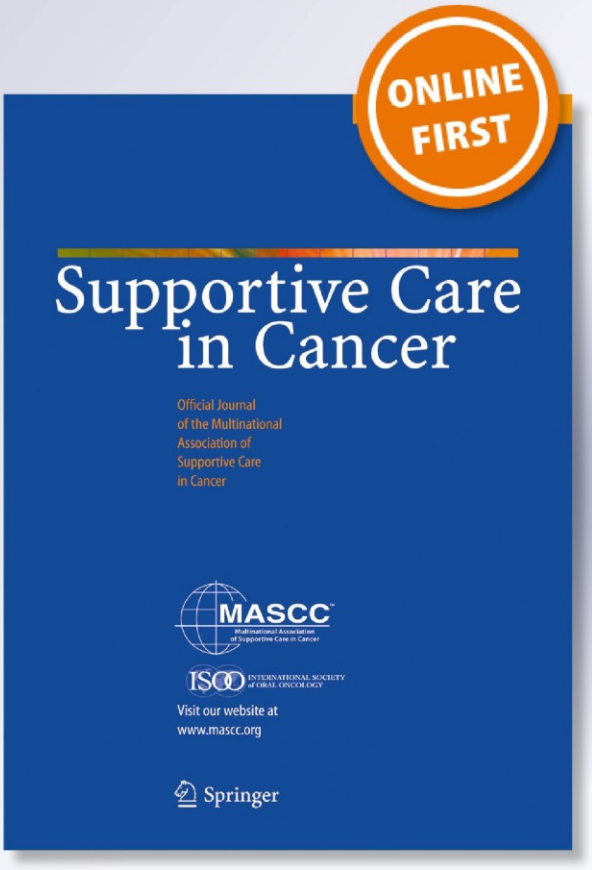
Agreement between personally generated areas of quality of life concern and standard outcome measures in people with advanced cancer

Ala' S Aburub, B. Gagnon, A. M. Rodríguez & Nancy E. Mayo

Supportive Care in Cancer

ISSN 0941-4355

Support Care Cancer
DOI 10.1007/s00520-016-3204-4



Springer

Support Care Cancer
DOI 10.1007/s00520-016-3204-4

ORIGINAL ARTICLE

Agreement between personally generated areas of quality of life concern and standard outcome measures in people with advanced cancer

Ala' S Aburub[1] · B. Gagnon[2] · A. M. Rodríguez[3] · Nancy E. Mayo[1]

Received: 22 October 2015 / Accepted: 1 April 2016

Abstract
Purpose People with advanced cancer experience different sequelae which have unique effects on quality of life (QOL). The patient-generated index (PGI) is a personalized measure that allows patients to nominate, rate, and value areas that have the most impact on QOL. Fatigue, pain, and aspects of physical function are among the top 10 areas with QOL impact. An area of validation that is lacking for the PGI is the extent to which spontaneously nominated areas of QOL that patients are concerned with, agree with ratings obtained from standard patient reported outcomes (PROs).

Methods Data from 192 patients were used to compare ratings on fatigue, pain, and physical function obtained from PGI to those from standard outcome measures.
Results Within one severity rating, agreement ranged from 32.1 to 76.9 % within the fatigue domain, 34.2 to 95.24 % for pain, and between 84.2 and 94.7 % for physical function. Of the 10 items where the PGI had the highest agreement, 7 came from the RAND-36. At the domain level, people nominating an area scored in the more impaired range on standard measures than people who did not.
Conclusion PGI gives comparable information as do standard measures.
Implications for cancer PGI provides important information to guide clinical care of the patient and also produces a legitimate total score suitable for research.

Electronic supplementary material The online version of this article (doi:10.1007/s00520-016-3204-4) contains supplementary material, which is available to authorized users.

✉ Ala' S Aburub
ala.aburub@mail.mcgill.ca

B. Gagnon
gagnon.bruno@crchuq.ulaval.ca

A. M. Rodríguez
Ana.rodriguez@mcgill.ca

Nancy E. Mayo
nancy.mayo@mcgill.ca

[1] School of Physical and Occupational Therapy, Division of Clinical Epidemiology, McGill University Department of Medicine, 687 Pine Ave W, Ross Pavilion R4.29, Montreal H3A 1A1, QC, Canada

[2] Département de Médecine Familiale et de Médecine d'urgence, Centre de Recherche sur le Cancer, Universite Laval, Centre de recherche du CHU de Québec, 9 rue McMahon, Local Qc, G1R 2J6, Québec 1899-6, Canada

[3] School of Rehabilitation Sciences, McGill University, 3654 Prom Sir-William-Osler, Montréal H3G 1Y5, Québec, Canada

Published online: 12 April 2016

Keywords Advanced cancer · Personalized measure · Patient-generated index · Quality of life · Patient-reported outcomes · Validity · Psychometric properties

Introduction

People with cancer experience a wide range of burdensome symptoms due to cancer itself and/or its treatments that negatively impact quality of life (QOL) [1]. Including emotional distress, people with cancer commonly experience fatigue, pain, and limitation in physical function [2, 3] A 2015 survey conducted on 528 individuals (57 % women; age range of 18 to 75 years) with different types of cancer showed that only half of the patients with symptoms such as fatigue, pain, or emotional distress were offered treatment [4]. This low rate was attributed to inability of the health care providers to routinely identify these symptoms.

In a recent study from our research group [5], we asked 192 people with advanced cancer to identify the areas of QOL most affected by their cancer. A total of 114 areas were nominated and the most prevalent were as follows: fatigue (39 %), sleep (23 %), pain (22 %), appetite (18 %), emotional health (15 %), work (14 %), recreation (8 %), socialization (8 %), eating (7 %), family relationships (6 %), and mobility (4 %). The heterogeneity of cancer impact is very high as even the top area, fatigue, was only nominated by 39 %. Of these areas, rehabilitation strategies are effective in targeting fatigue, pain, and physical function.

Cancer-related fatigue (CRF), a concern for 25 to 99 % of the cancer population [6, 7], is reduced by exercise [8, 9] and is therefore one of the symptoms for which there are effective interventions. In fact, the National Comprehensive Cancer Network guidelines recommend that to reduce CRF, people with cancer should do 30 min of physical activity at a moderate intensity, starting at low intensity, low duration, and progressing gradually [10, 11].

Pain was commonly identified for people with advanced cancer, ranging from 62 to 86 % [12, 13]. People experience pain as a complex symptom that negatively affects all aspects of function activity, participation in life's roles, social life, and emotional well-being [14]. Pain can be due to the cancer itself or the effects of treatment or to processes that are unrelated biologically to the cancer but heightened by emotional distress [15]. Treatment for pain is of primordial concern for cancer care.

The effect of cancer on physical function has been long documented. In 1978, a study on a sample of 805 patients with cancer showed that more than one third had difficulties arising from weakness and fatigue leading to limitations in mobility and self-care [2]. More recently, using data from NHANES, there is evidence that more than half of cancer survivors will have one or more difficulties in physical performance [3]. Older people experience greater physical impact and rate of decline from cancer than do younger people [16]. Implicated in decline in physical function is disuse, poor nutrition, biological, and cachexic state [17–19]. Physical function is the most usual target of rehabilitation and where there is the most evidence for effectiveness [20–22].

Routine use of patient-reported outcome (PRO) measures is the recommended method to avoid overlooking important information and under-referring patients for treatment [23]. Three types of PROs have been used in the cancer population: generic, cancer-specific, and personalized measures. Generic measures are those that identify common health states using a classification system completed by patients but with QOL impact weights derived from the perspective of the general population; examples are the EQ-5D from the EuroQoL group [24, 25] and the Short From 36-item Health Survey (SF-36) [26]. These measures yield a legitimate total score as the items are weighted.

Cancer-specific measures are those that were specifically developed to identify the sequelae of cancer; examples are the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) [27], EORTC QLQ-BR23, Functional Assessment of Cancer Therapy General Scale (FACT-G-version 4) [28], Functional Assessment of Anorexia Cachexia Therapy (FAACT) [29], McGill QOL Questionnaire (MQOL) [30–32], and Edmonton Symptom Assessment Scale (ESAS) [33]. All of these measures are fully standardized, in that everyone is asked the same questions with the same response options. A total score is derived by summing the ordinal values from the response options.

Personalized measures are completely individualized and do not have fixed questions; instead, people identify those areas of personal concern. These have been used in a variety of health conditions including cancer; examples are the patient-generated index (PGI) [34] and Schedule for the Evaluation of Individual Quality of Life (SEIQOL) Direct Weighting (SEIQOL -DW) [35, 36]. These measures have an advantage over simply asking patients about their concerns as they yield legitimate total scores. The areas nominated serve as a patient-specific health state classification system and the patients' priority ratings are used as weights. Of the personalized measures, the PGI is very simple to use and has evidence for validity at the level of the total score, sufficient reliability for group comparisons, but limited evidence as yet for responsiveness [37–39]. No study has yet validated the PGI at the item level in any health condition.

Cancer-specific measures have more face validity than generic measures in a clinical setting [40]. As cancer patients are all different and have different sequelae with varying impact on their lives, fully standardized measures may not necessarily identify areas that need to be addressed by the health care team. Personalized measures could bridge the gap between the structured questionnaire approach and the qualitative clinical interview which may not be consistent across providers and patients while yielding a score that can be used in an analytical framework.

To further support the value of using a measure like the PGI in research and clinical practice, this study addresses the relationship between what patients self-nominate and rate for severity using the PGI, and what would be ascertained from items on fully standardized measures. This information would contribute evidence towards the validity of personalized measures in the context of cancer.

Objective

The objective of this study of patients with advanced cancer was to estimate how well fatigue, pain, and physical

function identified on the PGI (a personalized measure) agree with ratings obtained from standard outcome measures (non-personalized measures).

Methods

This study is embedded within a longitudinal study of anorexia/cachexia in people with advanced cancer and impact on quality of life [41]. The study was approved by McGill University Faculty of Medicine Institutional Review Board. The data collected at study entry was used for these analyses. The methods have been reported previously [5, 41]. Subjects with advanced cancer of any origin were recruited before starting oncology treatment at two tertiary care university hospitals. Advanced cancer was defined as unresectable stage 3A, 3B, or 4 non-small-cell lung cancer; stage 3 or 4 upper gastrointestinal cancer; stage 4 colorectal, hepatobilliary, or head and neck cancers; breast and prostate cancers with visceral metastases; and all stages of pancreatic cancers. Excluded were people with an estimated life expectancy of less than 3 months, an Eastern Cooperative Oncology Group Performance Status Score > 3, symptomatic brain metastases, or difficulty with following instructions.

Measurement section

The personalized measure used in this study was patient-generated index (PGI). PGI was developed to measure the impact of a health condition on QOL [34]. PGI consists of three phases: (1) nomination of the top five areas of life affected by the health condition, in this case cancer; (2) rating of the severity of these 5 areas plus a 6th area for all other aspects affecting QOL, using a scale from 0 to 10, where 0 is as bad as possible and 10 is as good as possible; and (3) distribution of 12 tokens among all 6 areas based on the importance for improvement, with more tokens spent on highly important areas. A global index score is calculated by multiplying the rating score in phase 2 by the proportion of the 12 tokens allocated to that area and summing over the six areas, where 0 is poorest possible QOL and 100 represents best QOL. Our previous study showed that fatigue, pain, and physical function (mobility) were among the frequent areas identified by cancer patients using PGI [5]: 39.2, 21.6, and 3.5 %, respectively. The standard PROs that include items related to fatigue, pain, and physical function were EQ-5D, SF-36, ESAS, MQOL, FAACT, and the Multidimensional Fatigue Inventory (MFI −20). Two performance-based outcomes (PerfRO) were available for physical function: the 2-min walk test (2MWT) [42], and gait speed.

Statistical methods

To facilitate comparison across items, all measures were transformed to range from 0 to 10 (0 as the worst level and 10 as the best level). As the standardized measures varied in the number of response options (3, 5, or 6), PGI severity rating on the 0 to 10 scale was converted to match the number of categories on standardized measures (see Table 1). National Comprehensive Cancer Network (NCCN) guidelines and other studies on cancer populations endorse that, on a scale of 0–10 (where 0 is none and 10 is severe), a score of 4 or greater for either pain or fatigue is considered a concerning score and requires comprehensive assessments [10, 43]. Thus, in this study, with a reverse scale (where 0 is severe and 10 is none), a cut-point for the concerning level is 6. Therefore, in this study, a score 0–6 is considered a concerning level of fatigue or pain, and a score of 7–10 is considered a non-concerning level. No such guidance is available for physical function so, to be consistent, the same cut-points were used.

The PGI and standard PROs were compared at the item level and the domain level. At the item level crude agreement and positive and negative predictive values (PPV; NPV) were estimated for each of fatigue, pain, and physical function. To estimate PPV and NPV, we took the perspective that the value on the standard PRO item represented the "true" value, and the PGI area nominated was the value to be "tested." For example, PPV for fatigue was calculated as the proportion of the people who endorsed a concerning level of fatigue on a PRO item out of all people nominating fatigue on the PGI. The NPV for fatigue was calculated as the proportion of the people who did not endorse a concerning level of fatigue on the PRO item out of all people who did not nominate fatigue.

At the domain level, independent *t* tests were used to compare mean and standard deviations (SD) of total scores from subscales of standardized measures representing fatigue, pain and physical function, between people nominating and not-nominating those respective areas using the PGI.

Results

A total of 192 patients completed the PGI and the standard measures at baseline and their characteristics are presented in Table 2. Table 3 presents total scores for the PGI and other QOL measures used in this study, along with the correlation with the PGI. The mean value for the PGI was 37 (SD 25), and the mean value for the EQ-5D was 66 (SD 17). The value for the PGI was statistically significantly lower than all other QOL measures [5]. The correlation between the PGI and the other measures never exceeded 0.2.

Figure 1 shows the a box and whisker plot of the distribution of the severity rating for each of the PGI nominated areas: fatigue, pain, and physical function. The "box" delineates the

Table 1 Conversion between response options on standardized measures and PGI severity rating

Standardized measure	PGI
3 categories	0–3; 4–6; 7–10
5 categories	0–1; 2–3; 4–6; 7–8; 9–10
6 categories	0–1; 2–3; 4–5; 6–7; 8–9; 10

interquartile range, the median is indicated by a solid line, the mean by a broken line, and the "whiskers" indicate the range.

Table 4 shows the degree to which the severity rating on the PGI (see Fig. 1) agreed with the severity score on corresponding items from standard PROs, for people nominating each of the areas of interest: fatigue, pain, and physical function. Nine fatigue items were identified from our battery of standardized measures; for pain and physical function, 5 and 4 items were identified, respectively. For these standardized items, the number of response options ranged from 3 to 10.

For the fatigue items from the RAND-36 with 6 response options, the agreement proportions ranged from 29.5 to 39.7 % at similar severity level and from 61.5 to 76.9 % within one severity level. For the MFI fatigue items, agreement ranged from 9.0 to 37.7 % at similar severity level and from 32.1 to 72.72 % within one severity level. For pain items, the highest agreement was for the EQ-5D item "I have pain/discomfort" (35.7 %) at similar severity level and (95.24 %) within one severity level, while the lowest was for the ESAS item "No pain or worst pain possible." For physical function items from the RAND-36, the agreements ranged from 26.3 to 47.4 % at similar severity level and from 84.2 to 94.7 % within one severity level (Table 4).

Table 2 Demographic and clinical characteristics of the study participants (n = 192) [50]

Characteristics	n (%)
Age (63.8 ± 12.3)	
23–50	23 (12)
51–64	74 (39)
≥ 65	95 (49)
Gender	
Men	113 (59)
Cancer type	
Gastrointestinal cancer	91 (47)
Non-small cell lung carcinoma (NSCLC)	33 (17)
Ear, nose and throat cancer (ENT)	22 (11)
Breast	17 (9)
Hepatobilliary	15 (8)
Genitourinary cancer	10 (5)
Retroperitoneal	1 (0.5)
Thyroid	1 (0.5)
Unknown	2 (1)

Supplemental Table 1 presents the results of the PPV and NPV for identifying a concerning level of fatigue, pain, or physical function according to whether the area was nominated (PPV) or not (NPV) when completing the PGI. For example, if fatigue was nominated, the PPV for a concerning score across matching items ranged from 61.3 to 110 %; if not nominated, the NPV was lower, ranging from 34.3 to 69.5 %. For pain, only 1 of 5 matching items had a PPV of less than 92 %. For physical function, PPVs ranged from 84.2 to 89.5 % with NPV from 61.8 to 86.5 %.

Table 5 summarizes the results of the PGI to the 10 best performing standard items. Of these items, 7 came from the RAND-36 covering physical function (3 items), fatigue (2 items), and pain (2 items). For physical function, there was 94.7 % agreement within one severity level for "walking more than a kilometer," and the positive predictive value was 89.5 % (negative predictive value 61.8 %). Nominating fatigue has a positive predictive value of 100 % for two corresponding items from RAND-36.

Table 6 shows the results of an independent t test at the domain level, for the participants who nominated each of the areas: fatigue, pain, and physical function, on the PGI at the baseline assessment and for the participants who did not nominate these areas. People who nominated an area scored significantly lower on corresponding PROs than people who did not nominate the domain. For example, for fatigue domain, the average score of the vitality (RAND-36) subscale for the participants who nominated fatigue was significantly lower (42.3 ± 21.2) than the participants who did not nominate fatigue (56.4 ± 24.9); for general fatigue (MFI: higher values indicating more fatigue), the corresponding values were 14.1 (SD 4.1) and 11.3 (SD 4.9), respectively.

For the physical function domain, the average score on physical function (RAND-36) for the participants who nominated physical function was significantly lower (51.6 ± 27.9) than the participants who did not nominate physical function(72.0 ± 24.3). However, for the performance outcomes using the 2-min walk test and the gait speed, there were no differences between participants who nominated physical function or not (Table 6).

Discussion

We found that if people nominated an area on the PGI, the degree of agreement with the corresponding PRO items varied across the areas nominated and items matching the area (see Table 4). For example, for fatigue, there was high agreement between PGI and fatigue items from the RAND-

Table 3 Comparison between total scores on PGI and other QOL measures

QOL measures	Mean (SD)	Spearman's correlation with PGI and 95 % confidence interval (CI)
PGI	37 (25)	–
EQ-5D	66 (17)	0.16 (0.02 to 0.31)
RAND-36	65 (14)	0.22 (0.08 to 0.37)
MQOL-Existential	81 (15)	0.12 (−0.02 to 0.27)
MQOL-Single item (QOL item)	64 (27)	0.15 (0.01 to 0.3)
ESAS-Single item (QOL item)	64 (29)	0.18 (0.04 to 0.33)

PGI patient-generated index, *ESAS* Edmonton Symptom Assessment Scale, *MQOL* McGill QOL Questionnaire, *RAND-36* 36-Item Short Form Health Survey (SF-36), *EQ-5D* EuroQol-5D

36 and MFI and low agreement for ESAS and MQOL items. There was also high agreement between PGI and pain and physical function items from RAND-36 with low agreement for pain items from ESAS.

There are a number of explanations for the similarities and differences in the strength of agreement across items including differences in the number of response options, wording, and time frame queried. The PGI uses the 11-point scale as does ESAS and MQOL but agreement was lowest with these items. ESAS queries fatigue and the time frame is at the time of completion. The wording of the MQOL item does not directly refer to fatigue but rather to feeling physically terrible or well and the time frame is over the past 2 days.

For the items from RAND-36 and MFI, the response options were 6 and 5 respectively, and so severity categories were made for the PGI and this would have increased the agreement. However, the PGI agreed most closely with items from RAND-36 which queries the past 4 weeks. As QOL, what is being asked in the PGI, is not an instantaneous construct, it is likely the time frames correspond. The time frame for the MFI is current or past days (unspecified number). The EQ-5D refers to today. Future work on the PGI could include cognitive debriefing as to the time frame people are thinking about when responding as well as other aspects contributing to areas, severity rating, and weighting. There has been one study using cognitive interviews of 15 people with cancer which found that the interpretation of the severity rating of 10, "As good as could possibly be," could mean less impact than expected, satisfaction with the severity, or they were happy despite the area. The 0 rating. "As bad as could possibly be" meant a high level of severity, or impact on coping or on usual activities. The severity rating most often used was based on how they felt on the day the PGI was completed and not over the previous week as instructed. The instructions on spending tokens were understood but respondents identified difficulty in having to choose areas as some were dependent on others. This interviewing supported content validity, but recommended clarification of instructions during administration and ensuring that patients understood the task at hand [44].

We also found that there were at least 10 items where the agreement and predictive values with the PGI was very high (see Table 5). Of these 10, 7 came from the RAND-36 which is provides strong evidence for validity of the PGI as the RAND-36 (original version of the SF-36) is one of the most widely used and extensively validated measures of health-related quality of life. It is interesting to note that people who nominated an area (pain, fatigue, and physical function) scored significantly lower on corresponding PROs at the

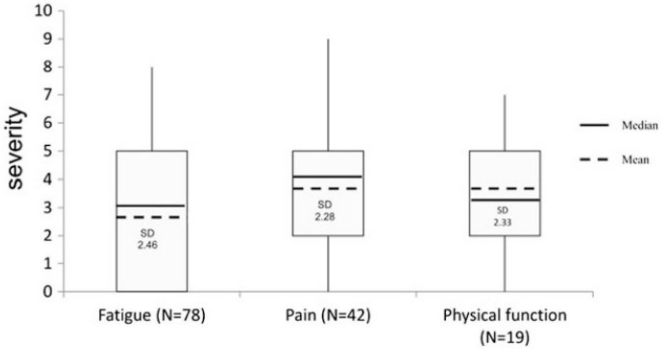


Fig. 1 A box and whisker plot of the distribution of the severity rating for each of the PGI nominated areas (fatigue, pain, and physical function)

Table 4 The comparison of severity rating between PGI and items from standard PROs

Areas	Number of response options	Source	Agreed *N* (%)	Δ ± 1 *N* (%)
Fatigue (n = 78)				
Did you feel tired?	6	RAND-36	31 (39.7)	60 (76.9)
Did you have a lot of energy?	6	RAND-36	23 (29.5)	48(61.5)
I feel tired	5	MFI	29 (37.7)	56 (72.7)
I tire easily	5	MFI	29 (37.7)	55 (71.4)
I think I do very little in a day	5	MFI	27 (35)	51 (66.2)
Physically, I feel only able to do a little	5	MFI	25 (32)	43 (55.1)
I do not feel like doing anything	5	MFI	11 (14.5)	30 (39.4)
No fatigue or worst fatigue possible	10	ESAS	7 (9.0)	25 (32.1)
Over the past two (2) days I have felt physically terrible or well	10	MQOL	13 (17.3)	29 (38.6)
Pain (n = 42)				
How much bodily pain have you had during the past 4 weeks?	6	RAND-36	13 (30.1)	31 (73.8)
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	5	RAND-36	10 (23.8)	25 (59.5)
I have pain/discomfort	3	EQ-5D	15 (35.7)	40 (95.24)
Physical well-being section; I have pain	5	FAACT	7 (16.6)	18 (42.8)
No pain or worst pain possible	10	ESAS	4 (9.8)	14 (34.2)
Physical function (n = 19)				
Walking more than a kilometer	3	RAND-36	9 (47.4)	18 (94.7)
Walking several blocks	3	RAND-36	7 (36.8)	16 (84.2)
Walking one blocks	3	RAND-36	5 (26.3)	16 (84.2)
Mobility	3	EQ-5D	8 (42.1)	16 (84.2)

To compare items with different response options we used this conversion: 3: PGI 0–3, 4–6, 7–10; 5: 0–1, 2–3, 4–6, 7–8, 9–10; 6: 0–1,2–3,4–5, 6–7, 8–9, 10

PGI patient-generated index *MFI* Multidimensional Fatigue Inventory, *ESAS* Edmonton Symptom Assessment Scale, *MQOL* McGill QOL Questionnaire, *RAND-36* 36-Item Short Form Health Survey (SF-36), *EQ-5D* EuroQol-5D

Table 5 Agreement parameters for best 10 performing items.

Items	Source	Agreed *N* (%)	Δ ± 1 *N* (%)	PPV (%)	NPV (%)
Walking more than a kilometer	RAND-36	9 (47.4)	18 (94.7)	89.5	61.8
Walking several blocks	RAND-36	7 (36.8)	16 (84.2)	84.2	72.4
Walking one block	RAND-36	5 (26.3)	16 (84.2)	89.5	86.5
Did you feel tired?	RAND-36	31 (39.7)	60 (76.9)	100	56.5
Did you have a lot of energy?	RAND-36	23 (29.5)	48 (61.5)	100	34.3
How much bodily pain have you had during the past 4 weeks?	RAND-36	13 (30.1)	31 (73.8)	92.9	70.4
During the past 4 weeks, how much did pain interfere with your normal?	RAND-36	10 (23.8)	25 (59.5)	92.9	57.8
I feel tired	MFI	29 (37.7)	56 (72.7)	93.5	42.8
I tire easily	MFI	29 (37.7)	55 (71.4)	93.5	35.6
I have pain/discomfort	EQ-5D	15 (35.7)	40 (95.24)	92.9	36.1

RAND-36 36-Item Short Form Health Survey (SF-36), *MFI* Multidimensional Fatigue Inventory, *EQ-5D* EuroQol-5D.

Table 6 The comparison between PGI severity score and the severity score from standard PROs at the domain level, for people who nominated fatigue, pain and physical function and for people who did not

Domains	Nominated mean (SD), [*n*]	Not nominated mean (SD), [*n*]	Pooled *t* test method *P* value
Fatigue			
Vitality (RAND-36)	42.3 (21.2), [78]	56.4 (24.9), [107]	<.0001
General fatigue subscale (MFI)	14.1 (4.1), [76]	11.3 (4.9), [103]	<0.001
Physical fatigue subscale (MFI)	13.8 (4.5), [75]	10.9 (4.9), [104]	<0.001
Pain			
Bodily pain (RAND-36 pain index)	40.4 (22.8), [38]	59.8 (28.9), [145]	0.0002
Physical function			
Physical function subscale (RAND-36)	51.6 (27.9), [17]	72.0 (24.3), [168]	0.0014
2-min walk test	115.1 (43.5), [17]	126.2 (36.8), [161]	0.2461
Comfortable speed	1.0 (0.38), [16]	1.1 (0.3), [159]	0.417
Fast speed	1.4 (0.35), [16]	1.5 (0.4), [158]	0.53

For RAND-36 subscales (vitality, pain, physical function), higher is better; for general and physical fatigue (MFI), higher is more fatigue. For performance measures (2-min walk test and gait speed) higher values are better

n sample size, *SD* standard deviation, *RAND-36* 36-Item Short Form Health Survey (SF-36), *MFI* Multidimensional Fatigue Inventory

domain level (see Table 6) than people who did not nominate an area, supporting construct validity. The average value on the RAND-36 Physical Function Index (PFI) was significantly lower in people who nominated physical function areas than who did not, but there was no difference in their performance on tests of walking capacity such as the 2-min walk test and the gait speed (Table 6). These performance outcomes test capacity to do simple activities at a sub-maximal intensity while the PFI queries some higher intensity activities such as climbing several flights of stairs, walking more an a kilometer, and doing vigorous activities.

This study has a number of limitations. Only 235 of 388 eligible patients consented (response rate 60.6 %), and of these 32 did not complete the initial evaluation. Thus, the group assessed could have differed from the group not assessed in important ways but these differences are unlikely to affect differentially the scoring of PGI and scoring of items on standard measures. People not entering the study likely have the same association between PGI areas and PRO measures.

Conclusion

The results indicate that PGI has high agreement with items for the RAND-36 and less agreement with items from other measures, likely owing to differences in time frame for response. The PGI has advantages for use in a clinical setting. It directly queries, in only a few minutes, the personal concerns of each patient, and to obtain the same information, it would be necessary to use a number of multi-item PRO measures. In a busy clinical setting, this personalized patient-centered outcome could be a valuable method of enhancing communication and guiding clinical care. In addition to its clinical relevance, the PGI does produce a legitimate total score but more validation is needed to determine if the PGI could be used alone, or as an adjunct to other QOL measures, to more specifically reflect the QOL impact and the effects of interventions targeting this important outcome.

Compliance with ethical standards

Funding This research was supported by a grant from the Terry Fox Research Institute and by the Cancer Research Society/Rob Lutterman Pancreatic Cancer Research Grant. B Gagnon is a recipient of "Chercheur-clinicien Boursier" award from Fond de Recherche Santé Québec, Québec, Canada.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

References

1. Smith T et al. (2007) The rationale, design, and implementation of the American Cancer Society's studies of cancer survivors. Cancer 109(1):1–12
2. Lehmann JF et al. (1978) Cancer rehabilitation: assessment of need, development, and evaluation of a model of care. Arch Phys Med Rehabil 59(9):410–419
3. Ness KK et al. (2006) Physical performance limitations and participation restrictions among cancer survivors: a population-based study. Ann Epidemiol 16(3):197–205
4. Zucca A et al. (2015) Medical oncology patients: are they offered help and does it provide relief? J Pain Symptom Manag 50(4):436–444

5. Aburub AS et al. (2016) Using a personalized measure (Patient Generated Index (PGI)) to identify what matters to people with cancer. Support Care Cancer 24(1):437–445
6. Donnelly S, Walsh D (1995) The symptoms of advanced cancer. Semin Oncol 22(2 Suppl 3):67–72
7. Morrow GR et al. (2005) Management of cancer-related fatigue. Cancer Investig 23(3):229–239
8. Mayo NE et al. (2014) Pedometer-facilitated walking intervention shows promising effectiveness for reducing cancer fatigue: a pilot randomized trial. Clin Rehabil 28(12):1198–1209
9. Cramp, F. and J. Daniel, Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev, 2008(2): p. Cd006145.
10. Cancer-related fatigue. (2003) Clinical practice guidelines in oncology. J Natl Compr Cancer Netw 1(3):308–331
11. Network, N.C.C., Clinical practice guidelines in oncology—cancer-related fatigue., 2009. V2.2009.
12. Di Maio M et al. (2004) Prevalence and management of pain in Italian patients with advanced non-small-cell lung cancer. Br J Cancer 90(12):2288–2296
13. Stromgren AS et al. (2004) Pain characteristics and treatment outcome for advanced cancer patients during the first week of specialized palliative care. J Pain Symptom Manag 27(2):104–113
14. Knudsen AK et al. (2009) Classification of pain in cancer patients—a systematic literature review. Palliat Med 23(4):295–308
15. Kocoglu H et al. (2002) Cancer pain, pathophysiology, characteristics and syndromes. Eur J Gynaecol Oncol 23(6):527–532
16. Lunney JR et al. (2003) Patterns of functional decline at the end of life. JAMA 289(18):2387–2392
17. Friedenreich CM, Orenstein MR (2002) Physical activity and cancer prevention: etiologic evidence and biological mechanisms. J Nutr 132(11 Suppl):3456S–3464S
18. McMichael AJ (2008) Food, nutrition, physical activity and cancer prevention. Authoritative report from World Cancer Research Fund provides global update. Public Health Nutr 11(7):762–763
19. McTiernan A (2008) Mechanisms linking physical activity with cancer. Nat Rev Cancer 8(3):205–211
20. Midtgaard J et al. (2015) Cancer survivors' experience of exercise-based cancer rehabilitation—a meta-synthesis of qualitative research. Acta Oncol 54(5):609–617
21. Salakari MR et al. (2015) Effects of rehabilitation among patients with advances cancer: a systematic review. Acta Oncol 54(5):618–628
22. Weis J, Giesler JM (2014) Rehabilitation for cancer patients. Recent Results Cancer Res 197:87–101
23. Dimoska A et al. (2008) Can a "prompt list" empower cancer patients to ask relevant questions? Cancer 113(2):225–237
24. Group EQOL (1990) EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 16(3):199–208
25. Gudex C et al. (1996) Health state valuations from the general public using the visual analogue scale. Qual Life Res 5(6):521–531
26. Ware JE Jr (2000) SF-36 health survey update. Spine (Phila Pa 1976) 25(24):3130–3139
27. Aaronson NK et al. (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85(5):365–376
28. Cella DF et al. (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 11(3):570–579
29. Ribaudo JM et al. (2000) Re-validation and shortening of the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire. Qual Life Res 9(10):1137–1146
30. Cohen SR, Mount BM (2000) Living with cancer: "good" days and "bad" days–what produces them? Can the McGill quality of life questionnaire distinguish between them? Cancer 89(8):1854–1865
31. Cohen SR et al. (1997) Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain. Palliat Med 11(1):3–20
32. Cohen SR et al. (1995) The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. Palliat Med 9(3):207–219
33. Bruera E et al. (1991) The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care 7(2):6–9
34. Ruta DA et al. (1994) A new approach to the measurement of quality of life. The Patient-Generated Index. Med Care 32(11): 1109–1126
35. Hickey AM et al. (1996) A new short form individual quality of life measure (SEIQoL-DW): application in a cohort of individuals with HIV/AIDS. BMJ 313(7048):29–33
36. Joyce CR et al. (2003) A theory-based method for the evaluation of individual quality of life: the SEIQoL. Qual Life Res 12(3):275–280
37. Ruta DA, Garratt AM, Russell IT (1999) Patient centred assessment of quality of life for patients with four common conditions. Qual Health Care 8(1):22–29
38. Phantipa Sakthong P (2014) Win Winit-Watjana, MD2, Kobkan Choopan, MSc (Clin Pharm)3, Usefulness of Patient-Generated Index for HIV to measure individual quality of life: a study from Thailand. V A L U E I N H E A L T H R E G I O N A L I S S U E S 3:101–107
39. Martin F et al. (2007) Twelve years' experience with the Patient Generated Index (PGI) of quality of life: a graded structured review. Qual Life Res 16(4):705–715
40. Machhin, P.M.F.a.D., Qulaity of life, second edition: the assessment, analysis and interpretation of patients reported outcomes. 2007.
41. Rodriguez AM, Mayo NE, Gagnon B (2013) Independent contributors to overall quality of life in people with advanced cancer. Br J Cancer 108(9):1790–1800
42. Bohannon RW, Wang YC, Gershon RC (2015) Two-minute walk test performance by adults 18 to 85 years: normative values, reliability, and responsiveness. Arch Phys Med Rehabil 96(3):472–477
43. Mock V et al. (2007) Cancer-related fatigue. clinical practice guidelines in oncology. J Natl Compr Cancer Netw 5(10):1054–1078
44. Tavernier SS, Totten AM, Beck SL (2011) Assessing content validity of the patient generated index using cognitive interviews. Qual Health Res 21(12):1729–1738

Supplemental Table 1 The positive and negative predictive value for the PGI areas

Areas	Source	Nominated		Not nominated		Test	
		Concerning score *a	Not concerning score **b	Concerning score °c	Not concerning score °°d	×PPV	××NPV
Fatigue							
Did you have a lot of energy?	RAND-36	78	0	71	37	100	34.3
Did you feel tired?	RAND-36	78	0	47	61	100	56.5
Physically, I feel only able to do a little	MFI	74	4	50	55	94.9	52.4
I feel tired	MFI	72	5	60	45	93.5	42.8
I tire easily	MFI	72	5	67	37	93.5	35.6
I think I do very little in a day	MFI	72	5	50	55	93.5	52.4
I don't feel like doing anything	MFI	70	6	32	73	92.1	69.5
No fatigue or worst fatigue possible	ESAS	50	28	47	61	64.1	56.5
Over the past two (2) days I have felt physically terrible or well	MQOL	46	29	40	68	61.3	63.0
Pain							
How much Bodily pain have you had during the past 4 weeks?	RAND-36	39	3	71	76	92.9	70.4
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	RAND-36	39	3	62	85	92.9	57.8
I have pain/ discomfort	EQ-5D	39	3	94	53	92.9	36.1
I have pain (Physical well being section)	FAACT	38	3	40	107	92.7	72.8
No pain or worst pain possible	ESAS	23	18	55	91	56.1	62.3
Physical function							
Walking more than a kilometer	RAND-36	17	2	65	105	89.5	61.8
Walking one block	RAND-36	17	2	23	147	89.5	86.5
Walking several blocks	RAND-36	16	3	47	123	84.2	72.4
Mobility	EQ-5D	17	2	40	130	89.5	76.5

***a** Concerning score (0-6) for people who nominated an area . ****b** Not Concerning score (7-10) for people who nominated an area. **°c** Concerning score (0-6) for people who did not nominate an area. **°°d** Not concerning score (7-10) for people who did not nominate an area **×PPV** Positive predictive value = a*/ (a*+**b)*100 **××NPV** Negative predictive value = °°d /(°c+°°d) *10.

Chapter 8 : RATIONALE AND PREFACE TO MANUSCRIPT 4

In Manuscript 2, the results showed that fatigue, pain, and physical function were among the top areas nominated by people with advanced cancer as impacting on QOL. In Manuscript 3, the main aim was to estimate, for people with advanced cancer, how well fatigue, pain, and physical function identified on the Patient Generated Index (PGI) (a personalized measure) agreed with ratings obtained from standard outcome measures (non-personalized or fully standardized measures). Data from 192 patients were used to compare ratings on fatigue, pain and physical function obtained from PGI to those from standard outcome measures such as PGI, RAND-36,EQ-5D, Edmonton Symptoms Assessment Scale (ESAS), McGill Quality of Life Questionnaire (MQOL). The results indicated that PGI has high agreement with items from the RAND-36 and less agreement with items from other measures (ESAS and MQOL) likely owing to differences in time frame for response. In a busy clinical setting, this personalized patient-centered outcome (e.g. PGI) could be a valuable method of enhancing communication, guiding clinical care, endorsing personal concerns of each patient and it only takes few minutes. In these two manuscripts, evidence was provided for the validity of the PGI at the item and at the domain level.

A challenge with using any measure of QOL to assess change, and in this context change among people with cancer, is that people may experience true change in their QOL due to cancer progression or change may occur because of adaption to the disease inducing a response shift. Using an individualized measure of QOL, such as the PGI, is one of the direct ways of identifying response shift [1], as these measures typically ask patients to nominate areas that

affect their QOL due to their disease, rate the severity of the nominated areas, and weight these areas in terms of desire for improvement.

Response shift is defined as the change in the meaning of a person's self evaluation of a target construct (e.g., QOL) over time, as a result of (1) changes in the internal standards (recalibration) of the measurement, (2) changes in the respondent's values (changes in importance of the items or component domains that constitute QOL concept (reprioritization), and (3) changes in the definition of the targeted construct (redefinition QOL) (reconceptualization) [2]. As an example of recalibration, a person with cancer may rate his/her fatigue prior to chemotherapy/radiotherapy as 7 on a scale of 0-10, where 0 no fatigue and 10 is severe. However, after experiencing chemotherapy/radiotherapy and the acute fatigue associated with these therapies, they later rate their fatigue level as 4 out of 10 even though in comparison to the 7 indicated prior to treatment, they actually have more, not less fatigue. The overwhelming fatigue experienced from chemotherapy led to a recalibration of the internal scale used to rate fatigue. For reprioritization, a person prior to a serious health condition may consider social and recreational activities more important than relationships with family, but after a cancer experience, the person reprioritizes relationships with family as more important. An example of reconceptualization is when a person defines good QOL as "having money and a new car" but after a cancer experience defines QOL as "being healthy and independent".

Sprangers and Schwartz have proposed a theoretical model of response shift and QOL [2] and this model was updated in 2004 by Rapkin and Schwartz [3], such that response shift occurs in the presence of a catalyst (e.g. event or health status change), which is influenced by antecedents (e.g. personal characteristics such as experience or expectation), mechanisms (e.g. coping or

adaptation), and appraisal (e.g. frame of reference) (See Figure 1 and 2). Response shift can be in the positive direction when a person rates their perceived QOL higher than expected regardless if there is improvement in health or not; or it can be in the negative direction if the perceived QOL is lower than the expected.

Oort and colleagues define response shift from two perspectives, measurement and conceptual. From the measurement perspective, response shift is defined as measurement bias and from the conceptual perspective as explanation bias [4]. A catalyst is considered an explanatory variable and antecedents and mechanisms are violator or confounder variables. They define response shift as a measurement bias if the violator variables (antecedents or mechanisms) rather than the true QOL effect observed QOL. This differs from response shift as an explanation bias which occurs if any variable other than the catalyst (explanatory variable) has an effect on the true QOL. Candidate variables would be part of the appraisal process where people change their goals, priorities, or frame of reference for valuing QOL [5].

Other researchers consider response shift a desired effect, something to be promoted, so that people can feel good about themselves and achieve satisfaction in their life despite impairments or other limitations and restrictions in life's roles [6-11].

Osborne et al. showed that people involved in a self management program experienced a positive response shift as result of learning better coping techniques and developing better skills to deal with their conditions [7]. Mayo et al. showed that over the course of the first-year post-stroke, 13% of people experienced a positive response shift while 15% experienced negative response shift and 67% no response shift [10]. The authors concluded that only the 13% with a positive response shift had a good outcome following stroke as they were able to consider their health to

be better over time despite the “bits of their body that didn’t work”. In general, people experience response shift to maintain their equilibrium after a major stressful event [1, 12, 13] thus, response shift should be looked at as a desired phenomenon.

There is a substantial literature on response shift dating back decades including a landmark text book [13]. The main methods of addressing response shift involve querying people or querying the data using statistical methods. In the context of this thesis, querying the people is most relevant. Statistical methods for response shift have been reviewed [1, 14].

The methods to obtain input from individuals experiencing change need to be designed into the data collection procedures and do involve additional respondent burden [15, 16] and, thus, may not be suitable for all populations.

Then-test is a retrospective method in which patients are asked at the post-test evaluation to re-rate their health at an earlier evaluation [17]. Then-test is relatively easy to administer and analyze, it provides the possibility of adjusting for response shift, and does not need large sample size [18]. However, Then-test leads to recall bias if patients have poor memory and are not able to recall their pervious heath state [19, 20]. Then-test reflects recalibration (change in internal standards) as the re-evaluation is based on the standards they now have whereas the original valuation was based on different standards. Response shift is calculated as the difference between the scores on the pretest and then-test[15]. The challenge with the Then-test is incorporating the findings in to the analysis. Would “Then-test adjusted change” be a legitimate outcome of a clinical trial?[21].

Successive comparison approaches such as pair-wise comparisons [22] and the card sort approach [23]. In pair-wise comparisons, people are asked to rate the relative importance of multiple areas presented pair-wise. The change in relative importance overtime is considered to represent reprioritization response shift. This method is reliable however it requires a lot of time to collect the data. In the card sort approach, patients are asked to order a list of life domains (>7) according to their importance to their life. Change in ordering reflects reprioritization response shift. This method is also time consuming and difficult to administer in patients with cognitive impairment [15].

A very direct approach is to ask respondents why two ratings on QOL may have differed [1]. A challenge is that people may not know, while others may have multiple reasons why change occurred.

The Then-test and the direct questioning methods are suitable for single items or very few items and would not be suitable for multi-item questionnaires. However, the availability of personalized or individualized measures provide a way of measuring response shift at a more global level. Personalized approaches allow patients to nominate, rate, and weight the important areas to their QOL.

Individualized measures can be used to detect reconceptualization and reprioritization response shift. For example, if patients change the weight (here the number of tokens) distributed across the nominated areas and there is no change in the content reprioritization response shift can be inferred. Reconceptualization response shift can be inferred if areas changed construct (e.g. people dropped areas or added new areas).

Little work has been done on response shift in the cancer population although the diagnosis, health impact, treatment, and transition into survivorship would act as strong catalysts for response shift. Therefore, the objective of manuscript 4 was to estimate the extent to which reconceptualization response shift occurred over time in cancer population and the impact of this response shift on estimated change in QOL.

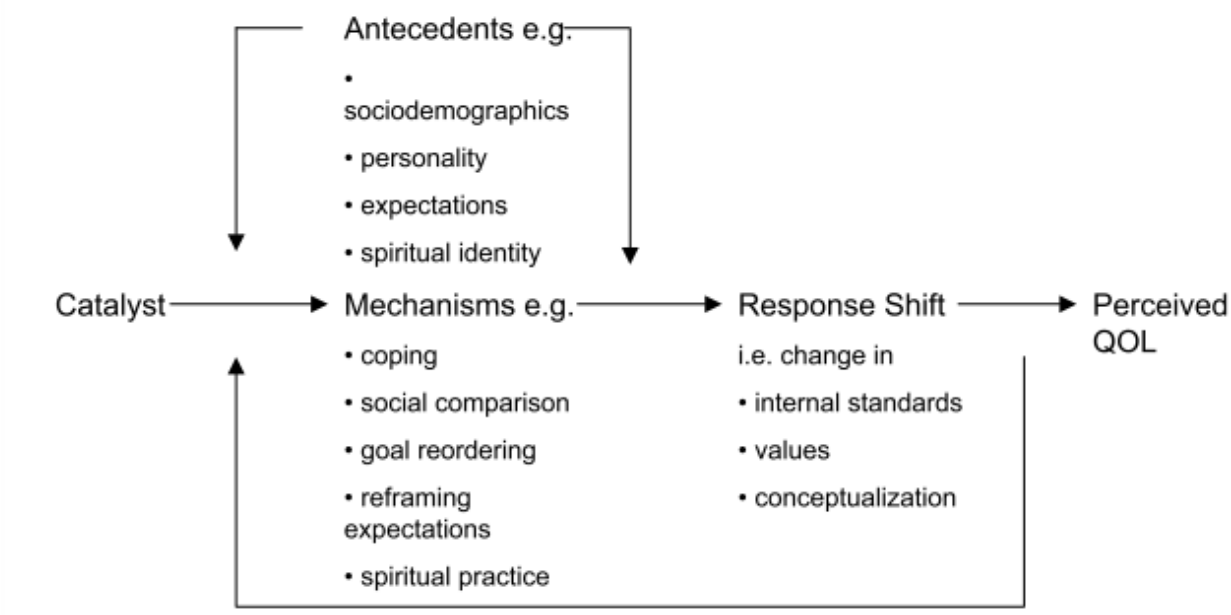


Figure 1: Sprangers and Schwartz (1999) theoretical model of response shift and quality of life [2]

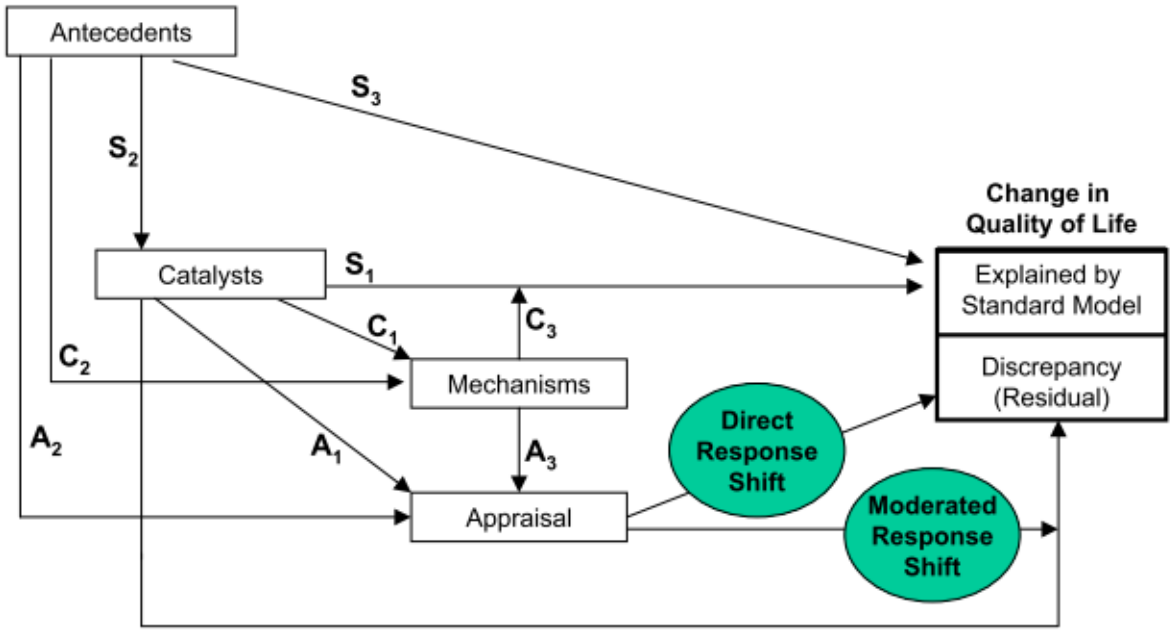


Figure 2: Rapkin and Schwartz (2004) theoretical model of response shift and quality of life "using a linear regression paradigm: Accounting for changes in Standard influences (S), Coping processes (C), and Appraisal (A) variables" [3]

References

1. Barclay-Goddard, R., J.D. Epstein, and N.E. Mayo, *Response shift: a brief overview and proposed research priorities.* Qual Life Res, 2009. **18**(3): p. 335-46.
2. Sprangers, M.A. and C.E. Schwartz, *Integrating response shift into health-related quality of life research: a theoretical model.* Soc Sci Med, 1999. **48**(11): p. 1507-15.
3. Rapkin, B.D. and C.E. Schwartz, *Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift.* Health Qual Life Outcomes, 2004. **2**: p. 14.
4. Oort, F.J., M.R. Visser, and M.A. Sprangers, *Formal definitions of measurement bias and explanation bias clarify measurement and conceptual perspectives on response shift.* J Clin Epidemiol, 2009. **62**(11): p. 1126-37.
5. Schwartz, C.E. and B.D. Rapkin, *Reconsidering the psychometrics of quality of life assessment in light of response shift and appraisal.* Health Qual Life Outcomes, 2004. **2**: p. 16.
6. Wilson, I.B., *Clinical understanding and clinical implications of response shift.* Soc Sci Med, 1999. **48**(11): p. 1577-88.
7. Osborne, R.H., M. Hawkins, and M.A. Sprangers, *Change of perspective: a measurable and desired outcome of chronic disease self-management intervention programs that violates the premise of preintervention/postintervention assessment.* Arthritis Rheum, 2006. **55**(3): p. 458-65.
8. Rochette, A., N. Korner-Bitensky, and M. Levasseur, *'Optimal' participation: a reflective look.* Disabil Rehabil, 2006. **28**(19): p. 1231-5.

9. Schwartz, C.E., et al., *Response shift theory: important implications for measuring quality of life in people with disability.* Arch Phys Med Rehabil, 2007. **88**(4): p. 529-36.

10. Mayo, N.E., et al., *Identifying response shift statistically at the individual level.* Qual Life Res, 2008. **17**(4): p. 627-39.

11. van Rijn, T., *A physiatrist's view of response shift.* J Clin Epidemiol, 2009. **62**(11): p. 1191-5.

12. Barclay-Goddard, R., et al., *Building on transformative learning and response shift theory to investigate health-related quality of life changes over time in individuals with chronic health conditions and disability.* Arch Phys Med Rehabil, 2012. **93**(2): p. 214-20.

13. Sprangers, C.E.S.a.M.A.G., *Adaptation to changing health, Response shift in quality of life research* 2002.

14. Schwartz, C.E., et al., *Guidelines for secondary analysis in search of response shift.* Qual Life Res, 2013. **22**(10): p. 2663-73.

15. Schwartz, C.E. and M.A. Sprangers, *Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research.* Soc Sci Med, 1999. **48**(11): p. 1531-48.

16. Ahmed, S., et al., *Using the Patient Generated Index to evaluate response shift post-stroke.* Qual Life Res, 2005. **14**(10): p. 2247-57.

17. Howard GS, D.P., *Response-shift bias: a source of contamination of self-report measures.* J Appl Psychol 1979. **64**: p. 144–50.

18. Schwartz, C.E., *Applications of response shift theory and methods to participation measurement: a brief history of a young field.* Arch Phys Med Rehabil, 2010. **91**(9 Suppl): p. S38-43.

19. Ahmed, S., et al., *Change in quality of life of people with stroke over time: true change or response shift?* Qual Life Res, 2005. **14**(3): p. 611-27.

20. hwartz CE, S.M., Carey A, Reed G, *Exploring response shift in longitudinal data.* Psychol Health 2004. **19**: p. 51-69.

21. Ahmed, S., et al., *Response shift influenced estimates of change in health-related quality of life poststroke.* J Clin Epidemiol, 2004. **57**(6): p. 561-70.

22. Edward, A.L., *The method of paired comparisons In: Techniques of Attitude Scale Construction. .* Appleton-Century-Crofts, New York, , 1957: p. 19–82.

23. Schwartz, C.E., *Preference value assessment: card sort approach. Copyrighted July 1996 by Frontier Science and Technology Foundation.* 1996.

CHAPTER 9 : MANUSCRIPT 4

Impact of Reconceptualization Response shift on Rating of Quality of Life Overtime.

Ala' S Aburub, Sara Ahmed, A M Rodríguez, B Gagnon, Nancy E. Mayo.

Abstract

Introduction: People with cancer may experience change in what constitutes quality of life (QOL) over time as a result of the cancer progression (true change) or adaptation to the experience, considered as a response shift phenomenon. As individualized measures are ideally suited to explore response shift, this study aimed to estimate the extent to which reconceptualization response shift occurred over time in a cancer population and the impact of this response shift on estimates of change on QOL measures.

Methods: 97 people with advanced cancer completed the study measures including the Patient Generated Index (PGI) at diagnosis (T1) and one year later (T2). Four response shift indicators were operationalized and tested for their impact on change in the PGI score, single indicators of global QOL, and the EQ-$5D_{index}$. Multivariate linear regression identified that dropping or adding areas was the most relevant response shift indicator. Models were adjusted for age and sex.

Results: Approximately 72% of people in this sample either added or dropped areas over time. People who dropped more than two areas had higher PGI scores at T2 than T1 (mean difference; 14; 95%CI: 1.9 to 30.2) while people who added areas showed a decrease (mean difference: -12.6 (95%CI: -25.2 to -1.0). Change in areas showed a similar effect on other measures of QOL but to a lesser extent and only the EQ-$5D_{index}$ decreased significantly (-9.8; 95%CI: -18.5 to -1.2) when areas were added using the PGI.

Conclusion: The results are consistent with the PGI framework as areas nominated tend focus on negative aspects of QOL. Those areas added would likely be those that are newly problematic leading to lower the PGI score at T2. The theory of cognitive homeostasis could explain the observation that when areas were dropped, QOL improved. In an attempt to maintain as high a QOL as possible, people refocus away from negative aspects thereby dropping those areas of QOL and reconceptualizing them as no longer impactful. The high prevalence of reconceptualization found in this study underlines the importance of considering response shift in studies that aim to evaluate QOL change over time in this population where QOL is of primordial importance

Introduction

The cornerstone of patient-centered care is the assessment of patient reported outcomes (PRO). In cancer, quality of life (QOL) is the most commonly assessed PRO, although assessed by measures that tap various domains including symptoms, function, and health perception[1-3]. QOL is a construct that can only be assessed from the patient's perspective. Many studies suggest that assessing QOL will improve communication between patients and the health care provider as well as facilitating the involvement of patients in decision making process.[4-6]. Several measurement tools have been used to assess QOL in cancer such as European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) [7] and Functional Assessment of Cancer Therapy [8]. These measures consist of standard questions that contain items that may not pertain to all patients or may not capture all aspects of QOL that are important to patients [9-12]. The use of an individualized measure could overcome this gap and the Patient Generated Index (PGI) is a very simple individualized measure that has been used in the cancer population[13].

A challenge with using any measure of QOL to assess change. In the context of people with cancer, people may experience true change due to cancer progression, or change may occur because of adaptation to the disease [14-19]. Change due to adaptation refers to a response shift phenomenon [4]. Response shift is defined as the change in the meaning of a person's self evaluation of a target construct (e.g., QOL) over time, as a result of (1) changes in the internal standards (recalibration) of the measurement, (2) changes in the respondent's values (changes in importance of the items or component domains that constitute QOL concept (reprioritization)),

and (3) changes in the definition of the targeted construct (redefinition QOL) (reconceptualization) [14].

Response shift can impact the psychometric properties of QOL measures, making them appear less reliable over time [20] and less correlated with other measures which themselves may change differently over time. Response shift can also alter the interpretation of QOL and the interpretation of the study results [20-24]. Response shift needs to be taken into account to: (1) understand the changes (magnitude and direction) in the construct (e.g. QOL), (2) differentiate between the true change and the response shift, (3) improve the interpretation of construct (e.g. QOL) over time, and (4) understand the effect of the response shift on the psychometric properties of QOL measures [14, 20, 22-27].

Using an individualized measure of QOL is one of the direct ways of identifying response shift [28], as these measures typically ask patients to nominate areas that affected their QOL due to their disease, rate the severity of the nominated areas, and weight these areas in terms of desire for improvement. All of these elements can change over time which would indicate, in the absence of change in severity, a response shift.

Two studies have provided information about response shift in a cancer population using PGI [29, 30] but in the context of validating the PGI, rather than as a specific focus of the study. In the first study, Camilleri-Brennan and colleagues assessed the validity and responsiveness of PGI in thirty-three patients with rectal cancer [29]. They found that pre-operation, participants nominated on average 3.2 areas with a median of 3 compared to 3.6 areas with a median of 4 three months post-operation [29]. In the second study, 86 adults with cancer receiving their first course of radiation therapy were recruited to evaluate the psychometric characteristics of the

individualized measures [30]. The results have shown that patients made on average 3 changes in the areas nominated in the first step of the PGI between the following time points ; pre-treatment to third week; third week to end of treatment; and pre-treatment to end of treatment [30].

Little work has been done on response shift in the cancer population although the diagnosis, health impact, treatment, and transition into survivorship would act as strong catalysts for response shift [14]. The purpose of this study was specifically to estimate the extent to which reconceptualization response shift occurred over time in cancer population and the impact of this response shift on estimated change in QOL.

Methods

This is a secondary analysis from data arising from a longitudinal study of anorexia/cachexia and QOL in people with advanced cancer[31]. The study was approved by McGill University Faculty of Medicine Institutional Review Board. The methods have been described previously [31, 32]. Briefly, people with advanced cancer of any origin post-diagnosis and before starting oncology therapy were recruited at two tertiary care university hospitals. People were excluded if their estimated life expectancy was less than 3 months, scored greater than 3 in the Eastern Cooperative Oncology Group Performance Status scale and having difficulty following the instructions. Participants were asked to complete several comprehensive QOL measures including patient generated index (PGI) at the baseline (T1) and one year later (T2).

Measures

Four types of measures of were used in this study: (i) QOL life and health related quality of life (HRQOL) measures; (ii) measures known to impact on QOL; (iii) indicators of

reconceptualization response shift; and (iv) potential confounders of age and gender. The primary outcome was the change in the PGI from T1 to T2, the variables under study are indicators of reconceptualization response shift.

QOL Measures

Patient Generated Index (PGI)

PGI requires three steps to complete. First, respondents are asked to nominate the top five areas that affected their QOL due to their disease. In this step, respondents are also asked to nominate one area that affected their QOL and not related to their disease. Second, respondents are asked to rate the severity of the nominated areas on a scale of 0-10, where 0 is severe and 10 is mild or not present. Third, respondents are asked to imagine that they have 12 tokens to distribute among the nominated areas where more tokens are given to the areas that they would like to improve the most and less to the least important areas. The global index score is calculated by multiplying the rating severity score in the second step by the proportion of the 12 tokens assigned to each area in the third step and then summing this across the six areas (five cancer related areas plus one for all non-cancer related areas). For people who did not use all 12 tokens, the weighting factors was the proportion of the token used. The total score is formed as the average of this token weighted severity score, transformed to range from 0 to 100, where 100 represents the best QOL [13]. As this index is conceptually equivalent to a preference –weighted index, a 5-point change would be considered clinically meaningful [33].

Edmonton Symptoms Assessment Scale (ESAS)

The Edmonton Symptom Assessment System (ESAS) is a cancer-specific clinical profile in which nine common symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, best quality of life, and shortness of breath) are rated 0 to 10 numerical rating scale with 0 being an absent symptom and 10 being the worst possible severity [34]. The QOL single item was used in this study. ESAS-QOL single item was multiplied by 10 and transformed to range from 0 to 100 with 0 as the worst level and 10 as the best level.

McGill Quality of Life Questionnaire (MQOL)

McGill QOL questionnaire was developed to measure the QOL at all stages of the disease trajectory for people with a life threatening illness [35-40]. MQOL consists of 16 self reported items and is based on a two day time frame. Each item is rated on a scale of 0 to 10; with 0 being the worst and 10 being the best. There are five MQOL sub-domains: physical symptoms (items 1-3), physical well-being (item 4), psychological symptoms (items 5-8), existential (items 9-14) and support (item 15 and16). The MQOL total score is the mean score of the five sub-domains. The MQOL contains a single-item scale (MQOL-single item) also scored from 0 to 10, constructed to measure overall QOL and is not included in the MQOL score. MQOL-single item was multiplied by 10 and then transformed to range from 0 to 100 with 100 being the best QOL.

<u>HRQOL Measure</u>

EQ-5D^{TM} consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each rated on a three-point ordinal scale (no problems, some problems, and extreme problems). The EQ-5D^{TM} describes 243 health states each with a unique index value

calculated using country-specific weights [41-43] with values for EQ-$5D_{index}$ ranging from -0.6 to 1.0 [41, 44]. The EQ-$5D_{index}$ indicates the health impact of cancer on QOL; the EQ-VAS was used for current health perception.

Measures of constructs that Impact QOL

The measures were chosen to represent the rubrics of the Wilson-Cleary Model for health-related quality of life. These rubrics are biological and physiological variables, symptom status, functional status, general health perception, which are theoretically linked to QOL. Also measured were personal factors (age and gender) and social support as an environmental factor. Biological rubric was represented by cancer type, symptoms were from the ESAS described above. For function, two performance-based measures of mobility were used. In addition four single indicators found useful in the context of recovering from stroke [45] were available, one for handling stress (coping) and three for participation (physical activity, work and driving). For health perception, the visual analogue scale rating for "health today" was used from the EQ-$5D^{TM}$, a generic measure of health-related QOL (HRQL).

Two -minute walk test(2MWT)

Walking tests are measures of functional walking capacity needed for activities of daily living. Here the 2 minute walk test (2MWT) was used as many could not complete a long walking time. Waling tests are valid and reliable measure and it has been used in healthy individuals and in different patient populations including cancer [46-54].

Gait Speed

Gait speed is a key feature of walking capacity [55, 56] derived from measuring the time to cover a specific distance. For comfortable gait speed, patients were asked to walk at their normal comfortable speed then at their maximum speed (as fast as they can) and the time is measured to

cover a 5 meters distance was recorded and converted to meters per second. Walking speed (gait speed) is considered a "vital" sign and predictive of health outcomes [55, 56].

Reconceptualization response shift

There is no specific way to define reconceptualization response shift in the context of the PGI and to move the field forward, four response shift variables (indicators) were operationalized: (i) change in the number of areas nominated from the baseline assessment; (ii) the number of new areas added; (iii) change in content of the areas; (iv) a composite response shift indicator derived from change in number of areas and change in content.

Statistical Analysis

To create the response shift indicator for change in content, the ratio of the number of new areas at T2 to the number of areas identified at T1 was calculated; this ratio could potentially range from 0 (no new areas) to > 1.0 if more new areas were added at T2 than were present at T1. As these response shift indicators represent different but correlated aspects of reconceptualization, their independent contributions to change in QOL cannot be estimated without an interaction term, which requires additional sample size and is very difficult to interpret. Therefore, a composite response shift indicator was derived by cross-tabulating the number of areas changed (7 categories) with the ratio for new areas that had 18 distinct values. Five distinct composite groupings emerged using both ratio and change.

A. 0.20-0.60 and - ≥ 2;

B. 0.25-0.80 and ± 1

C. 1.0 and 0;

D. 1.0-2.0 and +1;

E. 1.0-3.0 and + ≥2

Descriptive statistics were used to summarize the values on QOL and HRQL measures at T1 and T2 using means and SD and change scores on these measures were summarized using Box and Whisker Plots. The distribution on the four response shift indicators was also described, the change in the number of areas, number of new areas, ratio of new areas to T1 areas, and the composite indicator.

To identify whether there were factors that also changed from T1 and T2 that could have impacted directly on change in PGI (potentially contributing to true change), univariate linear regression models were used after verifying the assumptions. The factors assessed followed rubrics of the Wilson and Cleary model (personal factors, biological factors, symptom status change, functional status change, general health perception). Personal factors, biological and social factors were measured only at the baseline; all other variables were changed scores. All variables associated with change in PGI at $p<0.05$ were considered as important for explaining proportion of true change and were included in subsequent analyses.

To identify whether the variability in the response shift indicator, representing change in number of areas (range -4 to +3), contributed to change in PGI, over and above variables known to affect change, linear regression was used. The regression coefficients for dropping one area (-1 change) was not different from the referent category of 0 change, so these two categories were combined into one considered as “no change” and served as the referent category for further analyses. The regression coefficients for adding areas (+1, +2 and +3 changes) were also closely similar, so

only one category for adding areas was needed; the third category was for people who dropped two or more areas (-2, -3, -4 changes).

A multi-variate linear regression model was used to estimate the extent to which each of the four response shift indicators (adding new areas, change in number of areas, ratio, composite) , considered separately, impacted on change in PGI score. The model included age and sex and any significant univariate indicators of change in PGI. A second multi-variate model was used to estimate the extent to which the best response shift indicator from the PGI model impacted on change in the other measures of QOL and HRQL. The regression coefficients (β) and standard error (SE) were used to calculate 95% confidence intervals (CI). All statistical analyses were performed using SAS 9.3.

Results

A total of 192 participants completed the study measures at the baseline (T1); 104 participants completed the study measures at both T1 and one year later (T2). As 7 participants did not complete the last step of the PGI measure, assigning tokens, 97 participants were included in analyses.

The mean age of study participants was 62.8 ± 12.1 and 61% were men. The most common cancer type was pancreatic cancer (23%), followed by ear, nose, and throat cancer (ENT) (18%), colorectal (13%), non-small cell lung carcinoma (NSCLC) (10%) and breast cancer (10%).

Table 1 presents the estimates of QOL derived from study measures from 97 participants with data at T1 and T2. Three QOL measures (PGI, ESAS-QOL -single item and MQOL- single item) were analyzed. The mean score of the PGI was 41.2 (SD: 21.1) and 39.0 (SD: 21.6) at T1 and

T2, respectively. The mean PGI score was lower than the other QOL measures at each time points. The means at the two time points were closely similar. Also included was the one measure of HRQL, the EQ-5D$_{index}$, transformed to range from 0 to 100. The mean score of the EQ-5D was 66.7 (SD: 6.5) and 68.7 (SD: 17.0) at T1 and T2, respectively.

Figure1 shows the distribution change of the PGI, ESAS-QOL -single item and MQOL- single item, and EQ-5D$_{index}$ over one year period. All measures have a median of zero or close to zero. The mean change of the PGI, MQOL- single item and ESAS-QOL-single item were -2.2, -1.7 and -1.4, respectively; the mean change of the EQ-5D$_{index}$ was 2.2.

Table 2 presents the distribution of the response shift indicators. Out of 97 participants, 1 (1%) participants did not add new areas at T2, 21 (20%) added one new area, 27 (26)% added 2 new areas, 29 (27.9) added 3 areas, 15 (14.4%) added 4 new areas, and 11 (10.6) added 5 new areas. For the change in number of areas, 2 (2%) participants dropped 4 areas, 13 (13.4%) dropped 2 areas, 21 (21.6%) dropped one area, 27 had no change (27.8%); for those adding areas, the numbers for adding 1, 2, or 3 areas was 15 (15.5%), 14 (14.3%), 5 (5.1%), respectively. No one dropped 5 areas or added more than 3 areas. Also shown is the ratio and a composite response shift variable combining change in number of areas and change in content of the new areas added (ratio).

Table 3 shows the results of the univariate regression analyses to identify factors associated with change in PGI over one year period. Also included in this table is number of areas nominated at T1, which was not a significant univariate predictor of change in PGI.

Table 4 presents the results of the multivariate models to identify the effect of the response shift indicators on PGI change score adjusted for age and gender. None of the univariate predictors of change in PGI remained significant when included with the response shift indicators.

The first model tested the effect of adding new areas and analyses indicated no differences between adding 1, 2, 3, or 4 areas so this indicator was dichotomized. The β was -4.9 (95% CI: -9.4 to -0.3) indicating a significant decrease in PGI score when any areas were added.

For the change in areas, the original 5-level variable was reduced to 3-levels as the regression coefficients for adjacent categories showed that these were combinable. The β for participants who dropped more than one area, in comparison to those with no change, was +14.1 (95%CI: -1.9 to 30.2) indicating an increase in QOL rating that was of clinical relevance but borderline statistical significance ($p = 0.08$). The β for participants who added areas was -12.6 (95%CI: -25.2 to -1.0) indicating a large and significant decrease in QOL rating. Similar results were found for the other response shift indicators.

As the relevant categories for the composite indicator were very close to the categories for the change in area response shift indicator, and the former was easier to understand, this variable was tested for its impact on the global QOL measures and the EQ-5D$_{index}$. Table 5 presents these results and no effect was observed.

Discussion

A number of steps were carried out to address the complex issue of response shift using the PGI. First, we observed that a proportion of people made meaningful changes in their of QOL using

the PGI and in other related measures, where a change of 5 or more points out of 100 was considered meaningful [33] (see Figure 1).

Second, we demonstrated that there were changes in the number of areas nominated and the content of these areas, compatible with a response shift phenomenon (see Table 2). Approximately 72% of people in this sample either added or dropped areas after one year, as compared to baseline providing credence to the conclusion that people with advanced cancer experience reconceptualization response shift (see Table 2). These findings are in line with two studies on a cancer population, one of which showed that the number of areas increased over time [30] and a second study showing that the areas nominated changed [29].

Third, as there is no established metrics for response shift using individualized measures, we created four operational variables (see Table 2). The regression analyses demonstrated that the essence of reconceptualization came from adding or dropping areas and there is little contribution from which areas were included (see Table 4).

Fourth, we demonstrated that change in the symptoms of fatigue, depression, drowsiness, and poor appetite impacted on change in the PGI score, as did change in capacity to vigorous activities participate in usual roles (driving, recreational pursuits, and work). It is not surprising that change in these factors predicted change in PGI, as these were the factors most often identified as affecting QOL at baseline [32] (see Table 3).

Fifth, we observed that people who added areas at T2 had a lower PGI score at T2 (compared to T1) and people who dropped areas had a better score at T2. (see Table 4). This finding is consistent with the PGI framework as areas nominated tend focus on negative aspects of QOL,

thus areas added would tend to be those that are newly problematic leading to lower the PGI score at T2. The theory of cognitive homeostasis[57, 58] could explain the observation that when areas were dropped, QOL improved. This could indicate that people are attempting to maintain as high a QOL as possible by refocusing away from negative aspects dropping these areas as no longer being so important.

In support of cognitive homeostasis, was that global QOL ratings did not change as much as the PGI did with changing areas(see Table 5). This suggests that even in the presence of more problematic areas, people maintained their calibration on global indices. Additionally, people may not wish to declare, in front of an interviewer, that their QOL is poor or has deteriorated. They might also have changed their frame of reference over this time[20] period and, even in the presence of deteriorating health, felt themselves to be better off than others who they knew were ill or had died.

Of interest was that the impact of adding areas also decreased significantly the value of EQ-$5D_{index}$, but with a lesser magnitude than observed for the PGI. This could have been a chance finding as a number of statistical comparisons were made. However, the finding supports that adding areas is reserved from newly problematic areas and, in this case, areas that match the items on the EQ-5D. This could reflect true change or recalibration on the EQ-5D.

This study took a quantitative approach to response shift, the findings would have been greatly enhanced by adding a qualitative component to ask people how and why areas changed. Ahmed et al.[59] found that in a sample of 92 patients with stroke who completed PGI at 6 weeks and 24 weeks post stroke, approximately half nominated different areas at 24 weeks as compared to 6 weeks. Half of this group (n=46) were interviewed about their response shift experience at 24

weeks and for 13 (28%) the response shift was supported by information voiced during the semi structured interview [59]. For example, some patients indicated that they dropped areas, even though they were problematic as their new focus was now on only the most relevant areas. Other reasons for changing areas, unrelated to response shift were forgetting to nominate an area previously mentioned (n=8) or they had improved (true change; n=13).

The study sample here is unique as it targets only people with advanced cancer who at the time of entry into the study had not yet received any cancer treatment. This study is the first to evaluate response shift in people with advanced cancer and the first to attempt to systematically address metrics for response shift using individualized measures, in any clinical sample. The methods described here could serve as a model for other studies as replication is essential in any scientific process.

This study provided evidence that people with advanced cancer made a response shift (reconceptualization) and this is reasonable given that there are several potential catalysts[14] for the shift including disease progression, treatment side effects, and surviving.

A limitation of our study was that the sample size was small. This study was not designed *a priori* to test response shift hypotheses, and the small sample size arose from the nature of the condition itself which has a high mortality and considerable morbidity which themselves can act as catalysts for survivors. No other response-shift measures were administered, such as the "Then Test" [60] as the response burden would have been too high. Another limitation could be that the arguments with respect to changing areas and change in PGI scoring are circular but, in fact, the scoring algorithm is based on severity and on the priority for improvement assigned by

the respondent using the tokens and is, therefore, somewhat independent of the areas nominated or their number.

There were challenges in administering the PGI as some participants omitted the last stage, distributing tokens, some distributed too few or some too many. Those who distributed 0 tokens were removed from the analysis, those with an incorrect number had the score adjusted to the number of token actually distributed. We recommend that patients should be supervised when the PGI is administered to ensure no errors in completion.

Conclusion

People with cancer do reconsider what is important to them as they experience health and treatment challenges. Only one person had exactly the same profile of areas at the two time points. Some of this variation is simple measurement error and some is reconceptualization. Two different reconceptualization predominated. Some people (~15%) dropped 2 or more areas that they originally nominated and, as the PGI score improved (on average) by doing this, areas of high impact were dropped indicating a shift away from negative aspects of life. Some people (~35%) added areas and, as the PGI score was lower (on average), these new areas were those that were newly problematic. The observation that the reconceptualization did not affect global rating of QOL suggests a recalibration to maintain as high a QOL as possible in the presence changing health. The high prevalence of reconceptualization found in this study underlines the importance of considering the evaluation of the response shift in studies that aim to evaluate QOL change over time.

Table 1. Estimates of QOL and HRQL derived from study measures from 97 participants with data at baseline and one year later

Measures	**Baseline** Mean (SD)	**One year** Mean (SD)
Quality of life (QOL)		
PGI	41.2 (21.1)	39.0 (21.6)
ESAS-QOL -single item	67.0 (25.5)	66.0 (26)
MQOL-single item	67.1 (24.1)	66.0 (21.8)
Health-related quality of life (HRQL)		
EQ-5D	66.7 (16.5)	68.7 (17.0)

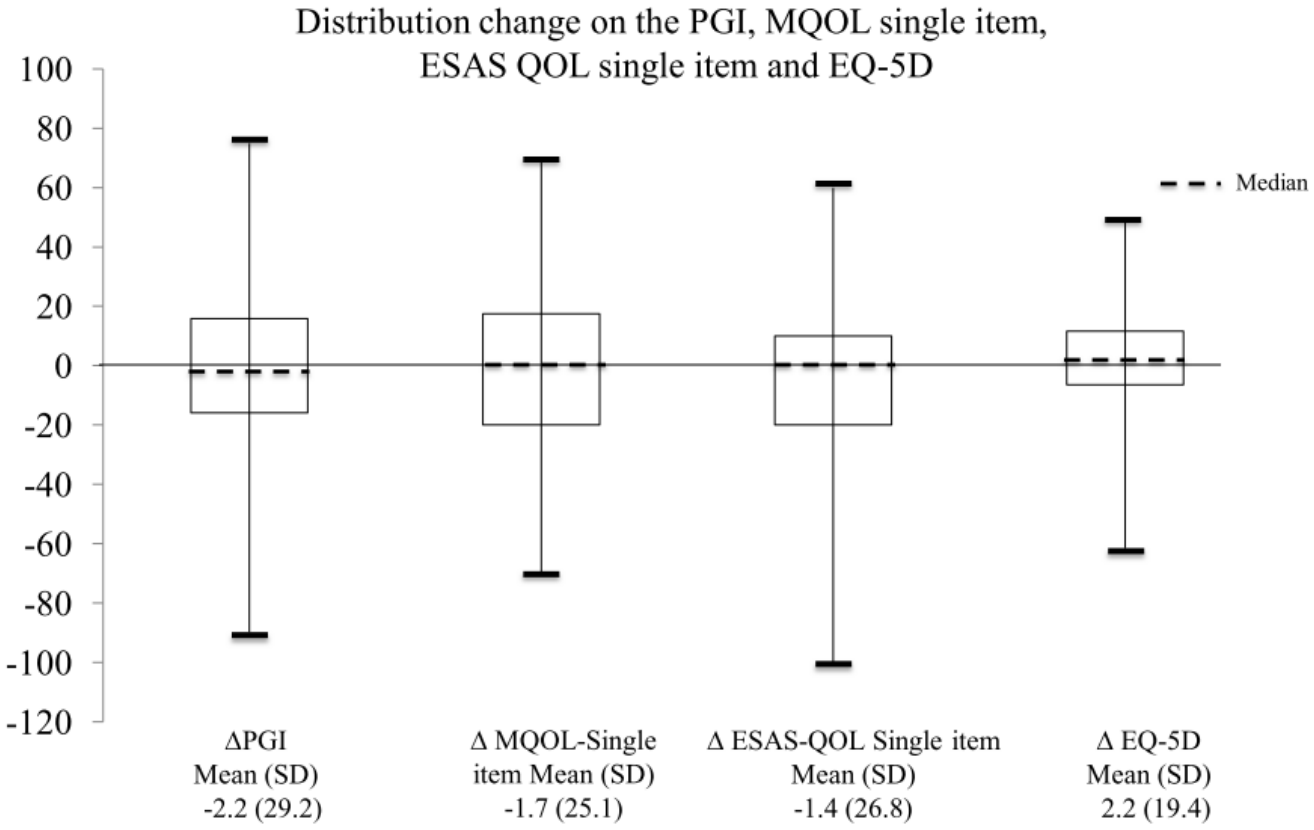


Figure 1 Distribution change on the QOL measures

Table 2 The distribution of the response shift indicators

Response shift indicators	N (%) (n=97)
Number of new areas added	
0	1 (1.0)
1	18 (18.6)
2	25 (25.7)
3	27 (27.8)
4	15 (15.5)
5	11 (11.3)
Number of areas change	
Dropped 4 areas	2 (2.0)
Dropped 2 areas	13 (13.4)
Dropped one areas	21 (21.6)
No change	27 (27.8)
Added one area	15 (15.5)
Added 2 areas	14 (14.3)
Added 3 areas	5 (5.15)
Ratio of new areas to areas at baseline	
0-0.5	32 (33)
0.6-0.8	26 (26.8)
1.0	15 (15.5)
1.25-1.66	14 (14.4)
2.0-3.0	10 (10.3)
Composite Response Shift Variable	
0.20-0.60 and - ≥ 2	15 (15.5)
0.25-0.8 and ± 1	43 (44.3)
1.0 and 0	11 (11.3)
1.0-2.0 and ± 1	9 (9.3)
1.0-3.0 and + ≥2 areas	19 (19.6)

Table 3 Factors associated with univariately with change in PGI over 1 year period.

Variable	β	SE	P value
Personal Factors (at baseline)			
Age (per year)	0.15	0.26	0.56
Male gender (men (n=60) vs. women)	2.5	6.3	0.73
Biological Factor (at baseline)			
Cancer Type			
Breast (n=10)	Referent		
Colorectal (n=13)	1.9	12.9	0.8
Ear, nose, and throat cancer (ENT) (n=18)	-9.9	12.2	0.4
Hepatobilliary (n=5)	-10.5	16.1	0.5
Non-small cell lung carcinoma (NSCLC) (n=10)	1.8	13.1	0.9
Ovarian (n=1)	-17.7	32.6	0.6
Pancreatic (n=23)	9.72	11.6	0.4
Prostate (n=2)	27.2	24.1	0.2
Retroperitoneal (n=1)	-4.00	32.6	0.9
Thyroid (n=1)	-73.6	32.6	0.03
Upper GI (n=9)	-5.8	14.3	0.7
Urological (n=2)	-12.3	24.1	0.6
Unknown (n=2)	15.8	31.1	0.6
Symptom Status Change (Higher is worse)			
Coping	-8.3	4.53	0.07
ESAS items			
Pain	-0.8	0.9	0.4
Fatigue	-2.1	0.8	0.01
Depression	-3.1	1.1	0.01
Anxiety	0.08	0.9	0.9
Drowsiness	-2.0	1.04	0.05
Appetite	-1.8	0.7	0.02
Shortness of breath	-1.3	1.0	0.2
Functional Status Change (Higher is worse)			
Vigorous activity	-11.3	3.7	0.00
Recreation	-11.3	3.7	0.00
Work activity	-9.6	3.2	0.00
Driving	-7.8	3.8	0.04
Performance measures Change (Higher is better)			
2MWT (per 10 meters)	4.0	3.1	0.2
Gait speed Comfortable (m/s)	-2.4	2.6	0.4
Gait speed Fast (m/s)	-5.0	3.1	0.1
Social Factors (at baseline)			
Is there someone to help you (yes	-1.5	8.0	0.8

Is there someone to take care	-0.2	0.1	0.2
I have felt supported (Higher is better)	0.13	2.7	0.9
General Health Perception Change (Higher is better)			
Health (EQ VAS; 0-100, per 10 unit)	2.8	1.2	0.03
Number of area at baseline	3.5	2.3	0.13

Table 4 Impact the response shift indicators on change in PGI score

Variable	β	SE	95% CI		P-value
Adding new areas model					
Adding any new areas vs. none	-4.9	2.3	-9.4	-0.3	0.03
Age	0.1	0.2	-0.3	0.6	0.6
Gender	-2.9	6.2	-15.0	9.2	0.6
Change in areas model					
Dropped 2 areas or more (n=15)	14.1	8.2	-1.9	30.2	0.08
No change or dropped one (n=48)	Referent				
Added areas (n=34)	-12.6	6.4	-25.2	-0.1	0.04
Age	0.1	0.2	-0.3	0.6	0.6
Gender	-3.8	6.1	-15.7	8.1	0.5
Ratio model					
Ratio (per 0.20 unit change)	-2.0	0.0	-4.0	-2.0	0.001
Age	0.3	0.2	-0.2	0.7	0.3
Gender	-5.2	6.1	-17.1	6.7	0.4
Composite indicator model					
0.0-0.8and - ≥2 (n=15)	14.3	8.0	-1.4	30.1	0.07
0-1.0 and ±1 (n=54)	Referent				
1.0-3.0 and +≥1 (n=28)	-14.6	6.6	-27.6	-1.7	0.02
Age	0.2	0.2	-0.3	0.6	0.5
Gender	-4.0	6.0	-15.8	7.8	0.5

Table 5 Impact of the response shift indicator (change in number of areas) on change in global ratings of QOL and on the EQ-5D$_{index}$

Parameter	β	SE	95% CI	P-value
ΔESAS-QOL-single item model				
Dropped more than one area	0.0	7.5	-14.8, 14.7	1.00
No change or dropped one area	Referent			
Added areas	-0.5	6.0	-12.2, 11.2	0.94
Age	-0.6	0.2	-1.0, -0.2	0.01
Gender	-8.8	5.6	-19.9, 2.2	0.12
ΔMQOL-single item model				
Dropped more than one area	4.1	7.3	-10.2, 18.5	0.57
No change or dropped one area	Referent			
Added areas	-9.0	6.0	-20.6, 2.7	0.13
Age	-0.2	0.2	-0.6, 0.3	0.42
Gender	-1.7	5.6	-12.6, 9.3	0.76
ΔEQ-5D$_{index}$ Model				
Dropped more than one area	3.3	5.6	-7.7, 14.3	0.55
No change or dropped one area	Referent			
Added areas	-9.8	4.4	-18.5, -1.2	0.03
Age	-0.3	0.2	-0.6, 0.1	0.11
Gender	-6.0	4.2	-14.2, 2.3	0.16

References

1. Joly, F., et al., *Quality of life and patient-reported outcomes in endometrial cancer clinical trials: a call for action!* Int J Gynecol Cancer, 2014. **24**(9): p. 1693-9.
2. Heydarnejad, M.S., D.A. Hassanpour, and D.K. Solati, *Factors affecting quality of life in cancer patients undergoing chemotherapy.* Afr Health Sci, 2011. **11**(2): p. 266-70.
3. Helgesson, O., et al., *Quality of life in cancer survivors as observed in a population study of Swedish women.* Scand J Prim Health Care, 2007. **25**(4): p. 220-5.
4. Lindblad, A.K., et al., *Focus on the individual--quality of life assessments in oncology.* Acta Oncol, 2002. **41**(6): p. 507-16.
5. Levine, M.N. and P.A. Ganz, *Beyond the development of quality-of-life instruments: where do we go from here?* J Clin Oncol, 2002. **20**(9): p. 2215-6.
6. Patel, K.K., D.L. Veenstra, and D.L. Patrick, *A review of selected patient-generated outcome measures and their application in clinical trials.* Value Health, 2003. **6**(5): p. 595-603.
7. Aaronson, N.K., et al., *The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.* J Natl Cancer Inst, 1993. **85**(5): p. 365-76.
8. Cella, D., et al., *Spanish language translation and initial validation of the functional assessment of cancer therapy quality-of-life instrument.* Med Care, 1998. **36**(9): p. 1407-18.
9. Bowling, A., *What things are important in people's lives? A survey of the public's judgements to inform scales of health related quality of life.* Soc Sci Med, 1995. **41**(10): p. 1447-62.

10. Donaldson, M.S., *Taking stock of health-related quality-of-life measurement in oncology practice in the United States.* J Natl Cancer Inst Monogr, 2004(33): p. 155-67.

11. Soni, M.K. and D. Cella, *Quality of life and symptom measures in oncology: an overview.* Am J Manag Care, 2002. **8**(18 Suppl): p. S560-73.

12. Frost, M.H. and J.A. Sloan, *Quality of life measurements: a soft outcome--or is it?* Am J Manag Care, 2002. **8**(18 Suppl): p. S574-9.

13. Ruta, D.A., et al., *A new approach to the measurement of quality of life. The Patient-Generated Index.* Med Care, 1994. **32**(11): p. 1109-26.

14. Sprangers, M.A. and C.E. Schwartz, *Integrating response shift into health-related quality of life research: a theoretical model.* Soc Sci Med, 1999. **48**(11): p. 1507-15.

15. Schwartz, C.E., et al., *The clinical significance of adaptation to changing health: a meta-analysis of response shift.* Qual Life Res, 2006. **15**(9): p. 1533-50.

16. Dabakuyo, T.S., et al., *Response shift effects on measuring post-operative quality of life among breast cancer patients: a multicenter cohort study.* Qual Life Res, 2013. **22**(1): p. 1-11.

17. Antoni, M.H., *Psychosocial intervention effects on adaptation, disease course and biobehavioral processes in cancer.* Brain Behav Immun, 2013. **30 Suppl**: p. S88-98.

18. Lechner, S.C., et al., *Adaptation of a Psycho-Oncology Intervention for Black Breast Cancer Survivors: Project CARE.* Couns Psychol, 2012. **41**(2): p. 286-312.

19. Naus, M.J., et al., *Cancer survivor adaptation model: conceptualizing cancer as a chronic illness.* J Clin Psychol, 2009. **65**(12): p. 1350-9.

20. Schwartz, C.E. and B.D. Rapkin, *Reconsidering the psychometrics of quality of life assessment in light of response shift and appraisal.* Health Qual Life Outcomes, 2004. **2**: p. 16.

21. Mayo, N.E., S.C. Scott, and S. Ahmed, *Case management poststroke did not induce response shift: the value of residuals.* J Clin Epidemiol, 2009. **62**(11): p. 1148-56.

22. Sprangers, M.A., *Response-shift bias: a challenge to the assessment of patients' quality of life in cancer clinical trials.* Cancer Treat Rev, 1996. **22 Suppl A**: p. 55-62.

23. Ring, L., et al., *Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients.* Health Qual Life Outcomes, 2005. **3**: p. 55.

24. Ahmed, S., et al., *Response shift influenced estimates of change in health-related quality of life poststroke.* J Clin Epidemiol, 2004. **57**(6): p. 561-70.

25. Schwartz, C.E. and M.A. Sprangers, *Methodological approaches for assessing response shift in longitudinal health-related quality-of-life research.* Soc Sci Med, 1999. **48**(11): p. 1531-48.

26. Oort, F.J., M.R. Visser, and M.A. Sprangers, *An application of structural equation modeling to detect response shifts and true change in quality of life data from cancer patients undergoing invasive surgery.* Qual Life Res, 2005. **14**(3): p. 599-609.

27. Ubel, P.A., Y. Peeters, and D. Smith, *Abandoning the language of "response shift": a plea for conceptual clarity in distinguishing scale recalibration from true changes in quality of life.* Qual Life Res, 2010. **19**(4): p. 465-71.

28. Barclay-Goddard, R., J.D. Epstein, and N.E. Mayo, *Response shift: a brief overview and proposed research priorities.* Qual Life Res, 2009. **18**(3): p. 335-46.

29. Camilleri-Brennan, J., D.A. Ruta, and R.J. Steele, *Patient generated index: new instrument for measuring quality of life in patients with rectal cancer.* World J Surg, 2002. **26**(11): p. 1354-9.

30. Tavernier, S.S., et al., *Validity of the Patient Generated Index as a quality-of-life measure in radiation oncology.* Oncol Nurs Forum, 2011. **38**(3): p. 319-29.

31. Rodriguez, A.M., N.E. Mayo, and B. Gagnon, *Independent contributors to overall quality of life in people with advanced cancer.* Br J Cancer, 2013. **108**(9): p. 1790-800.

32. Aburub, A.S., et al., *Using a personalized measure (Patient Generated Index (PGI)) to identify what matters to people with cancer.* Support Care Cancer, 2015.

33. Walters, S.J. and J.E. Brazier, *Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D.* Qual Life Res, 2005. **14**(6): p. 1523-32.

34. Bruera, E., et al., *The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients.* J Palliat Care, 1991. **7**(2): p. 6-9.

35. Cohen, S.R., et al., *Existential well-being is an important determinant of quality of life. Evidence from the McGill Quality of Life Questionnaire.* Cancer, 1996. **77**(3): p. 576-86.

36. Cohen, S.R., et al., *The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability.* Palliat Med, 1995. **9**(3): p. 207-19.

37. Cohen, S.R., et al., *Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain.* Palliat Med, 1997. **11**(1): p. 3-20.

38. Cohen, S.R. and B.M. Mount, *Living with cancer: "good" days and "bad" days--what produces them? Can the McGill quality of life questionnaire distinguish between them?* Cancer, 2000. **89**(8): p. 1854-65.

39. Cohen, S.R., et al., *Quality of life in HIV disease as measured by the McGill quality of life questionnaire.* AIDS, 1996. **10**(12): p. 1421-7.

40. Cohen, S.R., et al., *Changes in quality of life following admission to palliative care units.* Palliat Med, 2001. **15**(5): p. 363-71.

41. Dolan, P., *Modeling valuations for EuroQol health states.* Med Care, 1997. **35**(11): p. 1095-108.

42. Bansback, N., et al., *Canadian valuation of EQ-5D health states: preliminary value set and considerations for future valuation studies.* PLoS One, 2012. **7**(2): p. e31115.

43. Oremus, M., et al., *Health utility scores in Alzheimer's disease: differences based on calculation with American and Canadian preference weights.* Value Health, 2014. **17**(1): p. 77-83.

44. Shaw, J.W., J.A. Johnson, and S.J. Coons, *US valuation of the EQ-5D health states: development and testing of the D1 valuation model.* Med Care, 2005. **43**(3): p. 203-20.

45. Poissant, L., et al., *The development and preliminary validation of a Preference-Based Stroke Index (PBSI).* Health Qual Life Outcomes, 2003. **1**: p. 43.

46. Arcuri, J.F., et al., *Validity and Reliability of the 6-Minute Step Test in Healthy Individuals: A Cross-sectional Study.* Clin J Sport Med, 2016. **26**(1): p. 69-75.

47. Guerra-Balic, M., et al., *Reliability and validity of the 6-min walk test in adults and seniors with intellectual disabilities.* Res Dev Disabil, 2015. **47**: p. 144-53.

48. Gomes, E., et al., *Reliability and validity of 6MWT for outpatients with schizophrenia: A preliminary study.* Psychiatry Res, 2016. **237**: p. 37-42.

49. Olper, L., et al., *Validation of the treadmill Six-Minute Walk Test in people following cardiac surgery.* Phys Ther, 2011. **91**(4): p. 566-76.

50. Mossberg, K.A. and E. Fortini, *Responsiveness and validity of the six-minute walk test in individuals with traumatic brain injury.* Phys Ther, 2012. **92**(5): p. 726-33.

51. Kempen, J.C., et al., *Reliability of the walking energy cost test and the six-minute walk test in boys with Duchenne muscular dystrophy.* Neuromuscul Disord, 2014. **24**(3): p. 216-21.

52. Schmidt, K., et al., *Validity of the six-minute walk test in cancer patients.* Int J Sports Med, 2013. **34**(7): p. 631-6.

53. Nathan, S.D., et al., *Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis.* Respir Med, 2015. **109**(7): p. 914-22.

54. Butland, R.J., et al., *Two-, six-, and 12-minute walking tests in respiratory disease.* Br Med J (Clin Res Ed), 1982. **284**(6329): p. 1607-8.

55. Middleton, A., S.L. Fritz, and M. Lusardi, *Walking speed: the functional vital sign.* J Aging Phys Act, 2015. **23**(2): p. 314-22.

56. Fritz, S. and M. Lusardi, *White paper: "walking speed: the sixth vital sign".* J Geriatr Phys Ther, 2009. **32**(2): p. 46-9.

57. Martin, F., et al., *Twelve years' experience with the Patient Generated Index (PGI) of quality of life: a graded structured review.* Qual Life Res, 2007. **16**(4): p. 705-15.

58. Cummins, R., *Personal income and subjective well-being: A review.* Journal of Happiness Studies, 2000. **133–158.**(1).

59. Ahmed, S., et al., *Using the Patient Generated Index to evaluate response shift post-stroke.* Qual Life Res, 2005. **14**(10): p. 2247-57.

60. Howard GS, D.P., *Response-shift bias: a source of contamination of self-report measures.* J Appl Psychol 1979. **64**: p. 144–50.

CHAPTER 10: OVERALL DISCUSSION AND CONCLUSION

Quality of life (QOL) in people with cancer has become an important outcome for both clinical care and research as a way of summarizing across a wide range of physical and emotional sequelae that arise from the disease itself and from its treatment [1, 2].

The World Health Organization (WHO) defines quality of life as "the individuals' perceptions of their position in life, in the context of the cultural and value systems in which they live and in relation to their goals, expectations, standards and concerns"[3]. Using this definition, when there is a gap between patient's goals, expectations and achievements, QOL is affected [4].

QOL measures are of three types, full standardized, which can be generic or cancer-specific, and individualized. The Patient Generated Index (PGI) is one of two main individualized measures and is designed to identify personal QOL concerns and summarize their importance in a total score[5]. The validity of the PGI with respect to standard QOL measures has not been fully established for advanced cancer when QOL concerns predominate. The global aim of this thesis is to contribute evidence towards the applicability of the PGI in the context of evaluating QOL in cancer.

This thesis consists of four inter-related studies. The evidence on the psychometric properties of the PGI in the context of cancer was summarized systematically and reported in Manuscript 1. Two studies conducted as part of this thesis provided evidence of validity by comparing PGI to the standard measures at the total score and at the item levels. These results are presented in Manuscripts 2 and 3. A fourth study investigated the response shift phenomenon which was

made possible because of the nature of the PGI's assessment format and the results are reported in Manuscript 4.

The systematic review (Manuscript 1) set the foundation for the subsequent work carried out for this thesis. The review covered 27 studies reporting on the psychometric properties, including feasibility and applicability, of individualized measures in the context of cancer were summarized. The results of this review showed that individualized measures are feasible and acceptable among people with cancer. The top four QOL concerns across studies were family, health, finance, and work. Individualized measures are related in an expected way to other cancer-specific and generic measures tapping aspects of QOL. In general, correlations were low to moderate, depending on what correlated, total scores or subscales. The weak correlations were not surprising because individualized measures focus only on what is of concern to patients and fully standardized measures include items that may not be of individual concern. As a result scores on individualized measures tend to be lower than scores on standardized measures.

This was demonstrated in Manuscript 2 where the differences between the PGI and standardized measures ranged from -26.1 to -43.3. The correlations between the PGI and the standardized measures were also low and ranged from 0.12 to 0.22. This manuscript focused on total scores.

The literature review in Manuscript 1 also showed that the individualized measures are sensitive to change which could arise because lower scores provide more room for improvement. Magnitude of change is also affected by both true change and response shift. The response shift phenomenon was the topic of Manuscript 4.

The review also showed that the areas identified by the individualized measures covered a wide spectrum of concerns. This was supported by data reported in Manuscript 2 where the sample of 192 people identified at study entry 114 different areas, yet even the most prevalent area, fatigue, was nominated by only 39% of the sample. Of the top four domains identified from the systematic review (family, health, finance, and work), work and family were in the top 10 in this sample, and the others were nominated but with lower prevalence. These results speak to the heterogeneity of the cancer impact and would make individualized measures ideal for this population.

As indicated above, the systematic review set the foundation for the studies carried out using the data on hand. The review was unique in several ways. The WHO's International Classification of Functioning, Disability and Health (ICF) framework was used to harmonize the areas nominated into a standard nomenclature[6, 7]. The psychometric properties were appraised using, where possible, the guidelines from Consensus Based Standards for the Selection of Health Measurement Instruments (COSMIN). In addition, a formal meta-analysis was carried out to provide a summary estimate of the correlation, across studies, between the individualized measures and standard measures. For example, the pooled correlation between individualized measures and the global score on the SF-12 was 0.43 (95% CI: 0.42-0.45). The closest measure to the SF-12 that was available on the data used in this study was the SF-6D, derived from the SF-36, and the correlation was 0.22 (95% CI: 0.08 -0.37; see Manuscript 2). The lower correlation is likely a feature of the sample used in this thesis, which comprised people with advanced cancer and the PGI was the specific individualized measure used.

No study was identified from the systematic review that looked at validity at the area level. This was felt to be gap in the literature because the total score on the PGI is derived from the severity rating of the areas nominated. A logical next step would be to assess the agreement at the area level with items from standardized measures. This was the topic of Manuscript 3.

Manuscript 3 addressed the relationship between what patients self-nominate and rate for severity using the PGI and what would be ascertained from items on fully standardized measures. In the Manuscript 2, the results showed that fatigue and pain were among the top nominated areas by people with advanced cancer and, that although not in the top 10, physical function concerns were nominated by some. As rehabilitation professionals target physical function, this area was felt to be important to examine for agreement. In addition, existing standardized measures have many items relating to the physical domain. Thus, fatigue, pain and physical function were chosen for the assessment of the validity of the PGI at the item level. For each area, there were multiple items available from the standardized measures for comparison. For example for fatigue, agreement, within one severity rating, ranged from 32% to 77%, for pain, between 34% and 95%; and, for physical function, between 84% and 95%. There were 10 items was high (59% to 95%). Of these 10 items, 7 came from the RAND-36 which provides strong evidence for validity of the PGI as the RAND-36 (original version of the SF-36) is one of the most widely used and extensively validated measures of HRQL. At the domain level, people nominating an area scored in the more impaired range on standard measures than people who did not, support known groups validity.

The systematic review (Manuscript1) supported responsiveness of the individualized measures, that is they were sensitive to change when change occurred. Change in QOL is not a simple

calculation over two time points because change could come from different sources: true change owing to changes in health status, and change from response shift. No study from the systematic review investigated the response shift phenomenon yet the structure of individualized measures is ideal for this purpose.

The response shift phenomenon was the topic of Manuscript 4. Response shift is defined as the change in the meaning of a person's self evaluation of a target construct (e.g., QOL) over time, as a result of (1) changes in the internal standards (recalibration) of the measurement, (2) changes in the respondent's values (changes in importance of the items or component domains that constitute QOL concept (reprioritization)), and (3) changes in the definition of the targeted construct (redefinition QOL) (reconceptualization) [8].

Manuscript 4 focused only on reconceptualization response shift. The other types of response shift would have required additional data collection and/or interviews. For example, the "Then-test" [9] is a way of detecting recalibration [10] but the response burden would have been too high. The purpose of this Manuscript was specifically to estimate the extent to which reconceptualization response shift occurred over time in cancer population and the impact of this response shift on estimated change in QOL.

A step-wise approach was taken to investigate response shift. First, I demonstrated that people with advanced cancer made meaningful changes in their QOL using the PGI and in other related measures setting the stage in investigate sources of change. Second, I showed that all people changed the content of at least one area over time, potentially indicating a response shift. A major challenge in this thesis was the lack of established metrics for response shift using individualized measures. To move the field forward, four response shift variables were

operationalized: (i) change in the number of areas nominated from the baseline assessment; (ii) the number of new areas added; (iii) change in content of the areas; (iv) a composite response shift indicator derived from change in number of areas and change in content.

A key step in understanding change is to identify potential sources of true change. Variables known to contribute to QOL were assessed and several were identified as predicting change. These were included in further analyses.

To identify the independent contribution of "true change" variables and response shift variables, as series of multi-variate linear regression models were tested. The results revealed that only response shift variables contributed to change in PGI and none of the "true change" variables contributed. However, the main contributor was change in number areas, not content. People who added areas at one year (T2) had a lower PGI score at T2 as compared to baseline (T1), while those who dropped areas had a better score at T2. This finding is consistent with the PGI framework as areas nominated tend to focus on negative aspects of QOL, thus areas added would tend to be those that are newly problematic leading to lower the PGI score at T2. The theory of cognitive homeostasis[11, 12] could explain the observation that when areas were dropped, QOL improved. This could indicate that people are attempting to maintain as high a QOL as possible by refocusing away from negative aspects reflected by dropping these areas as no longer being so important. The results showed that people who dropped areas had a higher PGI score at T2 than T1 (Table 4 in Manuscript 4) and people who added areas had a lower PGI score. However, in support of cognitive homeostasis the global QOL ratings did not change as much as did the PGI, suggesting that even in the presence of more problematic areas, people maintained their calibration on global indices. Additionally, people may not wish to declare, in front of an

interviewer, that their QOL is poor or has deteriorated. They might also have changed their frame of reference over this time[13] period and, even in the presence of deteriorating health, felt themselves to be better off than others who they knew were ill or had died. Manuscript 4 provided evidence that people with advanced cancer made a response shift (reconceptualization) and this is reasonable given that there are several potential catalysts[8] for the shift including disease progression, treatment side effects, and surviving.

An interesting observation was that the EQ-$5D_{index}$ showed an impact of change in areas, similar to that observed for the PGI although to a lesser degree. When areas were added, the EQ-$5D_{index}$ decreased which would have occurred if the added areas were those included in the classification system for this measure (walking, usual activities, self-care, pain, anxiety/depression).

This study took a quantitative approach to response shift, the findings would have been greatly enhanced by adding a qualitative component to ask people how and why areas changed. Ahmed et al.[14] found that in a sample of 92 patients with stroke who completed PGI at 6 weeks and 24 weeks post stroke, approximately half nominated different areas at 24 weeks as compared to 6 weeks. Half of this group (n=46) were interviewed about their response shift experience at 24 weeks and for 13 (28%) the response shift was supported by semi structured interview [14].

For example, some patients indicated that they dropped areas, even though they were problematic as their new focus was now on only the most relevant areas. Other reasons for changing areas, unrelated to response shift were forgetting to nominate an area previously mentioned (n=8) or they had improved (true change; n=13).

Strengths and limitations of the thesis

The strength of this thesis was in the stepwise approach to investigating the richness of the PGI format for understanding QOL. I identified that there was quite good agreement between the areas of the PGI and items on standardized measures despite poor correlation at the total score level. This indicated that the area level provides the key to QOL and needs be further explored which led to the investigation of the response shift phenomenon. This work is completely novel in the field of response shift and makes an original contribution to this literature. Another strength of the thesis is the proposal of four metrics for operationalizing response shift. These methods could serve as a model for other studies as replication is essential in any scientific process.

The sample was also unique and quite large considering it was compromised entirely of people with advanced cancer for whom QOL is of primordial concern for making treatment and life decisions.

Finally, the analyses conducted for this thesis made use of existing data arising from a longitudinal study of anorexia/cachexia and QOL in people with advanced cancer[15]. This is a very ethical way of investigating new areas of research importance as people have already contributed the needed data and new people are not being recruited into studies that are developmental in nature.

The sample was unique, but limited in that only 235 of 388 eligible patients consented (response rate 60.6%) and, of these, 32 did not complete the initial evaluation. Thus, the group assessed could have differed from the group not assessed in important ways but these differences are

unlikely to affect differentially the scoring of PGI and scoring of items on standard measures (Manuscript 3). People not entering the study likely have the same association between PGI areas and PRO measures. Another limitation was the small sample size available for the analyses on response shift (Manuscript 4) but this study was not designed *a priori* to test response shift hypotheses.

There were challenges in administering the PGI as some participants omitted the last stage, distributing tokens, some distributed too few or some too many. We recommend that patients should be supervised when the PGI is administered to ensure no errors in completion.

Conclusion

This thesis supports that the PGI measures QOL from a different perspective than standardized measures. This different perspective is valuable in identifying what to matters to patients and in identifying how what matters changes over time. The PGI also provided an opportunity to investigate the effect of response shift beyond a measurement problem. For those who dropped areas, response shift is perhaps a desired phenomenon showing a coping mechanism; for others who added areas, this would indicate a need for clinical attention.

References

1. Lehmann, J.F., et al., *Cancer rehabilitation: assessment of need, development, and evaluation of a model of care.* Arch Phys Med Rehabil, 1978. **59**(9): p. 410-9.

2. Ness, K.K., et al., *Physical performance limitations and participation restrictions among cancer survivors: a population-based study.* Ann Epidemiol, 2006. **16**(3): p. 197-205.

3. World Health Organization, *Programme on Mental Health:.* WHOQOL User Manual. Geneva., 1998.

4. Calman, K.C., *Quality of life in cancer patients--an hypothesis.* J Med Ethics, 1984. **10**(3): p. 124-7.

5. Ruta, D.A., et al., *A new approach to the measurement of quality of life. The Patient-Generated Index.* Med Care, 1994. **32**(11): p. 1109-26.

6. Organization., W.H., *International Classification of Functioning, Disability and Health: ICF. World Health Organization.* 2008.

7. Organization., W.H., *International Classification of Functioning, Disability and Health, 2nd revision edn. Geneva: WHO. .* 2001.

8. Sprangers, M.A. and C.E. Schwartz, *Integrating response shift into health-related quality of life research: a theoretical model.* Soc Sci Med, 1999. **48**(11): p. 1507-15.

9. Howard GS, D.P., *Response-shift bias: a source of contamination of self-report measures.* J Appl Psychol 1979. **64**: p. 144–50.

10. Ahmed, S., et al., *Response shift influenced estimates of change in health-related quality of life poststroke.* J Clin Epidemiol, 2004. **57**(6): p. 561-70.

11. Martin, F., et al., *Twelve years' experience with the Patient Generated Index (PGI) of quality of life: a graded structured review.* Qual Life Res, 2007. **16**(4): p. 705-15.

12. Cummins, R., *Personal income and subjective well-being: A review.* Journal of Happiness Studies, 2000. **133–158.**(1).

13. Schwartz, C.E. and B.D. Rapkin, *Reconsidering the psychometrics of quality of life assessment in light of response shift and appraisal.* Health Qual Life Outcomes, 2004. **2**: p. 16.

14. Ahmed, S., et al., *Using the Patient Generated Index to evaluate response shift post-stroke.* Qual Life Res, 2005. **14**(10): p. 2247-57.

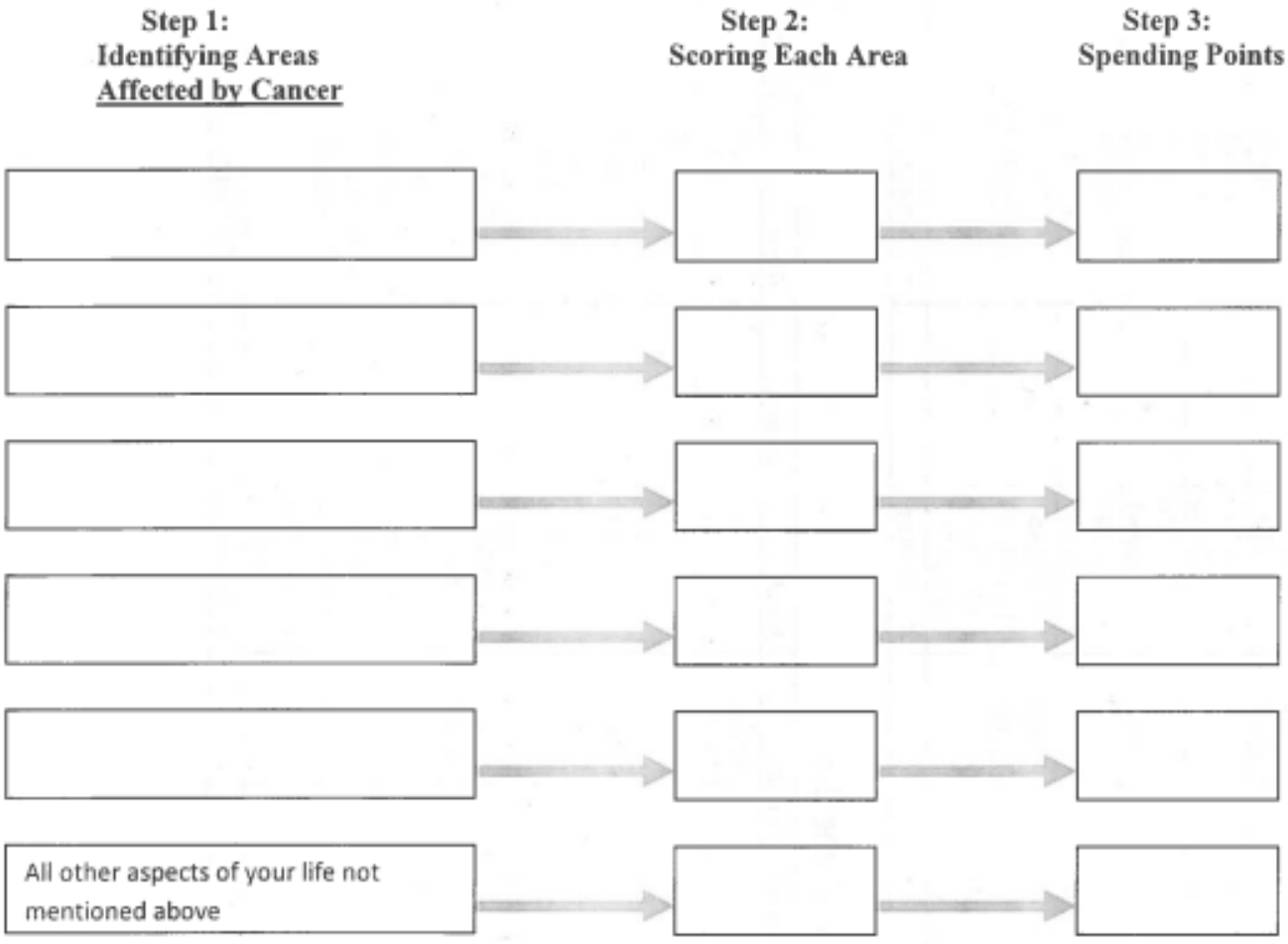
15. Rodriguez, A.M., N.E. Mayo, and B. Gagnon, *Independent contributors to overall quality of life in people with advanced cancer.* Br J Cancer, 2013. **108**(9): p. 1790-800.

THESIS MEASURES

Patient Generated Index (PGI)

Patient Generated Index Scoring Sheet

A participant's answers to the following steps will tell us how their life is affected by cancer.
Please refer to the instruction sheet how to ask these questions and complete the index.



*** Instructions for Interviewers*** Please see the page 3 for an example of how to complete the sheet.

Step 1

Questions to your participant:

"We would like you to think of the most important areas of your life that are affected by cancer.
Please give us up to 5 areas (responses)".

Instruction to the interviewer:

Please write down the responses in the boxes in the step 1 section.

Step 2

Questions to your participant:

"In this part we would like you to score the areas you mentioned in step 1. Also, please score all other areas of your life excluding the 5 areas previously mentioned. This score should ***show how much affected you were over the past MONTH.***
Please score each are out of 10 using the scale (see the page 3)".

Instruction to the interviewer:

Please show the scale to participant and write down the responses in the boxes in the step 2 section.

Step 3

Questions to your participant:

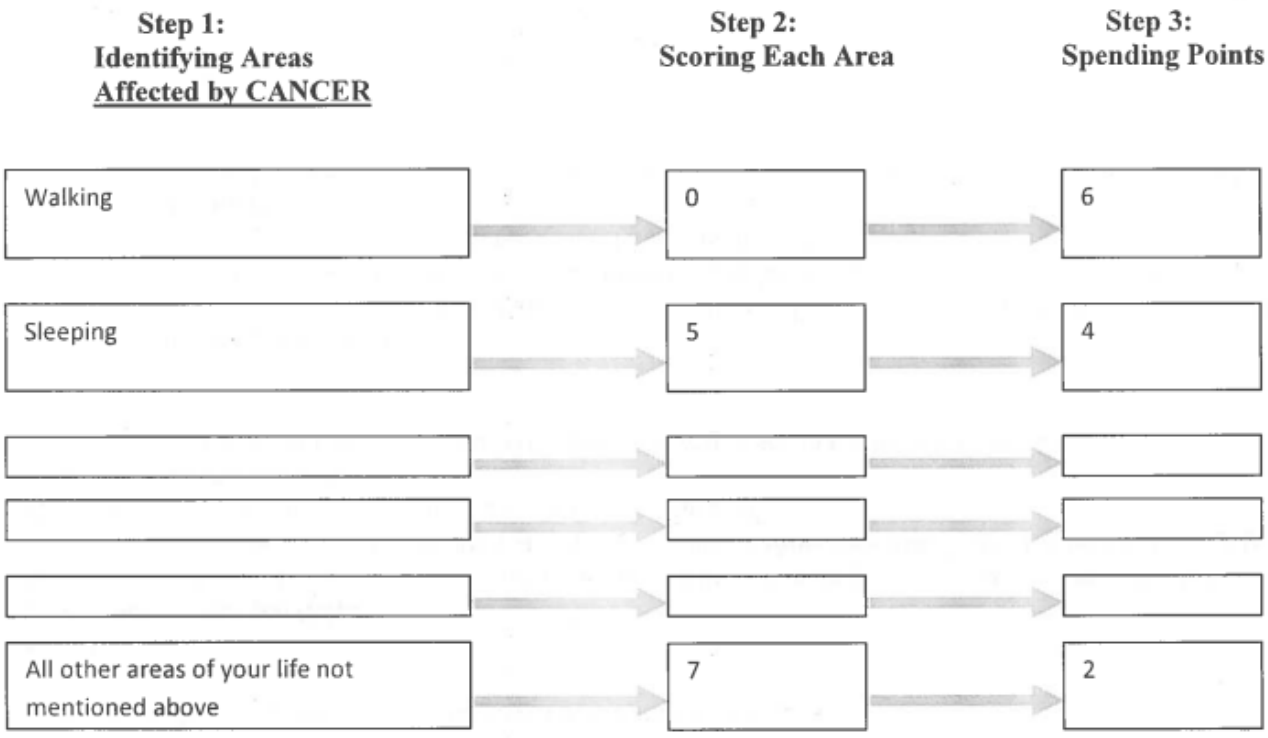
"Now, we would like you to imagine that any or all areas of your life could be improved. You have 12 imaginary points to spend to show which areas you would like to see improve and less on areas that are not so important. You do not have to spend points in every area. You cannot spend more than 12 points in total".

Instruction to the interviewer:

Please write down the responses in the boxes in the step 3 section and make sure the total score does not exceed 12 points.

Example:

- This participant identified 2 areas that were most important and affected by Cancer.
- 1. walking, affected the worst s/he could imagine, would like to improve a lot
- 2. sleeping, affected fairly, would like to improve a little
- 3. all other areas, between good and fair, would like to improve fairly



Edmonton Symptom Assessment System (ESAS)

Edmonton Symptom Assessment System (ESAS)

Please circle the number that best describes the state of your health during the last 24 hours:

No pain	0 1 2 3 4 5 6 7 8 9 10	Worst possible pain
No fatigue	0 1 2 3 4 5 6 7 8 9 10	Worst possible fatigue
No nausea	0 1 2 3 4 5 6 7 8 9 10	Worst possible nausea
Not depressed	0 1 2 3 4 5 6 7 8 9 10	Worst possible depression
No anxiety	0 1 2 3 4 5 6 7 8 9 10	Worst possible anxiety
Not drowsy	0 1 2 3 4 5 6 7 8 9 10	Worst possible drowsiness
Best appetite	0 1 2 3 4 5 6 7 8 9 10	Worst possible appetite
Best quality of life	0 1 2 3 4 5 6 7 8 9 10	Worst possible quality of life
No itching	0 1 2 3 4 5 6 7 8 9 10	Worst possible itching
No shortness of breath	0 1 2 3 4 5 6 7 8 9 10	Worst possible shortness of breath

McGill Quality of Life Questionnaire

McGILL QUALITY OF LIFE QUESTIONNAIRE

STUDY IDENTIFICATION #:_____ DATE: _____

Instructions

The questions in this questionnaire begin with a statement followed by two opposite answers. Numbers extend from one extreme answer to its opposite.
Please circle the number between 0 and 10 which is most true for you.
There are no right or wrong answers.
Completely honest answers will be most helpful.

EXAMPLE:

I am hungry:

not at all 0 1 2 3 4 5 6 7 8 9 10 **extremely**

- If you are not even a little bit hungry, you would circle 0.
- If you are a little hungry (you just finished a meal but still have room for dessert), you might circle a 1, 2, or 3.
- If you are feeling moderately hungry (because mealtime is approaching), you might circle a 4, 5, or 6.
- If you are very hungry (because you haven't eaten all day), you might circle a 7, 8, or 9.
- If you are extremely hungry, you would circle 10.

BEGIN HERE:

IT IS VERY IMPORTANT THAT YOU ANSWER ALL QUESTIONS FOR HOW YOU HAVE BEEN FEELING *JUST IN THE PAST TWO (2) DAYS*.

PART A

Considering all parts of my life - physical, emotional, social, spiritual, and financial - *over the past two (2) days* the quality of my life has been:

very bad 0 1 2 3 4 5 6 7 8 9 10 **excellent**

Please continue on the next page...

PART B: Physical Symptoms or Physical Problems

(1) *For the questions in Part "B", please list the* **PHYSICAL SYMPTOMS OR PROBLEMS** *which have been the biggest problem for you over the past* **two (2)** *days. (Some examples are: pain, tiredness, weakness, nausea, vomiting, constipation, diarrhea, trouble sleeping, shortness of breath, lack of appetite, sweating, immobility. Feel free to refer to others if necessary).*

(2) *Circle the number which best shows how big a problem each one has been for you* ***OVER THE PAST TWO (2) DAYS.***

(3) *If, over the past two (2) days, you had* **NO** *physical symptoms or problems, or only one or two, answer for each of the ones you have had and write "none" for the extra questions in Part B, then continue with Part C.*

1. Over the past two (2) days,
one troublesome symptom has been:_____.
(write symptom)

no problem 0 1 2 3 4 5 6 7 8 9 10 **tremendous problem**

2. Over the past two (2) days,
another troublesome symptom has been:_____.
(write symptom)

no problem 0 1 2 3 4 5 6 7 8 9 10 **tremendous problem**

3. Over the past two (2) days,
a third troublesome symptom has been:_____.
(write symptom)

no problem 0 1 2 3 4 5 6 7 8 9 10 **tremendous problem**

Please continue on the next page...

4. Over the past two (2) days I have felt:

physically terrible	0	1	2	3	4	5	6	7	8	9	10	**physically well**

PART C *Please choose the number which best describes your feelings and thoughts* ***OVER THE PAST TWO (2) DAYS.***

5. Over the past two (2) days, I have been depressed:

not at all	0	1	2	3	4	5	6	7	8	9	10	**extremely**

6. Over the past two (2) days, I have been nervous or worried:

not at all	0	1	2	3	4	5	6	7	8	9	10	**extremely**

7. Over the past two (2) days, how much of the time did you feel sad?

never	0	1	2	3	4	5	6	7	8	9	10	**always**

8. Over the past two (2) days, when I thought of the future, I was:

not afraid	0	1	2	3	4	5	6	7	8	9	10	**terrified**

9. Over the past two (2) days, my life has been:

utterly meaningless and without purpose	0	1	2	3	4	5	6	7	8	9	10	**very purposeful and meaningful**

10. Over the past two (2) days, when I thought about my whole life, I felt that in achieving life goals I have:

made no progress whatsoever	0	1	2	3	4	5	6	7	8	9	10	**progressed to complete fulfillment**

Please continue on the next page...

11. Over the past two (2) days, when I thought about my life, I felt that my life to this point has been:

completely worthless	0	1	2	3	4	5	6	7	8	9	10	**very worthwhile**

12. Over the past two (2) days, I have felt that I have:

no control over my life	0	1	2	3	4	5	6	7	8	9	10	**complete control over my life**

13. Over the past two (2) days, I felt good about myself as a person.

completely disagree	0	1	2	3	4	5	6	7	8	9	10	**completely agree**

14. To me, the past two (2) days were:

a burden	0	1	2	3	4	5	6	7	8	9	10	**a gift**

15. Over the past two (2) days, the world has been:

an impersonal unfeeling place	0	1	2	3	4	5	6	7	8	9	10	**caring and responsive to my needs**

16. Over the past two (2) days, I have felt supported:

not at all	0	1	2	3	4	5	6	7	8	9	10	**completely**

Please continue on the next page...

PART D

Please list or describe the things which had the greatest effect on your quality of life in the past two (2) days. Please tell us whether each thing you list made your quality of life better or worse during this time. If you need more space, please continue on the back of this page.

Thank you very much for your help.

Functional Assessment of Anorexia Cachexia Therapy (FAACT, Version 4)

FAACT (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
C6	I have a good appetite	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs	0	1	2	3	4
ACT2	I am worried about my weight	0	1	2	3	4
ACT3	Most food tastes unpleasant to me	0	1	2	3	4
ACT4	I am concerned about how thin I look	0	1	2	3	4
ACT6	My interest in food drops as soon as I try to eat	0	1	2	3	4
ACT7	I have difficulty eating rich or "heavy" foods	0	1	2	3	4
ACT9	My family or friends are pressuring me to eat	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
ACT10	When I eat, I seem to get full quickly	0	1	2	3	4
ACT11	I have pain in my stomach area	0	1	2	3	4
ACT13	My general health is improving	0	1	2	3	4

Multidimensional Fatigue Inventory (MFI)

MFI® MULTIDIMENSIONAL FATIGUE INVENTORY *am*

® E. Smets, B.Garssen, B. Bonke.

Instructions:

By means of the following statements we would like to get an idea of how you have been feeling **lately**.
There is, for example, the statement:

"I FEEL RELAXED"

If you think that this is **entirely true**, that indeed you have been feeling relaxed lately, please, place an **X** in the extreme left box; like this:

yes, that is true ☒1 ❑2 ❑3 ❑4 ❑5 **no, that is not true**

The more you **disagree** with the statement, the more you can place an **X** in the direction of "no, that is not true". Please do not miss out a statement and place only one **X** in a box for each statement.

1	I feel fit.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
2	Physically, I feel only able to do a little.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
3	I feel very active.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
4	I feel like doing all sorts of nice things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
5	I feel tired.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
6	I think I do a lot in a day.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
7	When I am doing something, I can keep my thoughts on it.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
8	Physically I can take on a lot.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
9	I dread having to do things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
10	I think I do very little in a day.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
11	I can concentrate well.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
12	I am rested.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
13	It takes a lot of effort to concentrate on things.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
14	Physically I feel I am in a bad condition.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
15	I have a lot of plans.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true

16	I tire easily.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
17	I get little done.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
18	I don't feel like doing anything.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
19	My thoughts easily wander.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true
20	Physically I feel I am in an excellent condition.	yes, that is true	❑1	❑2	❑3	❑4	❑5	no, that is not true

Thank you very much for your cooperation

EQ-5D ***index***

By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

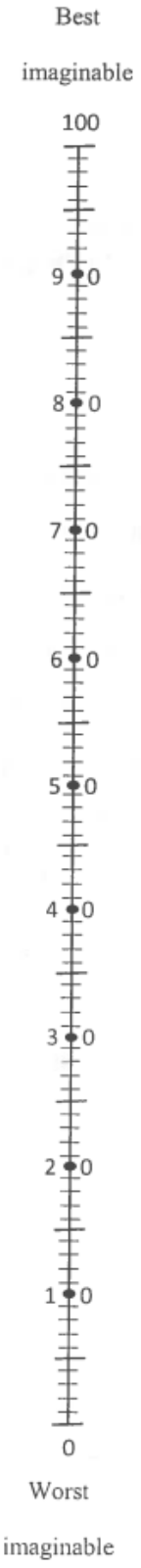
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health



RAND-36 Health Status Survey/ Canada

RAND-36 HEALTH STATUS SURVEY / CANADA

Questionnaire

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

	(circle one)
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?

	(circle one)
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same as one year ago	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a kilometer**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (circle one number on each line)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

	(circle one)
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past 4 weeks?

	(circle one)
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

	(circle one)
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of pep?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and blue?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

	(circle one)
All of the time.....	1
Most of the time.....	2
Some of the time.....	3
A little of the time.....	4
None of the time	5

11. How **TRUE** or **FALSE** is each of the following statements for you?

(circle one number on each line)

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5