What Constructs Are Represented in Multiple Sclerosis Specific Health-Related Quality of Life Measures?

Alaa Mohammad Arafah, B.Sc. (Occupational Therapist)
School of Physical and Occupational Therapy
Faculty of Medicine, McGill University, Montreal, Quebec, Canada
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ABSTRACT

Health-related quality of life (HRQL) is becoming a common outcome for many medical and rehabilitative studies. This is specifically true for multiple sclerosis (MS), one of the most common chronic neurological condition affecting young adults. As MS results in severe consequences, its management depends on careful assessment of the outcome of interest. Measures of HRQL should represent all domains of HRQL and should be based on a theoretical frame of reference.

The main objective of this content analysis study is to estimate the extent to which items in the MS-specific HRQL measures capture all domains of HRQL, using the International Classification of Functioning Disability and Health (ICF) and the Wilson-Cleary models as frames of reference. Items of 10 HRQL measures were linked to the ICF by a pool of 25 health professionals using a standardized procedure. Among the 550 items that were mapped, 44% represented symptoms, 34% represented functioning and 35% represented concepts of general health perception and satisfaction with quality of life. Only 6% of the items targeted environmental factors. Measures differed not only in the degree of representing the different components of HRQL but also in the ways of ascertaining a single construct, fatigue, one of the most distressing MS symptom.

ABRÉGÉ

La qualité de vie reliée à la santé (QRVS) devient de plus en plus l'objectif principal des recherches en réadaptation et en médicine. Les études portant sur la sclérose en plaque (SP) visent particulièrement des résultats pouvant améliorer la qualité de vie des personnes. En effet, la sclérose en plaque (SP) est une condition neurologique chronique qui affecte principalement de jeunes adultes. Cette maladie résulte en de sévères symptômes. Une meilleure compréhension de la gestion de ces symptômes dépend principalement de la précaution et de la précision des évaluations. Les mesures de qualité de vie reliée à la santé (QRVS) devraient représenter tous les domaines de ce qu'est la QRVS. De plus, ces mesures devraient se référer à un modèle théorique définit.

L'objectif principal de cette étude est d'estimer à quel point les mesures évaluant la qualité de vie reliées à la santé (QVRS) utilisées pour la sclérose en plaque permettent de saisir l'entièreté des domaines de la QVRS. Chaque item de ces mesures sera analysé en utilisant comme référence le modèle Classification internationale du fonctionnement, du handicap et de la santé (CIF) et le modèle Wilson-Cleary. Selon une méthodologie standardisée, vingt-cinq professionnels de la santé ont reliés au modèle ICF les items de 10 questionnaires évaluant la QVRS. Parmi ces 550 items, 44% représentaient des symptômes, 34% représentaient le niveau de fonctionnement, 35% portaient sur la conception de la santé et la satisfaction par rapport à la vie. Seuls 6% portaient sur des facteurs environnementaux. Les différents aspects de la QVRS étaient représentés différemment d'une mesure à l'autre. De plus, ces mesures divergeaient quant à leur définition de la fatigue, un des symptômes les plus affligeants de la sclérose en plaques.

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I would like to express my warmest gratitude to my supervisor Dr. Nancy Mayo for all the help and guidance she gave me and for all of the support and understanding she showed me during the past two years. Her doors were always open for my questions and concerns. Her patience and nurturing passion for knowledge and research had enlightened my journey and gave me a stimulating learning environment. She guided me and provided me with the required skills to master the expertise of a good researcher.

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PREFACE

There were many steps involved in the development of this manuscript based thesis. The thesis protocol was written by Aala Arafah, under the guidance of Dr. Nancy Mayo. Then a literature review was conducted, followed by data collection and analysis. The thesis was written by Alaa Arafah with extensive editing from Dr. Nancy Mayo. Carolina Moriello, Miho Asana, Ayse Kuspinar, and Shang Yuan Teng also contributed to the development of this thesis.

Organization of thesis

The primary objective of this thesis was to perform an in-depth content evaluation of the most commonly used health-related quality of life (HRQL) measures in the multiple sclerosis population. The secondary objective further examined the heterogeneity of ascertaining fatigue in the multiple sclerosis population. Each objective is independently addressed in two separate manuscripts. These manuscripts will later be submitted to scientific journals for publication. Additional chapters have been incorporated in this thesis in order to comply with the regulation of the Graduate and Postdoctoral Studies (GPS). It is required by the GPS to include a literature review and conclusion that is separate from the manuscript. Thus, it is unavoidable to have duplication of material in this thesis.

Chapter 1 is an introduction to multiple sclerosis, and its impact on quality of life. This chapter also describes the use of patient reported outcome measures in the evaluation of HRQL. This leads to a presentation of the challenges in measuring HRQL in multiple sclerosis. The ICF and the Wilson-Cleary models are introduced as the most suitable frames of reference in this study.

Chapter 2 presents a literature review on the available HRQL measures in the multiple sclerosis population. The major characteristics and psychometric properties of those measures are also presented in this chapter.

Chapter 3 states a general rationale for conducting a content examination of the most commonly used HRQL measures in the multiple sclerosis population. It also outlines the main objectives of the two manuscripts.

Chapter 4 consists of the first manuscript. It includes the text, figures, tables and references. The format of this manuscript follows the style of the journal *"Disability and Rehabilitation"*. The contents of this manuscript are related to performing in-depth content comparisons of HRQL measures using the ICF and the Wilson-Cleary models as frames of reference.

Chapter 5 presents the link or the connection between the conclusion of the first manuscript and the objective of the second manuscript.

Chapter 6 consists of the second manuscript. It includes the text, figures, tables and references. The format of this manuscript also follows the style of the journal *"Disability and Rehabilitation"*. This manuscript is related to further comparisons of measures of fatigue symptom, the most common and distressing symptom of multiple sclerosis. It states measurement problems and suggested solutions.

Chapter 7 includes a summary of findings and conclusions of both manuscripts. The appendices contain information that is not normally included in a manuscript. A complete list of appendices is presented in the table of contents.

CHAPTER 1

Overview of Multiple Sclerosis

1.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, autoimmune disease of the central nervous system (CNS) [1]. The body's immune system attacks the myelin surrounding the axons causing inflammatory lesions and damaging the myelin in patches. This will cause interruption or distortion of the neural signals leading to a variety of symptoms [2]. The etiology of MS is unknown, however, researchers believe that multiple factors play a role in triggering MS including infection [3]. There is also a genetic hypothesis as individuals who have a parent or sibling with MS have a greater risk of developing MS than the general population [4]. Environmental factors have shown to have an association with the onset of MS as individuals living further away from the equator have an increased risk of developing MS [5]. Moreover, it was shown that individuals who were born in a higher-risk country and migrated to a lower-risk country are more likely to keep the risk of the new region [5]. Individuals living in Canada, USA, New Zealand, some parts of Europe and Australia, have higher risk of having MS [6]. The prevalence of MS in Canada is 240 per 100 000 population [7]. Worldwide, MS is estimated to affect 2.5 millions of the population [6, 8].

MS is one of the most common chronic neurological condition affecting young adults [9]. It is usually diagnosed between the ages of 18 to 40, reaching its peak at the age of 30 [2]. MS is three times more likely to occur in women than in men [10]. There are four types of MS as illustrated in Figure 1.1. *Relapsing-remitting MS*, characterized by clear and well defined attacks followed by complete or partial remissions, 75% of persons are initially diagnosed with this type. *Primary-progressive MS*, characterized by slow and continuous worsening of the condition with no clear attacks or remissions, tends to occur in about 10% of persons diagnosed with MS. *Secondary-progressive MS*, about 50% of individuals diagnosed with relapsing-remitting MS will develop secondary progressive MS after 10-15 years of its onset. This type is characterized by steady worsening of the condition, with or without attacks and remissions. The last type is *progressive-relapsing MS*, the most severe and rare type of MS (occurs in about 5% of the persons diagnosed with MS). This type is characterized by steady worsening of the condition with clear attacks and without remissions [11].

1.2 MS Symptoms

MS is a variable and unpredictable disease; its symptoms vary greatly from one person to another and can change in severity within the same person. Therefore, there is no set pattern to MS. Symptoms of MS depend on the areas of the CNS that have been affected. MS symptoms are highlighted in Table 1.1 and 1.2. The most common symptoms are: fatigue, numbness, pain, decreased balance, spasticity, visual problem, bladder dysfunction, bowel dysfunction, sexual problem, cognitive decline and emotional changes [12-18.] Often, symptoms reach their maximal intensity within two weeks and then start to slowly resolve. In some cases, relapses may not remit for up to six months. The frequency of relapses is usually greater early in the disease, but can vary greatly among individuals with MS [2].

1.3 The New MS

Until only recently the diagnosis of MS was based on the presented clinical symptomatology and on the progression of abnormal neurological signs as investigated through neurological examination [1]. MS was often diagnosed after progression was evident and the management of MS was aimed at reducing acute relapses. Steroids were used to reduce inflammation and baclofen was used to reduce spasticity. However, two revolutionary dimensions played roles in improving the process of diagnosis and management of MS. In the mid-1980s, the introduction of magnetic resonance imaging (MRI) provided a window into the brain and from 1995 onward, MRI became the diagnostic standard for MS permitting myelin lesions to be identified early on in the course of the disease [19].

In addition, the introduction of disease modifying therapies (DMTs) permitted better management of the progression of MS [20].

Thus, people diagnosed after 1995, will receive this terrifying label possibly in advance of intrusive symptoms. Treatment may reduce the disability course of MS. Nevertheless, the emotional consequences may provoke more disability than the physical consequences and result in reduction of quality of life greater than expected from the physical disability alone.

1.4 MS Medical and Rehabilitative Managements

In 1993, the first DMT (Betaseron®) was approved for relapsing-remitting MS, followed by the approval of other DMTs; Avonex®, Copaxone®, Bebif®, Novantrone® and Tysabri® [20]. These agents which have immune-suppressive and/or immune-modulating effects work on reducing the rate and frequency of relapses and delaying the progression of physical disabilities [20, 21].

Other pharmaceutical approaches may focus on reducing the underlying symptoms e.g. antidepressant medication for depression, baclofen or tizanidine for spasticity and anticholinergics for overreacting bladder [22].

Rehabilitative approaches are also very essential in the management of MS. Depending on the symptoms and functional limitations, health professionals provide stretching and strengthening exercises, disease coping strategies, assistive devices, and education to assist persons with MS in taking control over their lives [23].

1.5 QOL of Persons with MS

With the development of DMTs and new imaging techniques, the life expectancy of persons with MS had been prolonged. Persons with MS are expected to live longer, yet their quality of life (QOL) is not promising. Quality of life is defined by the world Health Organization (WHO) as *"the individuals' perceptions of their position in life in the context of the cultural and value system in which they live and their relationship to their goals, expectations, standards, and concerns"*[*] [24].

As the progression of MS is heterogeneous and unpredictable, it can threaten

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[*] World Health Organization. *International classification of functioning, disability and health.* Geneva: WHO, 2001.

many aspects of the individual's life and well-being. MS substantially affects QOL as it impacts on health perception and on capacity to perform every day activities. After 10 years of MS diagnosis, up to 50% of persons with MS are restricted in their abilities to carryout household and employment responsibilities [25]. Aspects of health-related quality of life (HRQL) are greatly reduced in MS population. HRQL is referred to as *"the value assigned to duration of life as defined by the impairments, functional status, perceptions, and opportunities influenced by disease, injury, treatment, and policy"*[*] [26]. HRQL is generally distinguished from overall QOL by those aspects of life that are most likely to be affected by health. Domains outside of the purview of the health care system such as economic, family life and the employment are not parts of HRQL [27]. Physical function, social engagement, personal control, MS symptoms, sexual/intimacy, and emotional/mental health are all domains of HRQL that have been shown to be affected and altered by MS. Rudick et al [28] published in 1992 one of the earliest studies that examined HRQL in persons with MS. In this study, HRQL was compared across three chronic conditions: 68 persons with MS, 75 persons with rheumatoid arthritis, and 164 persons with inflammatory bowel disease. The study concluded that persons with MS had the lowest ratings of HRQL. This was also supported by Devins et al [29], who reported that persons with MS were less satisfied and more distressed by their condition than persons with other chronic conditions. Indeed, persons with MS were found to have significant lower ratings across all health dimensions of the SF-36 when compared to the general population [30]. In general, MS has a huge impact on the person's function and well-being; these dimensions should be addressed and highlighted when managing health care of these patients.

1.6 Measuring HRQL: The Application of Patient-Reported Outcome Measures

Changes in the regulation of the FDA, the Food and Drug Administration, had put more emphasis on developing drugs that aim at improving long-term outcomes that matter to patients, in addition to providing drugs that are safe and efficacious[31]. As patients value function, interventions should be aimed at

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[*] Patrick DL, Bergner M. Measurement of health status in the 1990s. *Annu.Rev.Public Health* 1990;11:165-83.

reducing impairments such as weakness, fatigue, and pain and increasing capacity for activity and participation in required and desired roles. Improvement in HRQL is the unanimous target of all health care interventions. This is true not only for MS but for chronic conditions in general, as the management of these conditions is palliative or rehabilitative rather than curative. Thus, increasingly, outcomes are focusing on evaluating parameters such as life-style, productivity and QOL and these constructs are best elicited from patients directly [32]. Researchers and clinicians are becoming more aware of the importance of incorporating the patient's perspective when measuring disease activity and impact. The patient's perspective provides unique information supplementing that obtained from physiological sources, clinicians, and family members. Each source provides a unique perspective. Clinicians analyze diseases and conditions from the perspective of the impact on body functions; caregivers may reflect on the impact of the disease on family life; but patients focus on the changes that they face in their everyday lives [33].

The FDA recognizes the importance of patients' perspectives and supports the use of patient-reported outcome measures (PROs). PROs represent *"patient's report of a health condition and its treatment"*[*] [31, 33, 34]. PROs contribute to the evaluation of treatment efficacy and effectiveness as they provide a unique indicator of the impact of chronic conditions. Most outcomes that are directly measured, such as lesion burden, muscle strength, or spasticity, do not provide insight into the impact of the MS on daily functioning at home or at work. Some interventions have a positive impact on some outcomes but have an adverse impact on aspects of the person's life; a PRO provides investigators with additional information regarding the positive or negative impacts of interventions on function and well-being [35]. PROs reveal more information that goes beyond simple counting of symptoms. This was illustrated in a study of the effect of interferon-beta on the QOL of persons with MS. QOL was evaluated in 111 persons with MS. The study concluded that even though the rate and frequency of

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[*] Food and Drug Administration. Draft Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *Federal register* 2006;71.

relapses had decreased, QOL was negatively influenced by interferon-beta, as treated patients reported lower ratings of mental and emotional functions [36].

The challenge with using PROs is to select appropriate measures that target clear and well defined constructs. Measures could target simple constructs such as “symptoms” or more complex concepts such as HRQL. HRQL is a multidimensional construct that parsimoniously encompasses many domains. The FDA developed guidelines for developing PRO measures of HRQL. One part of the FDA’s guidelines emphasizes the importance of basing the choice of measure on a clear conceptual framework [37, 31]. A conceptual framework explains the diagram of interaction or connection at four different levels; 1) item to item relation; 2) items to domain relation; 3) domain to domain relation; and 4) domains relation with the overall construct. For example, the item *difficulty dressing and undressing* could be grouped with another item *difficulty brushing teeth* within the domain of *self-care,* and *self-care* domain could be further grouped into the concept of *activities of daily living*. The application of valid HRQL conceptual model, explains which domains are strongly associated with each other, which domains have the biggest impact on the patient’s life, within specific conditions, and which intervention approaches are best suited for the management of that condition.

1.7 Models and Frameworks

Wilson-Cleary Model

In 1995, Wilson and Cleary proposed a conceptual model of patient outcomes [38]. The Wilson-Cleary model (WCM) links clinical variables, i.e. biological and psychological variables, with HRQL. As illustrated in Figure 1.2, the model suggests that physiological variables, symptom status, functional status, general health perception and overall QOL are linearly associated with each other and are considered as parameters influencing HRQL [39, 40]. Table 1.3 provides definitions and examples of WCM terms. The model acknowledges also the role of the characteristics of the individual and the characteristics of the environment on HRQL. As this model is a medical model, it is best suited to assist in the process of evaluating the effectiveness of interventions, as it provides a framework of the essential linkage between diagnosis and therapy.

The Wilson-Cleary model had been validated in patients with HIV [39]. This study examined the relations between four constructs of the HRQL conceptual model (symptom status, functional status, general health perception and overall QOL), using a sample of 917 patients with HIV. Information regarding participants' symptom status, functional status, general health perception and overall QOL were elicited form databases and other questionnaires. Structural equation modeling (SEM) was used to estimate the WCM. The result indicated that the WCM fits the data adequately and the relationships were significant between all constructs ($\rho < 0.05$) [39]. Thus, the model implies that symptom status, functional status, general health perception, and overall QOL are all dimensions of HRQL. Moreover, the Wilson-Cleary model had been validated in patients with heart failure [42]. Data from 293 patients with heart failure were analysed to examine variables driven from the Wilson-Cleary model and their association with HRQL. Results supported that symptom status, functional status, general health perception, and age were related to HRQL. An important finding of the study is that among the many clinical, physical and social variables of HRQL, symptoms and general health perception had the strongest and most consistent impact on HRQL [42].

ICF model

In 2001, the WHO approved the International Classification of Functioning Disability and Health (ICF) as a companion tool to the International Classification of Diseases (ICD-10) [41]. While the ICD-10 focuses on the diagnosis and physiological medical status of individuals, the ICF has functioning at its core. The ICF adopts a biopsychosocial model and provides a common international language for describing and coding functioning and disability at its most granular level. The ICF consists of two parts; each part is further classified into components (5 components in total) as illustrated in Figure 1.3.

Table 1.4 provides definitions and examples of ICF terms. The first part is *Functioning and Disability*, includes the components: *body function*, *body structure*, and *activity and participation*. The term *FUNCTION* is an umbrella term that covers the positive aspects of health (body structure and function, activities and participation), while the umbrella term *DISABILITY* covers the negative aspects of health (impairment of body structure and function, activity limitation and participation restriction). The second part is *Contextual Factors*, includes the components: *environmental factors*, and *personal factors*. The model suggests that these variables or components are bi-directionally associated with each other and that they shape the health status of individuals [24].

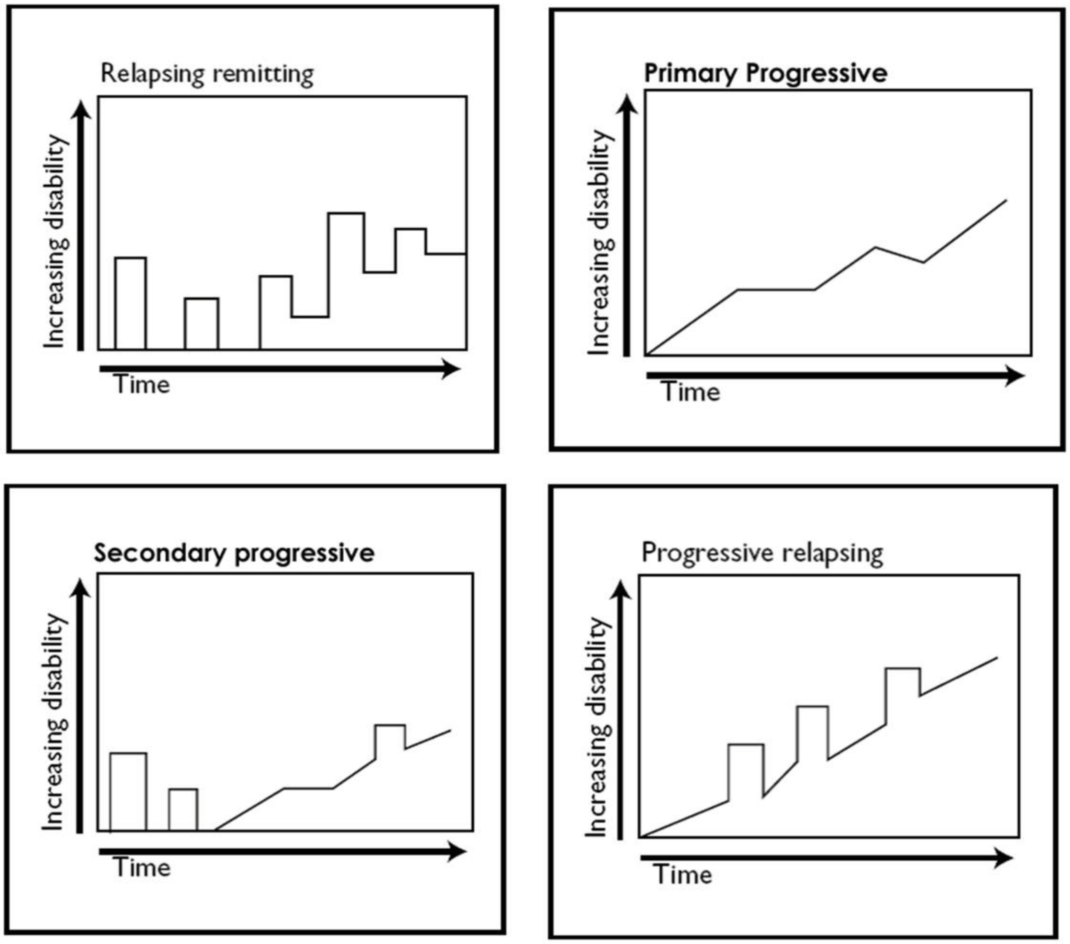
The ICF was developed in multiple languages; thus cultural and linguistic differences in these components have been identified and taken into consideration [43-45]. This new classification moves beyond the consequences of diseases approach and focuses on functioning as a major component of health. The ICF model has gone through multiple thorough revisions by an international assembly of experts around the globe. Thus this classification had been proven and accepted worldwide, and the content of this classification had been recognized and acknowledged by experts from all over the world.

Both the Wilson-Cleary and ICF models adopt a biopsychosocial approach. A combination of both of these two models, as demonstrated in Figure 1.5, could be used as a conceptual framework. Figure 1.4 shows that the WCM and the ICF models overlap. Biological and physiological variables and symptoms of the WCM are equivalent to impairments of body function and structure in the ICF. Functional status of WCM is the activity and participation of ICF. Both the WCM and ICF consider the important roles of the environmental and personal factors. While the WCM includes general health perception and overall QOL, the ICF considers them to be separate from functioning and disability. ICF presents QOL as personal satisfaction with their functioning, which is part of the WHO's definition of QOL. By putting these two models together the effectiveness of interventions could be appreciated from both medical and rehabilitative perspectives.

1.8 MS-HRQL Measures

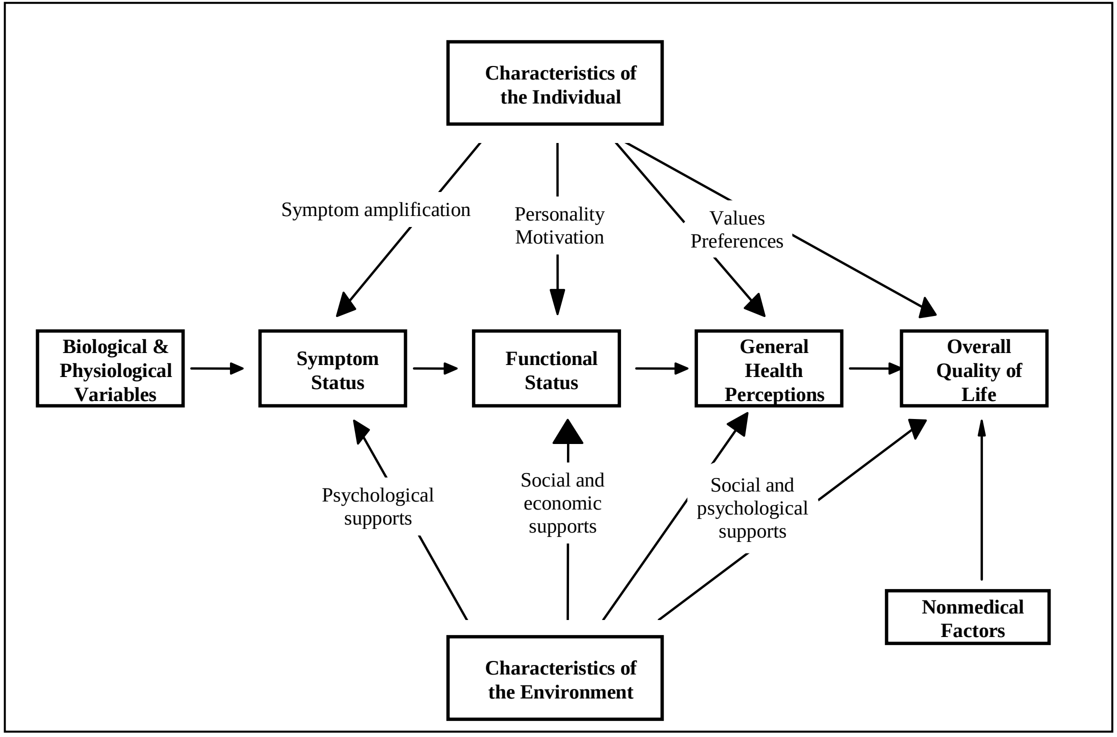
There are many measures of MS-HRQL which reflect not only the increased interest in this population, but also the growing appreciation of the importance of incorporating the person's perspective in outcome measurements. However, this increased number of MS-HRQL measures makes it more challenging for investigators and clinicians to choose measures that are best suited for their particular focus of clinical practice and/or research. On what basis should clinicians and researchers choose measures for evaluating disease activity and impact of interventions? The obvious criterion is that a measure should have supported psychometric properties. Measures should be reliable (reduce the amount of measurement errors present in scale scores), valid (measure the construct they were designed to measure) and responsive (able to detect changes over time) [46]. As important is that the measure has to target the domains of interest for specific population and/or intervention [47]. Measures should provide adequate coverage of all domains of HRQL [48]. HRQL is broadly understood to be a multidimensional concept; incorporating physical, psychological and social constructs. The impact of health condition is reflected in symptoms, functioning and well-being. Measures of HRQL should go beyond severity of symptoms and limitation in function to evaluate how individuals experience these manifestations in everyday lives, and how satisfied they are with their health status. Generic measures of HRQL (e.g. SF-36) do not include all relevant aspects of a specific condition. On the other hand, disease-specific measures capture symptoms that occur most often for a specific population. Thus, it is of a great benefit to examine the content of the available MS-HRQL measures and evaluate the multidimensionality of their contents.

Figure 1.1: Types of MS



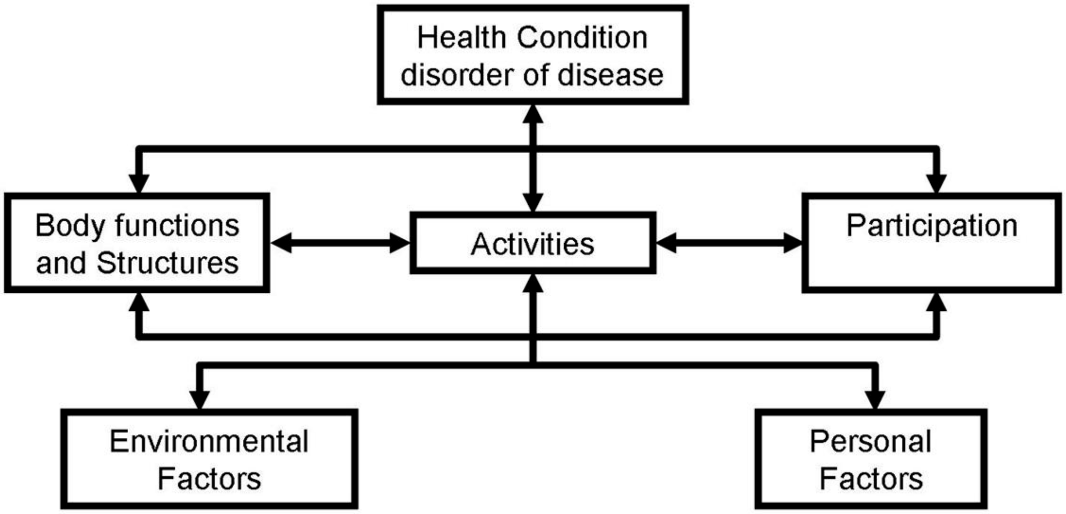
Adopted from Multiple Sclerosis Society of Canada
http://www.mssociety.ca/en/default.htm

Figure 1.2: Wilson-Cleary Model



Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA 1995; 273(1):59-65 [38]

Figure 1.3: The International Classification of Functioning Disability and Health



World Health Organization. International classification of functioning, disability and health. Geneva: WHO; 2001[24]

Figure 1.4: WCM and ICF

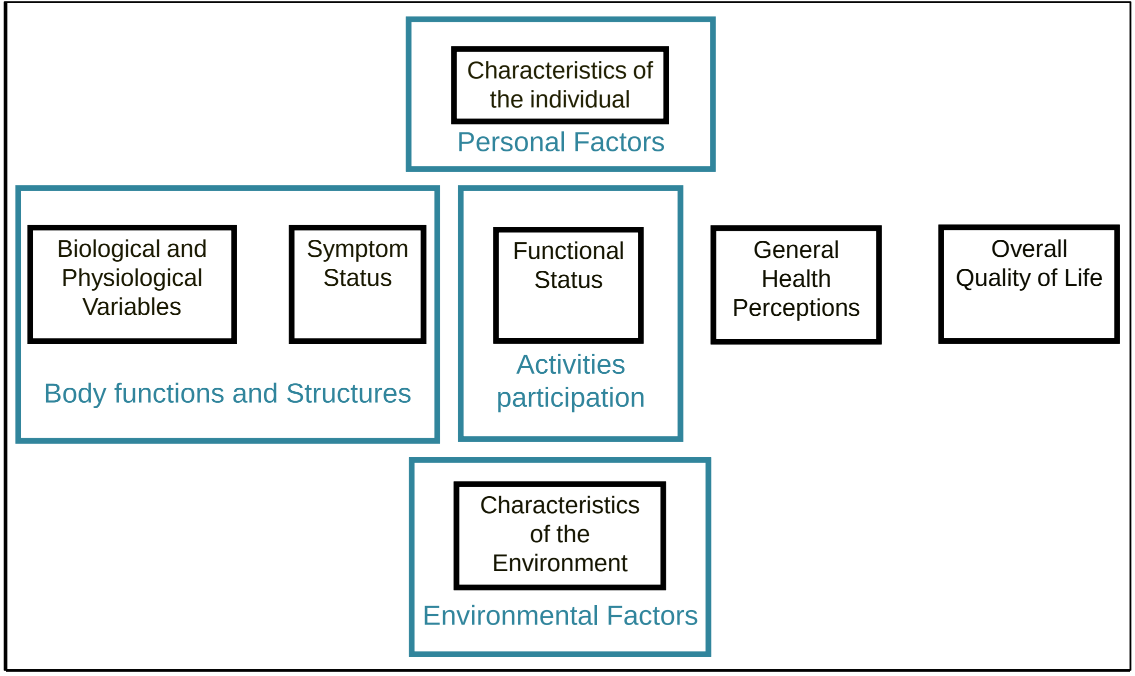


Table 1.1: Common Symptoms of MS

Common MS Symptoms **(**Prevalence**)**	
Fatigue **(**50% to 87%**)**	Mental fatigue Physical fatigue
Altered sensation **(**55%**)**	Tingling Pins and needles Numbness Pain Burning sensation
Visual Disturbances **(**50% to 90 %**)**	Diplopia Blurred vision Double vision Involuntary rapid eye movement
Spasticity **(**40% to 70%**)**	Muscle stiffness Muscle spasm
Balance & Coordination Problems **(**48% to 80%**)**	Vertigo Ataxia Tremor Clumsiness/Lack of coordination
Cognitive disturbances **(**43% to 59%**)**	Decreased concentration Decreased attention Poor judgment Poor reasoning
Emotional disturbances **(**16 % to 48 %**)**	Mood swings Irritability pseudobulbar affect
Bladder problems **(**80%**)**	Frequent /urgent needs Incomplete emptying Loss control
Bowel problems **(**35% to 54%**)**	Constipation Diarrhea Loss control
Sexual problems **(**75%**)**	Problem in arousal and orgasm

Table 1.2: Less Common MS Symptoms

Less Common MS Symptoms
Abnormal speech Slowing of speech Slurring of words Change in the rhythm of speech
Swallowing problems Dysphagia
Headache
Hearing loss
Seizure
Respiratory & breathing problems
Itching
Hemiparesis

Table 1.3: WCM Terminology

Term	Definition	Example
Biological & Physiological Variables	Changes that happen at the level of cells, organs and organs systems	Laboratory values, e.g. serum haemoglobin
Symptom Status	Patients' perspectives of their health conditions	Pain Shortness of breath
Functional Status	Capacity of the individual to perform functional, social or psychological tasks	Bathing Shopping
General Health Perception	Persons' global perceptions of their health, and it integrates the components of biological factors, symptoms and functional status	Rating of health status
Overall Quality of Life	Integration all of the pervious concepts; subjective well-being and satisfaction with life as a whole	Rating of satisfaction with quality of life

Table 1.4: ICF Terminology

Term	Definition	Example
Body Structure	Anatomical parts of the body	Muscles Limbs
Body Function	Physiological function of the body system	Muscle strength Mobility of joint function
Activity	Execution of a task or action by an individual	Walking long distances Writing
Participation	Involvement in a life situation	Carrying out household tasks Work and employment
Environmental Factors	Physical, social and attitudinal environment which people live	Product and technology for transportation
Personal Factors	Specific background of an individual's life	Age, race and gender

Chapter 2

Review on MS HRQL Measures

Health-related quality of life (HRQL) is becoming the choice of outcome when measuring the impact of conditions on functioning and well-being [33, 49, 50]. This is especially true for multiple sclerosis (MS), the most common and distressing chronic condition affecting the young population [9].

In the medical and rehabilitation fields, many approaches are carried out to try to improve or restore HRQL of persons with MS and thus HRQL measures are used to evaluate the effectiveness of their interventions. Nonetheless, findings of these studies are not promising. A meta analysis on the effectiveness of rehabilitation on persons with MS concluded that multidisciplinary rehabilitation did not have a positive effect on reducing the level of impairment, but it could improve the perceived level of activity and participation of these patients [51]. On the other hand, another meta analysis on the effectiveness of exercise on persons with MS, found that there was no evidence for the effectiveness of exercise at the activity and participation level [52].

In addition to methodological differences, the conflicting and inconclusive results of these meta analyses might have to do with the way that HRQL is being measured, and with the type of indices or measures used to capture this complicated construct.

2.1 Overview on HRQL measures in the MS population

There are many HRQL measures that have been developed for MS population. A literature review was conducted to extract the most commonly used HRQL measures in the MS population. The methods of extracting measures related to HRQL in MS population will be described in detail in Chapter 4 (manuscript 1). Briefly, a structured literature search was performed independently by two health professionals. The electronic search was conducted in MEDLINE, PsycINFO, CINAHL and EMBASE, using the following keywords: multiple sclerosis, quality of life, health related quality of life, measure, questionnaire, index, assessment, outcome and psychometric. The search was limited to articles published between 1980 and 2007 in the English language and excluded review articles. Measures were selected if they had supported psychometric properties as presented by at least two studies. The most commonly used measures were selected; thus measures had to be referenced by at least two studies not related to their developmental studies. Only HRQL measures that are specific for MS population were selected; thus generic measures of HRQL were excluded.

10 HRQL measures which met these criteria were identified, these measures are:

Multiple Sclerosis Quality of life Inventory (MSQLI)

The MSQLI is a comprehensive measure that combines the well-known generic measure, the SF-36, in addition to nine disease specific scales (Modified Fatigue Impact Scale (MFIS), MOS Pain Effect Scale (PES), Sexual Satisfaction Scale (SSS), Bladder Control Scale (BLCS), Bowel Control Scale (BWCS), Impact of Visual Impairment Scale (IVIS), Perceived Deficits Questionnaire (PDQ), Mental Health Inventory (MHI) and MOS Modified Social Support Survey (MSSS)) [53]. Contents of this measure were elicited from experts, patients and caregivers. In total, the MSQLI has 138 items, a shorter version of 81 items is also available. The MSQLI covers many domains including fatigue, pain, bladder/bowel function, emotional status, cognitive function, visual function, sexual satisfaction and socialization. All disease specific scales are scored using a five point likert scale, ranging from 0=normal to 5=total disability, except for mobility which is scored from 0 to 6. The total score ranges from 0 to 41. Reliability and validity of the MSQLI had been tested in a cohort of 300 MS patients [53]. All subscales were found to be reliable and valid. Internal consistency ranged from 0.67 to 0.97. Test-retest reliability ranged from 0.75 to 0.94. The content and construct validity of MSQLI were also supported. More recently, the MSQLI was tested and found to be reliable and valid in older MS patients and in patients with cognitive impairments [54, 55].

Functional Assessment of Multiple Sclerosis (FAMS)

The FAMS was adopted from the Functional Assessment of Cancer Therapy (FACT). It consists of 59 items capturing six domains related to mobility, symptoms, emotional well-being, general contentment, thinking fatigue and family/social wellbeing. The FAMS focuses on the psychosocial consequences of the condition. Items were generated by experts in addition to input from patients. Items are rated on a 5 point likert scale ranging from 0=not at all to 4=very much. Higher scores represent better QOL. The psychometric properties of the FAMS were tested on a sample of 121 persons with MS [56]. All of the subscales demonstrated very good reliability (alpha=0.90), and test-retest reliability ranged from 0.85 to 0.91. The correlation between FAMS and the SF-36 was 0.75, however, in non-ambulatory patients the correlation was lower than expected [56, 57]. The FAMS was found to have good responsiveness in both ambulatory and non-ambulatory patients [56, 57].

Multiple Sclerosis Quality of Life-54 (MSQOL-54)

Like the MSQLI, the MSQL-54 adopted the SF-36 in addition to 18 MS specific items that were chosen by experts. The MSQOL-54 covers the domains of health distress, cognition, pain, fatigue, sexual function and socialization. The MSQOL-54 is the most commonly used measure in the evaluation of HRQL in the MS population, and it had been translated into many different languages. Some items of the MSQOL-54 have dichotomous response options, other items are rated on a 3-7 point likert scale or a visual analogue scale. Each domain is scored separately and higher scores represent better QOL. The reliability and validity of this measure were tested in a sample of 183 persons with MS [58]. Internal consistency ranged from 0.75 to 0.96, except for the social functioning (0.68). Test-retest reliability exceeded 0.70, except for health perception (0.69). MSQOL-54 was found to have limited validity, as it showed low correlation with the Expanded Disability Status Scale (EDSS) [59]. The responsiveness of this measure was also criticized, as it showed marked floor and ceiling effects for the physical and sexual functions, respectively [60].

Hamburg Quality of Life Questionnaire in Multiple sclerosis (HAQUAMS)

The HAQUAMS consists of 38 items covering the domains of fatigue, cognition, emotion, mobility and social function. Content of this measure derived from persons with MS and from other measures. One item is rated by ranking the severity with respect to other symptoms. The rest of the items are rated on a 5 point likert scale ranging from 1= not at all to 5= very much. The items are weighted to generate the total score, and lower scores represent better QOL. The reliability of this measure was high when tested in a sample of 237 persons with MS [61]. The HAQUAMS had high correlation with the EDSS and the FAMS. This measure was also found to discriminate between persons with MS with and without cognitive impairment [61].

RAYS Scale

The RAYS scale consists of 50 items that are distributed in four subscales. These subscales cover the dimensions of physical, psychological, social-familial and additional concerns. Item generation was derived from clinicians, QOL experts and literature reviews. The items capture the level of impairment, and are rated on a 5 point likert scale ranging from 0= none to 4= extreme. The total score may range from 0 to 200. Psychometric testing of this scale was conducted on a sample of 50 persons with MS and 50 healthy controls. The internal consistency was found to range from 0.84 to 0.89 in all subscales. The RAYS was found to be highly correlated with the SF-36. However the physical subscale of the RAYS had moderate correlation with the EDSS. The scale was also found to distinguish between MS patients and healthy controls [62].

Performance Scales for Multiple Sclerosis (PS-MS)

The PS-MS consists of 27 items. It covers the domains of mobility, hand function, vision, fatigue, cognitive, bladder/bowel, sensory and spasticity symptoms. Its items are rated either on a 7 point likert scale, a dichotomous scale or a visual analogue scale. Lower scores represent better QOL. The psychometric properties of the PS-MS were tested in a sample of 274 persons with MS. Internal consistency was 0.78. Test-retest reliability ranged from 0.65 to 0.91. The PS-MS had a high correlation with the EDSS [63].

Multiple Sclerosis Impact Scale (MSIS-29)

The MSIS- 29 has 29 items that measure the physical health, psychological health and the impact of MS. Content of this measure derived from interviews with persons with MS [64]. Items are rated on a 5 point likert scale ranging from 1= not at all to 5= extremely. The total scores ranges from 0 to 100 with lower scores representing poorer QOL. The MSIS-29 was tested in a large sample of 766 persons with MS. It showed high internal consistency (0.89 – 0.91) and test-retest reliability (0.65 – 0.90). It also showed high correlation with the SF-36, FAMS and Barthel Index. The MSIS-29 was also suggested to have good responsiveness [65]. The MSIS-29 was found to be consistent across hospital based and community based samples [66].

Leeds Multiple Sclerosis Quality of Life (LMSQoL)

The LMSQoL index has only 8 items. It covers domains of emotion, health perception, fatigue, relationships and socialization. Items were generated from persons with MS as elicited in focus groups. Items are scored on a 4 point likert scale ranging from 1= very much to 4= not at all. Lower scores represent better QOL. The psychometric properties were tested in a sample of 200 persons with MS. Internal consistency was 0.79, and test-retest reliability was 0.85. The LMSQoL had low correlation with the SF-36 and MSQOL-54 [67, 68]. It was found to discriminate between persons with different types of MS [68].

Quality of Life Index MS-Version (QLI-MS)

This measure was developed to evaluate importance and satisfaction with various domains including physical, emotional, social, sexual, fatigue and pain. Item generation was based on a literature review. QLI-MS has 70 items that are rated on a 6 point likert scale ranging from 1= very dissatisfied/unimportant to 6= very satisfied/important. The internal consistency of the QLI-MS was found to be 0.90

and test-retest reliability ranged from 0.81 to 0.87 Moreover the QLI-MS had limited responsiveness [69].

Disability and Impact Profile (DIP)

The DIP has 78 items covering the domains of physical, cognition, emotional, social, sexual, visual, bladder/bowel and pain. Items were generated by a group of experts in disability and rehabilitation. Items are rated on a visual analogue scale. Scores are weighted to represent the level of severity and impact of MS. Psychometric evaluation of this measure was conducted in a sample of 73 persons with MS. Internal consistency ranged from 0.61 to 0.92. Test-retest reliability ranged from 0.61 to 0.87. The DIP had high validity and it was found to be more responsive than the SF-36 [70-72].

Overall, the available MS-HRQL measures differed in their core domains. Each measure fulfilled, to some extent, criteria of reliability, validity and responsiveness. Most measures offer a concession between ease of use (less number of items) and comprehensiveness of construct.

CHAPTER 3

Rationale and Objectives

Patient empowerment is a predominant feature of modern health care. Increasingly people seeking care wish to be well informed about their condition and share in the decision making process about treatment and its outcome [32]. From the person's perspective, perception of health and functioning are the yardsticks against which patients measure disease impact and treatment effectiveness. These concepts can only be captured using measures that are termed "patient-reported outcome measures" or PROs [35]. Health-related quality of life (HRQL) measures are ideal PROs because they capture a number of important constructs related to health and functioning parsimoniously and as a result they are often used to quantify the consequences of multiple sclerosis (MS). HRQL measures are increasingly being used by clinicians and researchers to evaluate the effectiveness of their interventions [48]. The challenge is to choose from the many HRQL measures available for the MS population [73].

With the introduction of the World Health Organizations (WHO) International Classification of Functioning, Disability and Health (ICF), which provides a universal and comprehensive framework for identifying components of functioning, disability and health, it is now possible to identify the content covered by measures of HRQL [41]. The Wilson-Cleary model is also very well suited in identifying dimensions of HRQL and quality of life [39]. As suggested by these models, HRQL is a multidimensional concept and hence the content of measures of HRQL should cover all of the dimensions of this construct [48]. Under the ICF model these dimensions are body functions and structures, activity and participation (or in their negative, impairments, activity limitations and participation restrictions). Satisfaction with these is included in the WHO definition of quality of life. Under the Wilson-Cleary model, these dimensions are symptoms (ICF impairments), functioning (ICF activity and participation) and general health perception (not defined by the ICF). A content comparison of the most commonly used HRQL measures would contribute valuable information to match measures to uses. Thus, the primary objective of this thesis is to estimate the extent to which items of MS-specific HRQL measures capture domains of symptoms, functioning and general health perception.

All MS-specific HRQL measures include items on fatigue, as fatigue is a central and distressing symptom of MS [18, 74, 75]. Fatigue is the main contributor to poor QOL in persons with MS, as it has a considerable impact on work, family and social life [76-78]. Despite its importance to MS, it remains challenging to define and measure and hence it would be of a great interest and relevance to MS to identify the different approaches used to capture fatigue. Thus, the secondary objective was to identify, in commonly used HRQL and fatigue indices, sources of heterogeneity in the assessment of fatigue in the MS population.

In summary, the objectives for this thesis are to:

(1) estimate the extent to which items of MS-specific HRQL measures capture domains of symptoms, functioning and general health perception; and

(2) identify sources of heterogeneity in the assessment of fatigue in the MS population as indicated by commonly used HRQL and fatigue indices,

Findings of these studies will lead to an improved framework for measuring HRQL and will provide a starting point for the development of “true” measures using modern psychometric approaches. The use of the comprehensive ICF classification and coding system will also facilitate electronic and systematic recording of functional status information.

CHAPTER 4
MANUSCRIPT 1

4.1 What Constructs Are Represented in Multiple Sclerosis Specific Health-Related Quality of Life Measures?

Alaa Mohammad Arafah, B.Sc., Occupational Therapist
Carolina Moriello, M.Sc.
Miho Asano, M.Sc.
Nancy E. Mayo, Ph.D.

School of Physical and Occupational Therapy,
Faculty of Medicine, McGill University
3654 Sir William Osler, Montreal, Quebec, Canada, H3G 1Y5

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Communication addressed to: Nancy E. Mayo, Ph.D.
James McGill Professor
Department of Medicine
School of Physical and
Occupational Therapy
McGill University
Division of Clinical Epidemiology
Division of Geriatrics
McGill University Health Center
Royal Victoria Hospital Site
Ross Pavilion R4.29
687 Pine Ave W
Montreal, QC, H3A 1A1
Tel. (514) 934 1934 36922
FAX (514) 843 1493
nancy.mayo@mcgill.ca

ABSTRACT

Purpose: Multiple sclerosis (MS) is one of the most common chronic neurological conditions affecting young adults. MS is a progressive and an unpredictable disease with severe consequences that reduce health-related quality of life (HRQL). HRQL is becoming an important outcome for the management of many chronic conditions including MS. HRQL is a multidimensional concept, with symptoms, functioning and general health perception at its core. One of the challenges in measuring HRQL in MS is that there are a large number of measures that have been developed to capture this construct. Thus, there is a need to assess how well the available MS-HRQL measures cover and address all components of HRQL that are important in the MS population.

Methods: A multi-rater, content analysis study was carried out using the International Classification of Functioning Disability and Health (ICF) and the Wilson-Cleary models as frames of reference. The content analysis had two components: a structured literature review to identify the measures, and a linkage of each item to the ICF using a standardized protocol.

Results: 550 items from 10 MS-HRQL measures were linked to the ICF. Some items were assigned to more than one component. 44% (range across measure 17% to 88%) captured the symptom component, 34% (range across measure 12% to 60%) captured the functioning component and 35% (range across measure 4% to 100%) captured concepts of general health perception and satisfaction with quality of life. Only 6% (range across measure 0% to 13%) of the items targeted environmental factors.

Conclusion: Heterogeneity of content and diversity of the degree of capturing different components of HRQL across measures were apparent in this study. Findings of this study would provide clinician and researchers with in depth insights when choosing the most suitable measures for their clinical trials.

INTRODUCTION

Multiple sclerosis (MS) is one of the most prevalent chronic neurological conditions affecting young adults [1]. MS is an acquired, inflammatory, demyelinating disease of the central nervous system (CNS) that is of an autoimmune origin [2]. The cause of MS is unknown. However, evidence points to multifactorial etiology, involving both genetic and environmental components [3]. MS affects 1 in 1000 people [4] and it is estimated that there are over 2.5 million persons with MS worldwide [5, 6]. MS is comparatively more common in Europe, North America, New Zealand and Australia. The prevalence of MS in the Northern United States and Canada is approximately 240 per 100 000 population [4]. MS is more common in women than men with a ratio of approximately 3:1 [7]. Incidence is high between the ages of 18-40 years, peeking at the age of 30 years [3].

MS has a wide spectrum of symptomatology that depends on location of affected areas of the CNS. Symptoms that predominate initially are sensory disturbances (tingling, pins and needles, numbness, burning sensations and pain), visual disturbances (visual blurring or loss, diplopia, involuntary rapid eye movement) and motor symptoms (muscle weakness and stiffness, fatigue, gait ataxia, poor coordination, impaired balance). Other symptoms may include cognitive impairments, speech difficulties and bladder, bowel and sexual disturbances [8-10]. As MS is a progressive and an unpredictable disease, it can result in severe consequences such as depression, limitation in usual activities and restriction in participation in life's roles [11, 12]. These sequelae impact to reduce quality of life (QOL) of the persons affected with MS and their families [13]. Studies have shown that persons with MS have notably poorer QOL than persons with other types of neurological conditions [14], notably in general health, vitality, physical function and socialization [15]. Within 10 years of MS diagnosis, up to 50% of people with MS are unable to fulfill household and employment responsibilities; within 15 years of diagnosis, about 50% are unable to walk independently and within 25 years, up to 50% are using a wheelchair [16].

Quality of life of persons with MS

The life expectancy of individuals with MS had been prolonged due to the development of new drugs that, to an extent, modify the course of this condition. Nevertheless, as the life expectancy of people with MS increases, more attention has been drawn to their QOL. The World Health Organization (WHO) defines QOL as *"the individuals' perceptions of their position in life in the context of the cultural and value system in which they live and their relationship to their goals, expectations, standards, and concerns*"* [17]. Health-related quality of life (HRQL) refers to those aspects of QOL that relate specifically to health. HRQL is defined as *"the value assigned to duration of life as defined by the impairments, functional status, perceptions, and opportunities influenced by disease, injury, treatment, and policy"*† [18]. HRQL refers to a multidimensional concept that represents the patient's overall satisfaction or perception of the impact of his health condition and its treatment on his function and well-being. QOL and HRQL are terms that have been used interchangeably without acknowledging that they are distinct constructs. HRQL excludes jobs, finance and other dimensions that are outside of health and health care.

Gruenewald et al reviewed the domains related to HRQL of those affected by MS [19]. This review focused on identifying the domains as perceived by persons themselves and their caregivers as elicited through interviews, focus groups or surveys. This review identified 16 qualitative studies and 51 questionnaire-based studies and identified the following domains: physical function (mobility, transfers, dressing), social function (participation in social activities, social support, social role, family life), personal control (autonomy, independency), MS symptoms (fatigue, pain, visual, cognitive, bladder/bowel control, spasticity, numbness), sexual/intimacy, and emotional/mental health (depression, anxiety, worry, distress). Therefore, MS has a huge impact on several health domains, which eventually leads to alteration of HRQL.

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[*] World Health Organization. *International classification of functioning, disability and health*. Geneva: WHO, 2001.

[†] Patrick DL, Bergner M. Measurement of health status in the 1990s. *Annu.Rev.Public Health* 1990;11:165-83.

Patient-reported outcome (PRO)

HRQL is becoming a common end-point for MS pharmaceutical trials where the effects go beyond safety and efficacy parameters [21]. HRQL can only be ascertained through self-report. The Food and Drug Administration (FDA) supports the use patient-reported outcome (PRO) measures to evaluate the effectiveness of new interventions [22-24]. The success of the application of PRO depends on the selection of appropriate questionnaires. The FDA provided some guidelines for developing measures that could be used as a reliable method to test the effectiveness of new interventions [24, 25]. The essential baseline of the development and use of PRO measures is that the measures' conceptual framework should be clear and well defined. Having a theoretical frame of reference would facilitate the applicability of concepts as reliable and valid outcome measures. A valid HRQL conceptual model would support and facilitate the understanding of relationships between concepts, assist in pointing the areas that have the greatest impact on patients' lives and provide the most relevant and appropriate approach for the management of patient care.

Models and frameworks

Wilson and Cleary proposed a conceptual model of HRQL [26]. Their model which is often referred to as the end-point model, integrates both biological and psychological aspects of health outcomes [27, 28]. It incorporates physiological variables, symptom status, functional status, general health perception and overall QOL, as illustrated in Figure 4.1. *Physiological variables* focus on the changes that happen at the level of cells, organs and organs systems. *Symptoms* are the patients' perspectives of their health conditions, which can only be educed through PRO. *Functional status,* is the capacity of the individual to perform functional, social or psychological tasks. *General health perception* and *overall QOL* integrate the previous variables and could be elicited subjectively from the patients. The Wilson-Cleary model suggests that those domains are linearly associated with each other. In addition, the Wilson-Cleary HRQL model links environmental and individual characteristics with the other variables. The Wilson-

Cleary model implies that symptom status, functional status, general health perception are dimensions of HRQL and this is one, albeit important factor, that contributes to overall QOL. This model could be used to identify those HRQL measures that best represent this conceptualization of HRQL.

Another more functional model is the International Classification of Functioning, Disability and Health (ICF) that was developed by WHO [29]. This model provides a global conceptual framework and a universal common language for describing and coding functioning, disability and health. The ICF adopts a biopsychsocial approach in describing functioning, disability as well as contextual factors (environmental and personal factors). The overall construct covered in the ICF is functioning which covers the components of body structure, body function, activity and participation, this is illustrated in Figure 4.2. *Body Structure/Function* refer to the anatomical/physiological parts of the body (e.g. muscle/decreased muscle strength). *Activity* refers to the execution of a task (e.g. reading). *Participation* refers to involvement in a life situation (e.g. school education). While *Function* covers the positive aspects of an individual health, *Disability* is used to represent the negative aspects. Thus according to the ICF *Disability* would cover the domains of *impairment of body function/structure*, *activity limitation* and *participation restriction*. The contextual factors include two components; the environmental factors and the personal factors. *Environmental Factors* refer to the physical, social and attitudinal environments which people live (e.g. accessibility to medication and medical services); while *Personal Factors* refer to the specific background of an individual's life (a list of personal factors is still under research but it is thought to include age, race, gender, est.) [17].

The ICF is best suited for the use as a frame of reference; as it has a unique classification system that allows us to capture and code functioning at its most granular level. The ICF was proven to be highly useful for coding and comparing concepts captured by functional and generic HRQL measures [30-34].

The Wilson-Cleary model and the ICF are both adopting a biopsychsocial approach. Both models target biological and psychological aspects of health, to a different extent. Figure 4.3 shows that biological/physiological variables and symptom status of the WCM are expressed by the ICF as impairments of body function and body structure. Functional status of the WCM is presented by the ICF as activity and participation. Both of these models acknowledge the important roles of environmental and personal factors. While the WCM includes general health perception and QOL, the ICF considers them to be distinct constructs reflecting personal satisfaction as included in the WHO's definition of QOL. Both models differ from one another in several ways: 1) while the Wilson-Cleary model is a medical model focusing more on the physiological aspect of health, the ICF puts more emphasis on functioning and disability; 2) the ICF framework expresses the relationship between health components in a dynamic way, where all items are related and influence one another [29]. On the other hand, the Wilson-Cleary model expresses a causal linear relationship between its components [26]. By putting these two models together, the impact of MS and its treatment can be appreciated from both the medical and rehabilitative perspectives and help with communication between these two disciplines about the health and well-being on their clients served.

MS-HRQL measures

In the past, the management of MS and indeed many other chronic conditions was aimed at relieving symptoms rather than at providing a cure for the underlying conditions. PROs, especially the HRQL measures become the best indicators of the progression of the condition and health experience [22, 35, 36]. Even now with the introduction of disease modifying drugs and powerful new imaging techniques, members of the health care community are aware that they are treating the whole person and are relying on the person's functioning and perception of health and health impact to make a judgment about treatment options and effectiveness [37]. One of the challenges in measuring HRQL in MS is that there are a large number of measures which have been developed to capture this construct. A review by

Gruenewald et al in 2004 indicated that 19 HRQL measures had been developed for the MS population [19]. Therefore, what characteristics should researchers consider when choosing the best HRQL measure?. First, measures should have strong psychometric properties (reliability, validity and responsiveness) [38]. Another essential principle in the selection of an appropriate measure needs to be based on the concepts contained in the measures and should not be primarily guided by their psychometric properties [39]. Thus, when choosing a HRQL measure, all concepts or dimensions of HRQL should be captured [40]. Clinicians and researchers can work better on improving HRQL if they are able to identify which variables are strongly associated with HRQL and which variable are less important to HRQL. Therefore, conceptualization of concepts related to HRQL is an essential step in the development and validation of HRQL measures [26]. The use of common and standard terms would allow professionals to record intervention goals and outcomes in a homogeneous manner. Only by having a clear and defined understanding of the dimensions of HRQL, measures can be used successfully in evaluating the effectiveness of interventions that are working on the enhancement of HRQL of patients with MS.

Content comparison of HRQL measures for MS is rarely presented in the literature [41, 42]. The reviews performed so far focused on comparing the psychometric properties. Thus, it is of a particular interest to assess how well the available MS-HRQL measures cover and address the HRQL domains that are important in MS population. Content comparison and detailed exploratory of contents of measures based on well defined and universally accepted frameworks would be valuable. Therefore, the objective of this study is to estimate the extent to which items in the MS-specific HRQL measures capture domains of symptoms, functioning and general health perception.

METHOD

Study design

A multi-rater, content analysis study was carried out. The content analysis had two components: a structured literature review to identify the measures, and a linkage of each item to the ICF using a standardized protocol [31, 44]. Delphi process was used to build consensus. The initial coding and consensus were done using e-mail surveys with health professionals from different clinical backgrounds.

Study Materials

The study materials consisted of the MS HRQL measures. Measures were selected if they met the following criteria: 1) had two published articles reporting on psychometric properties (reliability, validity and responsiveness); 2) were cited by at least two studies; 3) were published and validated in English (this is a feasibility criterion as raters and researchers are English speaking); 4) were available in hard copy or electronic copy. Generic measures of HRQL were excluded; as those measures do not include domains that are specifically affected in persons with MS

Procedure

The study was conducted following 4 steps, as illustrated in Figure 4.4:

Literature review: extraction of MS-HRQL measure

A structured literature review was performed independently by two researchers; to identify HRQL measures of MS population. The review was conducted using the following databases: MEDLINE, PsycINFO, CINAHL and EMBASE. The keywords searched were: multiple sclerosis, quality of life, health related quality of life, measure, questionnaire, index, assessment, outcome and psychometric. The search was limited to articles published between 1980 and 2007 in the English language and excluded review articles. Moreover, the research was supplemented by manual searches of the bibliography of intended articles. Articles were selected if they were primary studies focused on developing or evaluating measures related to HRQL in the MS population. Moreover, studies that reported the use of MS-HRQL measures were also included.

The identified measures were reviewed for their eligibility. A hard or electronic copy of the measures was obtained. If deemed necessary, permission of the measure's publisher was obtained for the use of those measures in the study.

Grouping items into common domains

After acquiring a copy of the MS-HRQL measures, their items were grouped together into common domains. Those domains were based on the ICF classification. This step was conducted to serve two purposes. First, it would facilitate the response rate of raters who would participate in the coding of items to the ICF. Seeing that, there were a large number of items to be coded to the ICF; their coding would be facilitated if they were clustered together.

The other purpose of performing this step was that it provided us with a picture of the heterogeneity of the wording of items capturing the same concepts and how measures differ in the way they try to assess a specific concept.

Coding items to the ICF

Coding items to the ICF was based on a mapping protocol that was developed by Moriello et al [31]. This protocol is listed in Table 4.1. The mapping protocol provides a guideline for the process of mapping items to the ICF, which involves the following steps:

Recruitment of raters

Health-care professionals were recruited by e-mail. Raters were recruited from different parts of the world (Canada, Germany, Saudi Arabia and Jordan), and from various clinical backgrounds (i.e. physicians, occupational therapists, physical therapists, nurses, epidemiologists and exercise physiologists). Those professionals have the knowledge and training to differentiate different aspects or components of health status of patients with MS. The protocol of ICF coding requires 10-15 raters to be involved in the process of mapping items to the ICF

(Table 4.1) [31]. However, as we expected to have a large number of items to be coded to the ICF, and in order to make it more convenient and feasible for the raters to complete the mapping exercise, we separated the items into three sets and assigned 10 raters per set. Hence 30 raters were needed to complete the mapping exercise.

A letter of invitation describing the objective and rationale of the study as well as the method and procedure of the study was sent to potential participants (refer to Appendix A1). Once a professional agreed to participate in the study, a training package was sent by e-mail. The training package included: 1) a Power Point presentation that explains the terminology of the ICF model along with rules for mapping; 2) an article by Cieza et al [44] describing the rules for mapping items to the ICF; 3) an Excel spreadsheet listing the items from the HRQL measures to be mapped; 4) a detailed time line. Participants were asked to work independently on providing an ICF code that correspond the best for each of the items of the MS-HRQL measures. Participants had about 6 weeks to complete this exercises and reminders were sent out one week and two days before the deadline.

ICF standardized coding system

Items of the MS-HRQL measures were coded to the ICF. The ICF provides a standard coding system for the various items on the different measures. The ICF currently has 1,424 categories of health outcomes. Each category defines a meaningful set of related physiological functions, anatomical structures, actions, tasks, or areas of life at the most granular level and is referred to as functional status indicator. As was mentioned before the ICF consists of four components (Body Function, Body Structure, Activity and Participation, and Environmental Factors). Those components are consequently structured into domains or chapters as illustrated in Figure 4.5. There are 8 chapters under Body Function, 8 chapters under Body Structure, 9 chapters under Activity and Participation, and 5 chapters under Environmental Factors. Within the chapters, the information is organized in categories. Thus when coding to the ICF, codes are preceded by the letters *b* signifying impairments of body function, *s* signifying impairments of body structure, *d* signifying activities and participation, and *e* signifying environmental factors. Each letter is followed by a numeric code representing the chapter number (a single digit), followed by the second level (two digits) and the third level (three digits) and the forth level (four digits). For example under the component of Activity and Participation there are those codes: *d4* mobility, *d450* walking, and *d4501* walking long distances. Thus the three or four-digit codes represent the degree of detail captured. For example dressing is a three-digit code (d540) and choosing appropriate clothing is a four-digit code (d5404). Whenever possible, a four-digit code is recommended to be chosen over a three-digit code to be as specific as possible in representing the coded item.

If the information provided by the item is not sufficient for making a decision about which ICF category the item should be coded as *nd* (not definable). Furthermore, items could be coded as *nd-gh* (not definable general health), *nd-ph* (not definable physical health), *nd-mh* (not definable mental health), or *nd-qol* (not definable quality of life).

Linking Rules

A structured and standardized approach of linking health status measures to the ICF was developed by Cieza et al in 2002, which had been updated in 2005 [30, 44]. A total of 8 linking rules have been established which could be used with different types of outcome measures [44].

Consensus

The Delphi technique was used to arrive at a consensus among raters on the best code for each item. Therefore, up to two rounds of consensus-building were conducted. The initial coding of items was conducted over a six-week period. In each of the consecutive round, participants had 4 weeks to respond and a reminder was sent out one week and two days before the deadline.

Delphi technique is a method for the collection of opinions on a particular topic [45]. It is considered the most reliable method for gaining consensus from a group of experts. In this study, the consensus rounds were conducted using an electronic exchange [46]. There are number of features that characterise the Delphi technique: 1) the Delphi is an iterative process where participants are provided with a series of survey questionnaires and controlled feedback. This way respondents are able to review their responses from previous rounds and modify them if needed [45]; 2) respondents must be relatively impartial so that the information provided reflects objectively their current knowledge and perception; 3) the sample should be heterogeneous to assure that the entire spectrum of opinion is determined [45]; 4) the Delphi techniques should aggregate expert opinion in an anonymous fashion. Anonymity provides respondents with a chance to present their opinion unbiased by the identities of other members; 5) the Delphi technique is analyzed by statistical aggregations of results to determine the consensus response of the group.

Percentage of crude agreement between raters was calculated for each item. As illustrated in Figure 4.6, agreement of greater than or equal to 70% was the target used to reflect an endorsed code. If the agreement was less than 70%, the Delphi technique was incorporated. In this exercise raters were asked to review their codes as well as the other codes suggested by other members, and decide if they would still implement their original codes or if they would adopt a code suggested by other members. This process was repeated until 70% of agreement was reached for the coded items, or it was determined that agreement was not achieved for the item.

Summary of concepts captured by each measure

For each of the measures, the percentages of items that cover symptoms, functioning and unclassifiable under the ICF were calculated. This latter group of items (unclassifiable under the ICF) were those potentially representing domains of health perception, global quality of life, global well-being and or satisfaction.

Those dimensions were based on the Wilson-Cleary and the ICF models, as shown in Figure 4.3. As the model indicated, symptoms, functioning and health perception were the components that produce the most impact on HRQL as reported by patients. Therefore, this study focused less on the contextual factors (environmental and personal factors). The biological and physiological variables were not studied as those variables are not included in PRO measures.

Analysis

Descriptive statistics were used to analyse the response rate of participants for each round. The percentage of crud agreement was calculated for each code. After the second Delphi round, the result were summarized. If the percentage of agreement was 70% or more, the suggested code was endorsed for that item, otherwise, the item was indicated as not having an endorsed code and the suggested codes along with the percentage of agreement for each code were reported. If a code was endorsed at a 4-digit level, then the 3-digit root of that code would be also endorsed as the ICF is hierarchically organized. Thus the lower-level categories share the same attributes of the higher-level categories.

It should be noted that there could be one or multiple constructs captured within the same item, and each construct has to be linked separately. Items that had single construct were referred to as *single unique items*, and their codes were referred to as *single unique codes*. Furthermore, we defined the *efficiency* of a measure, or the degree of compatibility to the ICF, as the ratio of items with single unique codes to the total number of items.

RESULTS

Identification of HRQL measures

The electronic literature searches in MEDLINE, PsycINFO, CINAHL and EMBASE conducted in May 2007 yielded 1052 hits. After applying the criteria for selected articles, 149 studies were included and original publications were checked. In these studies 20 MS specific HRQL measures were found. Among those measures only 10 met the selection criteria and 10 measures were excluded

(6 measures addressed a single domain, 3 were not commonly applied measures and one measure could not be reached in hard copy or electronic copy). The selected measures were the Multiple Sclerosis QoL Inventory (MSQLI)[51], the Functional Assessment of Multiple Sclerosis (FAMS)[52], the Multiple Sclerosis Quality of Life 54 (MSQOL-54)[53], Hamburg Quality of Life Questionnaire for Multiple Sclerosis (HAQUAMS)[54], the RAYS Scale[55], the Performance Scales for Multiple Sclerosis (PS-MS)[56], the Multiple Sclerosis Impact Scale (MSIS-29)[57,] the Leeds Multiple Sclerosis QoL (LMSQoL)[58], the Quality of Life –Index MS Version (QLI-MS- version)[59], and Disability & Impact Profile Questionnaire (DIP)[60]. Table 4.2 provides an overview of the major characteristics of the selected HRQL measures.

Grouping items into common domains

The total number of items of the selected MS-HRQL measures was 550. It should be noted that the SF-36 which is part of the MSQOL-54 and MSQLI was mapped in another study following the same mapping protocol and their results were included in this study.

After reviewing the items of all of the selected MS-HRQL measures, they were segregated and grouped into 18 domains; cognition (included 42 items), emotion (included 69 items), impairments (included 32 items), pain (included 16 items), autonomy (included 9 items), community (included 50 items), general health (included 38 items), quality of life (included 32 items), sexuality (included 22 items), arms/upper extremity (included 13 items), activity of daily living (included 43 items), leisure (included 7 items), fatigue (included 57 items), general motor (included 35 items), walking (included 19 items), working (included 24 items), environment (included 18 items) and others (items that did not fit into any of the previous domains), e.g. personal, spirituality and faith concepts (included 24 items). Furthermore, the previous domains were clustered into three sets and were designated to three groups of raters.

Recruitment of raters

Forty-eight health professional were approached to participate in the study and 25 agreed. It should be clarified that some raters completed more than one set of items. Thus overall, 11 raters completed the first set of items, 10 raters completed the second set and 9 raters completed the third set.

The professionals who participated in the study were from three countries (Montreal, Quebec, Canada (n=21); Kingston, Ontario, Canada (n=1), Jeddah, Saudi Arabia (n=2) and Amman, Jordan (n=1)). As illustrated in Table 4.3, participants were from various clinical backgrounds with varying experiences. With regards to the ICF, the majority of participants (n=19) had prior experience with the ICF and were enrolled in other previous mapping exercises. All participants were English speakers and/or completed a degree in English. All but three participants completed the whole process of mapping exercise.

Coding items to the ICF

Appendix Tables A1 to A19 present items of each measure with corresponding codes and percentages of agreements. Tables also present the stages of the mapping procedure where items were endorsed. Few items were endorsed in the initial mapping round and the majority of items were endorsed in the first and second Delphi rounds. The majority of the items of the MS-HRQL measures were endorsed. In total, 497 out of the 550 items (90%) were endorsed.

As shown in Table 4.4, 187 items were endorsed at the 4-digit level, and 229 items were endorsed at the 3-digit level with the percentage of agreement ranging from 70% to 100%. 37 items were coded as *nc* “not covered” and 18 items were coded as *nd-gh* “not definable general health’, or *nd-qol* “not definable quality of life”. In addition, 5 other items were coded as *pf* “personal factors”. 21 items were coded at the fist digit level; corresponding to the level of the chapters of the ICF. Overall, 53 items did not reach consensus on the best codes after the second Delphi round.

Table 4.4 also shows that the majority of items had single codes. Even though a good portion of those items contained more than one construct, not all constructs reached the critical level for endorsement. For example the item "*My fatigue symptoms keep me from being employed outside the home*", was coded b4552 representing the concept of "fatigue" but the other concept "employment" which is represented by the code d850 was not endorsed with only 56% agreement. This point determined the efficiency or compatibility of measures to the ICF. By taking the ration of items with single unique codes to the total number of items, the compatibility was found to range from 0% to 88% across measures. The most efficient measures were the LMSQoL and the FAMS, however, the LMSQoL had very few items and covered very few concepts. The MSIS-29 and the QLI-MS had 0% efficiency as more than one constructs were captured by their items and they had no single unique codes.

Table 4.4 also indicates that out of the 497 items that had endorsed codes, only 73 ICF categories were identified, i.e. only 5% of all existing ICF categories. Among those, 24 categories were selected from the component Body Function, 39 categories were selected from the component Activity and Participation and 10 categories were selected from the component Environmental Factors. None of the items were linked to the component Body Structure.

All 10 HRQL measures had items that were linked to Body Function and Activity and Participation components. All but four measures (MSQOL-54, PS-MS, LMSQoL and MSIS-29) included items that were linked to Environmental Factors component. Table 4.4 also shows the coverage of ICF categories by each selected measure. The RAYS scale had the most coverage of ICF categories, as it was linked to 33 different categories. On the other hand, the LMSQoL had the lowest coverage as it was linked to only 4 different ICF categories. Other measures had also limited coverage of ICF categories as their items were linked to 14 to 29 different ICF categories.

Representation of ICF components

Tables 4.5 to 4.7 represent the frequency of items coded to different ICF components at the third-digit level.

Under the component Body Function, Table 4.5, the MSQLI had the most coverage of this component, and the LMSQoL had the least coverage. The most coded ICF category was “b152 Emotional Function” as it was coded 45 times by the different measures. However, the PS-MS measure did not capture this category. The second most coded category was “b130 Energy function and derive” as it was coded 17 times by items from 8 of the selected measures. These two categories “emotion and energy” represent important symptoms in the MS population. Cognitive function affected by MS, namely memory and attention, were represented by all measures with the exception of the PS-MS and QLI-MS. The MSQLI had more detailed coverage of these aspects of cognition. Seeing function was only presented by 5 measures. Sensation of pain was represented by all of the measures with the exception of the PS-MS, LMSQoL and MSIS-29. Bowel function was covered by only 4 measures, and bladder function was covered by 7 measures. In terms of sexuality dysfunction, few measures included this symptom, however, this domain is also covered under the Activity and Participation component. Surprisingly, few measures captured muscle power and tone in their items. The least coded categories of Body Function component were “b110 Consciousness Function”, “b147 Psychomotor function”, “b535 Sensations associated with the digestive system” and “b730 Muscle power functions”. Only the last chapter of the Body Function component, *Chapter 8 Functions of the skin and related structures*, was not addressed by any of the measures. This chapter is not related much to MS population.

Table 4.6 presents the distribution of items across categories of Activity and Participation component. The DIP, HAQUAMS and RAYS measures had the most coverage of this component. The most cited categories were “d920 Recreation and leisure”, “d85 Remunerative employment”, “d450 Walking”, “d455 Moving around”, “d770 Intimate relationships”, “d760 Family relationships” and “d410 Changing basic body position”, respectively. These domains are affected tremendously by MS, yet some measure failed to include them. The least coded categories were “d155 Acquiring skills”, “d210 Undertaking a single task”, “d350 Conversation”, “d520 Caring for body parts”, and “d950 Political life and citizenship”. Overall, items from different measures were coded to categories from all of the different chapters of Activity and Participation component. However, there was not a single measure that captured categories related to all of these chapters, e.g. even though the DIP had good coverage, it did not include categories related to the fist two chapters “*Chapter 1 Learning and applying knowledge” and “Chapter 2 General tasks and demands”*.

Table 4.7 presents the distribution of items across categories of Environmental Factors component. This component had the least coverage with very few items coded to mainly the third chapter *“Chapter 3 Support and relationships”*. Other categories were related to financial assets “e165”, climate “e225”, individual attitudes “e410” and health care services “e580”.

Summary of concepts captured by each measure

Figures 4.7 to 4.16, illustrate the distribution of items of each measure across the different components of HRQL. The gray shaded areas represent those items that covered concepts beyond symptoms and function and targeted general health perception and quality of life. Figures show items that were coded as symptoms *“Body Function”*, functioning *“Activity and Participation”*, environmental Factors, Personal factors, not definable quality of life *“nd-qol”*, not definable general health *“nd-gh”*, and items not covered by ICF “*nc”*. It should be noted that some of the items that were coded under symptom, functioning or nc, but they were also found to target concepts of general health perception and QOL. For example, an item from the FAMS measure *“I am satisfied with how I am coping with my illness”* was coded as “*d240 Handling stress and other psychological demands”*. This item had two constructs: 1) coping presented by the coed *d240* and 2) satisfaction which reflects general health perception. Another example from the MSQOL-54 measure, the item *“Do you expect your health to get worse?”* was coded as *nc* under the ICF classification system, however this item represent general health perception when using the Wilson-Cleary model as a frame of reference.

Table 4.8 present a summary of the degree of capturing the different components of HRQL based on the ICF and the Wilson-Cleary models. In total we have a good distribution of items across the three major components of HRQL, i.e. symptoms, functioning, and general health perception. Out of the 550 items, 44% (range across measure 17% to 88%) captured the symptom component, 34% (range across measure 12% to 60%) captured the functioning component and 35% (range across measure 4% to 100%) captured concepts of general health perception and satisfaction with QOL. Only 6% of the items (range across measure 0% to 13%) targeted environmental factors.

Overall, 5 measures (MSQLI, FAMS, HAQUAMS, PS-MS and LMSQoL) had greater percentages of their items covering symptoms, then functioning, then general health perception. The MSQOL-54 had, more or less, even distribution of its items across the three components. The RAYS scale had even distribution of items across symptoms and functioning, but had very low covering of general health perception. The MSIS-29 and the QLI-MS had greater percentages of their items covering health perception/QOL more than symptoms and functioning. Lastly, the DIP had more coverage of symptoms, then general health perception, then functioning, respectively. The latter three measures (MSIS-29, QLI-MS and DIP) included many if not all items that ask patients about the level of importance or satisfaction with various health aspects. Formatting items this way resulted in having the majority of items of these measures go beyond symptoms and functioning.

DISCUSSION

The present study supports that there are indeed many HRQL measures developed for the MS population. The study provides an in depth comparison of the content captured by these measures using the ICF and the Wilson-Cleary models as frameworks. The ICF classification system was very appropriate and highly useful for capturing and coding the content represented in the items. Moreover, the the Wilson-Cleary model helped in explaining the other concepts that were not coded by the ICF. As a result, heterogeneity of content and diversity of the degree of capturing different components of HRQL across measures were apparent in this study.

Overall, 497 out of the 550 items of the MS-HRQL measures received codes and only 10% of the items were not coded to the ICF. This high degree of compatibility is somewhat surprising given that the taxonomical properties of the ICF were not used in the development of these measures, however, it reinforces the universality of the ICF in capturing content related to functioning. The items that were not linked to the ICF covered either content that related to QOL (coded nd-qol) or general health (coded nd-gh). However, other items that were not linked to the ICF were ambiguous and vague to an extent that health professionals did not agree on the most precise codes for those items. Other items covered very broad concepts and were only linked at the level of chapters. For example, the item *"I have difficulties learning new things"* was coded as *"d1 chapter of Learning and Applying Knowledge"*. These types of items are potentially not useful in a measure as they do not give enough level of specification and hence rating them would vary across people and time. Many other items contained more than one concept but only one concept reached the critical level for endorsement. As a result, there were many items with single codes but very few items with single unique codes. It is preferable to generate items that are simple, direct and only target one concept, for respondents to be able to provide consistent and reliable responses. Having items that are very broad, ambiguous or double-barrelled would result in imprecise measurement and unreliable data collection.

To have a better understanding of these items, cognitive debriefing (asking patients to think a laud when responding to questions) could be used to identify sources of misinterpretations and inconsistency.

The comparisons presented by this study are very useful, as they would provide clinicians and researchers with in depth insights when choosing the most suitable measures for their clinical practice and research. When choosing the appropriate measure, it is very essential to consider the specific type of intervention used, and the specific end-point targeted [30]. Having clear presentation of the content of measures would facilitate this selection process, as there would be information on which areas are covered more in depth and which areas are covered to a lesser extent and the degree of precision of each item. By using the information presented in Tables 4.5 to 4.7, clinicians and researchers could directly look up which HRQL measures attain the components or domains of interest to their studies. For example, the level of differentiation of the MSQOL-54 with regard to sexuality symptoms might be relevant in certain type of studies. In another example, we see that the DIP measure captures more concepts related to self care and household work, including bathing, toileting, dressing, eating, preparing meals and doing housework. This makes the DIP measure more relevant in certain rehabilitation disciplines, such as occupational therapy where the main focus of intervention is to increase and maintain activities of daily living. Some measures like the MSQLI, do not only show more precision in some domains, but they also show differentiation with regard to performance. The MSQLI allows researchers to capture the whole spectrum of performance, especially for walking, thinking and sexual performances, thus it is useful when testing persons with MS with various severity levels. Overall, we see that some measures are more differentiated and fine grained in some areas, while other measures address the domains in a parsimonious and screen-like fashion.

The content comparison also showed that environmental factors are seldom presented by HRQL measures. However, individual attitudes, family supports, use of assistive devices and climate are all important environmental factors that are addressed in may rehabilitation settings, e.g., social work and occupational therapy. Even though, environmental variables might be regarded as the least modifiable factors affecting HRQL, the previous findings should be taken into consideration when developing or modifying HRQL measures.

The comparison presented in this study also found that the FAMS and the RAYS measures had the least number of items that go beyond symptoms and functioning and cover other components of HRQL. Following were the measures: MSQLI, HAQUMS, LMSQoL, MSQOL-54, PS-MS, DIP, MSIS-29 and QLI-MS, respectively. However, some points should be stressed before drawing to conclusions when selecting the most suitable measures. The LMSQoL has only 8 items and it could be useful to supplement an evaluation when the focus of the evaluation is not HRQL but other components of health. The DIP, MSIS-29 and QLI-MS measures include the terms “satisfaction” and “importance”. These two terms are not captured by the ICF as they are referring to health perception and QOL. It was very challenging for raters to code these terms. Hence, patients responding to these items will be also faced by the same challenges and difficulties when answering such items. For example, when answering this question *“How satisfied are you with: Your ability to get around and go places?”*, a respondent might refer to his ability to go places and to the level of difficulties of moving around rather than to the level of satisfaction with his abilities. Or, having restricted their community participation, a respondent may say he or she is satisfied but in fact, does not go out at all anymore and has lowered expectations for satisfaction. Evaluations over time would be strongly affected by this change in expectation. On the other hand, the MSQOL-54 measure expresses its items in a more direct way e.g. *“Was your health a worry in your life?”* and *“Overall, how would you rate your own quality of life?*. Thus it might be appropriate to conclude that even though some measures do cover health perception and quality of life components, their items are not easily interpreted, and other measures reflect these components more clearly and precisely.

The ICF Research team and the WHO had recently developed ICF core sets for 12 common chronic conditions [47], and an ICF core set for MS condition was recently published in February, 2007 [48]. An ICF core set consists of the ICF categories that are most relevant and should be evaluated for specific conditions. In another word, the ICF core set for MS lists all domains that should be measured and evaluated in this population. The ICF core set for MS identifies 132 categories from the components of Body Function, Body Structure, Activity and Participation and Environmental factors. Our sample of MS HRQL measures captured only 64 or about 50% of the suggested ICF categories, these comparisons are illustrated in Appendix Tables A20 to A22. Thus, the ICF content examination of our selected measures could be compared to the ICF core set for MS, to support and facilitate the selection process.

It is acknowledged that there are some limitations to this study. The electronic search to extract HRQL measure used structured rather than systematic strategies. Yet, when compared to findings in other reviews on measures in MS [19, 40, 49], we included the most used MS-HRQL measures. The mapping protocol that we followed [31] requires 10-15 raters to perform the mapping exercise, however some of the tested items received 9 or 8 ratings. Having a large number of items to be coded restricted our sample of raters. Nonetheless clustering items into common domains made it easier for raters to code and resulted in few dropouts. The time restraints did not permit us from conducting a third Delphi round to try to reach consensus on those items that were not endorsed. In addition, the last two steps of the mapping protocol, cognitive debriefing and validation of the endorsed codes, are to be completed in future studies. The completion of these steps will add more creditability and reliability to our findings.

This study however, provided us with new insights on the available MS-HRQL measures. The content examination may serve further purposes other than the selection of measures. The other significant contribution of this study is that it will facilitate implementation of outcomes into electronic health records (EHRs) system [50]. At present, most of the data included in EHRs are related to demographics, diagnoses and drugs but not to function and well-being. Part of this problem is related to difficulties in translating results of HRQL and functional measures into electronically coded information. HRQL measures could enrich EHRs as they capture the essential component of physical, emotional and psychological health domains [32].

In conclusion, the comparison of MS-HRQL measures provided an interesting revelation of the heterogeneity of concepts attained by these measures. By coding items to the ICF, it was possible to identify how measures differed in the degree of coverage of the components of Body Function, Activity and Participation and Environmental Factors. We were also able to see with the help of the Wilson-Cleary model, how much these measures go beyond symptom and functioning and capture other concepts related to general health perception and QOL. Future studies on cognitive debriefing and validation of endorsed codes, would be valuable.

Figure 4.1: Wilson-Cleary Model [26]

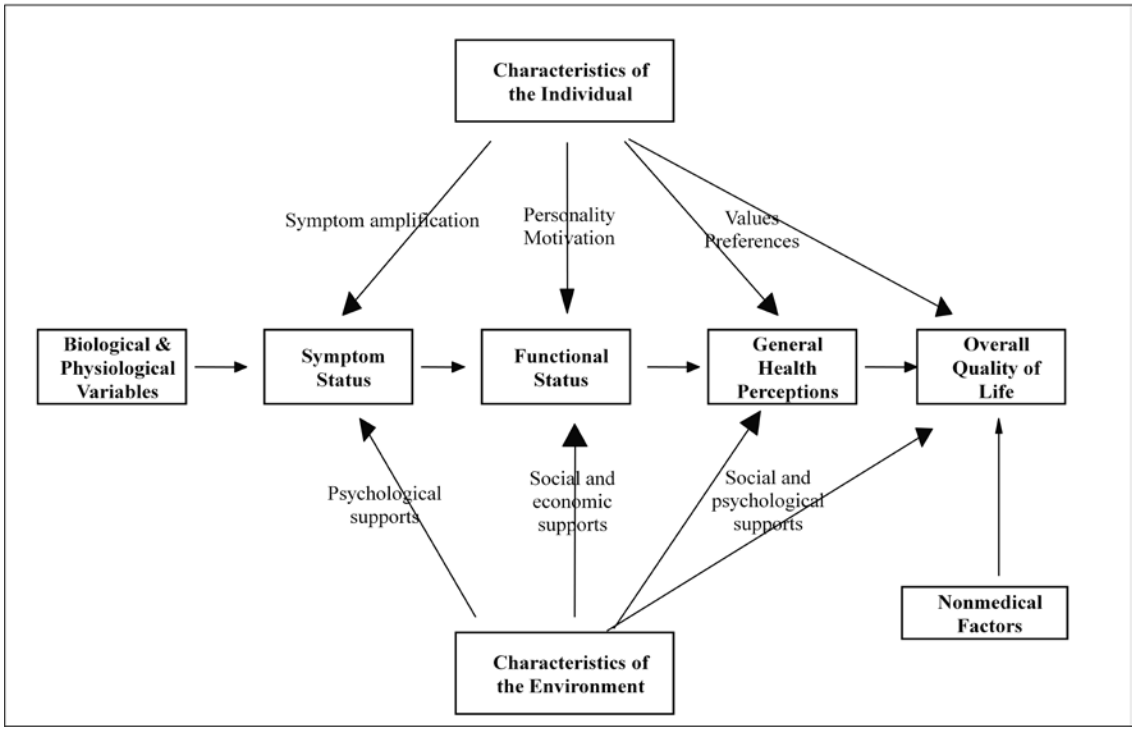


Figure 4.2: The International Classification of Functioning Disability and Health (ICF) [17]

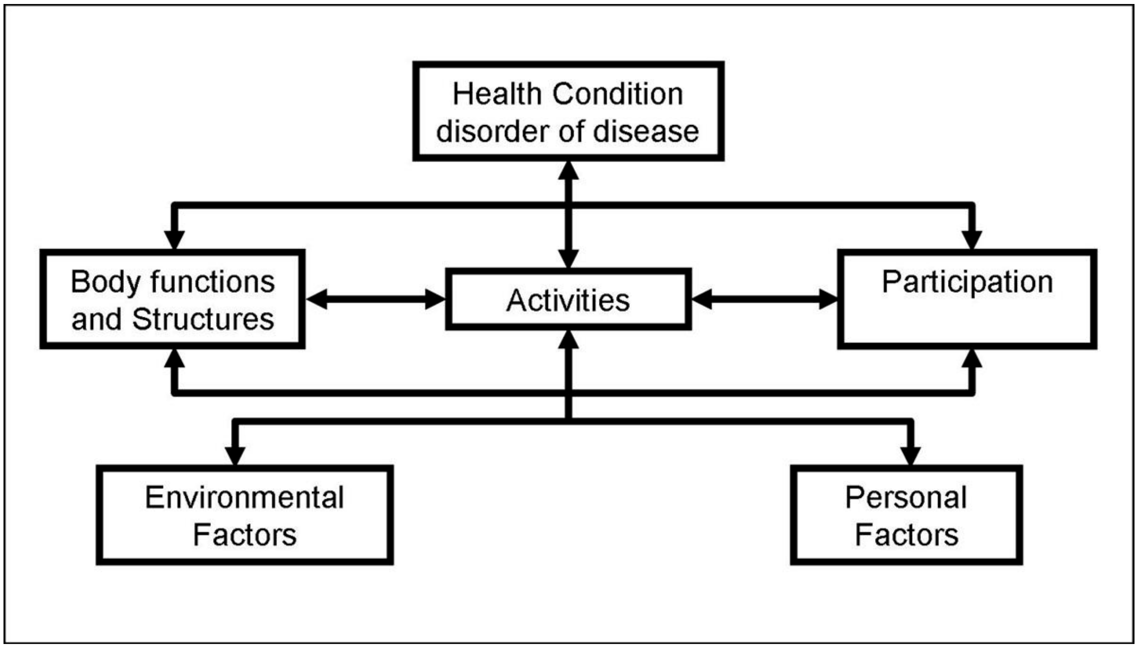


Figure 4.3: Components of HRQL based on the medical and rehabilitative Approaches

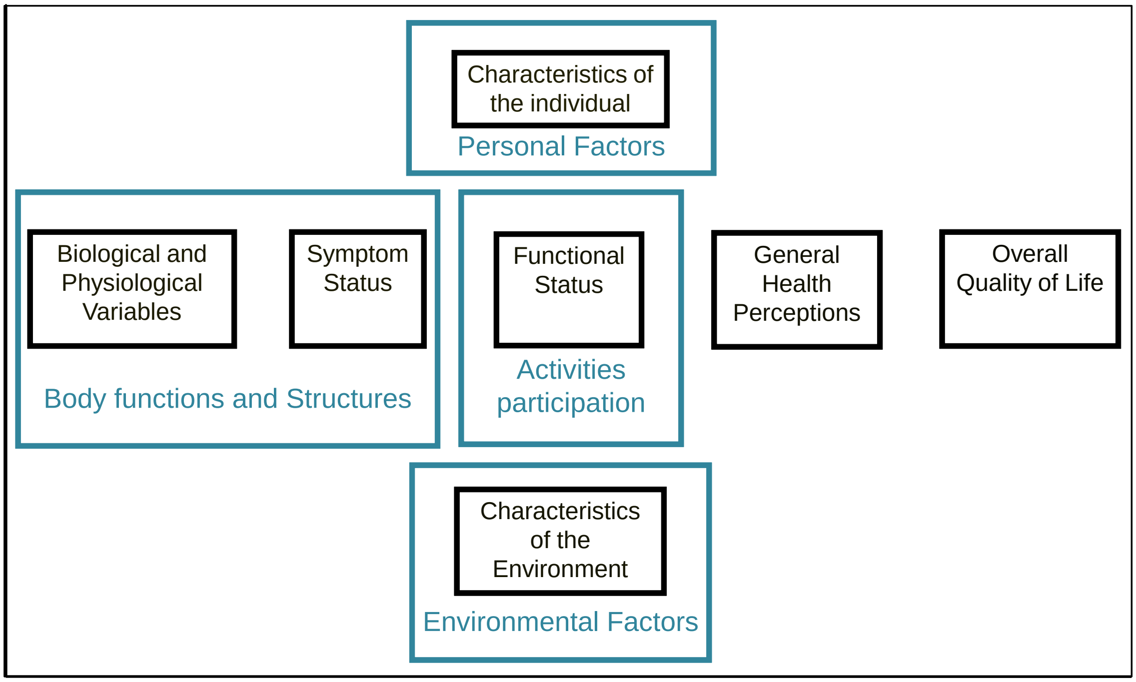


Figure 4.4: Study procedure

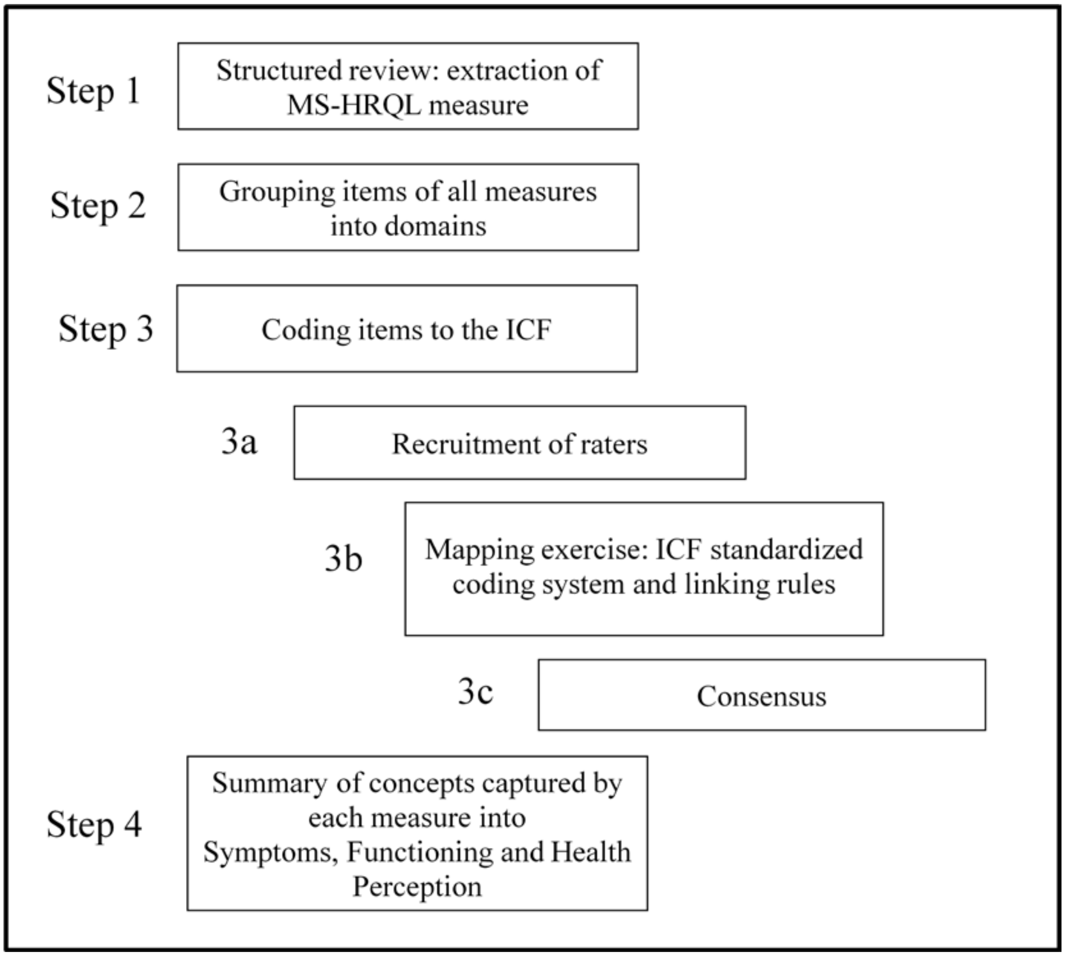
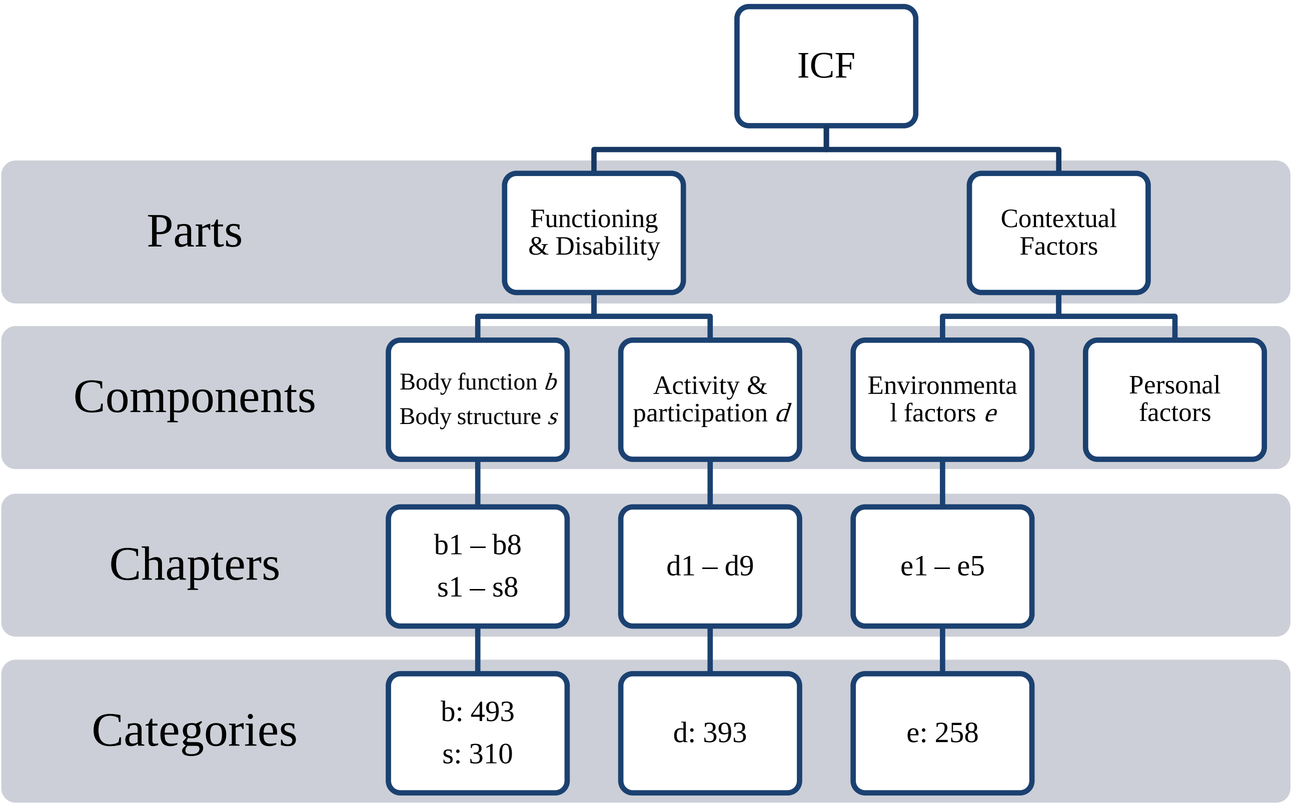


Figure 4.5: ICF classification system



Adapted from WHO, 2001 [17]

Figure 4.6: Delphi process for reaching consensus

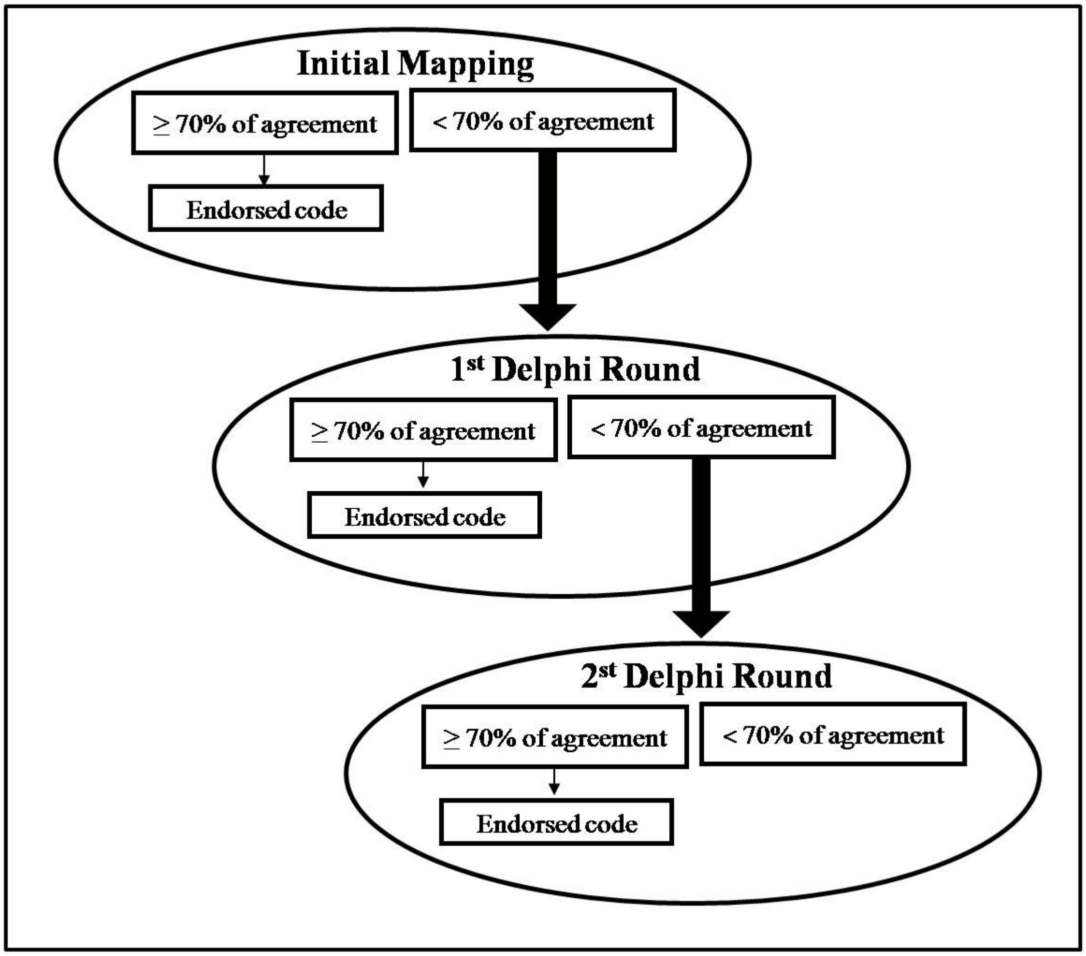


Figure 4.7 to 4.16: Presentation of concepts attained in MS HRQL measures

Figure 4.7: Presentation of concepts attained in **MSQLI** measure

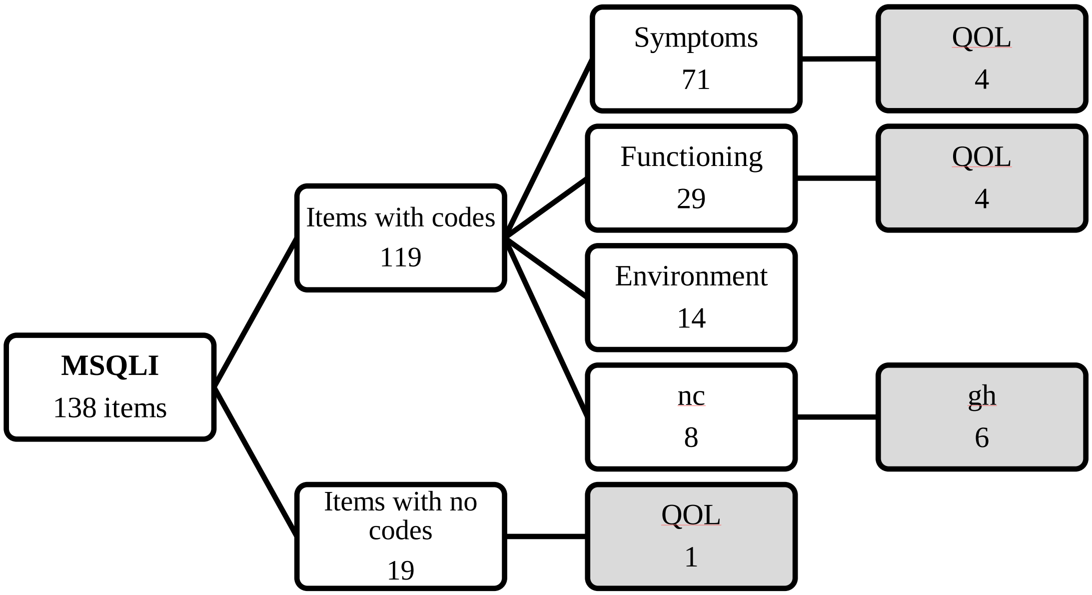


Figure 4.8: Presentation of concepts attained in the **FAMS** measure

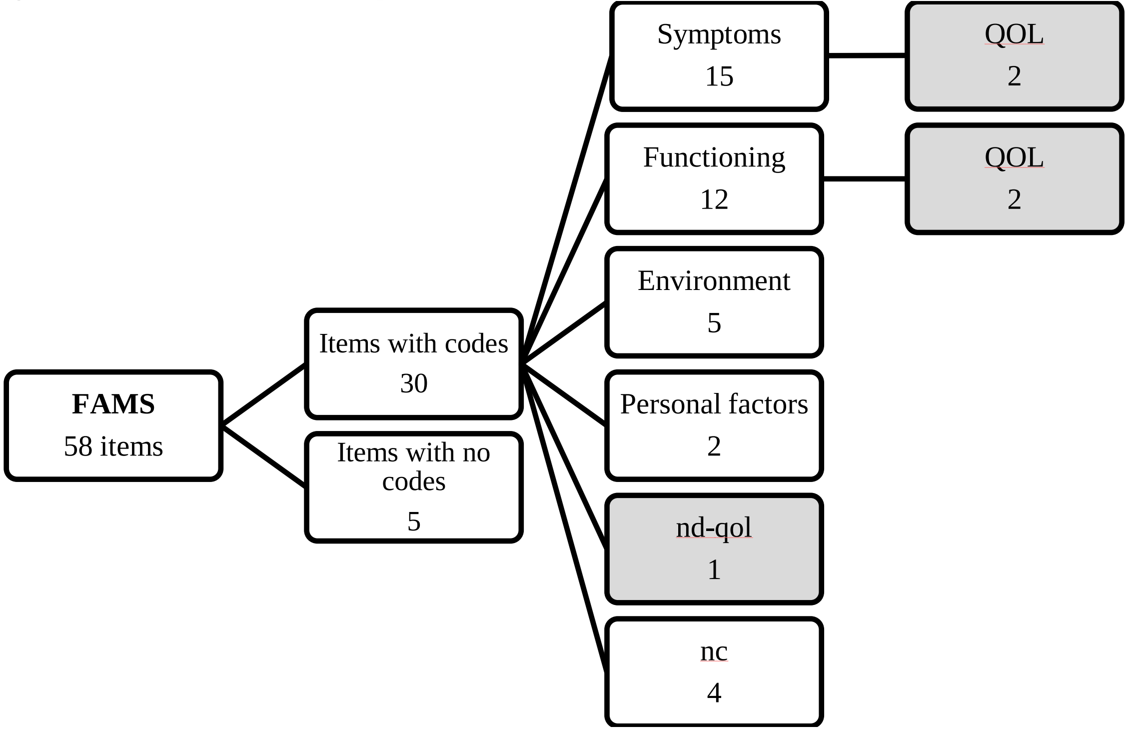


Figure 4.9: Presentation of concepts attained in the **MSQOL-54** measure

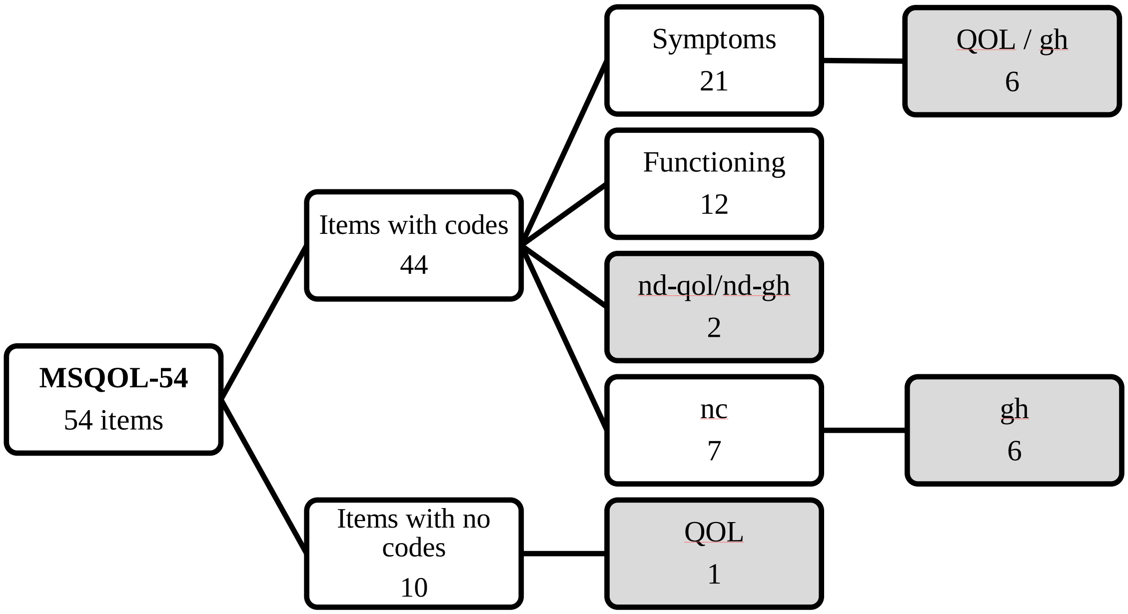


Figure 4.10: Presentation of concepts attained in the **HAQUAMS** measure

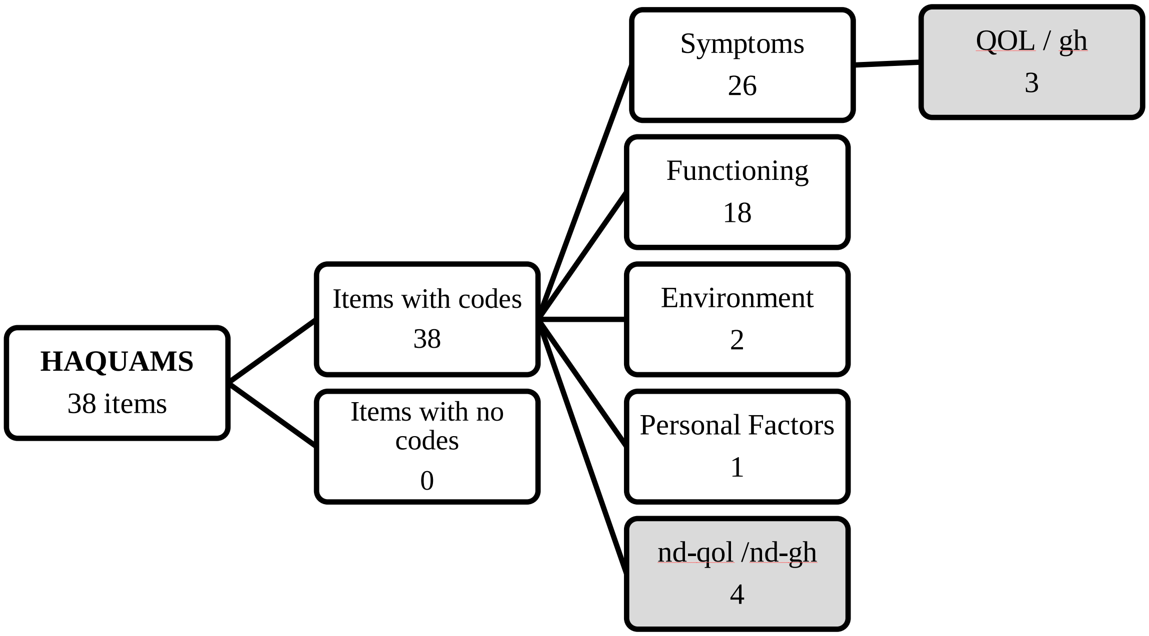


Figure 4.11: Presentation of concepts attained in the **RAYS** measure

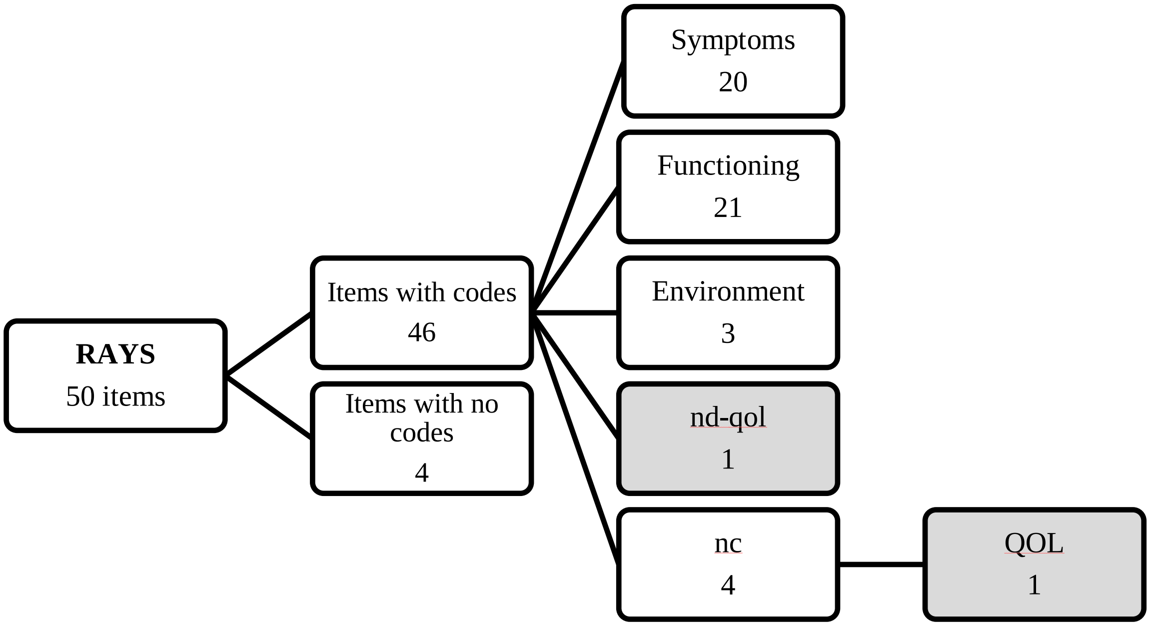


Figure 4.12: Presentation of concepts attained in the **PS-MS** measure

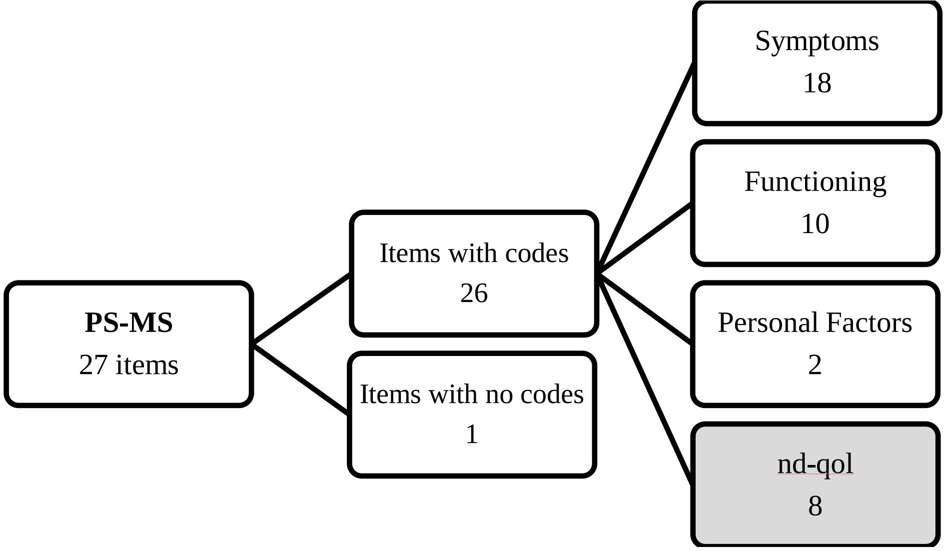


Figure 4.13: Presentation of concepts attained in the **LMSQoL** measure

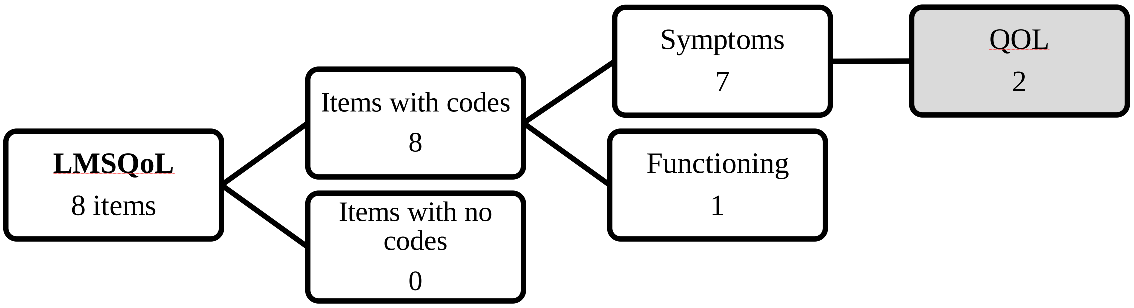


Figure 4.14: Presentation of concepts attained in the **QLI-MS** measure

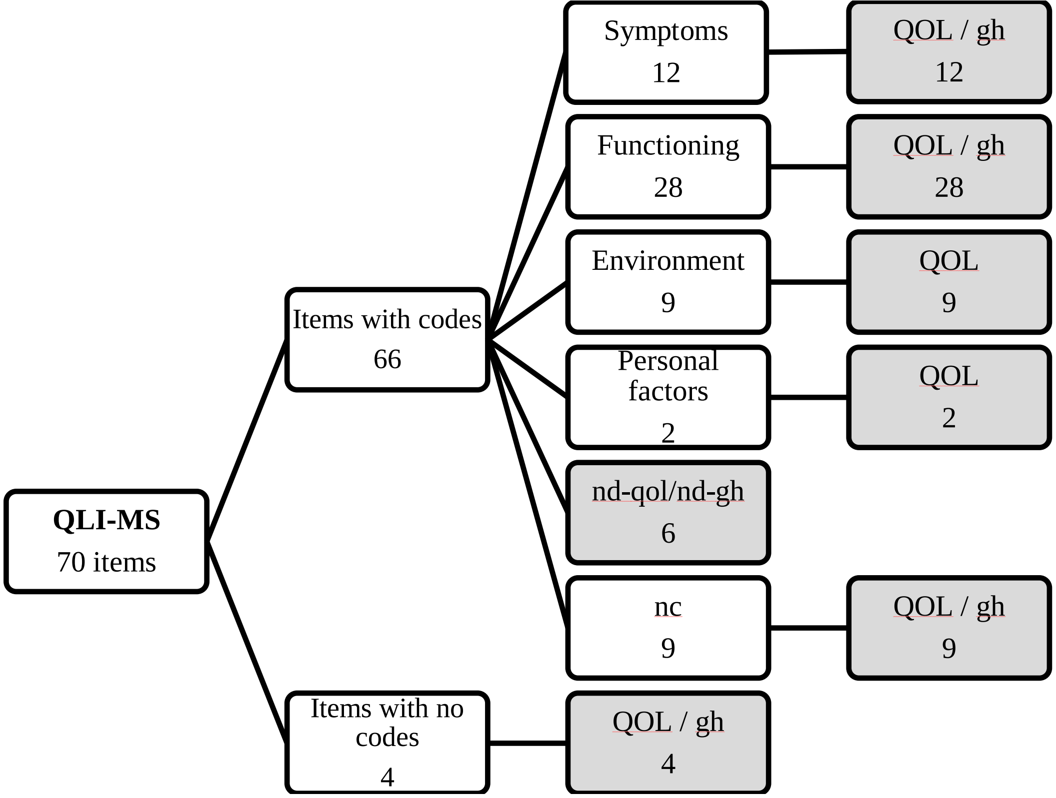


Figure 4.15: Presentation of concepts attained in the **MSIS-29** measure

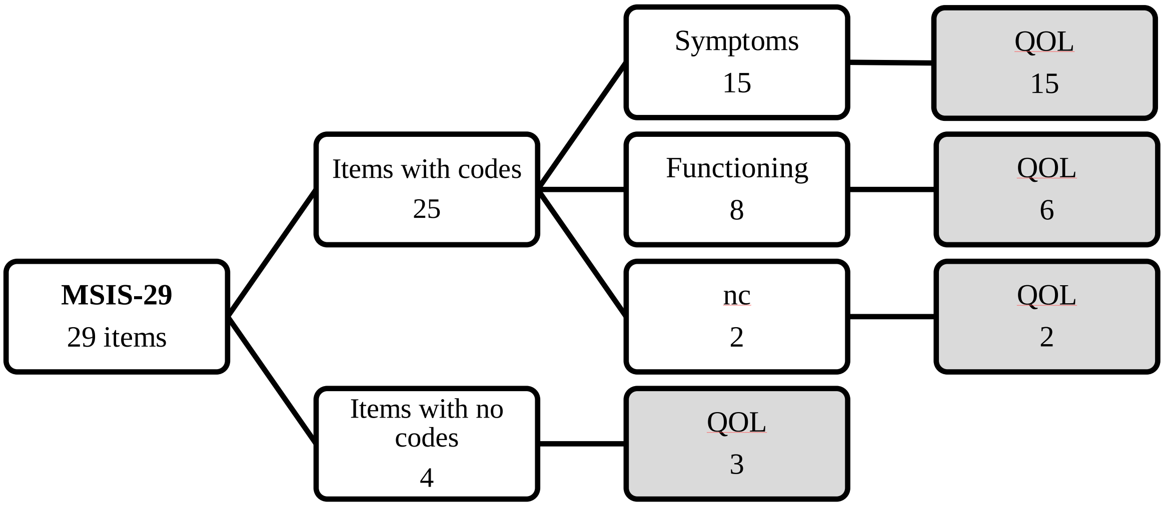
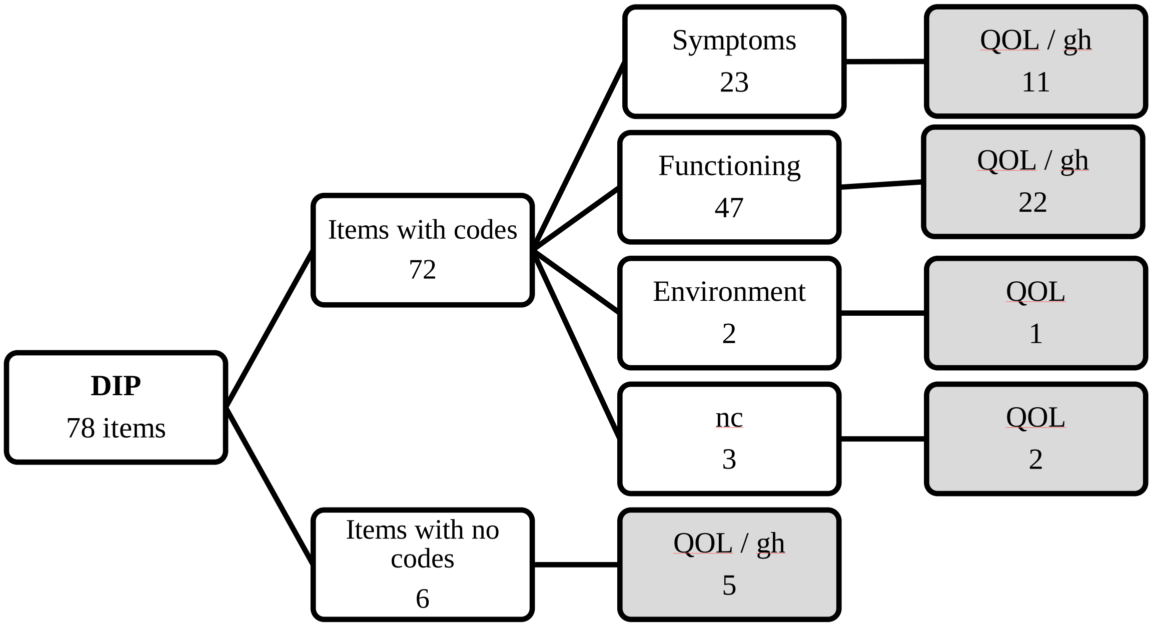


Figure 4.16: Presentation of concepts attained in the **DIP** measure



MSQLI: Multiple Sclerosis QoL Inventory; FAMS: Functional Assessment of Multiple Sclerosis; MSQOL-54: Multiple Sclerosis Quality of Life; HAQUAMS: Hamburg Quality of Life Questionnaire for Multiple Sclerosis; RAYS: The RYAS Scale; PS: Performance Scale; MSIS-29: Multiple Sclerosis Impact Scale; LEMSQoL: Leeds Multiple Sclerosis QoL; QLI-MS: Quality of Life Index-Multiple sclerosis Version; DIP: Disability and Impact Profile

nd: not definable; qol: quality of life; gh: general health; nc: not covered by ICF
Gray shaded areas represent items going beyond symptoms and functioning and covering general health perception and quality of life

Table 4.1: ICF mapping protocol [31]

Step	Procedure
Number of raters	10 to 15
Characteristics of raters	More than 2 disciplines represented; Mix of academic/research and clinician Should include persons with disability when relevant and appropriate (clients) Raters should all have a fundamental understanding of the ICF
Training	Presentation of ICF framework, definitions, coding structure, and coding rules.
Rating	Each rater must select codes independently without discussion with other raters.
Selecting codes	1st select all codes that could apply and 2nd to choose best code/s.
Selecting qualifiers	Same methodology as for selecting codes based on response options attached to the item being ICF coded (source item)
Consensus	A Delphi approach: by email, raters are shown their codes and the codes of others and provided with the opportunity to modify their choice; repeated until item reaches agreement among 70% of raters or further rounds will not improve the agreement
Endorsement of codes	Codes with 70% agreement or more would be endorsed as best codes until further data are available to modify the endorsement. Codes not endorsed by 70% of raters will be listed and identified as unendorsed.
Reporting agreement	Report the number of items for which agreement was achieved at the 100% level and the 70% level, at each consensus round of the Delphi procedure. Report items where no one code was endorsed.
Understanding items with no endorsed codes	Cognitive debriefing on the meaning of the item to the intended respondent (here persons with stroke)
Validity of endorsed codes	Test a sample of clients using the outcome measure and the ICF coded FSI, including qualifiers, to ensure that information was not lost in translation process.

Table 4.2: Overview on the major characteristics of the selected MS HRQL measures

Measure	No. of items	Time to complete (min)	Time frame	Psychometric properties	No. of supporting articles	No. of Citation
MSQLI[51]	138	45	Present, Past 4 weeks, Past year	Alphas: 0.67-0.97 Test-retest: 0.75-0.94 Good content and construct validity	4	12
FAMS[52]	58	20	Past week	Alphas: 0.82-0.96 Test-retest: 0.85-.091 Good construct, content and concurrent validity Good responsiveness	7	19
MSQOL-54[53]	54	11-18	Present, Past 4 weeks	Alphas: 0.75-0.96 Test-retest: 0.70-0.98 Limited validity Low responsiveness for EDSS ≥5	15	45
HAQUAMS[54]	38	25	Past week, Past 4 weeks, Past year	Alphas: 0.85-0.92 Test-retest:0.75-0.94 Good concurrent and discriminative validity	3	5
RAYS[55]	50	30	Past week	Alphas: 0.84-0.89 Limited construct validity Good discriminative validity	2	3
PS-MS[56]	27	10	Present compared to before developing MS	Alphas: 0.78 Test-retest:0.65-0.91 Good construct and discriminative validity	2	8
MSIS-29[57]	29	15	Past 2 weeks	Alphas: 0.89-0.91 Test-retest: 0.65-0.90 Good concurrent validity	9	20
LMSQoL[58]	8	5	Past month	Alphas: 0.79 Test-retest:0.85 Good discriminative validity	3	6
QLI-MS[59]	70	35	Present	Alphas: 0.90 Test-retest: 0.81-0.87 Limited responsiveness	2	7
DIP[60]	78	30	present	Alphas:0.61-0.92 Test-retest:0.61-0.87 Good discriminative validity Good responsiveness	7	11

MSQLI: Multiple Sclerosis QoL Inventory; FAMS: Functional Assessment of Multiple Sclerosis; MSQOL-54: Multiple Sclerosis Quality of Life; HAQUAMS: Hamburg Quality of Life Questionnaire for Multiple Sclerosis; RAYS: The RYAS Scale; PS: Performance Scale; MSIS-29: Multiple Sclerosis Impact Scale; LEMSQoL: Leeds Multiple Sclerosis QoL; QLI-MS: Quality of Life Index-Multiple sclerosis Version; DIP: Disability and Impact Profile

Table 4.3: Characteristics of participants

No.	Profession	Type of practice	Area of expertise
2	Physiotherapist	Researcher	Vascular diseases
5	Physiotherapist	Researcher	Pediatric / Adult Neurorehabilitation
2	Physiotherapist	Clinician	Oncology
2	Physiotherapist	Clinician	Orthopedics and sports injuries
1	Physiotherapist	Clinician	Geriatrics rehabilitation
1	Physiotherapist	Clinician	Pediatric rehabilitation
2	Exercise physiologist	Researcher	Geriatric neurorehabilitation
3	Occupational therapist	Researcher	Geriatric / Adult neurorehabilitation
1	Occupational therapist	Researcher	Obesity
1	Occupational therapist	Clinician	Pediatric neurology
2	Occupational therapist	Clinician	Mental health
1	Occupational therapist	Clinician	Geriatric
1	Epidemiologist	Researcher	Geriatric and neurorehabilitation
1	Neurosurgeon	Physician	Epilepsy and pediatric neurosurgery

Table 4.4: Summary of mapping of MS HRQL measures: distribution of codes along ICF components and levels of hierarchy

	Total	**MSQLI**	**FAMS**	**MSQOL-54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMSQoL**	**MSIS-29**	**QLI-MS**	**DIP**
No. of item	550	138	58	54	38	50	27	8	29	70	78
No. of items with no codes	53	19	5	10		4	1		4	4	6
No. of items with codes	497	119	53	44	38	46	26	8	25	66	72
Items endorsed at 4-digit level	187	58	24	23	13	16	2	5	10	13	23
Items endorsed at 3-digit level	229	41	22	12	18	25	15	3	13	34	46
Items endorsed at lower level	81	20	7	9	7	5	9		2	19	3
Items with single codes	427	117	52	43	35	44	3	8	25	66	69
Items with multiple codes	38	2	1	1	3	2	26				3
Items with single unique codes	193	40	35	19	21	22	3	7	0		31
Efficiency	193/552= 35%	40/138= 29%	37/58= 64%	19/54= 35%	21/38= 55%	22/50= 44%	3/27= 11%	7/8= 88%	0/29= 0	0/70= 0%	32/78= 40%
No. ICF categories	73	29	27	14	27	33	8	4	17	21	32
Body Function	24	15	13	7	13	13	6	3	9	5	11
Activity & Participation	39	13	10	7	12	17	2	1	8	12	20
Environmental Factors	10	1	4		2	3				4	1

[*] Blank spaces mean no entry

[#] The ICF component “body structure” is not included in this table; as none of the items if the MS HRQL measures was linked to this category

Table 4.5: The third-level of ICF categories from the component **Body Function** endorsed by MS HRQL measures

ICF Category		MSQLI	FAMS	MSQOL-54	HAQUAMS	RAYS	PS-MS	LMS QoL	MSIS-29	QLI-MS	DIP
b110	Consciousness function	1									
b126	Temperament & personality function	6	2	1	2	3		2	2	1	
b130	Energy and drive functions	5	6	2	3	1		2	1	2	
b134	Sleep functions	1	1			1			1		2
b140	Attention functions	5	1	3	1				1		2
b144	Memory functions	12	1	2	1	1					2
b147	Psychomotor function					1					
b152	Emotional functions	12	8	5	6	7		3	4	5	4
b160	Thought functions	4	1								
b164	Higher-level cognitive functions	3				1	1				1
b210	Seeing functions	2			2	1	3				2
b230	Hearing functions										2
b280	Sensation of pain	3	4	3	2	1				2	2
b330	Fluency and rhythm of speech functions					1				2	
b455	Respiratory muscle functions	7	1		1		2				
b525	Defecation functions	5			1		2				2
b535	Sensations associated with the digestive system		1								
b620	Urination functions	4	2		2	1	3		1		2
b640	Sexual functions			5	1						2

Table 4.5: The third-level of ICF categories from the component **Body Function** endorsed by MS HRQL measures (continued)

ICF Category		**MSQLI**	**FAMS**	**MSQOL-54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS-29**	**QLI-MS**	**DIP**
b730	Muscle power functions		1								
b735	Muscle tone functions				1	1	3				
b760	Control of voluntary movement functions	1							1		
b765	Involuntary movement functions								1		
b780	Sensations related to muscles and movement functions		1						2		

*Blank spaces mean no entry

Table 4.6: The third-level of ICF categories from the component **Activity and Participation** endorsed by MS HRQL measures

ICF Category		**MSQLI**	**FAMS**	**MSQOL -54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS -29**	**QLI-MS**	**DIP**
d155	Acquiring skills		1								
d163	Thinking	3									
d166	Reading	3									2
d170	Writing				1						2
d177	Making decisions	2				1					
d210	Undertaking a single task								1		
d230	Carrying out daily routine					1			1		
d240	Handling stress and other psychological demands		1			1				2	
d330	Speaking					1					2
d350	Conversation					1					
d410	Changing basic body position	1		1	1	2					7
d430	Lifting and carrying objects	1		1		2			1		2
d440	Fine hand use					1			1		
d445	Hand and arm use						2		1		2
d450	Walking	3		2	3	2			1		2
d455	Moving around	3		3	1	1					4
d460	Moving around in different locations									2	
d470	Using transportation		1		1	1			1		2
d475	Driving					1					

Table 4.6: the third-level of ICF categories from the component **Activity and Participation** endorsed by MS HRQL measures (Continued)

ICF Category		**MSQLI**	**FAMS**	**MSQOL -54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS -29**	**QLI-MS**	**DIP**
d510	Washing oneself										2
d520	Caring for body parts					1					
d530	Toileting										2
d540	Dressing		1		1						2
d550	Eating				1						2
d630	Preparing meals	1			1						2
D640	Doing housework	1		1	1	1					2
d660	Assisting others		1							2	
d710	Basic interpersonal interactions	1								1	
d750	Informal social relationships				2						1
d760	Family relationships		1		1			1		4	3
D770	Intimate relationships	5	2	1		1				4	
d820	School education									2	
d845	Acquiring, keeping and terminating a job									2	
D850	Remunerative employment	1	2			1	7			1	2
d870	Economic self-sufficiency									2	
D920	Recreation and leisure	4	1	3		3			1	2	2
d930	Religion and spirituality									2	
d950	Political life and citizenship		1								

*Blank spaces mean no entry

Table 4.7: The third-level of ICF categories from the component **Environmental Factors** endorsed by MS HRQL measures

ICF Category		**MSQLI**	**FAMS**	**MSQOL-54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS-29**	**QLI-MS**	**DIP**
e165	Assets										2
e225	Climate		1			1					
e3	*Support & Relationships*										
e310	Immediate family		1		1					2	
e320	Friends		1							2	
e325	Acquaintances, peers colleagues, neighbors and community members				1					3	
e340	Personal care providers and personal assistants	2									
e355	Health professionals					1					
e410	Individual attitudes of immediate family members		2								
e580	Health services, systems and policies									2	

[*] Blanc spaces mean no entry

Table 4.8: Summary of multiple sclerosis HRQL measures: distribution of items across components of HRQL

	Total	**MSQLI**	**FAMS**	**MSQOL-54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMSQoL**	**MSIS-29**	**QLI-MS**	**DIP**
No. of item	550	138	58	54	38	50	27	8	29	70	78
Symptoms *Body Function* n	243	71	30	21	26	20	18	7	15	12	23
(%)	*(44%)*	*(51%)*	*(52%)*	*(39%)*	*(68%)*	*(40%)*	*(67%)*	*(88%)*	*(52%)*	*(17%)*	*(29%)*
Functioning Activity & Participation n	186	29	12	12	18	21	10	1	8	28	47
(%)	*(34%)*	*(21%)*	*(21%)*	*(22%)*	*(47%)*	*(42%)*	*(37%)*	*(12%)*	*(28%)*	*(40%)*	*(60%)*
Environmental Factors n	35	14	5	0	2	3	0	0	0	9	2
(%)	*(6%)*	*(10%)*	*(9%)*		*(5%)*	*(6%)*				*(13%)*	*(3%)*
Health Perception & QoL n	191	15	5	15	7	2	8	2	26	70	41
(%)	*(35%)*	*(11%)*	*(9%)*	*(28%)*	*(18%)*	*(4%)*	*(30%)*	*(25%)*	*(90%)*	*(100%)*	*(53%)*

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CHAPTER 5
Integration of Manuscript 1 and 2

5.1 Research objectives of manuscript 1 and 2

Manuscript 1:

To estimate the extent to which items in the MS-specific HRQL measures capture domains of symptoms, functioning and general health perception.

Manuscript 2:

To explore, in commonly used HRQL and fatigue indices, sources of heterogeneity in the assessment of fatigue in the MS population.

5.2 Integration of manuscript 1 and 2

HRQL measures were found to be frequently used in the evaluation of disease progression and in the evaluation of effectiveness of new interventions [27-29]. These measures differed in the degree to which components of HRQL, symptoms functioning and general health perception were represented. In the first manuscript, an in depth content analysis of the most commonly used HRQL measures in the MS population was presented. The results provided clinicians and researchers with new insights on the heterogeneity of the content of these measures. Moreover, the diversity in the degree of coverage beyond symptoms and functioning was illustrated, using the ICF and the Wilson-Cleary models as frameworks.

The first study also provided an overall picture on how measures differed in the way of capturing a single domain. Thus we wanted to explore in more details how a single domain is measured differently across measures and indices. The symptom fatigue was chosen to be the domain of interest in the second manuscript, because fatigue is one of the most common and most distressing symptoms of MS. Fatigue was also shown in the first study to be represented differently by the different measures, as items measuring this domain were coded to different ICF categories.

Clinicians and researcher intending to measure fatigue in MS patients need to ensure that the indices chosen are measuring the right aspects of fatigue. Thus in the second manuscript, sources of heterogeneity in ascertaining fatigue in the MS population were explored. In the second study, variations across the selected measures and indices in the wording of items, constructs captured, unit of references, and response options were presented.

CHAPTER 6
MANUSCRIPT 2

6.1 Heterogeneity of Ascertaining Fatigue in the Multiple Sclerosis Population

Alaa Mohammad Arafah, B.Sc., Occupational Therapist
Ayse Kuspinar, B.Sc.
Shang Yuan Teng, B.Sc.
Nancy E. Mayo, Ph.D.

School of Physical and Occupational Therapy,
Faculty of Medicine, McGill University
3654 Sir William Osler, Montreal, Quebec, Canada, H3G 1Y5

Manuscript prepared for submission to the journal entitled Disability & Rehabilitation

Running Title: Heterogeneity of Ascertaining Fatigue in the Multiple Sclerosis Population

Communication addressed to: Nancy E. Mayo, Ph.D.
James McGill Professor
Department of Medicine
School of Physical and
Occupational Therapy
McGill University
Division of Clinical Epidemiology
Division of Geriatrics
McGill University Health Center
Royal Victoria Hospital Site
Ross Pavilion R4.29
687 Pine Ave W
Montreal, QC, H3A 1A1
Tel. (514) 934 1934 36922
FAX (514) 843 1493
nancy.mayo@mcgill.ca

ABSTRACT

Purpose: Fatigue is the main factor contributing to poor HRQL among people with MS. Nonetheless, fatigue remains difficult to define, measure, and manage. The sources of heterogeneity in the measurement of fatigue create a risk that the assessment method will impact on the results rather than characteristics of the people studied, the intervention, or time. The purpose of this study was to explore, in commonly used HRQL and fatigue indices, sources of heterogeneity in the assessment of fatigue in the MS population.

Methods: Fatigue Items from 9 HRQL measures and 1 fatigue specific index were linked to the ICF. Concepts, response options and unit of references were identified.

Results: Out of the 66 items, 57 items were coded to the ICF, and only 38 items were linked to the fatigue ICF categories. 23 items referred to the severity or the intensity level of fatigue, while 43 items referred to the impact of fatigue on function and well-being. The majority of measures rated their items on Likert scales with 4 to 7 options.

Conclusion: Many indices of HRQL and fatigue have been developed and are routinely used in the clinical practice. No two instruments are the same. Some instruments measure the severity, impact, or cause of fatigue, while other instruments measure a mixture of these. Having items that are very broad, ambiguous or double-barrelled would result in imprecise measurement and unreliable data collection.There is a need for a “true” measure of fatigue that harmonizes clinicians, researchers, and patients’ needs for measurement.

INTRODUCTION

Multiple sclerosis (MS) is one of the most common chronic autoimmune diseases of the central nervous system. It is estimated that there are more than 2.5 million people with MS world wide [1]. Its onset is most common between the ages of 18 and 40 years and it affects women more often than men [2]. Common symptoms and signs of MS are sensory disturbances, spasticity, fatigue, vertigo, diplopia, hemiparesis, tremor, ataxia, bladder/bowel/sexual disturbances and cognitive impairments [3-5]. Although the symptoms of onset vary and the progression is heterogeneous, unpredictable in timing, and uncertain in outcome, MS affects many of the domains of function with the ultimate impact on quality of life (QOL). The most common and disabling symptom of MS is fatigue affecting 50% to 87% of people with MS; up to 40% regard fatigue as their most distressing symptom [5, 6].

Fatigue substantially affects QOL as it impacts on work, family and social life; in one study, over 80% of people with MS stated that it was the main problem affecting their ability to work [7, 8]. Health aspects of QOL among people with MS have been reported to be lower than that of healthy people and also poorer than that of persons with other chronic conditions [9]. When compared to healthy individuals, persons with MS had significantly higher level of physical fatigue [10]. In fact, Turpin et al [11], found that fatigue was the main factor contributing to poor health-related quality of life (HRQL) among people with MS. This was also supported by Simone et al [12], who indicated that fatigue along with depression were the main predictors of poor HRQL as evaluated by MSQOL-54 scale. The impact of fatigue on HRQL was attributed to its effect on mood and on limiting capacity for physical and mental activity. Physical, mental and sensory impairments, and activity limitations ultimately affect participation in life’s roles and is likely one of the reasons why people with MS reported higher level of illness intrusiveness than individuals with rheumatoid arthritis and end-stage renal disease ($p < 0.01$) [9].

Although fatigue has an important impact on the lives of people with MS, it remains difficult to define, measure, and manage. Fatigue has been discussed and studied intensively in the medical and rehabilitative literature, nonetheless, there seems to be variability in the definition and or criteria for this symptom. Table 6.1 provides a sampling of the various definitions appearing in the literature. In many of these definitions, fatigue, tiredness, and lack of energy are used as synonyms. However, qualitative research suggests that people with chronic conditions do not necessarily equate these terms [13]. Another key concept from this list of definitions is that fatigue is effort related and impacts on physical activities. Fatigue could impede not only physical function, but also mental function as expressed by inability to concentrate or think clearly. Fatigue can also generate or worsen other symptoms of MS as there is a high degree of interdependence among MS symptoms. This is shown in Figure 6.1 which was adapted from the model of Crayton [13].

Fatigue is common in the general population, however, there are several unique features of the fatigue associated with MS. According to Krupp et al [14], in comparison to the fatigue experienced by healthy individuals, MS fatigue is: 1) more severe and more frequent; 2) a greater impediment to sustained physical functioning; 3) more often sudden in onset; 4) longer to recover; 5) precipitated or accentuated by heat or humidity; 6) sustained or chronic; and 7) not always correlated with other MS symptoms.

With these diverse components of the definition, quantifying fatigue in MS population is challenging as it is not easily isolated from other symptoms such as depression, sleepiness, cognitive impairment, and muscle weakness [15]. Also, unlike constructs such as muscle weakness or cognitive impairment which can be directly measured using specific tests, fatigue can only be assessed through self-report.

Because of the importance of fatigue to MS and because of the multidimensional impact on other symptoms and functions, measures of HRQL are often used in MS as they are well suited to depicting parsimoniously the impact of a health condition such as MS. There are at least 10 HRQL indices in use in the MS population and all but one included items on fatigue. Indeed, a review by Hjollund et al [16] on fatigue scales used for chronic conditions in the last three decades reported that among the 1086 studies published, 62% of the studies used 157 multidimensional scales (e.g.SF-36), and 58% used 71 fatigue specific scales. When fatigue is assessed as a "stand alone" construct in the MS population, it is most commonly assessed using the FSS or the MFIS. The latter fatigue index (MFIS) is, however, included in a MS specific HRQL battery. All of these measures are self-reported and are intended to reflect the individual's perception and experience of fatigue and its impact on daily life. Therefore, information on fatigue gleaned from these sources depends primarily on the nature of the questions asked. Additionally, the items included in the fatigue indices are based on the personal conceptualization of their developers and responses depend on the individual's interpretation when responding. This means that different fatigue indices might be measuring fundamentally different dimensions of fatigue or even different constructs.

As a result of these sources of heterogeneity and interpretation in the measurement of fatigue, there is a risk that the assessment method will impact on the results rather than characteristics of the people studied, the intervention, or time. Hence, it is of a great importance to evaluate content of measures and to conduct a careful examination of individual items to assure accuracy of information elicited.

The purpose of this study was to explore, in commonly used HRQL and fatigue indices, sources of heterogeneity in the assessment of fatigue in the MS population.

METHODS

The source of data for this study came from the fatigue items in commonly used MS-HRQL and MS fatigue indices.

To identify the MS-HRQL indices, a structured literature review was conducted in MEDLINE, PsycINFO, CINAHL and EMBASE databases in the period 1980 to 2007. The keywords searched were: Multiple sclerosis, quality of life, health related quality of life, measure, questionnaire, index, assessment, outcome and psychometric. Indices were selected if they have supported psychometric properties and if they were commonly used. The methods to identify items referring to fatigue have been described in detail in a previous manuscript [17]. Briefly, content analysis of the MS-HRQL was carried through linking each item to the International Classification of Functioning, Disability and Health (ICF) using a standardized mapping protocol [18, 19].

Here is an example on how fatigue could be coded using the ICF as a frame of reference. Under the component of body function there are these codes: *b4* sensory function and pain, *b455* exercise tolerance function, *b4552* functions related to susceptibility to fatigue at any level of exertion. Thus the code *b4552* represents the concept of *fatigability*. Moreover, the ICF captures the mental dimension of fatigue; the first chapter of body function represents the mental function *b1*, under which we have these codes: *b130* energy and drive functions, *b1300* energy level, and the code *b1301* motivation.

Overall, fatigue could be represented by the following codes:

b1300 Energy level

Mental functions that produce vigour and stamina.

b1301 Motivation

Mental functions that produce the incentive to act; the conscious or unconscious driving force for action.

b4552 Fatiguability

Functions related to susceptibility to fatigue, at any level of exertion.

A pool of 25 health professionals from different clinical backgrounds was drawn upon to code items from HRQL indices to the ICF. Each item received 8 to 11 independent ratings. Those Raters were instructed to identify all concepts contained in the item and link them to the most precise ICF categories. A Delphi process was used to arrive at a consensus on the most appropriate code. Percentage of agreement of more than or equal 70% was aimed at in order to have an endorsed code for a specific item. The initial coding and consensus were done using e-mail surveys.

To identify the MS fatigue indices not included in HRQL indices, PROQOLID data base was searched. PROQOLID provides an overview on the existing patient-reported outcome measures (PROs) that are available for specific populations and pathologies. The available fatigue indices were cross referenced with the term “Multiple Sclerosis” in PubMed to identify use in MS population. Three independent health professionals subsequently mapped the items on one MS specific fatigue index to the ICF using the same protocol [18].

The constructs represented by each item were identified. Three independent health professionals identified and classified the constructs captured by items. Consensus between raters was obtained. Finally, the response options for each index were identified.

RESULTS

Identifying MS-HRQL indices

A total of 1052 papers reporting the use of MS-HRQL measures were published between 1980 and 2007. In these studies, 20 MS-HRQL indices were found and only 10 indices met the selection criteria. Table 6.2 provides an overview of the major characteristics of selected MS-HRQL indices. The most commonly applied indices are the MSQOL-54, the FAMS, and the MSQLI. However the MSQOL-54 has only 5 items (9.25%) targeting fatigue concept. Out of the 58 items of the FAMS, 9 items (16%) measure fatigue. Out of the 138 items of the MSQLI, 25 items (18%) measure fatigue. It should be mentioned that the MSQLI consists of 10 scales; one of them is the Modified Fatigue Impact Scale (MFIS) which is an MS-specific fatigue index. Overall, 57 items addressing fatigue were included in MS-HRQL indices.

Identifying MS fatigue scales

PROQOLID search identified 8 MS fatigue indices. Table 6.3 provides a list of the fatigue indices, the frequency of use in the MS literature, and key psychometric properties. Two indices predominated in the literature, the FSS, used 86 times and the MFIS used 35 times. Of these, the MFIS is a part of a MS HRQL index so the FSS is the most widely used and relevant for this study stand alone fatigue index.

Coding items to the ICF

In total, 66 items were identified from all of the selected MS-HRQL and fatigue indices. Table 6.4 lists the items that were linked to the fatigue concept of the ICF, b130 and b4552. Out of the 66 items that were coded to the ICF, 14 items were linked to the code b1300, 3 items were linked to the code b1301 and 21 items endorsed the code b4552. Some items were linked to more than one concept (e.g. *Fatigue interferes with carrying out certain duties and responsibilities* was linked to b4552 (fatigability) and d230 (carrying out daily routine)). Table 6.5 provides a list of items coded to other ICF categories. Overall, 15 other ICF categories were identified; these categories covered mainly the components of body function and activity & participation. Moreover, 9 items did not reach consensus on the most appropriate codes; these items are listed in table 6.6. Interestingly among these items, two items stating the word “tired” did not reach consensus on the most appropriate code.

Classifying concepts: Severity vs. Impact

Among the 66 fatigue items, 23 items referred to the severity or the intensity level of fatigue, while 43 items referred to the impact of fatigue on function and well-being as shown in Table 6.7. One item from the FSS referred to the perceived cause of fatigue *"Exercise brings on my fatigue"*. In three HRQL indices, MSQOL-54, LMSQoL and QLI-MS, the items only captured severity of fatigue and no item targeted impact.

Response options

All but 2 of the 10 indices rated their items on Likert scales with 4 to 7 options. The HAQUAMS rated one item by ranking severity with respect to other symptoms. The PS-MS rated one item on a dichotomous scale (yes/no) and rated another item on a visual analogue scale (VAS). Interestingly, items from various indices differed also in frame of reference for quantification. For example, the MSQOL-54 and the SF-36 used *time* as the frame of reference (e.g. the response option in the MSQOL-54 and the SF-36 is *all of the time, most, a good bit, some, a little, none of the time*). In contrast, the RAYS used level of impairment as the reference frame (i.e. *none, mild, moderate, severe, extreme*).

DISCUSSION

ICF codes were endorsed for 57 items out of the 66 fatigue items. As was expected, items were linked to the categories of *energy and drive function* and *fatigability*. The finding of this study supports that fatigue has two dimensions; physical and mental; as 17 items were linked to *energy and drive function*, under the chapter of mental function, and 21 items were linked to *susceptibility to fatigue at any level of exertion*. 23 items were linked to 15 other ICF categories. These items reflect the impact of fatigue on activities and participation. There were 9 items that did not have endorsed codes as raters did not reach consensus on the most precise codes and raters suggested different codes for those items. Hence, respondents are going to face the same problem when interpreting and answering these questions. An interesting finding of this study is that out of the five items that stated the concept "tiredness", two of the items did not reach consensus. This was also inquired when conducting focus group on fatigue with patients with osteoarthritis [13]. When asked to describe their fatigue, one patient stated *“…when I get really fatigued it is not that I feel I’m tired, but I feel that if I don’t go lie down, I’ll fall down*” [13]. The terms fatigue and tiredness should be studied more to ascertain if they are indeed different constructs.

This study illustrated that there is heterogeneity in the way that fatigue is defined and measured. This is an important point to take into consideration as it has an impact on an individual’s health care and management. It is difficult to produce an effect on a symptom that cannot be measured accurately. Interventions aiming at reducing fatigue in the MS population may be under or over estimated due to the presence of measurement bias. Measurement bias might be induced due to lack of common vocabulary between patients and clinicians. Clinicians may assume that respondents understand and interpret the terminology used the same as was intended by the investigators [20]. Thus, we need to move toward having patient-reported outcome measures that reflect patients’ perspectives.

One way to overcome the discrepancy between patients and clinicians, is to apply the process of cognitive debriefing or interviewing using items selected from different HRQL and fatigue indices. Cognitive debriefing is conducted by asking people to think aloud when they answer questions [21]. Cognitive debriefing is a way of understanding the mental process that respondents follow when they formulate their answers. This will allow researchers to check if the wording of the item provides respondents with sufficient information to answer or if the item has incomplete concept coverage or was misleading. Consequentially, cognitive debriefing could be used to assure the accuracy of data collected using self-reported indices.

For example, one of the activities of daily living that is affected by fatigue is shopping. Different meanings of shopping were expressed when cognitive debriefing process was conducted with persons with stroke [18]. Interestingly, men focused on the mental aspect of shopping (e.g. remembering the items in the shopping list), while women focused on the physical aspects of shopping (e.g. reaching up the shelves and walking down the aisles). Therefore, the cognitive processes that respondents follow to interpret items need to be identified and considered when interpreting scores.

Tourangeau [22] presented *the question-and-answer model*; the most commonly cited model of how respondents answer survey question. This model suggests that there are four actions the respondents have to complete when answering questions: comprehension, retrieval, judgment and response. Measurement error could occur at any of these stages. Problem that might occur at the comprehension stage might be caused by double-barrelled questions. In our sample of items measuring fatigue in the MS population, 44% were doubled-barrelled questions (e.g. *I had difficulties falling asleep and/or awoke up in the middle of the night and/or awoke unrefreshed*). Ambiguity of wording of questions could be also another source inducing errors and inconsistency of responses (e.g. *Please indicate how true each statement has been for you during the past 7 days. I feel* ***weak all over***). Items should also be addressed so that respondents are able to retrieve information easily and accurately or else, items could induce problems at the retrieval stage (e.g. *I have had as much energy as usual*, what do we mean by “as usual”? Is it before the patients developed MS? What if he or she had MS for more than 20 years, how accurate would the response be?).

An important issue that also needs to be considered when attempting to measure fatigue is the phenomenon of response shift. Some constructs are strongly susceptible to response shift, such as fatigue and HRQL. Response shift could occur at any area where PROs are evaluated over a period of time [23-25]. Response shift refers to *“a change in the meaning of one’s self evaluation of a target construct as a result of (1) a change in the respondent’s internal standards of measurement(i.e. scale recalibration); (2) a change in the respondent’s value (i.e. reprioritization) or (3) a redefinition of the target construct (i.e. reconceptualization)”*[*] [26, 27]. Response shift could be induced when there is a change in the individual frame of reference, taking into consideration pervious experiences, present circumstances, and anticipated status. An example to

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[*] Spangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med* 1999;48:1507-15.

illustrate this point, consider asking a person with MS the following question, “*How satisfied are you with: Having enough energy for everyday activities?”* the person might answer that question as “very dissatisfied” taking into consideration that he is relatively young, quite active, wants to pursue his education and career and his energy level should match his activity and participation level. However, years after, this person might have developed other severe and more disabling symptoms, such as severe spasticity or hemiparesis, and he would rate the previous question as “somewhat satisfied” even though, his energy level might actually have deteriorated. What happened is that, over time, this component of HRQL has undergone reprioritization. Now, that person cares more about his ability to walk and move around more than his energy level. There are methods to identify and adjust for response shift but a discussion of these methods is beyond the scope of this paper. However, the work of Sprangers [27], Schwartz [26, 28, 29], Oort [30], Ahmed, and Mayo [23, 31-34] provide background into this important area.

Another challenge with measuring concepts such as fatigue and HRQL is the scoring method, as summing the ordinal response options across items does not yield mathematical quantities [35]. The modern psychometric approach is to use Item Response Theory (IRT) or Rasch modeling to create true measures of constructs such as fatigue [28]. To capture the complete construct, combining items from different measures would potentially yield a more accurate measure. In this process, items from different indices, measuring the same construct, are placed onto the same linear continuum [36]. Briefly, the Rasch model converts ordinal or categorical quantities into meaningful, interval like measures [28]. Andrich [36], Conrad [37], McHorney [38], and Cook [39] provided information on Rasch modeling and IRT which is beyond the discussion in this paper.

The results of this content investigation could be a starting point to develop a new measure of fatigue for the MS population. This new measure would be based on a universal common language, understood by professionals from different backgrounds, and incorporates patients' perspectives. The qualifiers of the ICF coding system could readily be used as a common metric. ICF qualifiers signify the magnitude of the level of severity of a particular category, and ranges from 0= no problem to 4=complete problem. For example the visual analogue scale of the assessment of fatigue could be linked to the code b4552. Then the values of this scale are transformed in to ICF qualifiers. As the scale ranges from 0= not at all, to 100= a great deal, using the ICF classification, level of fatigue ranges 0 to 4mm would receive the qualifier 0, from 5 to 24mm the qualifier 1, from 25 to 49mm the qualifier 2, from 50 to 95mm the qualifier 3, and from 96 to 100mm the qualifier 4.

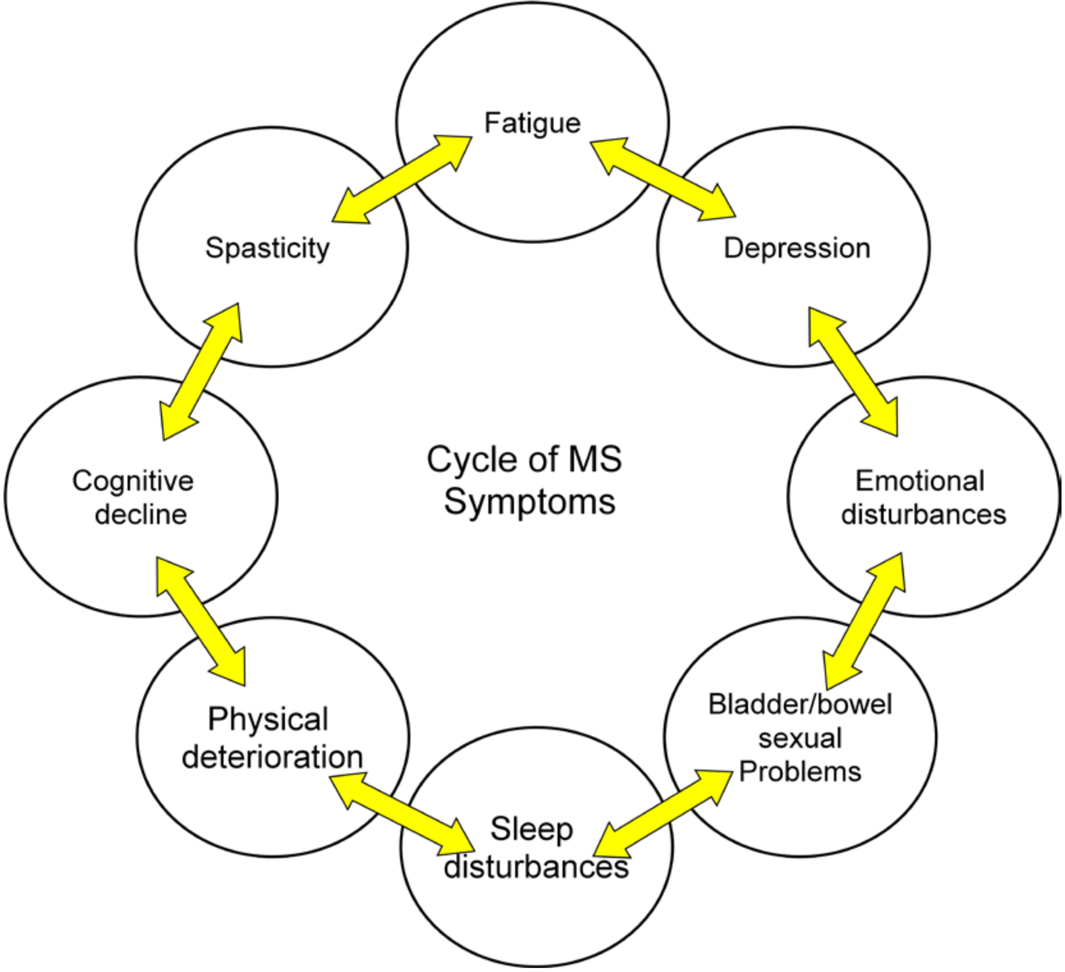
An exemplary study was conducted by Cieza et al, who used Rasch modeling to estimate the extent to which items addressing the category "energy and drive function" in rheumatoid arthritis patients, form a unidimensional, ordered interval scale, so called *ICF category interval scale* [40]. In that study, 19 items integrated from different PRO measures were hierarchically ordered using the Rasch model. The study found that 3 items, even though they had similar wording, were placed at different levels of the difficulty continuum. They implicated the different recall times and different response options as a reason for the different values. Easiest item had as the response option *time* (i.e. response option ranging from "none of the time" to "all of the time"). Items with the response option of *level of truth* (i.e. response option ranging from "yes, that is true" to "no, that is not true") were placed at higher level of difficulties. This implies that respondents might also find it more challenging to answer these questions as the response option is more abstract. In our sample of fatigue items there were 13 items with the response option "level of truth". Other items had also more challenging concepts such as satisfaction and importance. Cieza et al [40] found as well that items referring to the *impact* on activities and participation were placed at higher level of difficulties than items referring to the *severity* of symptoms. All of these issues should be taken into consideration when testing or developing PRO measures.

It is acknowledged that there were some limitations to this study. We conducted a structured rather than a systematic literature review to extract HRQL and fatigue indices. Nonetheless, previous reviews supported our findings regarding the most commonly used HRQL and fatigue indices [41-43]. There were also some limitations regarding the ICF mapping procedure. The ICF mapping protocol requires 10 to 15 raters to perform the mapping exercise, however, items of the FSS were coded by 3 raters. In addition the mapping protocol requires the completion of cognitive debriefing and validation of the endorsed codes. These two steps were not completed in this study. Conducting these steps will provide us with interesting insights regarding the ambiguity of the items that were not endorsed, and will support findings of this study.

There is clearly much to be done in the development of fatigue indices. One way to produce a valid and a universal index, which could be used in multidisciplinary medical and rehabilitation teams, is to have the ICF classification system as source of items, the ICF qualifiers as the frame of reference for the response options, and to use Rasch or IRT modeling to produce interval like scales.

In conclusion, even though fatigue is recognized as a major clinical problem in the MS population, it remains very challenging to define and measure. Many indices of HRQL and fatigue have been developed and are routinely used in the clinical practice. No two instruments are the same. Some instruments measure the severity, impact or cause of fatigue, while other instruments measure a mixture of these. Having items that are very broad, ambiguous or double-barrelled would result in imprecise measurement and unreliable data collection.There is a need for a “true” measure of fatigue that harmonizes clinicians, researchers, and patients’ needs for measurement.

Figure 6.1: The cycle of MS symptoms



Adapted from Crayton et al, 2004 [51]

Table 6.1: Definition of fatigue from the literature

Reference	Definition/Criteria
Comi et al, 2001[44]	Overwhelming sense of tiredness, lack of energy or feelings of exhaustion
Chaudhuri & Behan, 2004[45]	Difficulty initiating or sustaining voluntary effort
Krupp, 1988[14]	Feelings of physical tiredness and lack of energy distinct from sadness or weakness
Multiple Sclerosis Council, 1998[46]	A subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual or desired activity
Mills & Young, 2008[47]	Reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion. It is relieved by daytime sleep or rest without sleep. It can occur at any time but is usually worse in the afternoon. In MS, fatigue can be daily, has usually been present for years and has greater severity than any premorbid fatigue
Packer et al, 1994[48]	A state characterized by extreme tiredness, an overwhelming need to rest, a complete lack of energy, and a decreased capacity for physical or mental work
Dittner et al, 2004[43]	An extreme and persistent tiredness, weakness or exhaustion—Mental, physical or both.
Bakshi et al, 2000[49]	Subjective feeling of tiredness, and/or lack of energy after prolonged or excessive periods of either physical or mental activities.
Krupp et al, 1988[14]	MS fatigue is: 1) more severe and more frequent; 2) a greater impediment to sustained physical functioning; 3) more often sudden in onset; 4) longer to recover; 5) precipitated or accentuated by heat or humidity; 6) sustained or chronic; and 7) not always correlated with other MS symptoms
Flachenecker et al, 2002[50]	Fatigue: 1) is one of their most three most distressing symptoms; 2) occurs daily or on most of the day; 3) limits their activities at home or at work.

Table 6.2: Overview on the major characteristics of the selected MS HRQL measures

Measure	No. of items	No. of fatigue items	Time to complete (min)	Time frame	psychometric properties examined	No. of supporting articles	No. of Citation
MSQLI[52]	138	25	45	Present, Past 4 weeks, Past year	Alphas: 0.67-0.97 Test-retest: 0.75-0.94 Good content and construct validity	4	12
FAMS[53]	58	8	20	Past week	Alphas: 0.82-0.96 Test-retest: 0.85-.091 Good construct, content and concurrent validity Good responsiveness	7	19
MSQOL-54[54]	54	5	11-18	Present, Past 4 weeks	Alphas: 0.75-0.96 Test-retest: 0.70-0.98 Limited validity Low responsiveness for EDSS ≥5	15	45
HAQUA MS[55]	38	5	25	Past week, Past 4 weeks, Past year	Alphas: 0.85-0.92 Test-retest:0.75-0.94 Good concurrent and discriminative validity	3	5
RAYS[56]	50	4	30	Past week	Alphas: 0.84-0.89 Limited construct validity, Good discriminative validity	2	3
PS-MS[57]	27	3	10	Present compared to before having MS	Alphas: 0.78 Test-retest:0.89 Good construct and discriminative validity	2	8
MSIS-29[58]	29	3	15	Past 2 weeks	Alphas: 0.89-0.91 Test-retest: 0.65-0.90 Good concurrent validity	9	20
LMSQoL[59]	8	2	5	Past month	Alphas: 0.79 Test-retest:0.85 Good discriminative validity	3	6
QLI-MS-version[60]	70	2	35	Present	Alphas: 0.90 Test-retest: 0.81-0.87 Limited responsiveness	2	7
DIP[61]	78	0	30	present	Alphas:0.61-0.92 Test-retest:0.61-0.87 Good discriminative validity Good responsiveness	7	11

MSQLI: Multiple Sclerosis QoL Inventory; FAMS: Functional Assessment of Multiple Sclerosis; MSQOL-54: Multiple Sclerosis Quality of Life; HAQUAMS: Hamburg Quality of Life Questionnaire for Multiple Sclerosis; PS-MS: Performance Scales for MS; MSIS-29: Multiple Sclerosis Impact Scale; LEMSQoL: Leeds Multiple Sclerosis QoL; QLI-MS: Quality of Life Index-Multiple sclerosis Version; DIP: Disability and Impact Profile

Table 6.3: Overview on the characteristics of the fatigue-specific indices for MS

Measure		No. of items	No. of citation in MS	Psychometric properties	Reference
DUFS	Dutch Fatigue Scale	9	1	Alphas: 0.79-0.87 Test-retest: 0.72 discriminant validity was supported	Kos et al, 2003[62]
FSI	Fatigue Symptom Inventory	14	2	Alphas: 0.93-0.95 Test-retest**:** 0.40-0.75 discriminant validity was supported	Hann et al, 1998[63]; Johnson et al, 2006[64]; Schwartz et al, 1999[57]
FSS	Fatigue Severity Scale	9	86	Alphas: 0.81-0.89 Test-retest: 0.84 discriminant validity was supported	Krupp et al, 1989[65]; Taylor et al, 2000 [66]
WEIMuS	Würzburg Fatigue Inventory in MS	17	3	Alphas: 0.94 Test-retest:0.57-0.66 limited convergent and discriminant validity	Flachenecker and Meissner, 2002[67]; Flachenecker and Meissner, 2007[68]; Flachenecker et al, 2006[69]
MFIS	Modified Fatigue Impact Scale	21	35	Alphas: 0.80-0.95 Test-retest: 0.86 Good construct and discriminant validity	Kos et al, 2005 {5402]; Fischer et al, 1999[52]; Marrie et al, 2003[70]
VAS-F or LFS	Lee Fatigue Scale	18	2	Alphas: 0.94-0.96 discriminant validity was supported	Rammohan et al, 2002[71]; Benito-León et al, 2007[72]
MAF	Multidimensional Assessment of Fatigue	16	2	Alphas:0.93 Test-retest: 0.50-0.063 Limited content validity	Schwartz et al, 1996[73]; Benito-León J et al, 2007[72]
MFI	Multidimensional Fatigue Inventory	20	2	Alphas: 0.66-0.93 Good discriminant validity	Benito-León et al, 2007[72]; Trojan DA et al, 2007[74]

Table 6.4: Items coded to fatigue concept of the ICF

ICF code	No. of items	Items
B130 *Energy and drive function*	19	**FAMS** I have a lack of energy I feel tired I have trouble starting things because I am tired I have trouble finishing things because I am tired I feel motivated to do things I need to rest during the day **HAQUAMS** I am full of energy I have difficulties beginning or finishing things because I am tired I have to rest during the day **LMSQoL** I have had as much energy as usual I have felt tired **MSIS-29** How much have you been bothered by...Feeling mentally fatigued? **MSQLI:MFIS** Because of my fatigue during the past 4 weeks... I am less motivated to do anything that requires physical effort* Because of my fatigue during the past 4 weeks... I am less motivated to engage in social activities Because of my fatigue during the past 4 weeks... I am less motivated to do anything that requires thinking* **QLI-MS** How satisfied are you with: Having enough energy for everyday activities? How important to you is: Having enough energy for every day activities? **MSQLI:SF-36 & MSQoL-54** Did you have a lot of energy? Do you feel full of pep? **FSS** My motivation is lower when I am fatigued*

*items endorsed the code *b1301*, the rest of the items endorsed the code *b1300*

Table 6.4: Items coded to fatigue concept of the ICF (continued)

ICF code	No. of items	Items
B4552 *Fatigability*	21	**FAMS** I feel weak all over **HAQUAMS** What are your main complaints? Fatigue I have difficulties doing sports or running fast **MSQLI:MFIS** Because of my fatigue during the past 4 weeks...I have had to pace myself in my physical activities Because of my fatigue during the past 4 weeks...I am limited to do anything outside my home Because of my fatigue during the past 4 weeks...I have trouble maintaining physical effort for long periods Because of my fatigue during the past 4 weeks...I feel weak Because of my fatigue during the past 4 weeks...I am less able to complete tasks that require physical effort Because of my fatigue during the past 4 weeks...I have to limit my physical activities Because of my fatigue during the past 4 weeks...I require more frequent or longer periods of rest **PS-MS** Compare your current condition to your fatigue level before you developed MS My fatigue symptoms keep me from being employed outside the home **FSS** My motivation is lower when I am fatigued Exercise brings on my fatigue I am easily fatigued Fatigue interferes with my physical functioning Fatigue causes frequent problems for me My fatigue prevents sustained physical functioning Fatigue interferes with carrying out certain duties and responsibilities Fatigue is among my three most disabling symptoms Fatigue interferes with my work, family, or social life

FAMS: Functional Assessment of Multiple Sclerosis; HAQUAMS: Hamburg Quality of Life Questionnaire for Multiple Sclerosis; LEMSQoL: Leeds Multiple Sclerosis QoL; MSIS-29: Multiple Sclerosis Impact Scale; MSQLI-MFIS: Multiple Sclerosis QoL Inventory-Modified Fatigue Impact Scale; QLI-MS: Quality of Life –Index MS Version; MSQLI:SF-36: Multiple Sclerosis QoL Inventory-Health Status Questionnaire; MSQOL-54: Multiple Sclerosis Quality of Life; PS-MS Performance Scales for MS; FSS: Fatigue Severity Scale

Table 6.5: Items coded to other concept of the ICF

ICF code	*ICF category title*	**No. of items**	**Items**
b110	*Consciousness functions*	1	**MSQLI:MFIS** Because of my fatigue during the past 4 weeks...I feel less alert
b134	*Sleep functions*	1	**RAYS** I had difficulties falling a sleep and/or awoke up in the middle of the night and/or awoke un-refreshed
b140	*Attention functions*	2	**MSQLI:MFIS** Because of my fatigue during the past 4 weeks...I have difficulty paying attention for a long period of time Because of my fatigue during the past 4 weeks... I find it hard to concentrate
b144	*Memory functions*	1	Because of my fatigue during the past 4 weeks...I find that I am more forgetful
b160	*Thought functions*	2	Because of my fatigue during the past 4 weeks...I find it difficult to organize my thoughts when I am doing things at home or at work Because of my fatigue during the past 4 weeks...I feel slowed down in my thinking
b280	*Sensation of pain*	1	Because of my fatigue during the past 4 weeks...My physical discomfort is increased
b760	*Control of voluntary movement functions*	2	Because of my fatigue during the past 4 weeks...I am more clumsy and uncoordinated **FSS** Fatigue interferes with my work, family, or social life
d163	*Thinking*	3	**MSQLI:MFIS** Because of my fatigue during the past 4 weeks... I have been unable to think clearly Because of my fatigue during the past 4 weeks...I am less motivated to do anything that requires thinking Because of my fatigue during the past 4 weeks...I am less able to finish tasks that require thinking
d177	*Making decisions*	1	Because of my fatigue during the past 4 weeks...I find it difficult to make decisions
d230	*Carrying out daily routine*	2	**MSIS-29** How much have you been bothered by...Having to cut down the amount of time you spent on work or other daily activities? **FSS** Fatigue interferes with carrying out certain duties and responsibilities

Table 6.5: Items coded to other concept of the ICF (continued)

ICF code	***ICF category title***	**No. of items**	**Items**
d4	*Chapter of Mobility*	2	**FSS** Fatigue interferes with my physical functioning My fatigue prevents sustained physical functioning
d750	*Informal social relationships*	1	Fatigue interferes with carrying out certain duties and responsibilities
d845	*Acquiring, keeping and terminating a job*	1	Fatigue interferes with carrying out certain duties and responsibilities
d920	*Recreation and leisure*	3	**MSQLI:MFIS** Because of my fatigue during the past 4 weeks...I am less motivated to engage in social activities **FSS** Exercise brings on my fatigue **HAQUAMS** I have difficulties doing sports or running fast

FAMS: Functional Assessment of Multiple Sclerosis; HAQUAMS: Hamburg Quality of Life Questionnaire for Multiple Sclerosis; LEMSQoL: Leeds Multiple Sclerosis QoL; MSIS-29: Multiple Sclerosis Impact Scale; MSQLI-MFIS: Multiple Sclerosis QoL Inventory-Modified Fatigue Impact Scale; QLI-MS: Quality of Life –Index MS Version; RAYS: The RYAS Scale; MSQLI:SF-36: Multiple Sclerosis QoL Inventory-Health Status Questionnaire; MSQOL-54: Multiple Sclerosis Quality of Life; FSS: Fatigue Severity Scale

Table 6.6: Items with no endorsed codes

Measure	Items
FAMS	I am forced to spend time in bed
MSIS-29	How much have you been bothered by...Taking longer to do things?
PS-MS	Please rate how much your fatigue symptoms impact your quality of life
RAYS	I felt tired I have stayed in bed during the day
MSQLI:SF-36	I could not complete tasks I started Did you feel worn out? Did you feel tired?
MSQOL-54	Did you feel rested on waking in the morning?

FAMS: Functional Assessment of Multiple Sclerosis; MSIS-29: Multiple Sclerosis Impact Scale; PS-MS: Performance Scale for MS; RAYS: The RYAS Scale; MSQLI:SF-36: Multiple Sclerosis QoL Inventory-Health Status Questionnaire; MSQOL-54: Multiple Sclerosis Quality of Life; FSS: Fatigue Severity Scale

Table 6.7: Response categories and options of items ascertaining fatigue

Measure	Number of fatigue items	Response category Severity	Impact	Response option
MSQLI*	25	4		A
			21	B
FSS[#]	9	2	6	C
FAMS	8	3	5	D
MSQoL-54	5	5		A
HAQUAMS	5	1		E
		1	3	D
RAYS	4	1	3	F
PS-MS	3	1		G
			1	H
			1	I
MSIS-29	3	1	2	J
LMSQoL	2	2		K
QLI-MS	2	2		L/M

[*] Includes MFIS and vitality subscale of the SF-36

[#] 1 additional item on perceived cause of fatigue

A: 6 point Likert Scale; all of the time, most, a good bit, some, a little, none of the time.
B: 5 point likert Scale; never, rarely, sometimes, often, almost always.
C: 7 point Likert Scale: disagree to agree with no additional anchors
D: 5 point likert Scale; not at all, a little bit, some-what, quite a bit, very much.
E: severity with respect to other symptoms rank.
F: 5 point Likret scale: none, mild, moderate, severe, extreme.
G: 6 point Likert Scale; normal fatigue, minimal fatigue disability, mild, moderate, sever, total fatigue disability.
H: yes, no.
I: visual analogue scale; 0= not at all, 100= a great deal.
J: 5 point Likert Scale; not at all, a little, moderately, quite a bit, extremely.
K: 4 point likert scale: not at all, a little, quite a bit, very much.
L: 6 point Likert Scale; very dissatisfied, moderately dissatisfied, slightly dissatisfied, slightly satisfied, moderately satisfied, very satisfied.
M: 6 point Likert Scale; very unimportant, moderately unimportant, slightly unimportant, slightly important, moderately important, very important.

Table 6.8: Response options of items ascertaining fatigue

	Unit	**Scale range**					
A	time	none of the time	a little of the time	some of the time	a good bit of the time	most of the time	all of the time
B	time	never	rarely	sometimes	often	almost always	
C	Level of impairment	disagree					agree
D	Level of impairment (how true)	not at all	a little bit	some-what	quite a bit	very much	
E	Rank severity	1	2	3			
F	Level of impairment	none		mild	moderate	severe	extreme
G	comparison	normal fatigue	minimal fatigue disability	mild fatigue disability	moderate fatigue disability	severe fatigue disability	total fatigue disability
H	Presence of impairment	yes					no
I	impact	0= not at all					100= great deal
J	Level of impairment & comparison	not at all	a little		moderately	quite a bit	extremely
K	Level of impairment (impact)	not at all	a little		quite a bit	very much	
L	satisfaction	very dissatisfied	moderately dissatisfied	slightly dissatisfied	slightly satisfied	moderately satisfied	very satisfied
M	importance	very unimportant	moderately unimportant	slightly unimportant	slightly important	moderately important	very important

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CHAPTER 7

Summary and Conclusion

There is an increased interest in multiple sclerosis (MS) because MS is facing a new era where the possibility of detecting the onset of this condition early is increasing due to the introduction of the neuroimaging techniques [19]. In addition, the approval of disease modifying therapies had also played a role in enhancing the management of this condition [20]. MS is facing an increased prevalence in many regions around the world [8]; affecting mainly the young population [9]. The devastating effect of MS on functioning and well being is well documented in the literature [25, 28, 29]. MS was found to considerably reduce quality of life (QOL) of persons more than that of other chronic conditions [30]. Thus all of these factors make MS a hot spot for the research community. Researchers and clinicians are very interested in trying to reduce the effect of MS on health-related quality of life (HRQL), and many interventions are including HRQL as their main outcome.

To be able to produce an effect on HRQL, this construct needs to be measured accurately. Evaluation of pharmaceutical and rehabilitative interventions for MS depends on careful assessment of HRQL [32]. Many measures of HRQL are available for the MS population [73]. These measures have undergone psychometric testing, but there is still a question remaining as to which of these measures is best suited for different research purposes. As HRQL is a multidimensional construct, its measurement should cover all of its domains and components. Measures of HRQL should go beyond measuring symptoms and functioning and capture other components of HRQL that are related to general health perception and well being.

The use of the Wilson-Cleary model allows the identification of the different components of HRQL. In addition, the approval of the ICF by the WHO, permits the classification and coding of functioning, disability and health using a universal, well defined and standard frame of reference.

The objective of this study was to perform in depth content comparisons across the most commonly used HRQL measures in the MS population. Heterogeneity of ascertaining symptoms, functioning and general health perception across the selected measures was explored. In this study items of 10 commonly used HRQL measures were coded to the ICF using a standardized procedure. The majority of items were linked to the ICF. Measures differed in the degree of capturing the different components of HRQL. In general, most of the measures captured symptoms to a greater extent than functioning and general health perception.

Moreover, the different approaches of ascertaining a single symptom, fatigue, which is one of the most predominate symptoms of MS, was explored. The second objective of our study aimed at finding sources of heterogeneity of measuring fatigue across the most commonly used HRQL and fatigue indices. Results of that study showed that measurement of fatigue was challenging. Measures and indices differed in the wording of items and in the construct measured, i.e. severity versus impact. Indices also differ in the response options and unit of references. Many issues were brought up when attempting to measure fatigue. Issues were related to having items that reflect patients' perspectives, that are clear, unambiguous, and account for response shift. Different methods were suggested to produce a "true" fatigue measure, including cognitive debriefing and use of modern psychometrics such as Item Response Theory or Rasch modeling.

As with any study, there were limitations to this project. The literature review that was conducted followed structured rather than systematic approaches. A third Delphi round would have been beneficial as it could have resulted in the endorsement of more items. The number of raters was less than what was suggested in the ICF mapping protocol, for some of the items. In addition, the last two steps of the mapping protocol, namely cognitive debriefing and validation of endorsed codes, are yet to be completed in future studies.

Over all, this project provided a comprehensive review and content analysis of the most commonly used HRQL measures in the MS population. Findings were compared to the ICF core set of MS [79] to further assist clinicians and researchers when selecting the most suitable measures for their specific purposes. Results will also facilitate the integration of functional and HRQL outcomes in the electronic health records and will in turn enhance comparisons of health status across different studies, conditions, populations and medical services.

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Appendices
Recruitment Letter

Dear health professionals,
I am carrying out my Master's degree in Rehabilitation Science at McGill University with Dr. Nancy Mayo. This is a recruitment letter to invite to participate in our study.

We are studying the health related quality of life (HRQL) measures of patients with multiple sclerosis. We are estimating the extent to which the content of these measures go beyond symptoms and function and cover other domains related to HRQL, using the International Classification of Functioning, Disability and Health (ICF) as a frame of reference.

This project will help in providing a framework for content validation of HRQL measures. Moreover, the project will facilitate the selection of measures that will be appropriate for measuring the effectiveness of new interventions aiming at improving HRQL in persons with MS. Finally, this research will facilitate the integration of HRQL measures into Electronic Health Records system, which is a very efficient resource for obtaining information about the population health and health services.

The process of content validation of those measures will involve mapping the items of those measures to the ICF. There are mapping rules that were developed to allow raters to code items in a standardized way.

We truly appreciate if you would participate in our study by mapping items to the ICF.
Upon your agreement to participate, we will send you a training package that involves self-explanatory instructions of the ICF framework and its mapping procedure, in addition to the mapping rules that will assist you in this process.

It is acknowledged that there will be a large number of items to be coded to the ICF. However, those items will be grouped together into common domains. Many of the items differ only in wording, and will most likely map to the same code or not map at all. We will also offer incentive (a 30$ gift card from Amazon) for completing this exercise before a specific date.

We would appreciate it if you could provide us with contact information of any colleague that you feel might be interested in mapping. We would like to expand our mapping team.

Have a nice day

Sincerely,
Alaa Arafah, M.Sc. candidate
School of Physical and Occupational Therapy
McGill University,
Montreal, QC
Canada

Appendix Tables A1 to A19

Items from all measures and corresponding codes

Table A1.a: Items of the MSQOL-54 measure and corresponding codes

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Items endorsed at 4 digit level		
How much of the time during the past 4 weeks…		
Were you discouraged by your health problem?	b1522 *(100%)*	b152 *(100%)*
Were you frustrated about your health?	b1522 *(100%)*	b152 *(100%)*
Was your health a worry in your life?	b1522 *(100%)*	b152 *(100%)*
Did you feel weighted down by your health problems?†	b1522 *(89%)*	b152 *(100%)*
Did you have trouble keeping your attention on an activity for long?*	b1400 *(82%)*	b140 *(100%)*
How much of a problem was each of the following for you during the past 4 weeks?		
Lack sexual interest*	b6400 *(70%)*	b640 *(90%)*
Difficulty getting or keeping an erection	b6401 *(100%)*	b640 *(100%)*
Difficulty having orgasm*	b6402 *(80%)*	b640 *(100%)*
Ability to satisfy sexual partner†	d7702 *(89%)*	d770 *(89%)*
Inadequate lubrication	b6401 *(100%)*	b640 *(100%)*
To what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbors, or groups?	d9205 *(100%)*	d920 *(100%)*
Does your health limit you in doing vigorous activities (running, lifting heavy objects, participating in strenuous sports)?†	d9201 *(94%)*	d920 *(94%)*
Does your health limit you in climbing several flights of stairs?*	d4551 *(82%)*	d455 *(88%)*
Does your health now limit you in walking more than a kilometer?*	d4551 *(88%)*	d455 *(88%)*

Table A1.a: Continued

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Does your health now limit you in walking several blocks?*	d4500 *(75%)*	d450 *(100%)*
Does your health now limit you in walking one block?†	d4500 *(88%)*	d450 *(88%)*
How much of the time did you feel full of pep?†	b1300 *(81%)*	b130 *(94%)*
How much of the time did you have a lot of energy?*	b1300 *(76%)*	b130 *(88%)*
How much of the time has your physical or emotional health interfere with social activities?†	d9205 *(88%)*	d920 *(88%)*
<u>Items endorsed only at 3 digit level</u>		
How much of the time during the past 4 weeks…		
Have you had difficulty concentrating and thinking?		b140 *(90%)*
Have you had trouble with you memory?†		b144 *(100%)*
How much of the time during the past 4 weeks…Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?		b144 *(90%)* b140 *(70%)*
Overall, how satisfied were you with your sexual function during the past 4 weeks?†		b640 *(100%)*
During the past 4 weeks, how much did pain interfere with your enjoyment of life?		b280 *(100%)*
Does your health limit you in doing moderate activities (moving a table, pushing a vacuum, bowling, play golf)?†		d640 *(75%)*
Does your health limit you in lifting or carrying groceries?*		d430 *(81%)*
Does your health now limit you in bending, kneeling, or stooping?		d410 *(75%)*

Table A1.a: Continued

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
How much bodily pain have you had?*		b280 *(100%)*
How much did bodily pain interfere with your normal work due to pain?*		b280 *(100%)*
How much of the time did you feel very nervous? *		b152 *(100%)*
How much of the time did you feel calm and peaceful?		b126 *(88%)*

*Items endorsed in initial round

†Items endorsed in first round of Delphi consensus

Table A1.b: Items of the MSQOL-54 **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
Items endorsed at lower level	
Overall, how would you rate your own Quality of life?	nd-qol *(100%)*
Which best describes how you feel about your life as a whole?	nd-qol *(100%)*
In general, would you say your health is:	nc *(88%)*
Compared to one year ago, how would you rate your health now?	nc *(88%)*
To what extent has your physical health or emotional problems interfered with your normal social activities with family, friends?	nc *(75%)*
Do you seem to get sick easier than other people?	nc *(82%)*
Are you as healthy as anybody you know?	nc *(82%)*
Do you expect you health to get worse?	nc *(82%)*
Do you feel that your health is excellent?	nc *(82%)*
Items with no endorsed codes	
Did you feel rested on waking in the morning?	
Does your health now limit you in bathing or dressing yourself?	
Have you had any problems with work or other activities as a result of your physical health?	
Have you had any problems with work or other activities as a result of your emotional problems?	
How much of the time did you feel so down in the dumps that nothing could cheer you up?	
How much of time did you feel downhearted and blue?	
How much of time did you feel worn out?	
How much of time have you been a happy person?	
How much of time did you feel tired?	

nd-qol: not definable-quality of life; nc: not covered by ICF

Table A2.a: Items of the HAQUAMS measure and corresponding codes

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Items endorsed at 4 digit level		
What are your main complaints? Bladder Control	b6202 *(100%)*	b620 *(100%)*
What are your main complaints? Fatigue[*]	b4552 *(78%)*	b455 *(78%)*
Please indicate how true each statement has been for you during the past 7 days…		
I have to rest during the day	b1300 *(100%)*	b130 *(100%)*
I have difficulties doing sports or running fast[*]	d4552 *(100%)* d9210 *(78%)*	d455 *(100%)* d921 *(78%)*
I have difficulties standing[*]	d4104 *(78%)*	d410 *(78%)*
I have trouble cleaning my home[†]	d6402 *(100%)*	d640 *(100%)*
I have problems dressing and undressing	d5400 *(88%)* d5401 *(88%)*	d540 *(100%)*
I have trouble controlling my bladder[†]	b6202 *(75%)*	b620 *(100%)*
I have trouble controlling my bowels[*]	b5253 *(100%)*	b525 *(78%)*
I feel distance from my friends and family	d7500 *(89%)*	d750 *(89%)*
My condition impairs my relationships with others (friends, family)[†]	d7500 *(78%)*	d750 *(78%)*
I am losing hope about the fight against my illness[*]	b1265 *(82%)*	b126 *(82%)*
I can enjoy life[†]	b1265 *(78%)*	b126 *(78%)*
I am full of energy[*]	b1300 *(78%)*	b130 *(89%)*
Items endorsed only at 3 digit level		
What are your main complaints?...		
Difficulties in walking[†]		d450 *(100%)*

Table A2.a: Continued

Items	4 digit level *(% agreement)*	3 digit level *(% agreement)*
What are your main complaints?...		
Pain†		b280 *(100%)*
Coordination difficulties†		b760 *(100%)*
Blurred/Double vision		b210 *(100%)*
Spasticity†		b735 *(100%)*
Difficulties concentrating		b140 *(100%)*
Dad mood		b152 *(70%)*
Loneliness†		b152 *(90%)*
Please indicate how true each statement has been for you during the past 7 days…		
I have pain†		b280 *(100%)*
I have difficulties beginning or finishing things because I am tired		b130 *(100%)*
I have difficulties remembering things†		b144 *(100%)*
I have disturbed vision while watching TV or reading		b210 *(100%)*
I have trouble getting around in public places†		d470 *(75%)*
I have trouble walking around at home†		d450 *(100%)*
I can walk†		d450 *(100%)*
I have difficulties writing†		d170 *(100%)*
I have difficulties preparing a meal†		d630 *(100%)*
I have difficulties eating†		d550 *(100%)*
I am satisfied with my sex life†		b640 *(89%)*
I get support from friends or nieghbours†		e325 *(89%)*
I get support from my family†		e310 *(100%)*

Table A2.a: Continued

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Please indicate how true each statement has been for you during the past 7 days…		
Communication about my illness is poor with my family[†]		d760 *(100%)*
I feel separated[†]		b152 *(80%)*
I am scared because of my condition		b152 *(90%)*
I am depressed about my condition		b152 *(70%)*
I feel useless		b152 *(70%)*

[*] Items endorsed in initial round
[†] Items endorsed in first round of Delphi consensus

Table A2.b: Items of the HAQUMS **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
<u>Items endorsed at lower level</u>	
Compared to one year ago, how would you rate your health in general now?	nd-gh *(89%)*
Compared to 4 weeks ago, how would you rate your health in general?	nd-gh *(89%)*
What are your main complaints? Sensory disturbances	b2 *(100%)*
Please indicate how true each statement has been for you during the past 7 days…	
Disturbed sensation affected me	b2 *(100%)*
I have difficulties learning new things	d1 *(70%)*
I am content with my quality of life	nd-qol *(100%)*
I feel a sense of purpose in my life	pf *(89%)*
How far does MS affect your ability to live a normal life?	nd-qol *(89%)*

nd-gh: not definable-general health; b2: chapter of sensory function and pain; d1: chapter of learning and applying knowledge; nd-qol: not definable-quality of life; pf: personal factors

Table A3.a: Items of the PS-MS measure and corresponding codes

Items	4 digit level *(% agreement)*	3 digit level *(% agreement)*
<u>Items endorsed at 4 digit level</u>		
Compare your current condition to your fatigue level before you developed MS[†]	b4552 *(75%)*	b455 *(75%)*
My fatigue symptoms keep me from being employed outside the home	b4552 *(75%)*	b455 *(75%)*
<u>Items endorsed only at 3 digit level</u>		
My mobility symptoms keep me from being employed outside the home		d850 *(100%)* d4 *(75%)*
Compare your current condition to your hand function before you developed MS[†]		d445 *(100%)*
My hand function symptoms keep me from being employed outside the home[†]		d445 *(88%)* d850 *(75%)*
Compare your current condition to your vision before you developed MS[†]		b210 *(100%)*
My visual symptoms keep me from being employed outside the home		b210 *(100%)* d850 *(75%)*
Please rate how much your visual symptoms impact your quality of life		b210 *(78%)* nd-qol *(78%)*
My cognitive symptoms keep me from being employed outside the home		d850 *(88%)* b117 *(88%)*
Please rate how much your cognitive symptoms impact your quality of life		b164 *(78%)* nd-qol *(78%)*
Compare your current condition to your bladder/bowel function before you developed MS[†]		b620 *(88%)* b525 *(75%)*
My bladder/bowel symptoms keep me from being employed outside the home		b525 *(100%)* b620 *(100%)* d850 *(100%)*
Please rate how much your bladder/bowel symptoms impact your quality of life		b620 *(100%)* nd-qol *(78%)*

Table A3.a: Continued

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
My sensory symptoms keep me from being employed outside the home		d850 *(88%)* b2 *(100%)*
Compare your current condition to your level of spasticity function before you developed MS[†]		b735 *(100%)*
My spasticity symptoms keep me from being employed outside the home		b735 *(100%)* d850 *(75%)*
Please rate how much your spasticity symptoms impact your quality of life		b735 *(100%)* nd-qol *(78%)*

[*] No items endorsed in initial round
[†] Items endorsed in first round of Delphi consensus

Table A3.b: Items of the PS-MS **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
<u>**Items endorsed at lower level**</u>	
Compare your current condition to your mobility before you developed MS	d4 *(100%)*
Please rate how much your mobility symptoms impact your quality of life	nd-qol *(78%)*
Please rate how much your hand function symptoms impact your quality of life	nd-qol *(78%)*
Please rate how much your fatigue symptoms impact your quality of life	nd-qol *(89%)*
Compare your current condition to your level of cognition before you developed MS	b1 *(90%)*
Compare your current condition to your level of sensory function before you developed MS	b2 *(100%)*
Please rate how much your sensory symptoms impact your quality of life	b2 *(78%)* nd-qol *(78%)*
Date of Birth	pf *(100%)*
Gender	pf *(100%)*
<u>**Items with no endorsed codes**</u>	
Please circle the highest level of education you received	

d4: chapter of mobility; nd-qol: not definable- quality of life; b1: chapter of mental functions; b2: chapter of sensory functions and pain; pf: personal factors

Table A4.a: Items of the FAMS measure and corresponding codes

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Items endorsed at 4 digit level		
Please indicate how true each statement has been for you during the past 7 days…		
I have to limit my social activity because of my condition[*]	d9205 *(70%)*	d920 *(70%)*
I have strength in my legs[†]	b7303 *(88%)*	b730 *(100%)*
I have nausea[*]	b5350 *(81%)*	b535 *(81%)*
I feel weak all over	b4552 *(75%)*	b455 *(75%)*
I have pain in my joints[*]	b28016 *(72%)*	b280 *(100%)*
I am bothered by headaches[*]	b28010 *(72%)*	b280 *(100%)*
I am losing hope in the fight against my illness[*]	b1265 *(91%)*	b126 (91%)
I am able to enjoy life	b1265 *(100%)*	b126 *(100%)*
I feel motivated to do things[*]	b1301 *(91%)*	b130 (82%)
I have a lack of energy[*]	b1300 *(78%)*	b130 *(89%)*
I feel tired[†]	b1300 *(75%)*	b130 *(75%)*
I have trouble starting things because I am tired	b1300 *(88%)*	b130 *(88%)*
I have trouble finishing things because I am tired	b1300 *(100%)*	b130 *(100%)*
I need to rest during the day	b1300 *(100%)*	b130 *(100%)*
I have trouble concentrating[*]	b1400 *(70%)*	b140 *(100%)*
My thinking is slower than before[*]	b1600 *(90%)*	b160 *(100%)*
I am satisfied with my sex life	d7702 *(89%)*	d770 *(89%)*
I feel nervous[*]	b1522 *(70%)*	b152 *(90%)*
I worry that my condition will get worse	b1522 *(78%)*	b152 *(89%)*
I am sleeping well	b1343 *(75%)*	b134 *(100%)*
Heat worsens my symptoms[*]	e2250 *(78%)*	e225 *(78%)*

Table A4.a: Continued

Items	4 digit level *(% agreement)*	3 digit level *(% agreement)*
I have trouble controlling my urine†	b6202 *(88%)*	b620 *(100%)*
Urinate more frequently than usual*	b6201 *(78%)*	b620 *(89%)*
I am bothered by muscle spasms	b7801 *(100%)*	b780 *(100%)*
<u>Items endorsed only at 3 digit level</u>		
Because of my physical condition, I have trouble meeting the needs of my family†		d660 *(100%)*
I am able to work†		d850 *(75%)*
I have trouble walking†		d450 *(100%)*
I have trouble getting around in public places†		d470 *(75%)*
I have pain†		b280 *(100%)*
I am bothered by muscle pains†		b280 *(90%)*
I feel sad†		b152 *(100%)*
I feel useless		b152 *(70%)*
I feel overwhelmed by my condition		b152 *(100%)*
My work (include work at home) is fulfilling		d850 *(88%)*
I am enjoying the things I usually do for fun		b152 *(90%)* d920 *(70%)*
I am frustrated by my condition†		b152 *(100%)*
I have trouble remembering things†		b144 *(100%)*
I have trouble learning new tasks or directions†		d155 *(80%)*
I get emotional support from my family†		e310 *(100%)*
I get support from my friends†		e320 *(100%)*
My family has accepted my illness		e410 *(89%)*
I feel "left out" of things		b152 *(70%)*

Table A4.a: Continued

Items	4 digit level *(% agreement)*	3 digit level *(% agreement)*
I am satisfied with family communication about my illness		d760 *(100%)*
My family has trouble understanding when my condition gets worse[†]		e410 *(89%)*
I feel close to my partner (or the person who is my main support)[†]		d770 *(89%)*
I am satisfied with how I'm coping with my illness		d240 *(100%)*

[*] Items endorsed in initial round
[†] Items endorsed in first round of Delphi consensus

Table A4.b: Items of the FAMS **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
Items endorsed at lower level	
Please indicate how true each statement has been for you during the past 7 days…	
I feel trapped by my condition	nc *(90%)*
I have accepted my illness	pf *(89%)*
I am content with the quality of my life right now	nd-qol *(89%)*
I feel a sense of purpose in my life	pf *(78%)*
I am bothered by side effects of treatment	nc *(70%)*
I am bothered by the chills	nc *(80%)*
I am bothered by fevers	nc *(70%)*
Items with no endorsed codes	
I have to take my condition into account when making plans	
I feel ill	
I feel depressed about my condition	
I feel close to my friends	
I am forced to spend time in bed	

nc: not covered by ICF; pf: personal factors; nd-qol : non definable-quality of life

Table A5: Items of the LMSQoL measure and corresponding codes

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Items endorsed at 4 digit level		
I have felt good about my appearance	b1266 *(89%)*	b126 *(89%)*
I have felt worried about my health	b1522 *(100%)*	b152 *(100%)*
I have had as much energy as usual*	b1300 *(78%)*	b130 *(89%)*
I have felt tired†	b1300 *(75%)*	b130 *(75%)*
I have felt happy about the future	b1265 *(78%)*	b126 *(78%)*
Items endorsed only at 3 digit level		
My health has affected my relationships with my family†		d760 *(100%)*
I have felt lonely†		b152 *(90%)*
I have worried about other people's attitudes towards me		b152 *(78%)*

*Items endorsed in initial round
†Items endorsed in first round of Delphi consensus

Table A6.a: Items of the MSIS-29 measure and corresponding codes

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Items endorsed at 4 digit level		
In the past two weeks, how much have you have been bothered by…		
Difficulties moving about indoors?[†]	d4500 *(75%)*	d450 *(75%)*
Stiffness?[*]	b7800 *(73%)*	b780 *(82%)*
Tremor of your arms or legs?[*]	b7651 *(90%)*	b765 *(90%)*
Spasms in your limbs?[*]	b7801 *(70%)*	b780 *(70%)*
Having to depend on others to do things for you?	d2102 *(90%)*	d210 *(90%)*
Needing to go to the toilet urgently?[†]	b6202 *(88%)*	b620 *(88%)*
Feeling unwell?	b1522 *(100%)*	b152 *(100%)*
Feeling irritable, impatient, or short tempered?[*]	b1263 *(90%)*	b126 *(90%)*
Problems concentrating?[*]	b1400 *(70%)*	b140 *(100%)*
Lack of confidence?[*]	b1266 *(100%)*	b126 *(100%)*
Items endorsed only at 3 digit level		
In the past two weeks, how much have you have been bothered by…		
Being clumsy?		b760 *(100%)*
Heavy arms and/or legs?[†]		b780 *(80%)*
Limitations in your social and leisure activities at home?		d920 *(100%)*
Difficulties using your hands in everyday tasks?[†]		d445 *(88%)*
Having to cut down the amount of time you spent on work or other daily activities?[†]		d230 *(100%)*
Problems using transport (e.g. car, bus, train, taxi, etc.)?[†]		d470 *(88%)*
Problems sleeping?[†]		b134 *(88%)*

Table A6.a: Continue

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Worries related to your MS?		b152 *(100%)*
Feeling mentally fatigued?		b130 *(90%)*
Feeling anxious or tense?[†]		b152 *(100%)*
Feeling depressed?[†]		b152 *(100%)*
How much has your MS limited your ability to...Grip things tightly (e.g. turning on taps)?[†]		d440 *(100%)*
How much has your MS limited your ability to...Carry things?[†]		d430 *(100%)*

[*] Items endorsed in initial round
[†] Items endorsed in first round of Delphi consensus

Table A6.b: Items of the MSIS-29 **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
<u>Items endorsed at lower level</u>	
In the past two weeks, how much have you have been bothered by…	
Being stuck at home more than you would like to be?	nc *(75%)*
Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	nc *(70%)*
<u>Items with no endorsed codes</u>	
In the past two weeks, how much have you have been bothered by…	
Problems with your balance?	
Your body not doing what you want it to do?	
Taking longer to do things?	
How much has your MS limited your ability to...Do physically demanding tasks?	

nc: not covered by ICF

Table A7.a: Items of the RAYS measure and corresponding codes

Items	4 digit level *(% agreement)*	3 digit level *(% agreement)*
<u>Items endorsed at 4 digit level</u>		
I found it difficult to lift objects, bend, walk up stairs[*]	d4105 *(100%)* d4300 *(78%)* d4551 *(78%)*	d410 *(100%)* d430 *(100%)* d455 *(78%)*
Difficulty in bladder control limited my activities	b6202 *(88%)*	b620 *(88%)*
I suffered blurred or double vision	b2102 *(100%)*	b210 *(100%)*
I felt tired[†]	b1300 *(75%)*	b130 *(75%)*
Worm weather exacerbated my condition[*]	e2250 *(78%)*	e225 *(89%)*
I laughed or cried suddenly for no reasons[*]	b1520 *(90%)*	b152 *(100%)*
I spoke hopelessly of the future[*]	b1265 *(90%)*	b1265 *(90%)*
I reacted slowly to things said or done around me[*]	b1470 *(80%)*	b147 *(80%)*
I found it difficult to solve problems, make decisions, plan or learn mew information	b1646 *(70%)*	b164 *(70%)* d177 *(100%)*
I had difficulties falling a sleep and/or awoke up in the middle of the night and/or awoke un-refreshed[†]	b1343 *(75%)*	b134 *(100%)*
I did not enjoy activities that once brought me pleasure[†]	b1522 *(78%)*	b152 *(89%)*
I felt changes in my appearance make me unattractive	b1266 *(89%)*	b126 *(89%)*
I went out socially[*]	d9205 *(80%)*	d920 *(80%)*
I participated in social gathering[†]	d9205 *(89%)*	d920 *(89%)*
My sexual activities declined	d7702 *(89%)*	d770 *(89%)*
I was demanding, irritable and short-tempered to those around me	b1263 *(100%)*	b126 *(100%)*

Table A7.a: Continued

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
<u>Items endorsed only at 3 digit level</u>		
My driving is limited		d475 *(100%)*
My walking is limited[†]		d450 *(100%)*
I suffered pain or was uncomfortable[†]		b280 *(100%)*
I needed help to get up from a chair, get into a car, get out of bed[†]		d410 *(100%)*
I was unstable when walking[†]		d450 *(100%)*
I had difficulties with fine coordination of my hands (e.g. writing, buttoning, lacing my shoes)[†]		d440 *(100%)*
I suffered from muscle cramps or rigidity[†]		b735 *(90%)*
Due to speech or voice difficulties other found it hard to understand me[†]		b330 *(100%)*
I blamed or cursed myself[†]		b152 *(90%)*
I was afraid/frightened of what the near future holds for me		b152 *(100%)*
I had difficulties remembering details[*]		b144 *(100%)*
I devoted time and effort to grooming and personal appearance[†]		d520 *(100%)*
I felt sad or depressed		b152 *(100%)*
Physical problems occupied or bothered me		b152 *(100%)*
I worked /was employed		d850 *(100%)*
I took part in household chores[†]		d640 *(100%)*
I took part in leisure activities and hobbies		d920 *(100%)*
I used public transportation		d470 *(100%)*

Table A7.a: Continued

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
I took part in managing family and personal duties		d230 *(88%)*
I engaged in family and social conversation		d350 *(89%)*
I felt lonely[†]		b152 *(90%)*
I received emotional support from my family, friends, caretakers[†]		e320 *(89%)*
I was coping with my illness		d240 *(78%)*
My treating physicians was available to answer my needs[†]		e355 *(100%)*
I spoke with my family/friends about my illness[†]		d330 *(100%)*

[*] Items endorsed in initial round

[†] Items endorsed in first round of Delphi consensus

Table A7.b: Items of the RAYS **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
Items endorsed at lower level	
I had ‘accidents’ such as: dropping objects, falls, bumping into things	nc *(70%)*
I am burden to others	nc *(70%)*
I was satisfied with my achievements	nc *(89%)*
Generally I was satisfied with my quality of life	nd-qol *(89%)*
I felt my illness makes me disabled	nc *(89%)*
Items with no endorsed codes	
I have stayed in bed during the day	
I could not complete tasks started	
I listened to the news, read a newspaper, watched television	
I suffered/was bothered by the side-effects of my treatment/medications	

nc: not covered by ICF; nd-qol: not definable-quality of life

Table A8.a: Items of the QLI-MS measure and corresponding codes

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Items endorsed at 4 digit level		
How satisfied are you with: Your health care?	e5800 *(89%)*	e580 *(89%)*
How important to you is: Your health care?†	e5800 *(78%)*	e580 *(78%)*
How satisfied are you with: Having enough energy for everyday activities?†	b1300 *(100%)*	b130 *(100%)*
How important to you is: Having enough energy for every day activities?†	b1300 *(88%)*	b130 *(88%)*
How satisfied are you with: Your children?†	d7600 *(100%)*	d760 *(100%)*
How important to you is: Your children?†	d7600 *(100%)*	d760 *(100%)*
How satisfied are you with: Your sex life?	d7702 *(89%)*	d770 *(89%)*
How important to you is: Your sex life?†	d7702 *(78%)*	d770 *(78%)*
How satisfied are you with: The emotional support you get from people other than your family?	d7101 *(89%)*	d710 *(89%)*
How satisfied are you with: Your ability to take care of family responsibilities?	d2400 *(78%)*	d240 *(78%)*
How important to you is: Taking care of family responsibilities?	d2400 *(89%)*	d240 *(89%)*
How important to you is: Having a job (if unemployed, retired, or disabled)?	d8451 *(75%)*	d845 *(88%)*
How satisfied are you with: Your personal appearance?†	b1266 *(89%)*	b126 *(89%)*
Items endorsed only at 3 digit level		
How satisfied are you with: The amount of pain that you have?†		b280 *(100%)*
How important to you is: Having no pain?†		b280 *(70%)*
How satisfied are you with: Your ability to get around, go places?†		d460 *(100%)*

Table A8.a: Continued

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
How important to you is: Your ability to get around, go places?†		d460 *(88%)*
How satisfied are you with: Your ability to speak?		b330 *(80%)*
How important to you is: Your ability to speak?		b330 *(70%)*
How satisfied are you with: Your family's happiness?†		d760 *(100%)*
How important to you is: Your family's happiness?†		d760 *(100%)*
How satisfied are you with: Your spouse, lover, or partner?†		d770 *(100%)*
How important to you is: Your spouse, lover, or partner?†		d770 *(100%)*
How satisfied are you with: Your friends?†		e320 *(89%)*
How important to you is: Your friends?†		e320 *(89%)*
How satisfied are you with: The emotional support you get from your family?†		e310 *(100%)*
How important to you is: The emotional support you get from your family?†		e310 *(100%)*
How important to you is: The emotional support you get from people other than your family?		e325 *(100%)*
How satisfied are you with: How useful you are to others?†		d660 *(78%)*
How important to you is: Being useful to others?†		d660 *(89%)*
How satisfied are you with: The amount of worries in your life?†		b152 *(90%)*
How important to you is: Having no worries?		b152 *(70%)*
How satisfied are you with: Your neighborhood?†		e325 *(78%)*
How important to you is: Your neighborhood?†		e325 *(78%)*

Table A8.a: Continued

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
How satisfied are you with: Your job (if employed)?[†]		d850 *(88%)*
How satisfied are you with: Not having a job (if unemployed, retired, or disabled)?		d845 *(88%)*
How satisfied are you with: Your education?		d820 *(78%)*
How important to you is: Your education?		d820 *(78%)*
How satisfied are you with: How well you can take care of your financial needs?		d870 *(100%)*
How important to you is: Being able to take care of your financial needs?		d870 *(88%)*
How satisfied are you with: The things you do for fun?[†]		d920 *(100%)*
How important to you is: Doing things for fun?[†]		d920 *(88%)*
How satisfied are you with: Your peace of mind?		b152 *(80%)*
How satisfied are you with: Your faith in God?		d930 *(78%)*
How important to you is: Your faith in God?		d930 *(78%)*
How satisfied are you with: Your happiness in general?		b152 *(78%)*
How important to you is: Your happiness in general?[†]		b152 *(78%)*

[*] No items endorsed in initial round

[†] Items endorsed in first round of Delphi consensus

Table A8.b: Items of the QLI-MS **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
Items endorsed at lower level	
How satisfied are you with:Your health?	nd-gh *(89%)*
How important to you is: Your health?	nd-gh *(100%)*
How satisfied are you with: Your ability to take care of yourself without help?	d5 *(100%)*
How important to you is: Taking care of your self without help?	d5 *(88%)*
How satisfied are you with: The amount of control you have over your life?	nc *(80%)*
How important to you is: The amount of control you have over your life?	nc *(70%)*
How satisfied are you with: Your chances of living as long as you would like?	nc *(89%)*
How important to you is: Your chances of living as long as you would like?	nc *(89%)*
How satisfied are you with: Your family's health?	nd-gh *(78%)*
How important to you is: Your family's health?	nd-gh *(78%)*
How satisfied are you with: Your home, apartment, or place where you live?	nc *(88%)*
How important to you is: Your home, apartment, or place where you live?	nc *(88%)*
How important to you is: Having a happy future?	nc *(78%)*
How satisfied are you with: Your achievement of personal goals?	nc *(70%)*
How important to you is: Your achievement of personal goals?	nc *(70%)*
How satisfied are you with: Your life in general?	nd-qol *(100%)*
How important to you is: Being satisfied with life?	nd-qol *(100%)*

Table A8.b: Continued

Items	**Lower level codes** ***(% agreement)***
How satisfied are you with: Yourself in general?	pf *(89%)*
How important to you is: Are you to yourself?	pf *(89%)*
Items with no endorsed codes	
How important to you is: Your job (if employed)?	
How satisfied are you with: Your chances for a happy future?	
How important to you is: Peace of mind?	
How important to you is: Your personal appearance?	

nd-gh: not definable-general health; d5: chapter of self-care; nc: not covered by ICF; nd-qol: not definable-quality of life; pf: personal factors

Table A9.a: Items of the DIP measure and corresponding codes

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Items endorsed at 4 digit level		
Do you have worries about deterioration of your health?[†]	b1522 *(78%)*	b152 *(89%)*
How important to you is it that you sleep well?	b1343 *(75%)*	b134 *(88%)*
Can you stand up and sit down?[*]	d4103 *(78%)* d4104 *(89%)*	d410 *(100%)*
How important to you is it that you are able to stand up and sit down easily?	d4104 *(88%)*	d410 *(100%)*
Can you stand?[*]	d4104 *(88%)*	d410 *(88%)*
How important to you is it that you are able to stand easily?[*]	d4104 *(78%)*	d410 *(78%)*
Can you use the stairs?[*]	d4551 *(100%)*	d455 *(100%)*
How important to you is it that you are able to use the stairs easily?[*]	d4551 *(78%)*	d455 *(78%)*
Can you reach up high?[*]	d4452 *(90%)*	d445 *(90%)*
How important to you is it that you are able to reach up high easily?[†]	d4452 *(78%)*	d445 *(88%)*
Can you lift things?[*]	d4300 *(90%)*	d430 *(90%)*
How important to you is it that you are able to lift things easily?[†]	d4300 *(88%)*	d430 *(88%)*
Can you dress and undress yourself?	d5400 *(88%)* d5401 *(88%)*	d540 *(100%)*
How important to you is it that you are able to dress and undress yourself easily?	d5400 *(88%)* d5401 *(88%)*	d540 *(100%)*
Can you control your bladder?	b6202 *(88%)*	b620 *(100%)*
Can you control your bowel function?[†]	b5253 *(88%)*	b525 *(100%)*
How important to you is it that you are able to have full control of your bowel function?	b5253 *(88%)*	b525 *(88%)*

Table A9.a: Continued

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Are you capable of cleaning your own home?	d6402 *(100%)*	d640 *(100%)*
How important to you is it that you are able to clean your own home easily?	d6402 *(88%)*	d640 *(88%)*
How important to you is it that you have good relations with relatives and friends?	d7500 *(100%)*	d750 *(100%)*
How is your financial situation?	e1650 *(88%)*	e165 *(88%)*
How important is money to you?†	e1650 *(88%)*	e165 *(88%)*
Can you determine your own day-program?	b1641 *(70%)*	b164 *(70%)*
<u>Items endorsed only at 3 digit level</u>		
Do you have much pain?†		b280 *(100%)*
How important to you is it to have little or no pain?†		b280 *(80%)*
How important to you is it that you don't have to worry about your health?		b152 *(89%)*
How do you sleep?		b134 *(100%)*
Can you get in and out bed by yourself?		d410 *(100%)*
How important to you is it that you can get in and out bed easily?		d410 *(88%)*
Can you walk?†		d450 *(100%)*
How important to you is it that you are able to walk easily?†		d450 *(100%)*
Can you use your hands?†		d445 *(100%)*
How important to you is it that you are able to use your hand well?†		d445 *(88%)*
Can you eat independently?†		d550 *(100%)*
How important to you is it that you are able to eat by yourself easily?†		d550 *(88%)*

Table A9.a: Continued

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Can you wash yourself?†		d510 *(100%)*
How important to you is it that you are able to wash yourself easily?†		d510 *(88%)*
Can you go to the toilet without help?†		d530 *(100%)*
How important to you is it that you are able to go to the toilet yourself easily?†		d530 *(88%)*
How important to you is it that you have full control of your bladder function?†		b620 *(100%)*
Are you capable of preparing your own meals?†		d630 *(100%)*
How important to you is it that you are able to prepare your own meals?†		d630 *(88%)*
How is your sex-life?†		b640 *(100%)*
How important is your sex-life to you?†		b640 *(100%)*
How are your relations with your family?†		d760 *(100%)*
How important to you is it that you have good relations with your family?†		d760 *(100%)*
Can you maintain good relations with relatives and friends?		d760 *(78%)*
Can you travel (by car, bicycle, public transport, or any special transport)?†		d470 *(100%)*
How important to you is it that you are able to travel easily?†		d470 *(88%)*
Can you work (in a paid job)?†		d850 *(88%)*
How important to you is it that you are able to work easily?†		d850 *(75%)*
Can you do leisure activities?†		d920 *(100%)*
How important to you is it that you are able to spend your leisure time well?†		d920 *(88%)*

Table A9.a: Continued

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Can you hear?[†]		b230 *(90%)*
How important to you is it that you are able to hear well?[†]		b230 *(70%)*
Can you see?[†]		b210 (100%)
How important to you is it that you are able to see well?		b210 *(80%)*
Can you speak?		d330 *(90%)*
How important to you is it that you are able to speak easily?		d330 *(80%)*
Can you read?[†]		d166 *(100%)*
How important to you is it that you are able to read easily?[†]		d166 *(70%)*
Can you write?[†]		d170 *(100%)*
How important to you is it that you are able to write easily?[†]		d170 *(88%)*
How is your memory?[†]		b144 *(100%)*
How important to you is it that you have a good memory?		b144 *(70%)*
Can you concentrate?		b140 *(100%)*
How important to you is it that you are able to concentrate well?		b140 *(90%)*
How do you feel?[†]		b152 *(80%)*
How important to you is it that you are happy?[†]		b152 *(90%)*

[*] Items endorsed in initial round

[†] Items endorsed in first round of Delphi consensus

Table A9.b: Items of the DIP **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
<u>Items endorsed at lower level</u>	
Is your home adequate for you?	nc *(88%)*
How important to you is it that you have an adequate home?	nc *(75%)*
How important to you is it that you are able to determine your own day-program?	nc *(70%)*
<u>Items with no endorsed codes</u>	
Do you have visible deformities?	
How important to you is it to have no visible deformities?	
How is your physical condition?	
How important to you is it that you have a good physical condition?	
Do you feel that you can reach your goal in life?	
How important to you is it that you reach your goal in life?	

nc: not covered by ICF

Table A10.a: Items of the MSQLI-SF-36 measure and corresponding codes

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Items endorsed at 4 digit level		
Does your health limit you in doing vigorous activities (running, lifting heavy objects, participating in strenuous sports)?[†]	d9201 *(94%)*	d920 *(94%)*
Does your health limit you in climbing several flight of stairs?[*]	d4551 *(82%)*	d455 *(88%)*
Does your health limit you in climbing one flight of stairs?[*]	d4551 *(82%)*	d455 *(88%)*
Does your health now limit you in walking more than a kilometer?[*]	d4551 *(88%)*	d455 *(88%)*
Does your health now limit you in walking several blocks?[*]	d4500 *(75%)*	d450 *(100%)*
Does your health now limit you in walking one block?[†]	d4500 *(88%)*	d450 *(88%)*
How much of the time did you feel full of pep?[†]	b1300 *(81%)*	b130 *(94%)*
How much of the time did you have a lot of energy?[*]	b1300 *(76%)*	b130 *(88%)*
How much of the time has your physical or emotional health interfere with social activities?[†]	d9205 *(88%)*	d920 *(88%)*
Items endorsed only at 3 digit level		
Does your health limit you in doing moderate activities (moving a table, pushing a vacuum, bowling, play golf)?[†]		d640 *(75%)*
Does your health limit you in lifting or carrying groceries?[*]		d430 *(81%)*
Does your health now limit you in bending, kneeling, or stooping?[*]		d410 *(75%)*
How much bodily pain have you had?[*]		b280 *(100%)*
How much did bodily pain interfere with your normal work due to pain?[*]		b280 *(100%)*

Table A10.a: Continued

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
How much of the time did you feel very nervous?[*]		b152 *(100%)*
How much of the time did you feel calm and peaceful?[*]		b126 *(88%)*

[*] Items endorsed in initial round

[†] Items endorsed in first round of Delphi consensus

Table A10.b: Items of the MSQLI-SF-36 **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
Items endorsed at lower level	
In general, would you say your health is:	nc *(88%)*
Compared to one year ago, how would you rate your health now?	nc *(88%)*
To what extent has your physical health or emotional problems interfered with your normal social activities with family, friends?	nc *(75%)*
Do you seem to get sick easier than other people?	nc *(82%)*
Are you as healthy as anybody you know?	nc *(82%)*
Do you expect you health to get worse?	nc *(82%)*
Do you feel that your health is excellent?	nc *(82%)*
Items with no endorsed codes	
Does your health now limit you in bathing or dressing yourself?	
Have you had any problems with work or other activities as a result of your physical health?	
Have you had any problems with work or other activities as a result of your emotional problems?	
How much of the time did you feel so down in the dumps that nothing could cheer you up?	
How much of time did you feel downhearted and blue?	
How much of time did you feel worn out?	
How much of time have you been a happy person?	
How much of time did you feel tired?	

nc: not covered by ICF

Table A11: Items of the MSQLI-MFIS measure and corresponding codes

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Items endorsed at 4 digit level		
Because of my fatigue during the past 4 weeks...		
I feel less alert	b1102 *(100%)*	b110 *(100%)*
I have difficulty paying attention for a long period of time	b1400 *(100%)*	b140 *(100%)*
I have had to pace myself in my physical activities†	b4552 *(100%)*	b455 *(100%)*
I am less motivated to do anything that requires physical effort†	b1301 *(88%)*	b130 *(88%)*
I am less motivated to engage in social activities	d9205 *(78%)*	d920 *(78%)* b130 *(78%)*
I am limited to do anything outside my home	b4552 *(88%)*	b455 *(88%)*
I have trouble maintaining physical effort for long periods†	b4552 *(75%)*	b455 *(75%)*
I am less motivated to do anything that requires thinking	b1301 *(90%)*	b130 *(90%)* d163 *(70%)*
I feel weak†	b4552 *(88%)*	b455 *(88%)*
I find it difficult to organize my thoughts when I am doing things at home or at work	b1601 *(100%)*	b160 *(100%)*
I am less able to complete tasks that require physical effort†	b4552 *(75%)*	b455 *(75%)*
I feel slowed down in my thinking	b1600 *(90%)*	b160 *(90%)*
I find it hard to concentrate	b1400 *(80%)*	b140 *(100%)*
I have to limit my physical activities†	b4552 *(88%)*	b455 *(88%)*
I require more frequent or longer periods of rest†	b4552 *(88%)*	b455 *(88%)*

Table A11: Continued

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
<u>Items endorsed only at 3 digit level</u>		
Because of my fatigue during the past 4 weeks...		
I have been unable to think clearly		d163 *(80%)*
I am more clumsy and uncoordinated		b760 *(80%)*
I find that I am more forgetful		b144 *(100%)*
I find it difficult to make decisions		d177 *(100%)*
My physical discomfort is increased†		b280 *(90%)*
I am less able to finish tasks that require thinking		d163 *(90%)*

*No items endorsed in initial round
†Items endorsed in first round of Delphi consensus

Table A12: Items of the MSQLI-PES measure and corresponding codes

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Items endorsed at 4 digit level		
how much did these symptoms (unpleasant sensory symptoms) interfere with your...enjoyment of life	b1265 *(100%)*	b126 *(100%)*
Items endorsed only at 3 digit level		
How much did these symptoms (unpleasant sensory symptoms) interfere with your...		
mood		b126 *(80%)*
ability to walk or move around†		d450 *(100%)*
Sleep†		b134 *(100%)*
normal work (both outside your home and at home)		d850 *(75%)*
recreational activities†		d920 *(100%)*

* No items endorsed in initial round

†Items endorsed in first round of Delphi consensus

Table A13: Items of the MSQLI-SSS measure and corresponding codes

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Items endorsed at 4 digit level		
During the past 4 weeks, how satisfied have you been with…		
The amount of affection expressed physically in your relationship?[†]	d7105 *(100%)*	d710 *(100%)*
The variety of sexual activities you engage in with your partner?[†]	d7702 *(100%)*	d770 *(100%)*
Your sexual relationship in general?[*]	d7702 *(70%)*	d770 *(80%)*
Your sexual relationship in general, during the past 4 weeks?[*]	d7702 *(70%)*	d770 *(80%)*
Items endorsed only at 3 digit level		
Do you have a relationship with one primary partner?[†]		d770 *(100%)*

[*] Items endorsed in initial round
[†] Items endorsed in first round of Delphi consensus

Table A14: Items of the MSQLI-BLCS measure and corresponding codes

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Items endorsed at 4 digit level		
During the past 4 weeks, how often have you...		
Lost control of your bladder or had an accident?†	b6202 *(75%)*	b620 *(100%)*
Almost lost control of your bladder or had an accident?†	b6202 *(100%)*	b620 *(100%)*
Items endorsed only at 3 digit level		
During the past 4 weeks, how often have you...		
Altered your activities because of bladder problems?†		b620 *(88%)*
How much have bladder problems restricted your overall lifestyle?		b620 *(100%)*

*No items endorsed in initial round

†Items endorsed in first round of Delphi consensus

Table A15: Items of the MSQLI-BWCS measure and corresponding codes

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Items endorsed at 4 digit level		
During the past 4 weeks, how often have you...		
Been constipated?[†]	b5252 *(75%)*	b525 *(100%)*
Lost control of your bowels or had an accident?[†]	b5253 *(100%)*	b525 *(100%)*
Almost lost control of your bowels or almost had an accident?[*]	b5253 *(78%)*	b525 *(91%)*
Altered your activities because of bowel control problems?[†]	b5253 *(88%)*	b525 *(88%)*
Items endorsed only at 3 digit level		
How much have bowel problems restricted your overall lifestyle?		b525 *(100%)*

[*] Items endorsed in initial round

[†] Items endorsed in first round of Delphi consensus

Table A16: Items of the MSQLI-IVIS measure and corresponding codes

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
<u>Items endorsed at 4 digit level</u>		
During the past 4 weeks, how difficult did you find it to...		
Watch television or identify faces from a distance?[*]	b2100 *(90%)*	b210 *(100%)*
Identify house numbers, street signs, etc.?[*]	b2100 *(80%)*	b210 *(100%)*
<u>Items endorsed only at 3 digit level</u>		
During the past 4 weeks, how difficult did you find it to...		
Read or access personal letters or notes?[*]		d166 *(100%)*
Read or access printed materials, such as books, magazines, newspaper, etc.?[*]		d166 *(100%)*
Read or access dials, such as on stoves, thermostats, etc.?[†]		d166 *(100%)*

[*] Items endorsed in initial round
[†] Items endorsed in first round of Delphi consensus

Table A17: Items of the MSQLI-PDQ measure and corresponding codes

Items	**4 digit level** *(% agreement)*	**3 digit level** *(% agreement)*
Items endorsed at 4 digit level		
During the past 4 weeks, how often did you…		
Lose your train of thought when speaking?	b1603 *(70%)*	b160 *(80%)*
Have difficulty remembering the names of people, even ones you have met several times?	b1442 *(70%)*	b144 *(100%)*
Forget what you came into the room for? †	b1440 *(80%)*	b144 *(100%)*
Have trouble getting things organized?*	b1641 *(82%)*	b164 *(91%)*
Have trouble concentrating on what people are saying during a conversation?	b1400 *(70%)*	b140 *(100%)*
Miss appointments and meetings you had scheduled?	b1441 *(90%)*	b144 *(100%)*
Have difficulty planning what to do in the day?*	b1641 *(91%)*	b164 *(100%)*
Have trouble concentrating on things like watching a television program or reading a book?	b1400 *(70%)*	b140 *(100%)*
Forget what you did the night before?	b1441 *(70%)*	b144 *(100%)*
Have trouble getting started, even if you had a lot of things to do?	b1641 *(70%)*	b164 *(70%)*
find your mind drifting?†	b1400 *(80%)*	b140 *(100%)*
Forget to do things like turn off the stove or turn on your alarm clock?†	b1440 *(70%)*	b144 *(100%)*
Feel like your mind went totally blank?†	b1602 *(80%)*	b160 *(80%)*
Have trouble holding phone numbers in your head, even for a few seconds?*	b1440 *(91%)*	b144 *(100%)*
Forget what you did last weekend?*	b1441 *(73%)*	b144 *(100%)*
Items endorsed only at 3 digit level		
During the past 4 weeks, how often did you…		
Forget if you had already done something?†		b144 *(100%)*

Table A17: Continued

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Forget the date unless you looked it up?[†]		b144 *(100%)*
Forget what you talked about after a telephone conversation?[†]		b144 *(100%)*
Forget to take your medication?[†]		b144 *(100%)*
Have trouble making decisions?[†]		d177 *(90%)*

[*] Items endorsed in initial round
[†] Items endorsed in first round of Delphi consensus

Table A18.a: Items of the MSQLI-MHI measure and corresponding codes

Items	**4 digit level** ***(% agreement)***	**3 digit level** ***(% agreement)***
Items endorsed at 4 digit level		
During the past 4 weeks, how much of the time...		
Have you been in firm control of your behaviour, thoughts, emotions, feelings?*	b1521 *(100%)*	b152 *(100%)*
Have you felt emotionally stable?*	b1521 *(90%)*	b152 *(90%)*
Were you able to relax without difficulties?*	b1521 *(90%)*	b152 *(90%)*
Have you felt cheerful, light-hearted?	b1265 *(90%)*	b126 *(90%)*
Did you feel you had nothing to look forward to?*	b1265 *(70%)*	b126 *(70%)*
Have you been anxious and worried?	b1522 *(70%)*	b152 *(100%)*
Items endorsed only at 3 digit level		
During the past 4 weeks, how much of the time...		
Did you feel depressed?†		b152 *(100%)*
Have you felt loved and wanted?		b152 *(90%)*
How much of the time...Have you been very nervous person?		b152 *(100%)*
Have you felt tense or high-strung?		b152 *(100%)*
How much of the time...Have you felt calm and peaceful?		b126 *(88%)*
Have you been moody, or brooded about things?†		b152 *(80%)*
Have you been in low or very low spirit?		b152 *(80%)*
Were you a happy person?		b152 *(100%)*

*Items endorsed in initial round

†Items endorsed in first round of Delphi consensus

Table A18.b: Items of the MSQLI-MHI **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
Items endorsed at lower level	
During the past 4 weeks, how much of the time...Has your daily life been full of things that were interesting to you?	nc *(89%)*
Items with no endorsed codes	
During the past 4 weeks, how much of the time...Have felt restless, fidgety, or impatient?	
How much of the time...Have you felt down hearted and blue?	
How much of the time...Have felt so down in the dumps that nothing could cheer you up?	

nc: not covered by ICF

Table A19.a: Items of the MSQLI-MSSS measure and corresponding codes

Items	Lower level codes *(% agreement)*
Items endorsed only at 3 digit level	
How often is someone available...	
To help you if you are confined to bed?†	e340 *(78%)*
To show you love and affection?	d770 *(78%)*
To prepare your meals if you were unable to do it yourself?†	d630 *(75%)* e340 *(75%)*

#No items endorsed at 4-digit level
* No items endorsed in initial round
†Items endorsed in first round of Delphi consensus

Table A19.b: Items of the MSQLI-MSSS **not** endorsed at 4 or 3 digit level

Items	**Lower level codes** ***(% agreement)***
Items endorsed at lower level	
How often is someone available...	
To give you good advice about crisis?	e3 *(89%)*
To take you to the doctor if you needed it?	e3 *(100%)*
To have a good time with?	e3 *(78%)*
To give you information to help you understand a situation?	e3 *(100%)*
To confide in or talk to about yourself of your problems?	e3 *(78%)*
To hugs you?	e3 *(78%)*
To get together with for relaxation?	e3 *(89%)*
To give advice you really want?	e3 *(78%)*
To share your most private worries and fears with?	e3 *(78%)*
To turn to for suggestions about how to deal with a personal problem?	e3 *(78%)*
To do something enjoyable with?	e3 *(78%)*
To understands your problems?	e3 *(78%)*
Items with no endorsed codes	
How often is someone available...	
To listen to you when you need to talk?	
To help with daily chores if you were sick?	
To love and make you feel wanted?	

e3: chapter of support and relationships

Appendix Tables A20 to A22

Representation of MS ICF core set categories by MS- specific HRQL measures

Table A20: Representation of the MS ICF core set of the component **Body Function** by MS HRQL measures

ICF Category		MSQLI	FAMS	MSQOL-54	HAQUAMS	RAYS	PS-MS	LMS QoL	MSIS-29	QLI-MS	DIP
b110	*Consciousness function*	1									
b114	Orientation functions*										
b122	Global psychosocial functions*										
b126	Temperament & personality functions	6	2	1	2	3		2	2	1	
b130	Energy and drive functions	5	6	2	3	1		2	1	2	
b134	*Sleep functions*	1	1			1			1		2
b140	Attention functions	5	1	3	1				1		2
b144	Memory functions	12	1	2	1	1					2
b147	Psychomotor functions					1					
b152	Emotional functions	12	8	5	6	7		3	4	5	4
b160	Thought functions	4	1								
b164	Higher-level cognitive functions	3				1	1				1
b210	Seeing functions	2			2	1	3				2
b230	Hearing functions										2
b235	Vestibular functions*										
b260	Proprioceptive function*										
b265	Touch function*										
b280	Sensation of pain	3	4	3	2	1				2	2
b310	Voice functions*										
b320	Articulation functions*										
b330	Fluency and rhythm of speech functions					1				2	
b435	Immunological systems functions*										
b455	Respiratory muscle functions	7	1		1		2				
b525	Defecation functions	5			1		2				2

Table A20: Representation of the MS ICF core set of the component **Body Function** by MS HRQL measures (continued)

ICF Category		**MSQLI**	**FAMS**	**MSQOL-54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS-29**	**QLI-MS**	**DIP**
b535	*Sensations associated with the digestive system*		1								
b620	Urination functions	4	2		2	1	3		1		2
b640	Sexual functions			5	1						2
b710	Mobility of joint functions*										
b715	Stability of joint functions*										
b730	Muscle power functions		1								
b735	Muscle tone functions				1	1	3				
b750	Motor reflex functions*										
b755	Involuntary movement reaction functions*										
b760	Control of voluntary movement functions	1							1		
b765	*Involuntary movement functions*								1		
b770	Gait pattern functions*										
b780	Sensations related to muscles and movement functions		1						2		

#Blank spaces mean no entry

*ICF core set categories for MS that were not captured by the selected measures

Italic fonted categories are those captured by the selected measures but are not included in the ICF core set for MS

Table A21: Representation of the MS ICF core set of the component **Activity and Participation** by MS HRQL measures

ICF Category		**MSQLI**	**FAMS**	**MSQOL -54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS -29**	**QLI-MS**	**DIP**
d155	*Acquiring skills*		1								
d160	Focusing attention*										
d163	Thinking	3									
d166	Reading	3									2
d170	*Writing*				1						2
d172	Calculating*										
d175	Solving problems*										
d177	Making decisions	2				1					
d210	Undertaking a single task								1		
d220	Understanding multiple tasks*										
d230	Carrying out daily routine					1			1		
d240	Handling stress and other psychological demands		1			1				2	
d310	Communication with receiving spoken messages*										
d315	Communication with receiving non-verbal messages*										
d325	Communication with receiving written messages*										
d330	Speaking					1					2
d335	Producing nonverbal messages*										
d345	Writing messages*										
d350	Conversation					1					
d355	Discussion*										
d360	Using communication device and techniques*										
d410	Changing basic body position	1		1	1	2					7

Table A21: the third-level of ICF categories from the component **Activity and Participation** endorsed by MS HRQL measures (Continued)

ICF Category		**MSQLI**	**FAMS**	**MSQOL -54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS -29**	**QLI-MS**	**DIP**
d415	Maintaining a body position*										
d420	Transferring oneself*										
d430	Lifting and carrying objects	1		1		2			1		2
d440	Fine hand use					1			1		
d445	Hand and arm use						2		1		2
d450	Walking	3		2	3	2			1		2
d455	Moving around	3		3	1	1					4
d456	Moving around using equipment*										
d460	Moving around in different locations									2	
d470	Using transportation		1		1	1			1		2
d475	Driving					1					
d510	Washing oneself										2
d520	Caring for body parts					1					
d530	Toileting										2
d540	Dressing		1		1						2
d550	Eating				1						2
d560	Drinking*										
d570	Looking after one's health*										
d620	Acquisition of goods and services*										
d630	Preparing meals	1			1						2
d640	Doing housework	1		1	1	1					2
d650	Caring for household objects*										
d660	*Assisting others*		1							2	

Table A21: Representation of the MS ICF core set of the component **Activity and Participation** by MS HRQL measures (continued)

ICF Category		**MSQLI**	**FAMS**	**MSQOL -54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS -29**	**QLI-MS**	**DIP**
d710	Basic interpersonal interactions	1								1	
d720	Complex interpersonal interactions*										
d740	Formal relationships*										
d750	Informal social relationships				2						1
d760	Family relationships		1		1			1		4	3
D770	Intimate relationships	5	2	1		1				4	
d820	*School education*									2	
d825	Vocational training*										
d845	Acquiring, keeping and terminating a job									2	
d850	Remunerative employment	1	2			1	7			1	2
d855	Non-remunerative employment*										
d860	Basic economic transactions*										
d870	Economic self-sufficiency									2	
d910	Community life*										
d920	Recreation and leisure	4	1	3		3			1	2	2
d930	Religion and spirituality									2	
d950	*Political life and citizenship*		1								

$^{\#}$Blank spaces mean no entry

*ICF core set categories for MS that were not captured by the selected measures

Italic fonted categories are those captured by the selected measures but are not included in the ICF core set for MS

Table A22: Representation of the MS ICF core set of the component **Environmental Factors** by MS HRQL measures

ICF Category		MSQLI	FAMS	MSQOL -54	HAQUAMS	RAYS	PS-MS	LMS QoL	MSIS-29	QLI-MS	DIP
e110	Products or substances for personal consumption*										
e115	Products and technology for personal use in daily living*										
e120	Products and technology for personal indoor and outdoor mobility and Transportation*										
e125	Products and technology for communication*										
e130	Products and technology for education*										
e135	Products and technology for employment*										
e150	Design, construction and building products and technology of buildings for public use*										
e155	Design, construction and building products and technology of buildings for private use*										
e165	Assets										2
e210	Physical geography*										
e225	Climate		1			1					
e310	Immediate family		1		1					2	
e315	Extended family*										
e320	Friends		1							2	
e325	Acquaintances, peers colleagues, neighbors and community members				1					3	
e330	People in positions of authority*										
e340	Personal care providers and personal assistants	2									
e355	Health professionals					1					

Table A22: Representation of the MS ICF core set of the component **Environmental Factors** by MS HRQL measures (continued)

ICF Category		**MSQLI**	**FAMS**	**MSQOL -54**	**HAQUAMS**	**RAYS**	**PS-MS**	**LMS QoL**	**MSIS-29**	**QLI-MS**	**DIP**
e360	Health-related professionals*										
e410	Individual attitudes of immediate family members		2								
e420	Individual attitudes of friends*										
e425	Individual attitudes of acquaintances, peers colleagues, neighbours and community members*										
e430	Individual attitudes of people in positions of authority*										
e440	Individual attitudes of personal care providers and personal assistants*										
e450	Individual attitudes of health professionals*										
e455	Individual attitudes of health-related professionals*										
e460	Societal attitudes*										
e510	Services, systems and policies for the production of consumer goods*										
e515	Architecture and construction services, systems and policies*										
e525	Housing services, systems and policies*										
e530	Utilities services, systems and policies*										
e540	Transportation services, systems and policies*										
e570	Social security services, systems and policies*										
e575	General social support services, systems and policies*										
e580	Health services, systems and policies									2	
e590	Labour and employment services, systems and policies*										

[#]Blank spaces mean no entry

*ICF core set categories for MS that were not captured by the selected measures

Appendix Table A23: List of Abbreviations

MS	Multiple Sclerosis
QOL	Quality of Life
HRQL	Health-Related Quality of Life
WHO	World Health Organization
FDA	Food and Drug Administration
PROs	Patient-Reported Outcome Measures
WCM	Wilson-Cleary Model
ICF	International Classification of Functioning Disability and Health
MSQOL-54	Multiple Sclerosis Quality of Life 54
FAMS	Functional Assessment of Multiple Sclerosis
HAQUAMS	Hamburg Quality of Life Questionnaire for Multiple Sclerosis
LMSQoL	Leeds Multiple Sclerosis QoL
MSIS-29	Multiple Sclerosis Impact Scale
MSQLI	Multiple Sclerosis QoL Inventory
MFIS	Modified Fatigue Impact Scale
PES	MOS Pain Effect Scale
SSS	Sexual Satisfaction Scale
BLCS	Bladder Control Scale
BWCS	Bowel Control Scale
IVIS	Impact of Visual Impairment Scale
PDQ	Perceived Deficits Questionnaire
MHI	Mental Health Inventory
MSSS	MOS Modified Social Support Survey
SF-36	36-Item Short Form Health Survey
RAYS	RAYS Scale
QLI-MS	Quality of Life –Index MS Version
PS-MS	Performance Scales for Multiple Sclerosis
DIP	Disability & Impact Profile Questionnaire
FSS	Fatigue Severity Scale
List of Abbreviations of ICF Coding	
nd	Not definable
qol	Quality of life
gh	General health
nc	Not covered by ICF
pf	Personal factors