Graduate Theses, Dissertations, and Problem Reports

2006

Health -related quality of life in multiple sclerosis: Measurement, predictors and utilization in routine clinical practice

Vivek S. Pawar
West Virginia University

Follow this and additional works at: https://researchrepository.wvu.edu/etd

Recommended Citation

Pawar, Vivek S., "Health -related quality of life in multiple sclerosis: Measurement, predictors and utilization in routine clinical practice" (2006). *Graduate Theses, Dissertations, and Problem Reports*. 2508.
https://researchrepository.wvu.edu/etd/2508

Health-Related Quality of Life in Multiple Sclerosis: Measurement, Predictors and Utilization in Routine Clinical Practice

Vivek S. Pawar

**Dissertation submitted to the School of Pharmacy
at West Virginia University
in partial fulfillment of the requirements for the degree of**

**Doctor of Philosophy
in
Pharmaceutical Sciences**

**Lesley-Ann Miller, PhD, Chair
Gauri Pawar, MD
S. Suresh Madhavan, PhD, MBA
Jan Kavookjian, PhD, MBA
Iftekhar Kalsekar, PhD**

Department of Pharmaceutical Systems and Policy

**Morgantown, West Virginia
2006**

Keywords: Multiple Sclerosis, Health-Related Quality of Life, Clinical Practice

Abstract

Health-Related Quality of Life in Multiple Sclerosis: Measurement, Predictors and Utilization in Routine Clinical Practice

Vivek S. Pawar

There are a large number of patient-reported questionnaires to assess health-related quality of life (HRQoL) in patients with multiple sclerosis (MS). In order to make a recommendation for use in clinical practice, a comparison of their psychometric properties is necessary. In addition to accurate assessment, it is also necessary to identify factors that have a significant impact on HRQoL. Further, lack of use of HRQoL information in clinical practice warrants examination of attitudes and behavior of neurologists about HRQoL assessment and their intention to consider incorporating HRQoL information in their decision making. This study collected data from patients with MS as well as neurologists and consisted of two phases. Phase I involved collection of primary data from non-institutionalized patients with MS. Data from Phase I was used to measure HRQoL, identify factors affecting HRQoL, and compare the measures on their psychometric properties. A mail survey of neurologists was performed in Phase II. This data facilitated investigation of factors that have a significant influence on neurologists' intention to assess HRQoL information in clinical practice. Possible predictors of intention such as: attitude, subjective norms, perceived behavior control and practice characteristics were included. Based on analyses of Phase I, no measure emerged clearly or consistently better or worse than the others in terms of psychometric properties. Hence, a recommendation of one particular measure for use in MS-related clinical practice cannot be substantiated. The choice of a measure ultimately rests on the neurologist and may be related to their perception of its usefulness and their intention to use such information in the routine care. With respect to predictors of HRQoL, visual function among other factors was found to have a significant and independent impact on HRQoL in patients with MS. This suggests that visual screening should be performed periodically using patient-reported questionnaires in addition to conventional tests of visual acuity. Over 90% of neurologists reported that they did not use standardized HRQoL questionnaires in clinical practice. Organizations such as the American Academy of Neurology and fellow neurologists can exert significant influence on neurologists' intention to assess HRQoL information in clinical practice.

Dedication

This research is dedicated to:

My grandmother Geeta Phatak

My parents Suman and Sharad Pawar

My wife Anagha

Acknowledgements

At the culmination of one of my most treasured accomplishments, I would like to thank:

Dr. Lesley-Ann Miller: For being a friend and a great mentor.

Dr. Suresh Madhavan: For giving me the opportunity to pursue my dreams. Your department was a haven for this once lost graduate student. Thank you for your support and honesty.

Committee members: Dr. Gauri Pawar, Dr. Iftekhar Kalsekar and Dr. Jan Kavookjian

PSP faculty: Dr. Michael Smith and Dr. Ginger Scott

Dr. Irene Tessaro and everyone at Community Health Initiatives

Dr. Harvey Rapport and Dr. Robert Kee at the University of Louisiana at Monroe

Dr. Ganesh Samant: You have been my one constant friend since my first day in the United States. Thank you for your support.

Murali Sundaram, Sanjoy Roy, Dr. Mariam Hassan and Dr. Anna O. D'Souza: My "family" in Morgantown.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction and Study Objectives

Health-Related Quality of Life in Multiple Sclerosis

Multiple sclerosis (MS) being a progressive neurological disease with no cure, lends itself as an important area for health-related quality of life (HRQoL) research. The available treatments have only a modest effect on the course of the disease with MS patients reporting lower satisfaction with life, not only compared to people without any disease, but also those with chronic illnesses such as inflammatory bowel disease, rheumatoid arthritis, epilepsy, and diabetes (Hermann et al., 1996; Rudick, Miller, Clough, Gragg, & Farmer, 1992). There are several ways in which MS can have an impact on patients' HRQoL. MS causes a disturbance in normal physiological functioning due to symptoms such as motor sensory impairments, ambulatory problems, bowel and bladder problems, cognitive disturbances, sexual dysfunction, and vision problems. The progressive nature of the disease elicits a pervasive impact on patients' lives, with substantial negative consequences for family and working life, which can manifest during the most active and productive period of people's lives (Solari & Radice, 2001).

Within 10 years of onset, half of all MS patients are unable to fulfill household and employment responsibilities; within 15 years, half of the patients are unable to walk unaided; and within 25 years half require a wheelchair (Confavreux, Vukusic, Grimaud, & Moreau, 1999). MS patients can be under immense social strain as the need for help, risk of divorce, loss of contact with relatives, difficulty leaving the house, need for structural changes in the house and need for pension can increase with worsening disability (Stenager, Stenager, Knudsen, & Jensen, 1994). Since it usually occurs in young adults it can have an overwhelming influence on future productivity and personal development. The

unpredictable course which the disease follows makes it very difficult for patients to anticipate and deal with the periods of relapses and remissions (Benito-Leon).

Although no curative treatments exist for MS, a number of parenterally administered immunological drugs have been developed to curb the progression of the disease. These treatments however, are not without their shortfalls. Treatment with interferon beta which is administered via injections can produce side effects that may have a deleterious effect on a patient's quality of life irrespective of whether it is given daily or once a week. In addition, the side effects of this treatment seem to increase with time. Adverse effects such as cutaneous ulceration and local pain at the injection site as well as flu like symptoms have been reported in MS patients on interferon therapy (Logan-Club & Stacy, 1995; Inafuku, Kasem Khan, Nagata, & Nonaka, 2004; Gottberg, Gardulf, & Fredrikson, 2000).

Skin reactions in response to disease modifying therapy have the potential to evolve into serious lesions culminating in infection, necrosis, and in some circumstances requiring surgical repair (Frohman et al., 2004). In addition to local skin reactions, therapy with glatiramer acetate and mitoxantrone has also been associated with several adverse events. Systemic adverse events such as flushing, chest-tightness, sweating, palpitations and anxiety have been observed in patients on glatiramer acetate therapy (Munari, Lovati, & Boiko, 2004). Adverse events such as nausea, alopecia, infections, menstrual disorders, risk of cardiotoxicity and malignancy may occur following administration of mitoxantrone (Edan, Morrissey, & Le Page, 2004). Side-effects are rarely incorporated in the overall results of a trial or intervention. They are either listed separately or often ignored.

Physicians generally lean towards assessing physical disability in MS patients, but are skeptical about the additional benefits of measuring HRQoL (Barbotte, Guillemin, & Chau,

2001). HRQoL in MS has been known to correlate with measures of impairment and disability such as the Expanded Disability Status Scale (EDSS). However, this correlation has been found to vary from 2% to 29% (on the correlation coefficient) depending upon the presence of other influencing factors such as fatigue, cognition, mood disorders etc. (Benedict et al., 2005; Patti et al., 2003; Fruehwald, Loeffler-Stastka, Eher, Saletu, & Baumhackl, 2001). The EDSS has to be administered by the physician and as a result certain patient-centered domains of health which may contribute to HRQoL may be overlooked. This can be a problem because it has been noted that patients with multiple sclerosis and possibly those with other chronic diseases are less concerned than their clinicians about physical disability in their illness (Rothwell, McDowell, Wong, & Dorman, 1997).

MS patients identify role limitations, cognition and emotional problems as having a significant influence on their HRQoL in addition to just the physical manifestations of the disease. Murphy and colleagues have shown that these domains are substantially lower in patients with MS compared with controls, and that these changes correlate poorly with neurological impairment and disability as measured by the EDSS (Murphy et al., 1998). Thus, assessment of quality of life during routine care of MS patients might alert health professionals to less obvious burdens of the disease. These may include factors that are affected by the disease process, are more closely related to overall HRQoL, and may also be adversely affected by side effects of treatment.

Factors Affecting Health-Related Quality of Life in MS

Neuro-ophthalmologic manifestations are common and disabling in patients with MS. Any area of the visual system can be affected, including the optic nerves, chiasm, tracts and even optic radiations, leading to a variety of symptoms from blurring to distortion of vision (Nordmann, Saraux, & Roullet, 1987; Warner & Lessell, 1994). Although visual symptoms in MS may precede, occur at onset, or develop during the course of the disease, they may represent the most prominent symptoms of MS from the patient's point of view. Visual symptoms may cause difficulties with activities used in day-to-day life such as dressing, eating, writing, simple communications or interactions with others, and daily travel (Stelmack, 2001; Keeffe, Lam, Cheung, Dinh, & McCarty, 1998). In addition to daily activities and functional status, mood level and social relationships can particularly be affected by visual impairment (Carabellese et al., 1993). Given the wide-spread impact, it is not surprising that visual impairment has been found to be associated with overall HRQoL in MS patients. This was noted in studies which used visual subscales of the general or functional status measures to correlate with the overall quality of life scores (Rudick et al., 1992; Fischer et al., 1999).

Objective measurements of vision impairments, particularly measures of visual acuity and visual fields have also been commonly used to represent a patient's functional capabilities during treatment. The term objective is usually used when the variable is manifest, that is, a publicly observable and quantifiable attribute or behavior. Since many clinical treatment trials depend on such objective measures as primary study variables, there is a growing demand to include subjective patient-based visual function assessments, which can be accomplished with several questionnaires that have been developed exclusively for

this purpose (Massof & Rubin, 2001; 1993; USDHHS, 1993). These instruments include the

Visual Function Index (VFI) (Bernth-Petersen, 1981), Activities of Daily Vision Scale

(ADVS) (Mangione et al., 1992), 14-Item Visual Functioning Index (VF-14) (Steinberg et

al., 1994), and the National Eye Institute's Visual Functioning Questionnaire (VFQ)

(Mangione et al., 2001), among others.

Depression is one of the strongest predictors of HRQoL in patients with MS

(Lobentanz et al., 2004; Fruehwald et al., 2001). This can be due to several reasons

(Mitchell, Benito-Leon, Gonzalez, & Rivera-Navarro, 2005). It can impair motivation,

interest and concordance, thus retarding physical progress. It can also manifest itself at the

point where the patients have exhausted their resources to cope with the disease. Presence of

depression can distort an individual's view of their surroundings as well as their health,

leading to a more negative assessment of quality of life. The association may also be due to

the fact that HRQoL and depression are both typically associated with similar facets of

experience such as distress and suffering. A strong inverse correlation of depression with

generic and MS-specific quality of life measures has been shown (Amato et al., 2001; Bakshi

et al., 2000).

In the study by Bakshi et.al., the association of depression with lower quality of life

scores remained significant after adjusting for other factors like severity of neurological

disability and fatigue. Depressed patients with MS have also scored worse on various scales

such as energy, mental health, cognitive function, overall quality of life, sexual and

emotional function compared with non-depressed MS patients (Wang, Reimer, Metz, &

Patten, 2000). Additionally, studies have tried to correlate neurological disability with

impaired HRQoL in MS patients. Results from these studies have shown that neurological

disability has a significant influence on HRQoL (Brunet, Hopman, Singer, Edgar, & MacKenzie, 1996; Modrego, Pina, Simon, & Azuara, 2001).

Problem Statement

In order to determine the relative advantages and disadvantages of various HRQoL instruments, a comparison of their psychometric properties in the same population is necessary. Although researchers have examined the psychometric properties of each of these three health status measures to be compared, some limitations can be noted. Only three studies have compared the properties of HRQoL measures on the same cohort of patients. The Multiple Sclerosis Quality of Life – 54 items (MSQoL-54) was used in two of the three studies which provided conflicting evidence regarding its superiority over its comparators (Vickrey, Hays, Genovese, Myers, & Ellison, 1997; Nicholl, Lincoln, Francis, & Stephan, 2001). Moreover, neither of these studies evaluated the full spectrum of psychometric properties, particularly ignoring responsiveness, for the included HRQoL measures.

One study performed a comparison of all psychometric properties among three patient reported outcome (PRO) measures and found that the Multiple Sclerosis Impact Scale (MSIS-29) performed better than Functional Assessment in Multiple Sclerosis (FAMS) (Riazi, Hobart, Lamping, Fitzpatrick, & Thompson, 2003). The authors however, acknowledged the need for further evaluation of their work owing to the small sample size of the study. A number of instruments have been designed to measure HRQoL in MS patients with many being published in recent years (Nortvedt & Riise, 2003; Solari, 2005). As a result, physicians have a greater range of choices but limited information on which to base the selection of health status measures. Hence, it is necessary to perform a rigorous and all-

inclusive concurrent comparison of currently relevant MS-related HRQoL instruments for use in routine clinical care. MSIS-29 is one such currently relevant measure which has been validated in a number of settings and has been shown to have better psychometric properties compared to other commonly used HRQoL measures. MSIS-29 however, measures only physical and psychological impact of the disease and not HRQoL per se. Other relevant measures include: the Hamburg Quality of Life Questionnaire in MS (HAQUAMS) which was recently developed and is the only measure that addresses all domains relevant to patients with MS; and the ubiquitous Medical Outcomes Survey – Short Form 36 Items (SF-36) which has been extensively used in MS research.

In addition to accurate and efficient assessment of quality of life, it is also necessary to identify and focus on factors that affect the quality of life of MS patients. A number of studies have reported association of overall quality of life with impairment and disability as measured by neurological symptoms or measures of disability (Miller, Rudick, Cutter, Baier, & Fischer, 2000; Ozakbas, Cagiran, Ormeci, & Idiman, 2004; Janardhan & Bakshi, 2000; Modrego et al., 2001). Others have demonstrated that variables such as fatigue, depression and anxiety and disease course (Pfennings et al., 1999a) can also have an impact on quality of life while some conflict exists regarding the impact of cognitive impairment (Benito-Leon, Morales, & Rivera-Navarro, 2002; Kenealy, Beaumont, Lintern, & Murrell, 2002). Of these variables, only neurologic disability, fatigue and depression have been shown to contribute independently to overall HRQoL (Henriksson, Fredrikson, Masterman, & Jonsson, 2001; Merkelbach, Sittinger, & Koenig, 2002a; Janardhan & Bakshi, 2002). However, no evidence is available on whether visual impairment affects MS-related quality of life, irrespective of disability, depression and other important clinical features of the disease. Since visual

impairment is a common manifestation among MS patients and can have a significant impact on HRQoL such information may be relevant in the routine care of patients.

The past decade has seen an increase in the number of MS-related clinical trials with quality of life as one of the outcomes of interest (Leuschen, Filipi, & Healey, 2004; Panitch, Miller, Paty, & Weinshenker, 2004; Patti et al., 2004a). A number of disease-specific quality of life measures have also been developed for use in MS research (Solari, 2005; Nortvedt et al., 2003). One of the major issues in HRQoL assessment is the transfer of newly developed measures from medical research to clinical practice (Belli, Tamburini, & Paci, 1994). No studies of the perspectives of neurologists on quality of life assessment in clinical practice have been reported in the literature. Thus, in addition to developing HRQoL measures appropriate for use in routine practice, more information is needed about the attitudes and behavior of neurologists about HRQoL assessment and their intention to consider incorporating HRQoL information in their decision making.

Study Aims

PHASE I

Objective 1: To compare the HAQUAMS with the SF-36 and the MSIS-29 in terms of their psychometric properties (scaling assumptions, acceptability, reliability, validity and responsiveness) as well as the preference of MS patients for each of these instruments.

Objective 2: To investigate the impact of visual impairment, in addition to other possible predictors such as disability and depression, on overall HRQoL in patients with MS.

Objective 3: To determine predictors (visual impairment, disability, depression, demographic factors, duration of disease and comorbid conditions) of various MS-specific HRQoL domains including fatigue, mobility, mood and social function, in patients with MS.

PHASE II

Objective 1: To compare neurologists' preferences regarding the usefulness and practicality of various MS-specific HRQoL measures in clinical practice.

Objective 2: To report neurologists' knowledge of and current practices regarding MS-specific HRQoL measures.

Objective 3: To identify barriers and facilitators to the use of HRQoL information in the routine care of patients with MS.

Objective 4: To investigate whether neurologists' intention to use HRQoL information in the routine care of patients with MS is associated with social cognitive factors (attitudes, subjective norms and perceived behavior control).

This study pertains to all aspects of health-related quality of life and its assessment in patients with MS. First, in order to make a recommendation for clinical practice, Objective 1 for both Phase I and II compared two MS-specific HRQoL measures in terms of: (1) their psychometric properties; and (2) patient and physician preferences regarding their usefulness and practicality. Objective 2 for Phase I focused on correlates of HRQoL and its specific domains and helps elucidate the relative contribution of visual impairment to overall HRQoL. Finally, Objectives 2, 3 and 4 from Phase II investigated neurologists' attitude and practices regarding HRQoL information in MS and examine behavioral factors that have an impact on the neurologists' intention to use HRQoL questionnaires in the routine care of patients with MS.

Study Significance

The current study yields important results that can be used by health care professionals to decide which instrument to use when evaluating HRQoL in patients with MS in routine clinical practice. Head-to-head comparisons in the same population can help provide an evidence-based framework to guide researchers in selecting measures for variety of purposes (Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2004). Since the psychometric properties of the MSIS-29, HAQUAMS, and SF-36 will be assessed using the same cohort of patients receiving care at an outpatient clinic, the comparison will be easier to interpret. Another important aspect of this study is the comparison of responsiveness of the three measures, which is their ability to measure clinically important change over time. The responsiveness of MS-related quality of life measures in general has been examined in

10

context of clinical trials, after patients initiate specific treatments and are expected to improve (Riazi et al., 2003). Most instruments perform reasonably well in such situations.

Due to the focus on use of HRQoL measures in clinical trials, it becomes difficult to assess whether these instruments can be useful for patients who may show comparatively smaller changes in their health status during routine care or follow-up. This study will compare the properties of the measures in a clinical setting. As such; its conclusions may help researchers to determine if they exhibit stability in patients showing no change and with ongoing disease, in addition to having discriminative properties. Comparison of ease of use, time to completion, accuracy and preference of individual patients regarding each measure, along with the complete psychometric properties will help neurologists choose the right measure for their setting, per their requirements.

If visual function is found to be a significant independent predictor of HRQoL in MS patients, the study findings may have important implications for patient care. It will allow policy makers and treating physicians to determine whether visual impairment should be screened for periodically in MS patients using HRQoL measures, regardless of neurological disability and other clinical characteristics of the disease. Mild visual impairment may be overlooked during routine visits, but if accurately monitored and treated successfully, it may have a significant impact on the HRQoL of patients.

The physician's perception of HRQoL is important, especially because they are primary decision makers regarding the treatment that is administered (Bezjak, Ng, Taylor, MacDonald, & Depetrillo, 1997). Due to a multitude of chronic conditions that exist in the society today and presence of limited healthcare resources, data from HRQoL questionnaires can be useful in decisions whether to continue or withhold treatment or even approve new

medications and technology (Drummond, 1987). In addition to determining the

appropriateness of MS-specific PRO measures, phase II of this project will help to determine

key factors that affect the neurologists' intention to use HRQoL information in their clinical

setting. Since the data will be obtained from a nationwide survey of neurologists, it may also

be useful as the basis for developing large-scale evidence-based HRQoL related intervention

strategies to increase neurologists' utilization of MS-related HRQoL information in their

clinical practice.

Chapter 2: Background

About Multiple Sclerosis

Multiple sclerosis (MS) is one of the most common chronic neurological diseases in adults, affecting about one in 1000 people. There are an estimated 1.1 million MS patients worldwide (Mitchell et al., 2005). It is an acquired primary demyelinating disease of the central nervous system (CNS) in which myelin is the target of an autoimmune inflammatory process (Whitaker JN & Mitchell GW, 1997). Myelin is a fatty material that insulates nerves and allows them to transmit impulses rapidly. The speed and efficiency with which these impulses are conducted permits smooth, rapid and coordinated movements to be performed with little conscious effort.

The sites of the nerves where the demyelination occurs appear as hardened, sclerosed, or scarred areas in the CNS and spinal cord. It is the presence of these sclerosed areas or lesions at multiple sites within the CNS that gives the disease its name. These lesions have a predilection for the optic nerves, periventricular white matter, brain stem, cerebellum and spinal cord. The lesions track along small and medium vessels, with an influx of inflammatory cells occurring perivascularly. The inflammation involves lymphocytes, macrophages, and reactive astrocytes. Inflammation and demyelination leads to a disruption in the ability of the nerves to conduct electrical impulses thus causing the many symptoms of the disease (Jacobs & Galetta, 2004).

Clinical hallmarks of MS include: 1) a temporal profile of symptoms and neurological deficits occurring in multiple episodes, designated as a relapse or an exacerbation, followed by disappearance of the symptoms and restoration of normal function, called remission; and

2) the dissemination of lesions anatomically within the CNS. In other words, lesions must be clearly disseminated in time and space within the CNS for clinically definite diagnosis of MS. By definition, a relapse should last for at least twenty-four hours and can not be attributed to another cause. The severity of the relapse mainly depends on the area and the volume of the damage caused by the demyelination (Whitaker JN et al., 1997).

Clinical Symptomatology

MS affects different people in different ways, and symptoms can vary in the same person from day to day. The majority of patients with MS develop an increasing range of symptoms, many of which worsen slowly, resulting in progressive and complex disability. Symptoms of MS can be categorized into three different categories; 1) primary symptoms that stem from actual demyelination of the CNS including spasticity, weakness, tremor, ataxia, numbness, cognitive disabilities, bladder and bowel dysfunction, blurred and double vision, and occasionally apraxia (total or partial loss of the ability to perform coordinated movements or manipulate objects in the absence of motor or sensory impairment); 2) secondary symptoms which originate because of the presence of primary demyelination such as contractures, urinary tract infections, and obesity, and 3) tertiary symptoms which emanate from the psychological, vocational or marital stress of a chronic disease (Schapiro RT, Baumhefner RW, & Tourtellotte WW, 1997).

Primary neurological symptoms reflect the location of the lesion in the CNS; for example, visual loss reflects lesions of the optic nerve; hemi-, para-, or quadri-paresis; with or without bladder dysfunction, reflects a lesion of the spinal cord; vertigo or diplopia (double vision), corresponds to a lesion of the brain stem; and ataxia, a lesion of the

cerebellum (Weinshenker & Lucchinetti, 1998). As many as 50% of MS patients experience vision loss as an initial presenting symptom, while 80% eventually end up with some degree of visual impairment (McDonald & Barnes, 1992; Leibowitz & Alter, 1968; Sorensen, Frederiksen, Bronnum-Hansen, & Petersen, 1999). Neuro-ophthalmologic manifestations of MS can occur due to the impact of the disease in the afferent or the efferent visual system.

Afferent Visual System

The most common cause of vision loss in MS patients is optic neuritis (sometimes called retrobulbar neuritis) which is an episode of demyelination in the optic nerve behind the eyeball. Optic neuritis is frequently the initial manifestation of MS. Symptoms associated with optic neuritis include: loss of central vision acuity, pain associated with eye movement, abnormal color vision, visual field defects, altitudinal defects, and visual loss associated with increased body temperature (Uthhoff's phenomenon) (Jacobs et al., 2004). Ocular inflammation including anterior uveitis, posterior uveitis, and periphlebitis (sheathing or cuffing of the retinal veins) can also occur in MS patients (Jacobs et al., 2004).

Efferent Visual System

Visual symptoms as a result of the impact of MS on the efferent visual system include diplopia (double vision), internuclear ophthalmoplegia, nuclear palsies, one-and-a-half syndrome (caused by lesions in the pons), skew deviation and nystagmus (rapid, involuntary, oscillatory motion of the eyeball).

Epidemiology and Prevalence

MS is approximately two times more common in females than in males and recent data suggest that the prevalence among women is increasing (Noonan, Kathman, & White,

2002). The disease is unusual before adolescence, rises steadily in incidence from teens to

age thirty five, and declines gradually thereafter (Sadovnick, Dyment, & Ebers, 1997; Hauser

S, 1994). Onset of the disease is slightly later in males than in females. Marked differences

in the prevalence of MS exist between different populations and ethnic groups, with it being

more common among Caucasians (particularly those of northern European ancestry)

compared to other ethnic groups (Hogancamp, Rodriguez, & Weinshenker, 1997).

MS is a disease associated with temperate climates. In both hemispheres, it occurs

with much greater frequency in higher latitudes (above 40° latitude) away from the equator

(Kurtzke JF, 1977). Migration may also be one of the risk factors for MS. This is backed by

evidence that individuals who move from a region with one risk level to a region with a

higher or lower risk, in general, adopt the risk level of their new home. This is especially

true for people moving from a low-risk to a high-risk area (Gale and Martyn, 1995; Elian

et.al, 2003; Kurtzke JF, 1977).

Conflicting data exists as to whether MS is caused or triggered by an infectious agent

(viral or bacterial) (Granieri et.al, 2001; Munger et.al, 2004; Gilden 2005; Goldacre et.al,

2004). Others have explored whether environmental factors contribute to the onset of MS, or

the probability of MS attacks (Marrie RA, 2004; Casetta and Granieri, 2000). Some studies

suggest that relapses of MS are more likely in the warmer months and less likely in the

colder months (Abella-Corral et.al, 2005; Jin et.al, 2000). Pregnancy is associated with a

decrease in the risk for MS attacks, particularly during the third trimester, while the

postpartum period sees a significant increase in the risk (Salemi et.al, 2004). In certain

populations, a genetic marker, or trait, has been found to occur more frequently in people

with MS than in those who do not have the disease (Hogancamp et.al, 1997). No specific

gene however, has been identified that definitively confers susceptibility to MS (Dyment et.al, 2004; Giordano et.al, 2002). It is thought that aggregation of MS in certain geographical areas, ethnic populations, or families can be explained by common environmental exposure, shared genetic background, or a combination of susceptibility to both (Sotgiu et.al, 2004).

Clinical Course & Prognosis

People with MS can expect one of four clinical courses of disease, each of which can be mild, moderate, or severe. The first, Relapsing-Remitting Multiple Sclerosis (RRMS), is characterized by discrete clinical "attacks" or "relapses" followed by subsequent improvement. These attacks generally evolve over days to weeks and may be followed by complete, partial, or no recovery. Recovery may occur within weeks, months, or sometimes may not occur for two or more years. This is the most common form of MS at the time of initial diagnosis (NICE, 2003). The second possible course of the disease, Chronic Progressive MS, results in gradually progressive worsening without periods of stabilization or remission. Chronic progressive MS however, is largely an outdated term that describes any of the following forms of MS: 1) Secondary Progressive MS; 2) Primary Progressive MS or 3) Progressive Relapsing MS (PRMS).

Many years after onset, a majority of relapsing remitting MS patients will develop a slow, insidiously progressive neurological deterioration (usually progressive gait impairment) over many years, with or without clinical attacks superimposed. This is termed as Secondary Progressive and after 10 years, about 50% of people with relapsing remitting MS will have developed Secondary Progressive (National Institute for Clinical Excellence,

2003b). By contrast, Progressive Relapsing MS follows a progressive course right from the onset, punctuated by relapses. There is significant recovery immediately following relapses similar to Relapsing Remitting MS, but the disease gradually worsens between the occurrences of relapses. Finally, a minority of patients have Primary Progressive MS; which is characterized by a gradual worsening right from the onset, with the complete absence of distinct relapses or remissions. It is relatively rare and patients may show variation in rates of progression over time, occasional plateaus, and temporary minor improvements (National Institute for Clinical Excellence, 2003a).

The prognosis of MS is widely variable. Natural history studies prior to the use of current immunomodulatory treatment showed that, on average, patients achieved a disability score of six on the Expanded Disability Status Scale (EDSS) at a median of 15 years following diagnosis (Weinshenker, 1995). This score implies the requirement of unilateral assistance with ambulation. At the same point in time, about 10-15 % required the use of a wheel-chair, while 20-25 % remained unrestricted in their ambulation, a condition termed benign MS (Weinshenker BG, 1995). Other studies report that trends toward favorable outcomes have been found in patients with optic neuritis, sensory symptoms, and younger age at onset, which are all factors associated with Relapsing Remitting MS. On the other hand, factors associated with Primary Progressive MS, namely motor symptoms and older age have indicated unfavorable outcomes for the patients (Myhr et.al, 2001). Other clinical indicators of relatively good prognosis are female gender, complete recovery from attacks, few attacks, and long inter-attack intervals. Relatively poor prognostic factors also include male gender, predominant cerebellar and motor involvement, incomplete resolution of

attacks, progressive course of onset, frequent early attacks, and short inter-attack intervals (Weinshenker et.al, 2001).

Diagnostic Criteria for Multiple Sclerosis

There is no MS-specific diagnostic test, and the intermittent nature of the disease and high variability in presenting symptoms makes diagnosis difficult. Prior diagnostic criteria for MS have included a combination of both clinical and para-clinical studies. The Schumacher criteria were the first set of diagnostic criteria that were developed in 1965 to make a clinical diagnosis of MS (Thompson et al., 2000). These criteria require two or more episodes of neurological dysfunction at least one month apart or slow stepwise progression for more than six months, plus objective signs of neurological dysfunction on examination displaying dissemination in space (distinctly separate lesions). The diagnosis of MS was not backed by any definitive laboratory tests and was essentially a clinical one.

This was followed by a revision in 1983 by Poser and colleagues (Poser et al., 1983) in order to reflect the advances of para-clinical detection techniques such as Magnetic Resonance Imaging (MRI) which was still in its infancy. Poser and colleagues concluded that clinically definite MS requires two attacks and clinical evidence of two separate lesions, or two attacks with clinical evidence of one lesion and para-clinical evidence of another separate lesion. The revised criteria also included degrees of diagnostic certainty that were identified by categories ranging from clinically definite diagnosis to laboratory-supported definite MS, clinically probable MS, and laboratory-supported probable MS. None of these criteria was appropriate for the diagnosis of Primary Progressive MS, since the basic requirement of episodes of neurological dysfunction cannot be fulfilled.

These criteria were used for about two decades during which the science of imaging technology flourished. Neurologists were hampered by out-dated diagnostic paradigms due to the lack of use of advanced technologic tools (such as MRI). Since MRI shows many clinically silent lesions, it seemed logical to integrate MRI evidence into the diagnostic criteria to achieve an earlier diagnosis of MS. In July 2000, the International Panel on Diagnosis of MS was convened in London, United Kingdom to reassess the Poser criteria and to develop new criteria (McDonald et al., 2001). The panel emphasized that para-clinical evidence like MRI, along with analysis of cerebrospinal fluid (CSF), and visual evoked potentials (VEP), add to clinical diagnosis and may be essential in making a definite diagnosis when clinical presentation alone is not sufficient.

One objective of the panel was to create diagnostic criteria suitable for use by practicing physicians and also for clinical trials. As such, the new McDonald criteria also include a scheme for the diagnosis of the Primary Progressive type of MS. In a prospective study of patients suffering from a clinically isolated syndrome, Dalton and colleagues addressed the added value of the McDonald diagnostic criteria as compared to the Poser criteria (Dalton et al., 2002). The authors supported the clinical relevance of the newer criteria based on higher specificity, positive predictive value, and accuracy for clinically definite MS.

Disease Management

Management of MS may be divided into categories consisting of 1) treatments that affect the long-term course; 2) treating exacerbations; and 3) symptomatic management and rehabilitation.

<u>Treatments that affect the long-term course of the disease</u>

The goal of therapy in patients with MS is to prevent relapses and progressive worsening of the disease (Thompson AJ, Murray TJ, McDonald WI, & Polman C, 2001). Drug treatments can reduce future disease activity for many individuals with relapsing forms of MS, including those with secondary progressive disease who continue to have relapses. These agents decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Disease progression can be treated by administering immunomodulatory drugs namely interferon beta-1a [Avonex & Rebif], interferon beta-1b [Betaseron], and glatiramer acetate [Copaxone] (Thompson AJ et al., 2001).

Copaxone represents an alternative to interferon beta therapy for patients with relapsing remitting MS. Mitoxantrone is an anti-neoplastic agent that exerts potent immunomodulatory effects, and it has been suggested that it may provide a safe treatment alternative for patients with Relapsing Remitting MS, who experience rapid and severe worsening of their disease despite interferon therapy (Correale, Rush, Amengual, & Goicochea, 2005). The risk of cardio-toxicity at higher cumulative doses however, limits the duration of treatment with this drug (Avasarala et al., 2003). All these treatments have been approved by the United States Food & Drug Administration (USFDA) for treating patients with MS (Galetta & Markowitz, 2005).

<u>Treatment for exacerbations</u>

At least 80 to 85% of people with MS have an exacerbation at some time during the course of the disease (Polman). Exacerbations are usually treated with corticosteroids, which may be used as "rescue" therapy, given as monthly boosters in patients who respond poorly

to the immunomodulators (Stangel & Gold, 2005). Corticosteroids are widely used for treatment of acute relapses because of their potent immunosuppressive and anti-inflammatory properties (Pozzilli, Marinelli, Romano, & Bagnato, 2004).

Adrenocorticotropic hormone (ACTH) was the first agent to be helpful in recovery from acute exacerbations. However, intravenous methylprednisolone has become the intervention of choice in recent years, especially because it can be given as a short course (typically 3-5 days), has a rapid onset of action, and is associated with relatively fewer side-effects. Possible mechanisms of action of IV methylprednisolone include restoring the integrity of the blood-brain barrier (Miller et al., 1992), eliciting an inhibitory effect on demyelination (Richert et al., 2001) and possibly, remyelination promotion (Zivadinov, 2005; Stangel et al., 2005). According to the Multiple Sclerosis International Federation (MSIF) Medical Management Committee, plasmapheresis should be considered for those rare cases that present with acute, fulminant symptomatology and do not respond to intravenous steroids.

Symptomatic Management & Rehabilitation

Treating optic neuritis with intravenous (IV) methylprednisolone provides short-term benefits for MS patients with visual problems. In one clinical trial, visual function returned faster in the IV methylprednisolone group compared to oral corticosteroids and placebo, resulting in slightly better vision in visual field testing, contrast sensitivity, and color vision at six months. This difference however, did not last at the end of one year (Beck et al., 1992). The use of corticosteroids and immunomodulatory agents in patients with optic neuritis may also reduce the frequency and severity of developing clinically definite MS (CDMS) (Arnold, 2005). Diplopia in its acute phase can be treated with an eye-patch or with

occlusion of an eyeglass lens. Patients who experience severe diplopia accompanied by symptoms such as vertigo or weakness can also be treated with a course of IV corticosteroids (Jacobs et al., 2004). Medications such as gabapentin, baclofen, memantine, and clonazepam may alleviate symptoms associated with severe nystagmus (Averbuch-Heller et al., 1997).

Identification and treatment of other symptoms besides visual dysfunction is also considered throughout the disease course. Drugs used to relieve common MS symptoms include: (1) muscle relaxants (baclofen, dantrolene) and benzodiazepines (diazepam, clonazepam) to relieve spasms and stiffness; (2) anti-cholinergics, urinary tract anti-spasmodics (oxybutynin), and anti-diuretic hormones (vasopressin, desmopressin) for treating urinary problems; (3) Selective Serotonin Reuptake Inhibitors (SSRIs) (citalopram, fluoxetine, paroxetine, sertraline) and tricyclic antidepressants (imipramine, amitriptyline) for treating MS associated depression and anxiety; (4) CNS stimulants (pemoline, modafinil) for fatigue; (5) anti-convulsants (carbamazepine, phenytoin, acetazolamide) and tricyclic antidepressants for neuropathic pain; and (6) laxatives (bisacodyl) for bowel irregularities (Fox & Cohen, 2001).

Quality of Life (QoL) Research

Historically, the term quality of life has been used in areas of politics, sociology, anthropology and psychology (Bullinger, 2002). Pigou first mentioned it in 1920 with regards to government support for the lower class and its impact on their lives as well as on the national finances (Wood-Dauphinee, 1999). Social science literature also provides many meanings of quality of life ranging from individual fulfillment and satisfaction with life – the satisfaction of basic human needs, the ability to lead a 'normal life' to the quality of the external environment (Bowling, 2001). Social indicators research which developed during the 1960s onwards focused on the importance of measuring subjective well-being as well as external, or objective circumstances of life such as housing, leisure activities, work, the environment and so on. The concerns with subjective indicators led to the first large surveys of life satisfaction, happiness, quality of life and the 'good life' among adults and older people.

The development of quality of life research is characterized by three phases. The first phase in the mid-1970s saw the rise of philosophical work regarding what quality of life is and how to measure it (Bullinger, 2002). In 1977, 'quality of life' became a keyword in the Medical Subjects Headings of the US National Library of Medicine MEDLINE Computer Search System (Wood-Dauphinee, 1999). The second phase corresponds with a more explicit assessment of quality of life and the corresponding development of measurement instruments. Finally in the 1990s, the third phase evolved and was distinguished from the other phases by the inclusion of quality of life instruments/measures in several types of clinical studies.

Health-Related Quality of Life (HRQoL)

Research on valued states of existence has reported that health is among the most valued states, and among the most important areas of life and of quality of life nominated by people (Bowling A & Windsor J, 2001). In a national opinion survey on quality of life related to choice of where to live, Rogerson (Rogerson RJ, Findlay AM, Coombes MG, & Morris A, 1989) found that healthcare provision ranked third in importance among the respondents. In order to narrow its operationalization in clinical research studies, quality of life in this regard is referred to as health-related quality of life (HRQoL).

Health-related quality of life is considered to be a multi-dimensional concept which represents a subjective perception reported by the patients. Mirroring the World Health Organization (WHO) definition of health, Greer (1984) has defined HRQoL as the social, emotional and physical well-being of the patients following treatment. Kaplan on the other hand noted that quality of life as it relates to health, was concerned with the impact of the disease and treatment on disability and daily functioning. Bullinger et.al. (2002) found that HRQoL focused on the impact of perceived health on the individual's ability to live a fulfilling life. Bowling (2001) defined HRQoL as optimum levels of mental, physical, role (e.g. work, parent, career etc.) and social functioning, including relationships and perceptions of health, fitness, life satisfaction and well-being. It should also include some assessment of the patient's level of satisfaction with the treatment, outcome, health status and with future prospects.

The term HRQoL allows us to distinguish widely valued aspects of life which do not fall under the health domain. Although low income, lack of freedom or a good quality environment can adversely affect health, these problems are often distant from health or

medical concerns (Guyatt, Feeny, & Patrick, 1993). Hence, people (clinicians) who assess the impact of disease and treatment on lives of the patients use the term HRQoL. The focus stays on HRQoL, although when ill or diseased, almost all aspects of life can become health-related for the patient (Guyatt et.al, 1993).

Advantages of Assessing HRQoL in Routine Clinical Practice

Measurement of HRQoL in routine practice can have a number of potential benefits to both the clinician and the patient. Clinicians may often stay unaware of significant changes in patient functioning (Nelson et al., 1987), social and even more so, psychological problems (el Mallakh, Wright, Breen, & Lippmann, 1996; Paykel & Priest, 1992; Maguire, Walsh, Jeacock, & Kingston, 1999). While patients may want physicians to ask them about their problems with functioning and well being, such inquiry rarely occurs (Schor, Lerner, & Malspeis, 1995). Quality of life instruments can aid in evaluating quality of care, assessing acceptability of treatment, and in determining the need for physiotherapy or psychological support (Moore, Wolfson, Alexandrov, & Lapierre, 2004). Patients and physicians may have different priorities regarding a certain treatment course or the effect of illness on their lives (Rothwell et al., 1997; Gulick, Cook, & Troiano, 1993), and patients are likely to assign varying importance to different outcomes.

Evidence has shown that patients may not comply with prescribed treatments unless they are actively included in the therapeutic process, understand their condition and its treatment and are motivated to do so (Stanton, 1987; Morrow et al., 2004). Patient-based measures of health present patients with clear information on a range of problems allowing them to learn more about their condition as well as its symptoms and treatment. Such

measures can also provide a standardized method by which physicians can gain information on patients' assessment of their own health, and thus may be useful as a starting point in patient assessment and diagnosis. In these respects, HRQoL information can promote shared decision making and may positively influence doctor-patient communication (Greenhalgh & Meadows, 1999). Using patient-based measures of health to incorporate patients' views in treatment decisions will not only empower them, but can also improve satisfaction with care and adherence to treatment (Stimson, 1974). Health-related quality of life information can also be used to identify aspects of the disease which may otherwise go unattended as they lack clinical relevance, but may be important in explaining disease severity or coping problems (Higginson & Carr, 2001). Health-related quality of life measures can thus complement, rather than replace, clinical evaluation by demonstrating the importance of signs or symptoms to the individual patient (Moore et al., 2004).

HRQoL Assessment

Patrick and Bergner (1990) have noted that the health of the nation cannot be determined specifically with reference to the structure and process of the health care system and require assessment of health and quality of life outcomes. In light of the effect of social inequities and restrictions to health care, they emphasized the use of appropriate and inclusive measures of HRQoL. The second phase in the evolution of quality of life research during the 1980s involved the construction and testing of instruments designed to measure health and HRQoL.

Generic Measures

Measures which are implicitly or explicitly geared to assess HRQoL are usually referred to as generic measures or broader measures of health status. Generic measures are broadly applicable across different medical treatments (Prasad, Rentz, & Revicki, 2003) or health interventions (Pickard, Johnson, & Farris, 1999; Kauppinen, Sintonen, & Tukiainen, 1998), and across demographic (Izquierdo-Porrera et al., 2005; De Oliveira, Barbiere, Santos, Faresin, & Fernandes, 2005) and cultural subgroups (Baker, Jacoby, Gorry, Doughty, & Ellina, 2005). Generic measures have been used in a large number of different populations especially subjects with chronic conditions such as rheumatoid arthritis (Kosinski, Keller, Hatoum, Kong, & Ware, Jr., 1999), multiple sclerosis (Miller et al., 2003), and chronic obstructive pulmonary disease (COPD) (Domingo-Salvany et al., 2002). An example of a generic measure is the Sickness Impact Profile (SIP) which assesses the sickness-related dysfunction in twelve different categories, producing a score for each category. Categories may be aggregated under umbrella terms such as the physical dimension score, the psychosocial dimension score, and an overall score (Miller et al., 2003).

Other commonly used generic health status measures are the Nottingham Health Profile (NHP) (Teixeira-Salmela et al., 2005) and the Medical Outcomes Survey Short Form – 12 & 36 items (SF-12 & SF-36) (Domingo-Salvany et al., 2002; Kosinski et al., 1999). Such wide utilization makes generic quality of life instruments invaluable methods of measurement. Since these measures permit the comparison of different populations and different programs, they are ideal in policy analysis and decision making situations. Continued use of generic measures allows policy makers to compare benefits of different health interventions and facilitate resource allocation decisions. Cummulative knowledge of

HRQoL outcomes will establish the relative burden of diseases which impact our society and the relative success of interventions targeted towards such illnesses. An important constraint of generic measures however, is that they are unable to identify disease-specific aspects that are essential for the measurement of certain outcomes.

Disease-Specific Measures

Disease-specific measurement scales have the goals of being more clinically and socially significant in relation to specific conditions and of being able to discriminate more finely between patients' levels of severity of a particular condition. Since a universal questionnaire for eliciting relevant health status information for a number of conditions would be enormous, use of disease-specific quality of life measures allow brevity. Although it seems intuitive that these measures would be automatically more sensitive to change than the more wide-ranging generic instruments, studies in various disease areas have found conflicting evidence regarding such an assumption (Bessette et al., 1998; Fitzpatrick, Ziebland, Jenkinson, Mowat, & Mowat, 1993a; Hagen, Smedstad, Uhlig, & Kvien, 1999; Harper et al., 1997). Additionally, their narrow focus may mean that they could miss unexpected problems, such as adverse drug reactions. It has therefore been suggested that generic measures, such as SF-36 should act as the core of the outcome measurement, that is to have disease-specific measures be used together with a generic measure. Several disease-specific measures have been developed for a number of conditions including cancer, arthritis and MS (Aaronson N, 2002).

Quality Standards for HRQoL Measures

The choice of a quality of life measure is determined by the research question and the application of measurement in clinical research, practice or policy analysis. HRQoL measures may be used to discriminate among respondents at a point in time, to predict future outcomes and/or events, and to measure changes over time (Kirshner & Guyatt, 1985). The quality standards that a HRQoL measure should meet vary according to the objective of measurement and the specific environment of application. Over the years, the rigors to which quality of life measures should be developed and continually evaluated have been investigated. Tully and Cantrill (1999) stress the importance of continuously evaluating HRQoL instruments, even if they have been in long use in order to provide ongoing evidence of their validity and to ensure that their language and content remains relevant to ever-changing cultures. The following sections will review the measurement properties against which HRQoL measures are judged.

Scaling Assumptions

Scaling assumptions are used to test whether the items are correctly grouped into scales measuring a unique underlying dimension for example, physical function, and if they can be summed without weighting or standardizing to produce a score. Scaling assumptions are examined by determining whether items in each scale have roughly similar distributions of item responses; display equivalence of item means and standard deviations; and possess item internal consistency.

Acceptability

Acceptability of HRQoL measures is determined by the range and distribution of its scores. A measure is considered acceptable if the observed scores are well distributed, and if

mean scores are near the mid-point for each scale. Acceptability of HRQoL questionnaires is also determined by floor and ceiling effects. Floor and ceiling effects represent the percentages of the sample scoring the lowest and highest possible scores respectively, and reflect the extent to which scores cluster at the bottom or the top of the score range. The presence of floor and ceiling effects indicates that the measure may not be able to discriminate between subjects (Mao, Hsueh, Tang, Sheu, & Hsieh, 2002). Floor and ceiling effects over 20% are generally considered unacceptable (McHorney, Ware, Jr., Lu, & Sherbourne, 1994).

Validity

Validity is a statement of confidence that the measure reflects the underlying concept it is supposed to measure rather than something else. It is not a statement about the measurement operations, but a statement about the interpretation about the instrument's score. Validation evidence can be divided into three types namely construct-related, content-related, and criterion-related (Aaronson N, 2002).

Construct validity refers to the degree to which the measure provides results the way it should. It includes face validity which refers to what an item appears to measure based on its manifest content. One of the simpler forms of construct validity is known-groups or concurrent validity. This is based on the principle that certain groups of patients may be anticipated to score in a different manner than others. An instrument is said to be valid if it is sensitive to such differences. Investigators usually select patients in whom differences may be anticipated within groups and as a result even small-sized studies can provide sufficient evidence to confirm that the observed differences are unlikely to be due to chance. It is not the p-value but the magnitude of the differences that is relevant in these situations (Fayers

31

PM & Machin D, 2000). Inter-correlations are used to measure the other two types of construct validity. When a measure correlates well with other measures of the same construct it is said to have convergent validity, and when it correlates poorly with other measures of some other construct it is said to have divergent validity. Advance specification of expected differences based on specific logical relationships among relevant concepts or constructs is necessary to establish this type of validity.

Criterion validity involves assessing an instrument against the true value, or against some standard that is accepted as providing an indication of the true values for the measurement and is divided into concurrent validity and predictive validity (Fayers PM et al., 2000). Concurrent validity means agreement with the true value or "gold standard". Predictive validity, a type of criterion validity is the degree to which a test can predict how well an individual will do in a future situation for e.g. future health status. It is determined by the degree of correspondence between the assessment instrument and the specific criteria used for future performance.

Reliability

Reliability refers to the extent to which a measure yields the same score each time it is administered, all other things being equal. Conceptually, a test score contains a "true-score" component and an "error" component. To the extent that random error is large, a test score will be unstable and hence unreliable. There are two basic ways to evaluate test reliability; internal consistency reliability and reproducibility (e.g. test-retest reliability, inter-observer and intra-rater reliability). Internal consistency reliability is the most frequently used estimate of a measure's reliability. The measure of internal consistency is the average degree of association among the items on a test. Cronbach's alpha, which is an index of

internal consistency of the items, is a popular statistical test of reliability of an instrument.

Commonly accepted minimal standards for reliability coefficients are 0.70 for group

comparisons and 0.90-0.95 for individual comparisons (Aaronson N, 2002). The

interpretation of alpha is that a higher value implies that the responses are more consistent,

and the sum of the item responses yields a score for the underlying dimensions that the items

represent. A low alpha coefficient usually indicates the item does not come from the same

conceptual domain (Williams JI, 1989).

Responsiveness

Responsiveness is also referred to as sensitivity to change and is an important part of

the longitudinal validation of a HRQoL instrument. Responsiveness is the instrument's

ability to detect change, that is, whether the measure can detect differences in outcomes, even

if those differences are small. Analyzing and interpreting changes in health status measures

can be a problem for all longitudinal observational case studies, cohort studies, clinical trials,

or health services evaluation. Changes in physiologic measures such as blood pressure can

be interpreted in terms of prognostic implications and well-established or pre-determined cut-

off point. Changes in generic HRQoL measures are more difficult to interpret, although

small changes in portions of the measure for example the physical or mental scale can be

quite useful. Single score or aggregated measures can make it difficult to identify which

items or components are responsible for change. Even if changes in the scores are found to

be sensitive, the relative magnitude of the change can be difficult to ascertain for example,

how much more meaningful is a five-point difference from a three point difference (Patrick

& Deyo, 1989).

Responsiveness of disease-specific measures may be easier to interpret, because the items on such a measure are closely associated with the clinical measures of the disease activity such as time to walk 8 feet and visual acuity testing in MS patients. Self-assessed improvements by patients which are a common measure of change may be more closely associated with a disease-specific measure compared to a generic HRQoL measure (MacKenzie, Charlson, DiGioia, & Kelley, 1986). In situations where a battery of HRQoL instruments is used, interpreting changes can be cumbersome due to different results presented by the constituent measures of the battery. This is especially difficult when multiple comparisons or statistical tests are necessary (Guyatt, Veldhuyzen Van Zanten, Feeny, & Patrick, 1989). Responsiveness of health status measures in clinical research has been assessed using various sensitivity-to-change coefficients including effect size (ES) (Kazis, Anderson, & Meenan, 1989), standardized response mean (SRM), paired t value (Liang, Fossel, & Larson, 1990; Guyatt, Walter, & Norman, 1987), Guyatt's Responsiveness Index (GRI) (Guyatt et al., 1987), t-value for independent change scores, receiver operating characteristic area curve and correlation coefficients (Spearman's ρ or Pearson's r) (Scrimshaw & Maher, 2001).

For a measure to have clinical usefulness it must not only have the above-mentioned psychometric properties, but it also must be simple, quick to complete, easy to score, and provide useful clinical data. It is imperative that all validation reports describe the conditions under which the validation was conducted, including the demographic characteristics of the sample, and the range of illness or symptoms experienced in the sample.

Choice of HRQoL Measure

Choosing a quality of life measure involves two major decisions: 1) should the measure be generic in nature or should it be disease/condition specific; and 2) whether the measure is sensitive to and appropriate for the patients seen in the particular practice or setting. While designing an optimal strategy for research, investigators need to assign priority weights to measurement objectives. The preference of a generic or disease specific measure depends not only on the psychometric properties described in the previous section, but also the research question at hand. Project aims, methodologic concerns, and practical considerations usually determine the relative use of generic and disease-specific measures in an investigation. Generic measures may be particularly useful for population-based studies used in shaping social policy decisions or in instances where allocation of resource decisions are to be made for large numbers of people (Albrecht, 1996).

Problems may arise, however, if such scales are administered to a broad range of persons with different diseases and chronic conditions like MS and arthritis. Since such populations may place different emphasis on the more generic concepts of health, it may be preferable to use standardized, generic instruments with disease-specific supplements. In the case of quality of life assessment in routine clinical practice, the intelligent approach is to use both generic and disease-specific quality of life measures. This will allow researchers to compare the group of interest with national norms while still staying sensitive to the condition in question. In summary, major factors in selecting a quality of life measure include: the intended use of the results, method of administration, ease of use, psychometric properties (reliability, validity and responsiveness) and the appropriateness of the scale for

the patients being studied and for the location in which it is used (McSweeney & Creer, 1995).

MS-Related Health and Functional Status Measures

  The first quality of life study in the area of MS was published by Rudick et.al. in 1992 (Rudick et al., 1992). This was followed by an increased use of quality of life measures based on the belief that such studies contribute knowledge essential to the health and healthcare of MS patients that is not captured by traditional measures of disease disability. A review by Nortvedt and Riise (Nortvedt et al., 2003) identified 33 different questionnaires used to measure quality of life, of which ten were specifically designed for MS patients.

  This list included the following MS-specific health related quality of life (HRQoL) measures: 1) DIP: Disability and Impact Profile; 2) FAMS: Functional Assessment of Multiple Sclerosis: 3) HAQUAMS: Hamburg Quality of Life Questionnaire in Multiple Sclerosis: 4) LMSQoL: Leeds Multiple Sclerosis Quality of Life; 5) MSQLI: Multiple Sclerosis Quality of Life Inventory; 6) MSIS-29: Multiple Sclerosis Impact Scale; 7) MSQoL-54: Multiple Sclerosis Quality of Life Inventory- 54 Items; 8) QLI-MS: Quality of Life Index- Multiple Sclerosis; 9) QOQL: Quality of Life Questionnaire for Multiple Sclerosis and 10) RAYS: a quality of life scale for MS patients.

  The most commonly used scales in MS measure impairment (objective clinical signs and symptoms), disability (behaviors that are altered or prevented within the illness), or HRQoL (an individual's assessment of how a health problem and its treatment affect the ability to perform valued activities and roles) (Balcer, 2001).

Generic and Disease-Specific Measures

The Medical Outcomes Survey Short Form -36 (SF-36) is considered to be a gold standard generic measure of health status and has been adapted cross-culturally in MS (Ware, Jr. & Sherbourne, 1992; Sharrack, Hughes, Soudain, & Dunn, 1999b; Nortvedt et al., 2001; Brunet et al., 1996; Pfennings et al., 1999b; Pfennings et al., 1999b). It is comprised of 36 items selected from a larger pool of items used by the RAND Corporation in the Medical Outcomes Study (MOS). The SF-36 includes eight domains: 1) physical functioning; 2) role limitations due to physical problems; 3) bodily pain; 4) general health perceptions; 5) vitality; 6) social functioning; 7) role limitations due to emotional problems; and 8) mental health. It also includes a single item that provides an indication of perceived change in health. Factor analyses of the SF-36 health survey provide strong support for a two-factor model of health, with physical health reflected primarily by measures of physical functioning, pain and role limitations due to physical health problems, and mental health reflected primarily by measures of emotional well-being and role limitations caused by emotional problems. Physical and mental component summary scales for the SF-36 health survey scales can thus be derived.

Several studies have shown that problems specific to MS patients are not completely captured by such generic measures, thus rendering them less sensitive and less useful. The physical scale has been known to display marked floor effects for severely disabled patients (Nicholl et al., 2001; Nortvedt, Riise, Myhr, & Nyland, 1999) and the use of the two summary scales seems to be problematic in MS (Nortvedt, Riise, Myhr, & Nyland, 2000; Hobart, Freeman, Lamping, Fitzpatrick, & Thompson, 2001). Hence it is imperative that

MS-specific measures be used to assess quality of life in such patients, either alone or in conjunction with generic measures.

The Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS) is one such MS-specific instrument which was developed as a self-administered questionnaire for HRQoL assessment in MS patients presenting at outpatient clinics (Gold et al., 2001). The HAQUAMS consists of 38 items, 28 of which address the major dimensions of HRQoL in MS, mainly fatigue and thinking, upper and lower limb mobility and mood. The ten additional items assess sensory symptoms, bladder and bowel control, sexuality, recent health changes, disturbed vision and a general self-rating of handicap. All subscales of this measure showed universally high internal consistency reliability except for the mobility scores which were less consistent over time (Gold et al., 2001). Construct validity was supported by associations with other scales as well as objective clinical measures. The HAQUAMS also showed no floor or ceiling effects in all of its five scales showing its applicability over a wide range of disease status.

A follow-up to the validation study by Gold (Gold et al., 2001) found that the scores on the self-reported form of HAQUAMS had satisfactory reliability, but showed a marked discrepancy when compared to scores on clinical rating scales in MS patients with cognitive dysfunction (Gold, Schulz, Monch, Schulz, & Heesen, 2003). It has been used as a HRQoL measure in order to examine the impact of aerobic training on quality of life, among other outcomes in MS patients (Schulz et al., 2004). The use of HAQUAMS, despite its promising psychometric properties, has been limited only to quality of life research studies in Germany. It is the only disease-specific measure besides the FAMS, which addresses all domains of health related quality of life in MS and hence may be a potential candidate for use in routine

care of MS patients in the United States. Since it has only been validated in the German

population, the next logical step would be to test its psychometric properties in English

speaking patients in order to facilitate cross-cultural adaptation.

The Multiple Sclerosis Impact Scale (MSIS-29) is a relatively new disease-specific

questionnaire that measures the physical and psychological impact of MS from the patient's

perspective (Hobart, Lamping, Fitzpatrick, Riazi, & Thompson, 2001). It was developed

using the standard psychometric approach which involved reducing an item pool generated

from people with MS. Its psychometric properties have been evaluated among randomly

selected, geographically stratified members of the Multiple Sclerosis Society (MSS) by

means of large independent postal surveys. It is simple, easy to administer and takes only a

few minutes to complete. Hobart (Hobart et al., 2004) found that it took two minutes and

forty-four seconds to complete in a sample of ten patients (Range= 1 minute 45 seconds to 4

minutes 26 seconds). It was developed to facilitate administration directly to patients in a

clinical or research setting or via a postal survey.

Although the MSIS-29 was found to have acceptable psychometric properties in a

random sample of the MSS, a limitation of this study was that the presence of clinically

definite MS in patients could not be confirmed. Separate studies in the following years tested

the psychometric properties of the MSIS-29 in hospital-based samples (Riazi, Hobart,

Lamping, Fitzpatrick, & Thompson, 2002; McGuigan & Hutchinson, 2004). Riazi (Riazi et

al., 2002) evaluated the psychometric properties of the MSIS-29 in three hospital-based

samples classified as those admitted for rehabilitation, those obtaining corticosteroid therapy

and a postal survey of patients with Primary Progressive MS. These properties were then

compared with data obtained from a community based sample in an earlier study (Hobart et

al., 2001). Expected differences in mean scores were obtained between the three hospital

samples with patients in rehabilitation having the worst scores. In the rehabilitation sample,

the correlation between the MSIS-29 physical scale and the SF-36 physical functioning scale

and the Expanded Disability Status Scale (EDSS) was found to be lower that expected. The

attenuation of this correlation was believed to be due to the limited score distribution of the

SF-36 (range 0 to 65). Overall, the psychometric properties (scaling assumptions,

acceptability, reliability and validity) of the MSIS-29 scales were similar in both the

community and the hospital samples.

Another study out of Ireland compared the responsiveness of MSIS-29 in addition to

these psychometric properties (McGuigan et al., 2004). Responsiveness was evaluated by

comparing mean scores at two time points and was found to exhibit at least moderate effect

size in the static group and the changed group. These studies provide evidence of acceptable

psychometric criteria and preliminary evidence of responsiveness of the MSIS-29 in various

settings. Moreover, it has been found to be useful in assessment of the physical impact of

MS in daily life (Hoogervorst, Zwemmer, Jelles, Polman, & Uitdehaag, 2004).   According to

Hobart (Hobart et al., 2004), head-to-head comparisons of the psychometric properties of the

MSIS-29 and other MS specific outcome measures will help to determine the relative

advantages of different instruments in order to facilitate evidence-based choice of measures.

Functional Status Measures

The consequences of a chronic illness such as MS on the life of the patient can be

systematically described using the World Health Organization's International Classification

of Impairments, Disabilities and Handicaps (ICIDH) (Wood, 1980). The ICIDH is a

classification of "disablements" and covers three dimensions: 1) body structures or functions, i.e. impairments; 2) personal activities, i.e. disability; and 3) participation in society, i.e. handicap. Accurate clinical assessment of disability experienced by patients with MS is of great importance in interventions or pharmacological research and also in clinical practice to identify problems that may be amenable to treatment (Rossier & Wade, 2002). Disability in MS patients however, does not necessarily arise only from impairments (signs or symptoms of MS) but can also occur due to impact on activity domains such as dexterity, communication, work, leisure/domestic activities and personal activities of daily living.

The most commonly used measure of neurological impairment in MS clinical trials is the EDSS (Solari, 2005). The EDSS was derived from the Disability Status Scale (DSS) originally introduced by Kurtzke (Kurtzke, 1955) and its ratings range from 0.0 to 10.0, with 0.5 unit increments (except between 0 and 1). For a rating lower than 4.0, the EDSS score is based on scores from eight functional systems: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual and mental function. Scores above 4.0 are highly dependent on the patient's ambulation status – primarily the ability to walk certain distances and a dependence on assistive devices.

In spite of its dominance in MS research, the Kurtzke scale is documented to have many weaknesses. It has been argued that the Kurtzke EDSS is not a general measure of disability since it uses information derived from the level of impairment to allocate the first three levels and this may be invalid given the variable link between disability and impairment. The six higher grades concentrate on mobility which is just one aspect of disability, while the final grade is death, which is not a disability (Rossier et al., 2002). Since the scores above 4.0 are primarily based on ambulation status, EDSS shows reduced

41

sensitivity to detect change in neurological impairment within this range (Balcer, 2001).

Studies have shown that simple timed measures of dexterity or mobility are much more

sensitive to change (Cutter et al., 1999; Goodkin, Hertsgaard, & Seminary, 1988).

The EDSS has limited reliability partly due to poor judging of distances (the main

differentiating feature between grades) by patients and doctors (Sharrack & Hughes, 1997;

Noseworthy, Vandervoort, Wong, & Ebers, 1990). The quantitative distances between

scores of the EDSS are on an ordinal or a noncontinuous scale, and as a result of this,

summary statistics such as mean and standard deviation may not be entirely appropriate for

reporting such scores (Balcer, 2001). Lastly, it takes time to complete, and requires a trained

neurologist because the functional systems analysis also needs to be completed (Rossier et

al., 2002).

Other commonly used clinical scales in MS research include The Scripps

Neurological Rating Scale (NRS) (Sipe et al., 1984), The Ambulation Index (AI) (Friedman

et al., 2005) and the Functional Independence Measure (FIM) (Granger, Cotter, Hamilton,

Fiedler, & Hens, 1990). The NRS is a reliable and valid measure of impairment and

disability but is unresponsive, while the AI which is a reliable and valid ambulation-related

disability scale is only weakly responsive. The FIM on the other hand was found to be

reliable and responsive, but is rather cumbersome to administer with a limited content

validity (Sharrack et al., 1999b).

The National Multiple Sclerosis Clinical Outcomes Assessment Task Force

developed the Multiple Sclerosis Functional Composite (MSFC) in light of the perceived

problems with existing disability measures (Fischer, Rudick, Cutter, & Reingold, 1999;

Rudick, Cutter, & Reingold, 2002). The scale has three components that yield objective and

quantitative results 1) the Timed 25-Foot Walk; 2) the 9 Hole Peg Test (9-HPT) and 3) the 3-second paced auditory serial addition test. The MSFC can be administered by trained technicians as well as other non-physician personnel. The testing time is about 15 minutes and required facilities to include a quiet examination room with a table or desk and a hallway for the Timed 25-Foot Walk Test. The MSFC has also been validated against patient-reported quality of life measures (Miller et al., 2000). Strong correlations were found with the SIP and SF-36 physical dimensions while significant but slightly weaker correlation was observed with the emotional functioning scale of the SIP.

In order to incorporate a measure focusing on disability in patients with MS, the Guy's Neurological Disability Scale (GNDS) was developed (Sharrack & Hughes, 1999a). The GNDS is based on the concept that disability in MS is multi-dimensional and can be considered in several separate categories. The authors identified twelve separate functional domains of mutually exclusive human functions which can be commonly observed in patients with MS namely: cognition, mood, vision, speech, swallowing, upper limb function, lower limb function, bladder function, bowel function, sexual function, fatigue and "others" to cover disabilities resulting from impairment of less defined systems such as pain, spasms, vertigo, etc.. The GNDS was found to be scientifically sound, displaying good to moderate validity, reliability and responsiveness. The GNDS can be either administered by an interviewer or self-administered, with both formats displaying good psychometric properties (Rossier et al., 2002). The necessary time to perform the GNDS has been documented to be nine minutes, with an additional five minutes required for scoring (Rossier et al., 2002).

Measures of Self-Reported Visual Function

Vision targeted patient-based activity assessments did not occur in the literature before 1980, but the following decades have seen the development of several patient-based visual function assessment instruments and their use in studies among patients with visual impairments (Massof et al., 2001). The National Eye Institute - Visual Function 51-item questionnaire (NEI-VFQ) was the first instrument developed specifically for vision-impaired patients which included items that assess patients' ability to cope emotionally and psychologically with their vision loss. This was administered to patients in the Optic Neuritis Treatment Trial (ONTT) cohort (Cole, Beck, Moke, Gal, & Long, 2000). Self-reported visual dysfunction on the 51-item NEI-VFQ as well as its short-form version Visual Function Questionnaire – 25 items (VFQ) was found to be common among those patients who developed clinically definite MS in the ONTT.

The VFQ consists of 25 items presented in the format of a Likert scale and patients are asked to rate the level of difficulty of particular visual symptoms or activities such as difficulty looking at or using a computer (Mangione et al., 2001). The following vision-targeted subscales are generated: global vision rating (1 item), difficulty with near vision activities (3 items), difficulty with distance vision activities (3 items), limitations in social functioning due to vision (2 items), role limitations due to vision (2 items), dependency on others due to vision (3 items), mental health symptoms due to vision (4 items), driving difficulties (3 items), limitations due to peripheral (1 item) and color vision (1 item), and ocular pain (2 items). It also contains an appendix of additional items from the original version that can be used to expand the scales up to a total of 39 items. The questionnaire can be self-administered by paper and pencil, and also through a personal or telephone interview.

The interviewer format takes approximately ten minutes to administer, while the self-administered format has not been times because it is yet to be tested psychometrically.

The interviewer-administered format of the VFQ was found to have internal consistency and validity comparable to the original 51-item version in a sample of patients with evidence of an underlying eye disease such as diabetic retinopathy and age-related cataracts. This format has also been used to assess and compare self-reported visual function between MS patients and an eye-disease free reference group (Balcer et al., 2000). Mean VFQ composite and selected sub-scale scores with the exception of color-vision, were found to be worse in MS patients compared with the eye-disease free group.

Measures of Depression

Depression screening questionnaires are appropriate for many research efforts due to the cost and time intensive nature of clinically diagnosing depression (Vahle, Andresen, & Hagglund, 2000). Standardized instruments of depression measure depressive symptomatology rather than clinical depression and are commonly used to screen people with disabilities. The Center for Epidemiologic Studies- Depression Scale (CES-D) which was derived from previously validated longer depression scales, is the most widely used questionnaire for depression screening (Vahle et al., 2000; BECK, WARD, MENDELSON, MOCK, & ERBAUGH, 1961; Raskin, Schulterbrandt, Reatig, & McKeon, 1969; BECK et al., 1961). The instrument consists of 20 symptom items associated with depression which are indicative of personality attributes such as self-esteem, state anxiety and trait anxiety (Orme, Reis, & Herz, 1986). The focus of the CES-D is on current symptoms (Kohout, Berkman, Evans, & Cornoni-Huntley, 1993), in that patients rate the frequency of each

symptom item over the past week as a score ranging from 0 (rarely or none of the time) to 3 (most or all of the time). A low average administration time of less than seven minutes leads to a reduction in administrative and respondent burden (Kohout et al., 1993).

The CES-D has been used among individuals with various disabling conditions including spinal cord injury, stroke and MS (Holicky & Charlifue, 1999; Shinar et al., 1986; Romberg, Virtanen, & Ruutiainen, 2005; Patten, Fridhandler, Beck, & Metz, 2003). The validity and reliability of the CES-D were tested in a large sample of MS patients, general practice patients and healthy workers (Verdier-Taillefer, Gourlet, Fuhrer, & Alperovitch, 2001). The four factors of the questionnaire explained more than 50% of the variance in each of the sample groups. Reliability was found to be excellent with Cronbach's α of 0.90 in patients with MS. The positive predictive value of the questionnaire was evaluated in patients who were candidates for disease-modifying MS treatment (Pandya, Metz, & Patten, 2005). The CES-D result was impressive, with 38 (74.5%) of a total of 47 patients with a positive test result were found to have a depressive disorder.

Psychometric Comparison of HRQoL Measures

Only three reported studies have concurrently compared the psychometric properties of MS-specific HRQoL measures. Riazi et.al. (2003) examined and compared the full range of psychometric properties of the MSIS-29 with the 59-item FAMS and the SF-36. The analysis however, was limited only to the physical and psychological scales from each of these measures in order to ensure that only similar domains were being compared. The comparison was performed in a sample of adults with clinically definite MS who were consecutively admitted to a hospital for rehabilitation or intravenous steroid treatment. The

authors examined the complete set of psychometric properties including scaling assumptions, acceptability, reliability, convergent and discriminant construct validity, and responsiveness. Patients were asked to complete the questionnaires on admission and discharge (rehabilitation) or on admission and six weeks later (steroids).

A substantial floor effect (20%) was detected for the SF-36 physical function scale, but not for the physical scales of the other measures. The reliability of the mobility scale of FAMS was lower than the acceptable level set for this study. With regards to responsiveness, the MSIS-29 performed better compared to the SF-36 and FAMS in both the physical and psychological scales. This evidence suggests that the MSIS-29 is more likely to detect clinically significant changes in the impact of MS. Relative efficiency statistics indicated that the other scales were 26% (SF-36 physical function) and 63% (FAMS mobility) as efficient at detecting change as the MSIS-29 physical scale. Although the MSIS-29 displayed better psychometric properties than the other measures, the authors have acknowledged the need for continuing comparisons among MS-specific HRQoL measures.

Another study of psychometric properties of MS related health status measures, evaluated the reliability, scale score distributions and the relationship of the measures to a set of specifically designed criterion variables (Vickrey et al., 1997). The quality of life measures included the SF-36 as the generic measure and the Quality of Life Questionnaire for Multiple Sclerosis (QOLQ) and the Multiple Sclerosis Activities of Daily Living Scales (MS-ADL scales) as the disease-specific measures. The study involved sending a mail survey to 171 patients with definite MS who attended the Multiple Sclerosis Clinic at the University of California at Los Angeles (UCLA). The SF-36 was supplemented with three scales which covered dimensions felt by expert opinion and a review of literature to be

highly relevant to individuals with MS (Vickrey, Hays, Harooni, Myers, & Ellison, 1995).

The SF-36 with supplemental scales showed marked floor and ceiling effects on the role

limitations due to physical problems and role limitations due to emotional problems scales,

respectively. The MS-ADL also showed noteworthy ceiling effects on a couple of scales,

while the QOQL showed no discernable floor or ceiling effects.

Results from relative validity analysis and the stepwise regression procedure

indicated that the disease-targeted components (cognitive function scale, mobility and self-

selected physical problems scales from the QOQL and the MS-ADL social and social (help)

scales) of HRQoL in MS contributed important unique information to researchers. Although

supplementing SF-36 with certain disease-specific components was found to be useful, no

one measure was clearly and consistently superior or worse than others in terms of reliability

and construct validity. One important limitation of this study was that the authors did not

evaluate the responsiveness of these measures to change. This makes it difficult to

generalize the findings of this study to all studies of MS, particularly those which are

longitudinal in nature.

The MSQoL-54, FAMS and EuroQol (standardized outcome measure developed by

the EuroQol Group) were administered to 128 MS patients in contact with a rehabilitation

ward or a consultant in rehabilitation medicine (Nicholl et al., 2001). The purpose of this

study was to assess the relative importance of the EuroQol (EQ-5D) compared to a MS-

specific and a generic quality of life questionnaire. The EQ-5D failed to perform well, owing

to the three point scale which was found to be lacking in discrimination within a highly

disabled sample. Since the visual analogue health state scale on the EQ-5D did not show

high correlations with any other mood or disability measures, the claim that it measures quality of life remained unsubstantiated.

The MSQoL-54 was found to have large floor effects on the physical health and role limitations due to the physical problems subscales. The FAMS motility subscale however, had no noticeable floor effects even though a large percentage of the study sample were restricted to a wheelchair (66.6 %). Some patients found certain items in all three questionnaires to be offensive due to their obvious limitations. The FAMS was found to be the better of the three questionnaires owing to the presence of a number of subscales relevant to MS and the lack of floor and ceiling effects. Since this study included a number of disabled MS patients, the generalizability of the results to patients with milder symptoms is suspect. Additionally the important property of responsiveness of these measures was left out of this analysis.

Use of Quality of Life Information in Clinical Practice

Knowledge of usefulness of health related quality of life (HRQoL) assessment in clinical practice such as documentation of the natural history of a disease, evaluating treatment effectiveness and improving clinical case management has been present since the early nineties. There have been attempts to move the formal evaluation of quality of life assessment into the clinical setting, but it has been difficult to anticipate the impact of such assessments in physician-behavior and patient care as well as decision making (Greenfield & Nelson, 1992). A shift towards HRQoL assessments, in order to be accepted by clinicians should not only benefit the patients, but also enhance the clinician's ability to function. This requires that the argument for use of HRQoL measures should be made on practical basis and

not purely on theoretical grounds (Hayes, 1998). Although some evidence of practicality of MS-related HRQoL measures is available from studies comparing their psychometric properties, there remains a need for a study exploring a neurologist's behavior and attitude in relation to QOL information.

Assessments of the behavior and attitude of physicians regarding routine measurement of HRQoL in patients with chronic conditions such as cancer (Bezjak et al., 1997; Bezjak et al., 2001), hematopoietic stem cell transplantation (Lee et al., 2004), diabetes (Meadows, Rogers, & Greene, 1998) and rheumatoid arthritis (Russack et.al; 2003) have been well documented. Such studies have provided varying results regarding physician use, knowledge and attitude regarding quality of life information in treating patients with chronic conditions. In a survey of general practitioners (GP) and practice nurses, it was found that almost half of the personnel were unclear as to how the health outcomes data obtained during routine care of patients with diabetes was used. In terms of outlook towards QOL information, the results conveyed that both GP's and nurses showed a positive overall attitude towards health outcome measurement (Meadows et al., 1998). Another study in a hospital setting found that most physicians had poor knowledge of quality of life assessment instruments and this was influenced mainly by the age of the physician and the department of practice. Young physicians and those working in oncological departments seemed to have more knowledge about health status measures (Belli et al., 1994).

Oncology practice has made great strides relating to research regarding quality of life assessment in clinical care of cancer patients. Bezjak and colleagues have published a series of research publications regarding the perspectives of oncologists regarding the use of quality of life information in clinical practice using the MD-QOL, a self-administered questionnaire

developed specifically for this purpose (Bezjak et al., 1997; Bezjak et al., 2001; Bezjak et al., 1997; Bezjak, Taylor, Ng, MacDonald, & Depetrillo, 1998; Taylor, Macdonald, Bezjak, Ng, & Depetrillo, 1996). The MD-QOL was constructed on the basis of in-depth interviews with sixty American and Canadian oncologists and was designed to assess physician perceptions of QOL and QOL information. Another study among rheumatologists noted that although 63% felt that patient self-report questionnaires were useful in clinical decision making, 48% of the respondents stated that none of their patients completed HRQoL self-reports in routine care. Only 19% of the rheumatologists had at least 50% of their patients complete self-report health status measures. Older rheumatologists were found to be most likely to endorse patient self-report questionnaires (Russak et al., 2003).

Quality of life information has been known to provide useful information to researchers by adding to existing clinical knowledge. Velikova and colleagues found that a larger proportion of patients in the intervention group (those who regularly completed HRQoL measures) showed clinically meaningful improvement in their HRQoL. Better HRQoL and emotional functioning was attributed to the indirect impact of patient-physician communication. Another randomized controlled trial in epilepsy patients at a neurology clinic found that routine use of the SF-36 provided physicians with new information in 63 per cent of the patients in the intervention group (Wagner et al., 1997). Thus, the routine use of health status measures enhanced patient care by prompting changes in therapy in 13% of the patients and by facilitating communication with physicians. The HRQoL has also been reported to be useful for informing patients of common reactions and choices made by patients with similar diagnosis (Bezjak et al., 2001).

It has been noted that HRQoL instruments are not commonly used in routine care of patients with MS. In order to achieve this practice, it is important to assess the neurologists' attitude, beliefs and barriers to the use of HRQoL information. However in order to gain a complete understanding of the neurologists' intention to assess HRQoL information, a complex approach that considers several factors may be required. Social psychological models such as the Theory of Planned Behavior (TPB) may be helpful in such situations to better identify the key determinants of behavioral intention. The TPB proposes that an individual's behavior is predicted by the strength of their intention to behave in that way. There are three variables that predict behavioral intention: attitude, subjective norms and perceived behavioral control, which in turn can be predicted from an individual's belief. Attitude towards a behavior is said to be a result of the belief about the likely outcome of the behavior (behavioral beliefs) weighted by an evaluation of the importance of the consequence (outcome evaluation). Subjective norm is assumed to be predicted from beliefs about the views of other important individuals or groups (normative beliefs) weighted by a persons motivation to comply with these groups (motivation to comply).

Perceived Behavior Control (PBC) is predicted by beliefs about factors likely to facilitate or inhibit the behavior (control beliefs) weighted by the person's evaluation of the power that each of these factors has to affect their behavior (power). The TPB is commonly used to study behavioral intentions and behavior in patients but has also been found to be relevant to healthcare providers as well (Millstein, 1996). Hu and Chau, 1999 used the TPB to investigate technology acceptance among physicians who practiced in public tertiary hospitals in Hong Kong and found that attitude and perceived behavior control are important predictors of this behavior. Another study utilized the framework of the TPB to examine

predictors of physicians' adherence to national guidelines for management of employees with mental health problems (Rebergen et al., 2006).

Another such model, the Transtheoretical Model of Change (Prochaska, DiClemente, & Norcross, 1992) has been used to conceptualize the process of intentional behavior change among health care professionals. Park and colleagues (2003) found this model to be useful in establishing future interventions to help understand and guide physician's behavior towards increasing adoption of smoking cessations interventions with their patients. Similarly Price and colleagues (2006) used the model to identify Ohio obstetricians/ gynecologists' use of nicotine replacement therapy with pregnant smokers. The Transtheoretical Model of Change focuses on the decision making of the individual where the stage construct is the key organizing construct of the model. The Transtheoretical Model defines change as a process involving progress through a series of five stages: precontemplation, contemplation, preparation, action and maintainence and has been used in the past to improve physician delivered counseling (Keller, Donner-Banzhoff, Kaluza, Baum, & Basler, 2000) and adherence to cancer screening guidelines among healthcare professionals (Honda & Gorin, 2006; Hersberger, Botomino, Mancini, & Bruppacher, 2006).

Precontemplation is the stage, in which people are not intending to take action in the foreseeable future. People in this stage are generally uninformed or under-informed about the consequences of the behavior in question. In the contemplation stage, people are intending to change in the next six months, while in the preparation stage they are intending to take action in the immediate future, usually measured as the next month. Action is the stage in which people have made specific modifications in their behavior within the past six months and since action is observable, behavior change often has been equated with this

stage. The final stage is that of maintenance in which people are working to maintain the behavior change for a long time. Behavior change is rarely a discrete, single event and an individual moves gradually from being uninterested (precontemplation stage) to considering a change (contemplation stage) to deciding and preparing to make a change. Most people find themselves recycling through the stages of change several times before the change becomes truly established. The Transtheoretical model also incorporates an intervening or outcome variable called decisional balance (the pros and cons of change). These decisional balance measures have become critical constructs in the Transtheoretical model. The pros and cons combine to form a decisional "balance sheet" of comparative potential gains and losses where the balance between the pros and cons varies depending on which stage of change the individual is in.

Chapter 3: Methods

Conceptual Model

The focus of this study was health-related quality of life (HRQoL) in non-institutionalized patients with multiple sclerosis (MS) and is illustrated by the conceptual model in Figure 1. Health-related quality of life is a multi-dimensional concept which can be measured by any one of several patient reported outcome (PRO) measures. Health-related quality of life may be influenced by several factors, especially in a progressive disease such as MS. One objective was to determine factors that have an *independent* and *significant* impact on HRQoL. As such, the influence of clinical, demographic and other relevant factors was investigated.

Measurement of HRQoL and identification of its predictors is relevant beyond the realm of research and may be very useful if incorporated into clinical practice. Incorporation into practice will depend upon the *choice* of the measure and the *intention* of neurologists to use such information. Deciding on a HRQoL measure for use in routine practice can be an arduous task and may be best addressed by facilitating evidence-based choice. This was accomplished by comparing currently relevant measures on various psychometric properties as well as preferences of MS patients and neurologists regarding these measures. Preferences regarding their relevance, usefulness, wording, and length were assessed.

Simplifying such decisions may not be sufficient to promote acceptance of HRQoL among neurologists. It is necessary to understand what other factors may be associated with the willingness of neurologists to utilize HRQoL information. These were investigated by

Factors affecting HRQoL
Clinical Factors:
Disability, Depression, and Visual Impairment

Demographic Factors:
Age, Gender, Marital and Employment Status

Other Factors:
Duration of disease, Comorbid Conditions

Health-Related Quality of Life in Multiple Sclerosis

Application of HRQoL in clinical practice

Choosing a suitable patient reported outcome questionnaire in the routine care of MS patients

Psychometric Properties: Acceptability, Scaling Assumptions, Reliability, Validity and Responsiveness

Patient Preferences: Length, wording, Relevance to Daily Functioning

Physician Preferences: Usefulness, Wording, Length

Intention of the neurologists to assess HRQoL information in patients with MS

Stage of Change (TTM)

Attitudes (TPB)

Subjective Norms (TPB)

Behavior Control (TPB)

Demographic Factors:
Age, Gender

Other Factors:
Experience, Patient Load, Participation in MS-Related Clinical Trial, Place of Practice

– · – · – · – = PHASE I
═══════ = PHASE II

Figure 1: Conceptual Model

56

using a framework of the Theory of Planned Behavior (TPB) and the Transtheoretical Model of Change (health behavior theories).

Phase I involved collection of primary data from a sample of non-institutionalized MS patients. Data from Phase I was used to measure HRQoL, identify factors affecting HRQoL, compare the HRQoL measures on their psychometric properties, and assess patient preferences. A mail survey of neurologists was performed in Phase II. This data facilitated investigation of: neurologist preferences regarding the HRQoL measures used in Phase I; intention of neurologists to use HRQoL information in practice; and factors that have a significant influence on this behavioral intention.

Phase I

Research Design

The study design was longitudinal involving a convenience sample of patients with multiple sclerosis (MS) at a large university hospital. The study involved completion of a battery of patient-reported outcome (PRO) measures and quantitative tests of motor function by the patients at the time of enrollment (Baseline, Time 1). Those patients who successfully completed baseline assessments were asked to complete selected self-report questionnaires via mail three to six months later (Time 2). A monetary reimbursement was given to all participants following successful completion of questionnaires and/or tests at each time point. The timeline for this study was March 2006 to October 2006.

Study Population

Patients were included in this study if they were diagnosed as having clinically definite MS and were treated for MS by at least one of the staff neurologists prior to baseline data collection. Clinically definite MS was confirmed by neurologists using the McDonald's diagnostic criteria (discussed in the background section). Following identification of this population, patients were excluded for any of the following reasons: 1) patients who had an exacerbation (relapse) in the four weeks prior to enrollment; 2) those less than 18 years of age; 3) those who were not literate in English; 4) those who were pregnant; and 5) those who were not willing, or were unable to complete a series of questionnaires owing to cognitive or functional limitations. These exclusion criteria were adapted from previous MS literature (Patti et al., 2003). One hundred and sixteen patients meeting these criteria were identified from the records of the outpatient neurology clinic at Ruby Memorial Hospital in Morgantown, West Virginia. The sample consisted of those MS patients who were seen regularly at the clinic, including those having a recent diagnosis of MS being seen for a second opinion, as well as patients referred for consultation about management of MS. Approval for the study was obtained from the West Virginia University Institutional Review Board (WV-IRB).

Two weeks prior to their scheduled appointment patients were mailed a letter printed on university letterhead, endorsed by their attending neurologist (Appendix A). The letter provided a short description of the study and encouraged patients to participate. It also asked them to account for some additional time during their upcoming visit, if they were interested in taking part in the study. Physician endorsement was utilized in order to improve chances of patient participation. Following their arrival at the outpatient clinic at Ruby Memorial

Hospital, the attending staff neurologist reminded the patient about the study and introduced them to the principal investigator (PI). The PI then described the study to the patient and invited them to participate. Informed consent statements were read to patients who were willing to participate and patient signature was obtained before any questionnaires or tests were administered.

Instrument Selection

Selection of Measures for Psychometric Comparison

Selection of a HRQoL instrument generally depends upon the specific context in which the instrument is going to be used (Holcik and Koupilova, 1999). Since the focus of this study was HRQoL assessment in routine clinical practice, brevity of the instrument was one of the main inclusion criteria. Questionnaires that were too long would be tiresome to complete and might decrease the number of subjects willing to participate. The candidate quality of life measures were also required to be self-administered, valid, available in English, and previously applied in a sample of patients with MS. Based on these criteria, the SF-36 was selected as the generic measure while HAQUAMS and MSIS-29 were selected as the MS-specific quality of life measures. The HAQUAMS is one of the few MS-specific measures that addresses most relevant domains of HRQoL. The MSIS-29 has been shown to have good psychometric properties in comparison to commonly used measures such as the Multiple Sclerosis Quality of Life – 54 Items (MSQ0L-54) and the Functional Assessment in Multiple Sclerosis (FAMS). Finally, in absence of a gold standard HRQoL measure in MS, the SF-36 was chosen as a generic comparator for this study.

<u>Reasons for Exclusion of Other HRQoL Measures</u>

FAMS although commonly used has been shown to have lower reliability on its motility scale compared to the MSIS-29 (Riazi et al., 2003). Additionally, eleven items of HAQUAMS were derived from it, as such FAMS was not chosen as a comparator in this psychometric comparison. The MSQoL-54 was excluded due to poor psychometric evidence and the respondent burden (patients have to complete 54 items) that it poses. The MSQoL-54 was developed as a disease-specific quality of life measure for MS and consists of the 36 items of the SF-36 and an additional eighteen condition-specific items. However, in comparison with the SF-36, the MSQoL-54 was found to have no better psychometric properties than the former and hence excluded. It was found to display marked floor and ceiling effects and poor responsiveness and in addition, its sexual function and satisfaction scales had a high proportion of missing data. Additionally, the MSQoL-54 overall quality of life scale showed only moderate correlations (r= 0.34 to 0.45) with four measures of varying constructs (Expanded Disability Status Scale, Functional Independence Measure, London Handicap Scale, General Health Questionnaire) implying that it does not address a single underlying construct (Freeman, Hobart, & Thompson, 2001). From among the other HRQoL measures specific to MS, the Multiple Sclerosis Quality of Life Inventory (MSQLI) was not included due to its length (takes approximately forty-five minutes to complete) and RAYS Quality of Life Scale in Multiple Sclerosis due to absence of validity and reliability studies in more than one setting.

<u>Selection of a Outcome Measure for Objectives 2 and 3</u>

Total and sub-scale HAQUAMS scores were used as quality of life outcome variables (dependent variable) for Objectives 2 and 3. The HAQUAMS was chosen for this purpose over SF-36 and MSIS-29 because; not only is it MS-specific but it also addresses aspects of patients other that just physical and psychological functioning. Although commonly used, the SF-36 is still considered as a generic measure of quality of life, while MSIS-29 is reported to be a measure of physical and psychological impact of MS and not of overall quality of life

Data Collection

The protocol for phase I involved the completion of a battery of PRO measures, and quantitative tests of motor function by all patients who consented to participate in the study. Data was collected in a private area at the neurology clinic at Ruby Memorial Hospital. First, the PI administered the Guys Neurological Disability Scale (GNDS) (see Appendix B), and the Visual Function Questionnaire (VFQ) (see Appendix C) to the patients. Each patient was then asked to complete the Centers for Epidemiological Studies- Depression Scale (CES-D) (see Appendix D). The CES-D assesses depressive symptoms and is *not* a clinical measure of depression. The terms *depressive symptoms* and *depression* will be used interchangeably for the purpose of this study. An additional questionnaire (see Appendix E) gathered information regarding age, gender, race, employment status, marital status, number of comorbid conditions, and duration of the disease.

Comorbidity data were collected by asking the respondent specifically if they were ever diagnosed or treated for the presence of any of a number of disease conditions (see Appendix F). For the final analysis, comorbidities for each patient were calculated as a

simple count of twelve common chronic diseases. These diseases included: arthritis, diabetes, asthma, chronic obstructive pulmonary disease, high blood pressure, high cholesterol, back problems, stomach ulcers, sexually transmitted disease, cancer, thyroid problems and any category of heart disease. Duration of disease was expressed as the time since diagnosis with MS. Patti and colleagues (2004b) have suggested that most patients with MS remember the exact year they were diagnosed. However, it is more difficult to know exactly when the onset of the disease occurred. The instructions for each questionnaire were reviewed with the patients and the PI sat in a nearby area and was available to clarify any questions that the patients had while completing the questionnaires.

Following the completion of the questionnaires, the patients were asked to complete two quantitative tests of motor function from the Multiple Sclerosis Functional Composite (MSFC): the Timed 25-Foot Walk Test and the 9-Hole Peg Test (9-HPT). The MSFC is a three-part, standardized, quantitative, assessment instrument for use in clinical studies, particularly clinical trials of MS. The instructions for each quantitative test of motor function were given exactly as they appeared in the MSFC manual. The Timed 25-Foot Walk is a quantitative mobility and leg function performance test in which the patient was directed to one end of a clearly marked 25-foot course and was instructed to walk the marked distance quickly, but safely. The time was calculated from the initiation of the instruction to start till the patient reached the 25-foot mark. This task was immediately administered again by having the patient walk back the same distance. This test allowed the use of assistive devices if necessary and the score was the average of the two completed trials. Total administration time of the test varied from one to five minutes depending on the ability of the patient.

Both, the dominant and the non-dominant hands of the patient were tested twice using the 9-HPT (a total of four trials). The patient was asked to sit at a table with a small, shallow container holding nine pegs and a wood or plastic block with nine empty holes in it. The patient was then asked to pick up the pegs, one at a time as quickly as possible and put them into the nine holes and once all the pegs were in place, the patient was to remove them one at a time as quickly as possible and replace them in the shallow container. The time to complete this activity from start to finish was recorded. The score on the 9-HPT was calculated as the average score (time of completion) of the four trials. Administration time for this test was usually less than ten minutes, and varied depending on the ability of the patient. During the administration of these tests (Timed 25-Foot Walk & 9-HPT), only the PI and the patient were present in the testing room and all potential external distractions were kept to a minimum.

Following these assessments, the patients were given a booklet (see Appendix G) which contained three health-related quality of life (HRQoL) questionnaires along with a business reply envelope. These questionnaires were randomly ordered in each booklet and consisted of: (1) the Medical Outcomes Survey Short Form- 36 items (SF-36); (2) the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS); and (3) the Multiple Sclerosis Impact Scale (MSIS-29). Additionally, information regarding approximate time of completion and opinion regarding ease of use and relevance of content for each of the questionnaires in the booklet was also collected. Questions assessing these additional properties were included at the end of each HRQoL questionnaire. Patients were asked whether they considered each questionnaire to be long, complex or difficult to complete. The responses of these questions were on a scale of 1 to 3 (where 1=not at all,

63

2=somewhat and 3=very much so). Questions relating to patient preference and assessment of practicality have been adapted from pervious research for the purpose of this study (Cooley et al., 2005; Bouchet, Guillemin, Paul-Dauphin, & Briancon, 2000). The patients were asked to complete this booklet at home and return it in the mail within one week.

Three to six months following the initial assessment (Time 2), all patients who successfully completed all questionnaires and tasks at the time of the first assessment, were mailed a second booklet containing the same set of three quality of life questionnaires, again randomly ordered. The patients were asked to send the booklet back by mail in the accompanying business reply envelope within one week of receiving it. This was done in order to examine the responsiveness of the three measures (SF-36, HAQUAMS and MSIS-29).

Instrument Scoring

Medical Outcomes Survey Short Form (SF-36)

The SF-36 consists of eight sub-scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. These sub-scales are scored such that a higher score indicates a better health state, for example, functioning scales are scored so that a high score indicates better functioning and the pain scale is scored so that a high score indicates freedom from pain. Scoring for each sub-scale in the SF-36 was performed in the following steps

(1) Data Entry: Data was entered as coded in the questionnaire.

(2) Recoding for ten items that require recoding: Item recoding is the process of deriving the item values that will be used to calculate scale scores. Recoding involves changing out-of-

range values to missing, reverse coding of items and substituting person-specific estimates for missing items.

(3) Dealing with missing data: It is recommended that a scale score be calculated if the respondents answer at least half of the items in a multi-item scale (or half plus one in the case of scales with an odd number of items)

(4) Computing a raw score: This score is a simple algebraic sum of responses for all items in a particular sub-scale

(5) Transformation of scale scores: The raw scales are transformed to a 0-100 scale in order to convert the lowest and highest possible scores to 0 and 100 respectively. Scores between these values represent the percentage of the total possible score achieved. This was calculated using the following formula:

Transformed Scale = $\dfrac{\text{(Actual raw score- lowest possible raw score)}}{\text{Possible raw score range}} \times 100$

Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS)

The final English version of the HAQUAMS consists of 38 items which are used as the basis for computation of five subscale scores reflecting major dimensions of HRQoL in MS: fatigue/thinking (four items), lower limb mobility (five items), upper limb motility (five items), social function (six items) and mood (eight items). Most items are scored from one to five where "1 = not at all" and "2 = very much". A total of eight items (item numbers 15, 23, 25, 26, 34, 35, 36 and 37) are positively worded for example, "I am satisfied with my sex life" or "I get support from my family". Sub-scale raw scores were computed by first recoding the positively worded questions, so that high scores indicate a low quality of life in all questions. Mean scores were then computed for all subscales and mean substitutions were

allowed for missing items. Subscales were not calculated if more than 20% of the items were missing (Gold et al., 2001).

Multiple Sclerosis Impact Scale (MSIS-29)

The MSIS-29 was used to calculate two scores; physical impact score and psychological impact score (Hobart et al., 2004). The physical impact score was calculated by summing item numbers 1 through 20. This score was transformed to a score on a scale of 0-100 using the following formula:

$$\frac{100 \text{ x (observed score} - 20)}{100 - 20}$$

As in case of the physical impact score, the psychological impact score was calculated by summing items 21 through 29, and then transformed to a score on a scale of 0-100 using the following formula:

$$\frac{100 \text{ x (observed score} - 9)}{45 - 9}$$

Guy's Neurological Disability Scale (GNDS)

The GNDS is divided into twelve separate categories each with an interview and scoring section. Each sub scale was scored from 0 to 5, representing disability grades ranging from "0 = normal status" to "5 = total loss of function: maximal help required". An overall score of the patients total disability was obtained by summing up all different sub-scores giving a sum score ranging between 0 (no disability) and 60 (maximum possible disability) (Sharrack et al., 1999a).

Visual Function Questionnaire (VFQ)

The VFQ was scored in a two step process. First, the original numeric values from the survey were re-coded following scoring rules outlined in Table 1. A higher score represents better functioning. Each item was converted to a 0-100 scale so that the lowest and highest possible scores were set at 0 and 100 points. This format allows scores to represent to the achieved percentage of the total possible score. In other words a score of 50 represents 50% of the highest possible score. Following this procedure, items within each sub-scale were averaged together to create 12 sub-scale scores. Items contributing to each specific sub-scale are presented in Appendix H. In the case of missing data, the items were not taken into account when calculating scale scores. A sub-scale score was generated only when at least one item was answered within that sub-scale. The VFQ sub-scale scores were generated based on the average of all items in the sub-scale that the respondent answers.

Centers for Epidemiological Studies Depression Scale (CES-D)

The Centers for Epidemiological Studies – Depression scale can be scored in three steps. First, sixteen items in this instrument are assigned one value in the following manner for each response category; rarely or none of the time (less than one day) = 0; some or a little of the time (1-2 days) = 1; occasionally or a more moderate amount of time (3-4 days) = 2 or more or all of the time (5-7 days) = 3. For four items, namely questions 4, 8, 12 and 16, this scoring is reversed. Once the value is assigned for each item, a total is computed by adding the values for each of the twenty items. The resulting score usually ranges between zero and sixty. The total is not computed if more than four answers are missing. Higher scores on the CES-D indicate higher levels of distress (depressive symptomatology and not clinical depression).

Analysis for Phase I: Objective 1

For Phase I, Objective 1, the following five psychometric properties were examined and compared for the SF-36, HAQUAMS and MSIS-29: scaling assumptions; acceptability; validity; reliability; and responsiveness.

Scaling Assumptions, Acceptability and Patient Preferences

Item internal consistency was examined by calculating the Pearson's *r* between each item and total scale score. An item correlation with its domain (total scale score) of at least 0.30 was considered a valid indicator of scaling success (Riazi et al., 2003). Descriptive analyses were performed for floor and ceiling effects (percentage of respondents having the lowest and highest possible scores respectively), time of completion and patient opinion regarding ease of use and relevance of content of the PRO measures. Floor and ceiling effects less than 20% were considered as a criterion of acceptability in this study (McHorney et al., 1994).

Validity

Construct validity (convergent and divergent validity) was tested using multitrait-multimethod (MTMM) analysis (CAMPBELL & FISKE, 1959; Langfitt, 1995; Campbell DT & Fisk DW, 1959). The MTMM is simply a matrix or table of correlations arranged to facilitate the interpretation of the assessment of construct validity. The MTMM makes it possible to examine both convergent and divergent validity of various scales simultaneously using one matrix. The general principle of this technique is that two or more methods, for example different instruments can each be used to assess the same traits such as quality of life aspects, items or subscales (Fayers PM et al., 2000).

In the present study, scales assessing both, similar and different dimensions were chosen from each measure based on scale names. The physical and psychological sub-scales from each of the HRQoL measures were used: SF-36 physical functioning, MSIS-29 physical impact scale and the HAQUAMS upper and lower mobility subscales. Convergent validity was examined as the average of the correlations among pairs of scales measuring the same concept. Divergent validity was tested by comparing validity coefficients between scales measuring different dimensions. An example of divergent validity is to compare the mental health scale (SF-36) with the lower limb scale (HAQUAMS). It would be expected that comparisons of similar domains will display higher intercorrelations, while comparisons of differing domains will exhibit lower intercorrelations. Convergent validity was also established by observing the intercorrelations between the mobility subscales of SF-36, HAQUAMS and MSIS-29 with the scores of the patients on the quantitative tests of motor function from the multiple sclerosis functional composite (Timed 25-Foot Walk and the 9-hole Peg Test).

Concurrent validity was compared for all measures by examining differences in HRQoL scores across level of disability and level of ambulation. Disability, for the purpose of this study was defined using patient self-report on the GNDS which is a new clinical disability scale for patients with MS. Disability grades on the GNDS were classified as having no disability (score of 1 to 12), mild disability (score of 13 to 24), moderate disability (score of 25 to 36), severe disability (score of 37 to 48) and total loss of function (score of 49 to 60) (Sharrack et al., 1999a). Similarly, responses of the participants on question 7 of the GNDS allowed us to categorize each of the participants in one of three groups based on ambulation status: (1) able to walk independently (corresponding to a score of 0 to 2 on

question 7 of GNDS); (2) requiring either a unilateral or bilateral support to walk (corresponding to a score of 3 or 4 on question 7 of GNDS); or (3) confined to a wheelchair (corresponding to a score of 5 on question 7 of GNDS).

Relative validity (relative efficiency) analysis was also performed. This analysis provides an estimate of the sensitivity of the different PRO measures to important clinical differences measured on external criteria such as level of disability. It was expected that patients reporting a lower grade of disability on the GNDS would report better HRQoL compared to the other patients. Analysis was performed using analysis of variance (ANOVA), which compared the scale scores between all three HRQoL measures for the different disability grades and one way ANOVA *F*-ratios were computed for each scale. These *F*-ratios were then compared as a basis for evaluating the relative sensitivity (validity) of individual scales to the known group differences. The relative validity was reported as the ratio of the *F*-ratio of each scale to the *F*-ratio of a designated reference scale, usually the scale with the smallest *F*-ratio. Standard parametric methods may be used to analyze quality of life data, as recent evidence has shown that non-parametric testing methods produce results similar to those presented by standard parametric tests (Walters & Campbell, 2004). Additionally, *post hoc* comparisons were performed to identify which ambulation groups differ significantly from each other. Duncan's multiple-range test which is a specialist multiple comparison test that maintains a low overall type I error was utilized. A significance level of $p = 0.05$ was used for this analysis.

Reliability

Cronbach's alpha (α) coefficients were calculated for the total and subscale scores of the included measures to estimate the internal consistency reliability. Evidence of

satisfactory internal consistency reliability was set at the criterion of $\alpha > 0.70$ (Nunnnally JC, 1978; Bennett et al., 2003; Meyer-Rosberg et al., 2001). Cronbach's α coefficient of 0.80 or greater was used as a more rigorous indicator of satisfactory internal consistency reliability of the instruments.

<u>Responsiveness</u>

All psychometric properties specified above, except for responsiveness, were assessed using cross-sectional data obtained at baseline (Time 1). Responsiveness of the three measures was assessed using self-report data at two time points i.e. at baseline (Time 1) and at three to six months following the initial assessment (Time 2). Change scores were calculated as the difference between baseline (Time 1) and Time 2 scores for each domain of the three questionnaires. Responsiveness was assessed using the following statistics: ES and SRM (Kazis et al., 1989; Liang et al., 1990). At Time 2, each patient was asked to respond to a transition question adapted from a study in rheumatoid arthritis (Fitzpatrick, Ziebland, Jenkinson, Mowat, & Mowat, 1993b): "Thinking of any overall effects MS may have on you; how would you describe yourself compared with the last time you completed these questionnaires: Do you feel that you are much better, slightly better, the same, slightly worse or much worse?" The ES is a standardized measure of change obtained by dividing the average change between the initial and follow-up measurement by the standard deviation of the initial measurement. The SRM is also a standardized measure of change which is calculated by dividing the average change between initial and follow-up measurements by the standard deviation of the change scores. These measures are commonly used in study designs in which health status measures are administered at two points in time (Stratford, Binkley, & Riddle, 1996), and hence are appropriate for this objective. ES has also been

used as a responsiveness measure in an earlier comparison of MS related quality of life measures (Riazi et al., 2003). Usually an ES of approximately 0.20 is considered to be a small change, one of 0.50 indicates a moderate change, and those of 0.80 or above reflect a large change (Cohen J, 1977).

Sub-scales for each of the PRO measures were examined in terms of ES and SRM, among a sub-sample of patients stratified into one of the following two groups on the basis of their response to the transition question: (1) Worse: those patients who reported worsening in their health status (those who reported slightly worse or much worse in response to the transition question); (2) Better: those who considered themselves to have stayed the same (those who reported much better or slightly better or the same). Investigators have often used such indices because such questions have been shown to be useful bench-marks against which to compare change scores on health status instruments (Guyatt et al., 1987; MacKenzie et al., 1986).

Analysis for Phase I: Objectives 2 and 3

Objective 2 for Phase I was to identify predictors of HRQoL in patients with MS and to determine the relative contribution of visual impairment on HRQoL in addition to depressive symptomatology, level of disability and other clinical factors. This was achieved by constructing a hierarchical regression model. Hierarchical regression models involve entry of one predictor variable or a block of variables at a time, based on some *a priori* criteria. Each step is a separate regression model and the resulting model is similar to the model which is obtained by adding all variables simultaneously. An additional advantage of such models over the multiple linear regression approach is that a change in R^2 is computed

at each step. This allows researchers to test whether a significant amount of additional variance is accounted for by the variable or variables entered at that step.

In this model, the dependent variable was the HRQoL score on the HAQUAMS, and the independent variables were: (1) visual impairment as measured by the visual function questionnaire (VFQ); (2) as measured by the Guy's Neurological Disability Scale (GNDS); (3) age; (4) gender; (5) marital status; (6) race; (7) employment status; (8) depression; and (9) duration of the disease.   Bivariate analyses were performed to examine the extent to which the individual variables were associated with overall HRQoL. Pearson's correlations were computed to examine the intercorrelations between the predictor variables and the HRQoL scores. The degree of association between nominal and interval variables were assessed by using the eta squared statistic. Eta squared is a measure of strength of relationship based on sums of squares computed in analysis of variance and can be interpreted as the percent of variance in the dependent variable explained linearly or nonlinearly by the independent variable. The significance of the level of correlation in this case was determined by the F-test analysis of variance.

If a given variable had an association with the significance level of $p \leq 0.10$, that variable was included in the multiple regression analysis. The exceptions to this rule were disability as measured by the GNDS and depression score on the CES-D, based on their significant associations with quality of life as evidenced by past research. The selected independent variables were then entered into the model in blocks, with all variables within a block entered in a single step

The change in R^2 showed the amount of unique variance explained by every new variable or block added to the model. Because one focus of this objective was the relation

73

between the HRQoL and visual impairment, the score on the VFQ was added last in the model. The change in R^2 for visual impairment (VFQ score) represented the unique variance explained by visual impairment when all other factors were accounted for.

Separate multiple linear regression analyses were performed to determine factors that have a significant impact on the various domains of HRQoL for Phase I, Objective 3. The domains of quality of life were identified by the HAQUAMS: fatigue, upper mobility, lower mobility, mood and social function. The selection process of the independent variables for each of the five regression models was similar to that for Phase 1, Objective 2.

Phase II

Research Design

Phase II of this project was a cross-sectional survey of neurologists with descriptive and analytic components. Data from one section of the survey was used in conjunction with Phase I which compared properties of three HRQoL measures in patients with MS.

Study Population

Surveys were mailed to neurologists currently working in the United States. The list of neurologists was supplied by SK&A Information Services Inc., a private mailing list firm located in Irvine, California. This firm researches, formats and maintains contact and profiling information for over 2 million healthcare providers, including 600,000 physicians.

Sample Size Calculation

Sample size was calculated using the following formula:

$$SS = \frac{Z^2 \text{ x (p) x (1-p)}}{C^2}$$

Where,

Z = Z value

p = population proportion, expressed as a decimal

c = confidence interval, expressed as a decimal

The sample size for the study using a 95% confidence level (Z = 1.96 for a 95%

confidence level) and a 5% confidence interval (c = 0.05) was estimated. The population

proportion (p) is the percentage of people in the population who will provide a given

response to a survey question. Since there was no population proportion for the sample, a

conservative estimate of 50% ($p = 0.5$) was used. Substituting these values for Z, p and c in

the above formula, the sample size was estimated to be 384. A response rate of about 25%

was assumed. This was a conservative estimate as compared to the mean response rate of

54%, typically seen in published surveys of physicians (Asch, Jedrziewski, & Christakis,

1997).

Survey Questionnaire Development & Validation

The survey instrument used was a five page questionnaire consisting of six sections

(see Appendix J). Information was collected on neurologists': opinion regarding two

HRQoL questionnaires which were used in Phase I of this study, attitudes, subjective norms

and perceived behavior control regarding HRQoL assessment in patients with MS; intention

to assess HRQoL information in patients with MS; perceived barriers and facilitators to HRQoL assessment; current behavior regarding HRQoL assessment and inclination to use HRQoL information in clinical practice; knowledge regarding specified HRQoL questionnaires; and socio-demographic information (age-group, gender, practice site, years in practice, participation in MS clinical trials, and patient load per week).

The members of the research committee which included one neurologist and four health outcomes researchers, were approached to asses the clarity, readability and the appropriateness of the instrument. This was done in order to improve the face and content validity, assess the relevance of the questions and clarity of the instructions and ease and time to completion. These results were then used to make further improvements in the questionnaire.

Study Procedures

Approvals for all Phase II survey related material was obtained from the WVU Institutional Review Board in July 2006. Three thousand mailing labels were purchased from SK & A, and a simple random sample of 2,400 neurologists was produced using Microsoft Excel's random number generator function. The decision to include 2,400 neurologists in the final sample was taken in order to meet the sample size requirement of 384, assuming a 25% response rate.

The questionnaires mailed to the neurologists were printed on colored paper and accompanied by a personalized cover letter on WVU letterhead (Appendix I), describing the study and encouraging them to complete the survey. Neurologists were asked to return it anonymously in an accompanying pre-addressed postage paid envelope. Four weeks

following the contact, a second mailing consisting of the survey instrument, cover letter and a pre-addressed postage paid envelope was sent to all non-responding neurologists.

At the end of eight weeks following the initial mailing, all respondents were broken down into three groups: Non-respondents: those who did not return the survey; Returned but not applicable: this group included those who indicated that they were not involved in the routine care of patients with MS or when the survey was returned as undeliverable by the postal service; and Returned responses: this group included those who returned the survey (either partially or entirely filled out). At the end of data collection, the response rate was calculated by dividing the total number of respondents in the returned responses group by the total number of eligible respondents (2400 – respondents in the returned but not applicable group).

Study Variables

Operationalization of the variables for the descriptive and analytic components of the study is listed below:

The variables for the descriptive study are as follows:

Neurologists' opinion regarding the usefulness, length and the wording of two MS-specific HRQoL measures were assessed using three questions on a 7-point Likert scale (Page 1 of the questionnaire). A list of potential barriers and facilitators to the utilization of HRQoL information were adapted from previous research (Bezjak et al., 2001). Six items formed the barriers scale while the facilitators scale consisted of the remaining four items. Each statement was rated on a 7-point Likert scale reflecting the degree to which each item is perceived to be a barrier or facilitator to HRQoL assessment where '1 = Strongly Disagree'

to '7 = Strongly Agree'. Barrier items addressed issues such as difficulty in scoring HRQoL questionnaires and irrelevance of such information to neurologists. (Barrier and facilitator items can be found on Page 4 of the questionnaire)

Current behavior regarding HRQoL assessment in patients with MS and categorization of the neurologists based on their knowledge and inclination to use HRQoL information (Page 4 of the questionnaire). Neurologists' knowledge of and experience with using specified HRQoL measures used in MS were also assessed. These questionnaires were identified from the literature as being the most commonly used in MS research. The list consisted of generic as well as MS-specific quality of life measures (Page 5 of the questionnaire)

Socio-demographic characteristics (Page 5 of the questionnaire): Gender, age group, primary practice site, number of MS patients seen per week, participation in MS-related clinical trial, year of board certification and number of years in practice. The independent and dependent variables for the study of the neurologist's intention to use HRQoL information in patients with MS were operationalized as follows:

Dependent Variable

Intention to use HRQoL information: Behavioral intention was measured by a single question on a seven point Likert scale where '1 = strongly disagree' and '7 = strongly agree'. (last item on page 3 of the questionnaire).

Independent Variables

An elicitation study was conducted among eight neurologists at the neurology clinic at West Virginia University to assess attitude, subjective norms and perceived behavior control.

78

Indirect measures of attitude were used by conducting separate interviews with several neurologists and neurology residents at the West Virginia University Neurology Clinic. The interviewees were asked about their beliefs regarding the consequences of assessing HRQoL information using validated formal questionnaires in routine practice. Using the results of the elicitation interviews seven attitudes were identified that are common among neurologists about the consequences of assessing HRQoL information in patients with MS during routine practice. Neurologists were asked to make judgments regarding each of these consequences (outcomes): an assessment of how strongly they agreed that an consequence would occur if they assessed HRQoL information in patients with MS; and an assessment of how desirable or undesirable each outcome is in their opinion (outcome evaluation). Questions regarding outcomes were constructed on a seven point Likert scale where '1= strongly disagree' and '7= strongly agree'. Outcome evaluations were measured on a scale of -3 to +3 where '-3= extremely undesirable' and '+3 = extremely desirable'. Product scores for each of the seven consequences were computed by multiplying the neurologists' probability rating regarding the outcome by the outcome evaluation score. These scores were then summed to create the attitude score. (Items 2 through 8 on pages 2 and 3)

Subjective Norms

Two salient referents were identified from the elicitation interviews. One was the American Academy of Neurology (AAN), which is a medical specialty society for neurologists and the other was colleagues or other neurologists. Neurologists were asked to assess the position of these referents with respect to HRQoL assessment in MS patients and

how motivated they were to adhere to those positions. Both judgments were scored on seven-point bipolar scales. The scales ranged from '1 = strongly disagree' to '7 = strongly agree' for the position assessments and from '1 = not at all' to '7 = very much' for the motivation assessments (Items 9 and 10 on page 3). The score for social norms was computed by summing across the neurologists' position rating and the motivation measure.

Perceived Behavior Control

Neurologists were asked whether the decision to assess HRQoL information from patients with MS was beyond their control. Responses were scored on a seven-point Likert scale where '1 = strongly disagree' to '7 = strongly agree'. They also assessed whether it was difficult or easy to assess HRQoL information in their patients with MS on a seven-point scale where '1= extremely difficult' and '7= extremely easy'. The two scores were averaged to give the perceived behavior control score.

Analysis for Phase II

To determine whether there was any difference in the opinion of neurologists regarding the HAQUAMS and MSIS-29, the Wilcoxon signed rank test was utilized. Statistically significant differences were identified at $p < 0.05$. The Wilcoxon signed rank test also referred to as the Wilcoxon matched pair test, is a non-parametric technique used to test the median difference in paired data. This test was utilized due to the non-normality of the responses to these items. Wilcoxon signed rank test is the non-parametric counterpart of the paired t test. The assumption of normality is avoided in the Wilcoxon signed rank test, because the test is based on rank order of the differences rather than the actual value of differences.

Frequency distributions for categorical data and means and standard deviations for continuous variables were calculated using descriptive analyses to present an overall picture of barriers and facilitators of HRQoL information use, knowledge and current behavior regarding HRQoL assessment in patients with MS.

Multiple linear regression analysis was used to determine the predictors of behavioral intention. Linear regression is a statistical technique for measuring the strength of a linear relationship between a dependent variable (Y) and one or more independent variables (X_1, X_2, X_3 … X_n). The dependent variable is the one being affected (intention to use HRQoL information) and the independent variables are the causes of that effect. The independent variables included in the model were: attitude; subjective norms; perceived behavioral control; primary practice site; years in practice as a neurologist; age; participation in a MS trial and number of patients seen per week.

Regression Diagnostics

All regression models were inspected for assumptions of normality using the Shapiro-Wilk W test. One assumption of linear regression analysis that assures that the *t*-tests are valid is that residuals are normally distributed. The *p* value of the Shapiro-Wilk test statistic is based on the assumption that the distribution is normal. Assumption of normality was rejected if $p \leq 0.05$ for the Shapiro-Wilk (*W*) statistic. The White test which is a formal test for the presence of heteroscedasticity was performed to establish homogeneity of the variance of residuals. Significance of the test statistic ($p \leq 0.05$) for the White test indicated that the variance is not homogenous. Variance inflation factor (VIF) values were used for each predictor to detect possible multicollinearity among predictors in the model.

Multicollinearity is when variables are highly correlated and multicollinearity statistics expose the redundancy of variables and the need to remove variables from the analysis. Increased multicollinearity leads to difficulty in partitioning out the individual effects of independent variables. The VIF measures how much multicollinearity has increased the variance of a slope estimate. The VIF ranges from 1 to infinity, where a high VIF value (>1) indicates that the variable may be affected by multicollinearity. The VIF value less than 4.0 is a common rule of thumb for acceptable multicollinearity in a regression model (Fisher JC & Mason RL, 1981).

Power Considerations

Concurrent validity of PRO measures

A priori power analysis are conducted in order to ascertain sample size required to perform the analyses necessary at a level of power desired prior to the start of the study. In order to perform sample size calculations, researchers need to decide upon an alpha level; the desired power, and the effect size. Alpha is the probability of making a Type I error that is rejecting the null hypothesis when it is true. Effect size is a name given to a family of indices that measure the magnitude of a treatment effect and unlike significance tests; these indices are independent of sample size. Cohen (Cohen J, 1988) established a measure of effect size termed Cohen's *d*, which is the number of standard deviations separating two group means. Although there is no universally accepted criteria for determining whether a given d is large enough, researchers often use Cohen's recommendations of small ($d= 0.2$), medium ($d= 0.5$) and large ($d= 0.8$) effect sizes. A conservative effect size ($d=0.3$) along with a target power of 0.8 and alpha level of 0.05 was selected for comparing patients classified into groups by

disability levels as well as ambulation levels. Using these criteria produced the sample size estimate of 111 subjects for Phase I, Objective 1.

Regression analyses for Phases I and II

The anticipated effect size index for regression is denoted by f^2, where f^2 reflects the proportion of variance accounted for by some source in the population (PVs) relative to the residual variance proportion (PVe), such that $f^2 = PVs/PVe$. For Phase I, the hypothesis being tested was that the correlation of the visual impairment and other independent variables with the overall quality of life score in the population to which the results are to be generalized is zero. For a set of predictors explaining 20% of the variance in the dependent variable, f^2 is 0.25, and with nine predictors, a sample size of 72 subjects was necessary to achieve a power of 0.8 and 89 subjects to achieve a power of 0.9 for Phase I, Objective 3 of this study.

For Phase II, Objective 4, the hypothesis being tested was that the correlation between the independent variables (attitude, subjective norms, perceived behavior control and demographic variables) and the intention to assess HRQoL information is zero for the population to which the results are to be generalized. For a set of predictors explaining 20 percent of the variance in the dependent variable, f^2 is 0.25, and with eight predictors, a sample size of 66 subjects was necessary to achieve a power of 0.8 and 84 subjects to achieve a power of 0.9.

All power analyses were performed by using G*Power, a general power analysis program (Erdfelder, 1996). The G*Power program uses the number of predictors in the analysis and expected effect size to calculate sample requirements. It should be recognized however, that several rules of thumb exist to guide sample size selection in studies examining

relationships between variables of interest. For testing individual predictors and assuming a medium-sized relationship, a conservative estimate of sample size is $N > 50 + 8$ m (N= sample size, m is the number of independent variables) (Green SB, 1991). Although Green's formula is comprehensive, there are a few other guidelines that may be considered. For regression equations using six or more predictors, Harris (1985) recommends an absolute minimum of ten participants per predictor variable. Still others have suggested a minimum total sample of 400 (Cohen & Cohen, 1984) while some have declared a minimum of forty subjects per predictor (Tabachnick BG & Fidell LS, 1996a). Generally speaking, such rules are only approximations and the number of observations required may change based on two important factors, the effect size (large or small) and the correlations among predictors (e.g. multicollinearity).

Chapter 4: Results

Phase I

Sample Characteristics

One hundred and thirty-six patients with MS agreed to participate in this study and completed the self-report measures and the quantitative tests of motor function in the clinic. Of these, 116 patients returned the completed HRQoL questionnaires in the mail. Table 1 shows the characteristics of the patients who completed both the in clinic assessments and the HRQoL questionnaires. The mean age for this group was 44.8 years (range = 19 to 79 years) with over 70% of them being women. Sixty-two participants failed to complete the questionnaires at follow-up, leaving only 54 patients who completed the questionnaires at both time points (Time 1 and Time 2).

Almost all of the participants were White (97.4%), while the remaining 2.6% were African-American. Fifty-six percent of the participants were currently married and 33.6% were currently working for pay; either full-time or part-time. Of those who were unemployed, 75% mentioned that multiple sclerosis (MS) was the main reason for unemployment. The mean duration of having MS was 8.8 years (range = 0 to 41). Approximately 43% of the sample reported having no comorbidites, while 12.3% of the patients said that they had at least three comorbid conditions from the checklist described in the methods section. Based on the scores on question 7 (regarding lower limb problems) in the Guys Neurological Disability Scale (GNDS), almost 16% of the participants were restricted to a wheelchair, 27.6% used some type of aid for walking while 56% could walk independently.

Table 1: Characteristics of the sample

Variable	N (%)
Sample Size	116 (100.0)
Gender	
Female	82 (70.7)
Age (in years)	
Mean (SD)	44.8 (13.8)
Range	19-79
Race	
White	113 (97.4)
Marital Status	
Married	65 (56.0)
Employment	
Unemployed due to MS	57 (49.1)
Unemployed	19 (16.4)
Employed	39 (33.6)
Ambulation	
Walks unaided	65 (56.0)
Walks with aid	32 (27.6)
Uses wheelchair	19 (16.4)
Duration of MS since diagnosis (years)	
Mean (SD)	8.8 (8.5)
Range	0-41
Comorbid conditions	
0	46 (43.4)
1	32 (30.2)
2	15 (14.2)
3 or more	13 (12.3)

SD= Standard Deviation
MS= Multiple Sclerosis

Comparison of Health-Related Quality of Life Questionnaires

Acceptability

Mean scale scores and percentage of scores at the floor and ceiling are shown in

Table 2. Scales for all HRQoL questionnaires had relatively small floor and ceiling effects

except for the SF-36 role-physical function (59.5%) and role-emotional (39.7%) scales. The

floor effects for the Hamburg Quality of Life Questionnaire in Multiple Sclerosis

(HAQUAMS) upper mobility (14.7%) and social function (12.9%) scales were slightly high,

but were still below the maximum value of 20% set as a criterion for this study.

The HAQUAMS upper mobility scale however, did not display any ceiling effects

(0.0%). Ceiling effects for scales measuring similar domains were 0.9% for the Multiple

Sclerosis Impact Scale (MSIS-29) physical impact scale, 5.2% for the SF-36 physical

function scale and 6.9% for HAQUAMS lower mobility. The HAQUAMS lower mobility

scale had the smallest floor effect (1.7%), followed by the MSIS-29 physical impact scale

(3.5%), SF-36 physical function scale (8.6%) and the HAQUAMS upper mobility scale

(14.7%).

With regards to the psychological domain, floor and ceiling effects for the

HAQUAMS mood scale fell in between those of SF-36 and MSIS-29. SF-36 displayed the

least floor effects on the mental health scale (0.0%), while this percentage was 0.8 for the

HAQUAMS mood scale and 2.6 for the MSIS-29 psychological impact scale. Only 0.9 % of

the respondents had a maximum score on the MSIS-29 psychological impact scale compared

to 1.7% on the HAQUAMS mood and 2.6% on the SF-36 mental health scale.

There were marked differences in the acceptability for the HAQUAMS and SF-36

social function scales. The HAQUAMS social scale had much higher floor effects than the

Table 2: Acceptability for HRQoL Measures (n=116)

Scale	No. of Items	Mean	SD	Percent Scoring Minimum	Percent Scoring Maximum	Cronbach's Alpha
SF-36						
Physical Function	10	41.0	31.1	8.6	5.2	0.87
Role-Physical	4	23.3	35.0	59.5	12.1	0.87
Bodily Pain	2	56.3	27.7	1.7	14.7	0.87
General Health	5	45.3	23.1	0.9	0.0	0.87
Vitality	4	39.9	21.0	2.6	0.0	0.87
Social Functioning	2	57.5	25.9	3.5	12.1	0.86
Role-Emotional	3	45.7	44.1	39.7	35.3	0.88
Mental Health	5	62.8	22.1	0.0	2.6	0.87
HAQUAMS						
Fatigue	4	11.8	4.1	1.7	3.5	0.82
Lower Mobility	5	14.1	6.1	1.7	6.9	0.80
Upper Mobility	5	10.6	5.0	14.7	0.0	0.79
Social Function	6	13.0	5.5	12.9	0.8	0.84
Mood	8	21.6	7.9	0.8	1.7	0.79
MSIS-29						
Physical	20	42.8	26.1	3.5	0.9	0.84
Psychological	9	42.0	24.7	2.6	0.9	0.84

No. = Number
SF-36= Medical Outcomes Survey Short Form – 36 Items
HAQUAMS= Hamburg Quality of Life Questionnaire in MS
MSIS-29= Multiple Sclerosis Impact Scale

SF-36 social functioning (12.9% vs. 3.5%) but significantly lower ceiling effects (0.8% vs.

12.1%). When comparing the HAQUAMS fatigue and SF-36 vitality scales a pattern opposite

to the one for the social functioning domain was observed. The HAQUAMS fatigue scale had

lower floor effects (1.7% vs. 2.6%) but higher ceiling effects (3.5% vs. 0.0%) compared to

the SF-36 vitality scale.

Reliability

Cronbach's alpha for the scales and summary scales are also shown in Table 2. A

majority of the scales exceeded the internal consistency reliability criteria of 0.80 set for this

study. Only the upper mobility and the mood sub-scales for the HAQUAMS did not meet

these recommendations, however the alpha values were 0.79 for both scales, which is still

high enough to be considered acceptable. With regards to scales measuring physical and

psychological domains, the SF-36 scales had the highest values of Cronbach's alpha

followed by the MSIS-29 and HAQUAMS. The SF-36 vitality scale and social functioning

scales had a slightly higher internal consistency reliability coefficients compared to their

HAQUAMS counterparts: 0.87 vs. 0.82 for the HAQUAMS fatigue scale and 0.86 vs. 0.84 for

the HAQUAMS social scale.

Scaling Assumptions

For all sub-scales, frequency distributions for the items were almost the same; items

within each scale had similar means scores and standard deviations (see Table 3). The

percentage of missing data was highest for the HAQUAMS lower (18.1%) and upper (3.5%)

mobility scales. The percentage of missing responses for all the remaining scales ranged

from 0.0 to 2.6%. Scales measuring the physical dimension of HRQoL displayed better

item-total correlations for the HAQUAMS (Range = 0.67-0.87) compared to the SF-36

Table 3: Scaling Assumptions for HRQOL Measures (Total N=116)

Scale	Item Mean Scores	Item SD	% Missing	Item Total Correlation
SF-36				
Physical Function	1.3-2.5	0.6-0.8	0.0-0.9	0.59-0.86
Role-Physical	1.2-1.3	0.4-0.5	0.0	0.63-0.75
Bodily Pain	3.6-4.0	1.4	0.0-0.9	0.89
General Health	2.4-3.0	1.0-1.4	0.9-2.6	0.44-0.75
Vitality	2.9-3.4	1.3-1.4	0.0-0.9	0.64-0.75
Social Functioning	3.2-3.4	1.2	0.0-2.6	0.55
Role-Emotional	1.4-1.5	0.5	0.0	0.74-0.86
Mental Health	3.4-4.7	1.4-1.5	0.0-0.9	0.53-0.78
HAQUAMS				
Fatigue	2.4-3.3	1.2-1.3	0.0-0.9	0.60-0.72
Lower Mobility	2.5-4.0	1.4-1.5	0.9-18.1	0.68-0.87
Upper Mobility	1.6-2.8	1.0-1.4	0.0-3.5	0.67-0.82
Social Function	2.0-2.5	1.3-1.4	0.0-2.6	0.38-0.74
Mood	2.2-4.0	1.1-1.4	0.9-2.6	0.59-0.78
MSIS-29				
Physical	2.0-3.3	1.2-1.5	0.9-2.6	0.58-0.82
Psychological	2.5-2.8	1.2-1.4	0.9	0.13-0.80

SF-36= Medical Outcomes Survey Short Form – 36 Items
HAQUAMS= Hamburg Quality of Life Questionnaire in MS
MSIS-29= Multiple Sclerosis Impact Scale

physical function (Range = 0.59-0.86) and MSIS-29 physical impact scale (Range = 0.58-0.82). Similar observations were made for the psychological scales: item-total correlations for the HAQUAMS mood scale ranged from 0.59 to 0.78 and from 0.53 to 0.78 for the SF-36 mental health scale. Item 21 (In the past two weeks, how much have you been bothered by feeling unwell) of the MSIS-29 psychological impact scale had a very low correlation with the total scale score (0.13).

The HAQUAMS fatigue scale had item-total correlations (Range = 0.60 to 0.72) similar to that of the SF-36 social function scale (Range = 0.64 to 0.75). With respect to the social functioning dimension, item 25 of the HAQUAMS social scale (I get support from friends and neighbors) had an item-total correlation of 0.38, while the highest correlation within this scale was 0.74 for item 29 (I feel separated). The average item-total correlation for the two items of the SF-36 social function scale (items 6 and 10) was 0.55. Overall, the item-total correlations for all scales except for item 21 of the MSIS-29 exceeded the target criterion of 0.30.

Construct Validity

This study attempted to provide evidence that the HAQUAMS and MSIS-29 scales measure the underlying constructs of physical and emotional impairments that they are known to represent. Table 4 depicts the matrix comparing the physical and mental scales for SF-36, HAQUAMS and MSIS-29. All scale correlations within and across the measures were statistically significant at the $p \leq 0.05$ level. Evidence of convergent validity was drawn from examination of the coefficients in the monotrait-multimethod triangles, enclosed by the solid lines. For example, the coefficient of -0.69 corresponding to row 2 and column 1

Table 4: Construct Validity of SF-36, HAQUAMS and MSIS-29 Physical and Psychological Scales

Instrument/Scale	1	2	3	4	5	6	7
1) SF-36 Physical Function							
2) HAQUAMS Upper Mobility	<u>-0.69</u>						
3) HAQUAMS Lower Mobility	<u>-0.82</u>						
4) MSIS-29 Physical Impact Scale	<u>-0.79</u>	0.76	0.82				
5) SF-36 Mental Health	**0.31**	*-0.29*	*-0.33*	*-0.41*			
6) HAQUAMS Mood	*-0.54*	**0.58**	**0.58**	*0.71*	<u>-0.51</u>		
7) MSIS-29 Psychological Impact Scale	*-0.50*	*0.54*	*0.54*	**0.70**	<u>-0.68</u>	0.62	

Note: N=116
SF-36= Medical Outcomes Survey Short Form – 36 Items
HAQUAMS= Hamburg Quality of Life Questionnaire in MS
MSIS-29= Multiple Sclerosis Impact Scale
Monotrait-Multimethod correlations are underlined: Correlations between two scales of two different questionnaires measuring similar constructs
Multitrait-Monomethod correlations are in bold: Correlations between two scales of the same questionnaire measuring different constructs
Multitrait-Multimethod correlations are italicized: Correlations between two scales of two different questionnaires measuring different constructs

of Table 4 indicates the correlation between two scales measuring a *similar trait or construct* (physical function and upper mobility) using *multi or different methods* (SF-36 and HAQUAMS). The construct validity for the physical sub-scales for all three questionnaires was found to be consistent with the predictions. The upper mobility scale of HAQUAMS correlated more highly with the SF-36 physical function scale ($r = -0.82$) compared to the physical impact scale of the MSIS-29 ($r = -0.79$). The negative correlation coefficients were expected because a higher overall score indicates better quality of life on the SF-36 but poorer quality of life on both, the HAQUAMS and MSIS-29. The correlation between the physical scales (Range= 0.69-0.82) was higher than the correlations among the physical and the psychological scales (Range= 0.31-0.71). However, this was not the case with the psychological scales. The correlation among the mood subscales was substantial (Range= 0.51-0.68) but not as high as observed for the physical domain scales.

To demonstrate divergent validity the multitrait-multimethod and the multitrait-monomethod correlation coefficients must be lower than the monotrait-multimethod correlation coefficients. In other words, the correlation coefficient between two scales of the same or different questionnaires, measuring *different* underlying constructs must be lower than the correlation between two scales from different questionnaires measuring the *same* underlying construct. For example, the correlation coefficient between the MSIS-29 physical and psychological impact scales (0.71 in Table 4) and between the MSIS-29 physical and SF-36 mental health scale (-0.41 in Table 4) must be higher that the correlation coefficient between the MSIS-29 physical impact and SF-36 physical function scales (-0.79 in Table 4). In Table 4, multitrait-monomethod correlations are bolded, while multitrait-multimethod correlations are italicized and are represented in the rectangle enclosed by the broken lines.

As would be expected, most of the scales that are supposed to measure different underlying constructs are weakly to moderately correlated, independent from the method that is used (range = 0.29 to 0.58). The only exception to this is the HAQUAMS mood scale, whose correlation of 0.70 with the MSIS physical impact scale (see row 6/column 4) is higher than its correlation with the SF-36 mental health (0.51) and MSIS-29 psychological impact scales (0.62).

<u>Criterion Validity</u>

Objective Tests of Motor Function and Depression Scale

Convergent validity of the physical scales of all three questionnaires with respect to the quantitative tests of motor function such as Timed 25-Foot Walk Test and 9-Hole Peg Test (9-HPT), ranged from 0.28 to 0.39 (see Table 5). The SF-36 physical function scale had the highest correlation with 9-HPT (-0.42) followed by the MSIS physical impact scale (0.41). It was expected that the HAQUAMS upper mobility scale would correlate strongly with the 9-HPT scores, however, this correlation was found to be lower compared to that of the other scales (0.33). The HAQUAMS lower mobility scale on the other hand, correlated as expected with the scores on 25-Foot Walk Test. This correlation coefficient was matched by the SF-36 physical function scale (-0.39) and was higher that the correlation between MSIS-29 physical impact scale and 25-Foot Walk Test (0.28). Evidence for divergent validity of scales measuring physical dimensions was provided by their correlations with scores on the depression scale (Range = 0.30 to 0.44). The psychological scales for all three questionnaires exhibited strong correlations with the Centers for Epidemiological Studies – Depression Scale (CES-D) (refer to Table 5). The correlation was strongest for the MSIS-29 psychological impact scale (0.71) and lowest for the HAQUAMS mood scale (0.62).

Table 5: Concurrent Validity of SF-36, HAQUAMS and MSIS-29 Physical and Psychological Scales against External Criteria

Instrument/Scale	CES-D	9-HPT	25-Foot Walk
1) SF-36 Physical Function	-0.38[†]	-0.42[†]	-0.39[†]
2) HAQUAMS Upper Mobility	0.32[†]	0.33[†]	0.29[†]
3) HAQUAMS Lower Mobility	0.30[†]	0.33[†]	0.39[†]
4) MSIS-29 Physical Impact Scale	0.44[†]	0.41[†]	0.28[†]
5) SF-36 Mental Health	-0.68[†]	-0.27[†]	-0.02
6) HAQUAMS Mood	0.62[†]	0.48[†]	0.11
7) MSIS-29 Psychological Impact Scale	0.71[†]	0.34[†]	0.07

[†] Significant at *p < 0.01*
CES-D: Centers for Epidemiological Studies- Depression scale
9-HPT: 9 Hole Peg Test & 25-Foot Walk Test: Objective clinical tests of motor function
Note: Negative correlations between external criteria variables (CES-D, Timed 25-Foot Walk Test and 9-HPT) and SF-36 are due to differences in scoring. Higher scores indicate better quality of life on the SF-36 but higher level of depressive symptomatology and poorer physical function
SF-36= Medical Outcomes Survey Short Form – 36 Items
HAQUAMS= Hamburg Quality of Life Questionnaire in MS
MSIS-29= Multiple Sclerosis Impact Scale

Correlations for scales measuring the psychological dimension of HRQoL were low to moderate with measures of motor function (Range = 0.02 to 0.48). Negative correlations between SF-36 and CES-D as well as the quantitative tests of motor function were due to the inverse relationship between them as a result of scoring methods. Higher scores on the SF-36 indicate better quality of life but poor physical function according to CES-D and the tests of motor function.

Degree of Disability

Mean scores on the HRQoL measures for the sub-groups classified by disability of the disease using GNDS are shown in the Table 6. Since the overall sample was less severe, the participants were classified in to three groups: No Disability (N=40); Mild Disability (N=54) and Moderate Disability (N=22). For the scales on all questionnaires, ordering mean scores tended to follow the hypothesized order of better HRQoL scores in the group having no disability, with progressively lower scores in the groups reporting mild and moderate disability.

There were significant group differences on scores for all scales ($p \leq 0.01$). The physical impact scale of the MSIS-29 and the physical function scale of the SF-36 had the highest relative validities of all scales, 7.5 and 5.8, respectively. The relative validity coefficients for the HAQUAMS were 4.9 for the upper mobility scale and 4.8 for the lower mobility scale. However, the overall QoL score for the HAQUAMS had the highest relative validity coefficient (= 8.2) of all scales, indicating that it most sensitive to discriminate between groups of MS patients based on disability. The mental health scale of the SF-36 was the least sensitive to group differences in disability scores. Overall, all scales of the

Table 6: Relationship between HRQoL Scores and Disability (Concurrent Validity)

	Level of Disability				
Scale	None (N=40)	Mild (N=54)	Moderate (N=22)	F-Ratio[a]	Relative Validity[b]
SF-36					
Physical Function	65.9[c]	32.2[d]	17.5[e]	33.0	5.8
Role-Physical	46.9[c]	14.4[d]	2.3[d]	19.6	3.4
Bodily Pain	71.0[c]	53.1[d]	37.4[e]	13.6	2.4
General Health	57.5[c]	43.7[d]	26.8[e]	16.0	2.8
Vitality	50.3[c]	37.9[d]	26.1[e]	11.7	2.1
Social Functioning	69.1[c]	57.9[c]	35.8[e]	14.5	2.5
Role-Emotional	60.0[c]	45.7[c]	19.7[e]	6.5	1.1
Mental Health	69.7[c]	62.7[c]	50.7[e]	5.7	1.0
HAQUAMS					
Fatigue	9.4[c]	12.0[d]	15.5[e]	22.7	4.0
Lower Mobility	9.6[c]	15.5[d]	18.6[e]	27.5	4.8
Upper Mobility	7.5[c]	10.8[d]	15.6[e]	27.9	4.9
Social Function	10.3[c]	13.4[d]	17.5[e]	15.0	2.6
Mood	17.1[c]	22.0[d]	28.8[e]	21.2	3.7
Total QoL	10.7[c]	14.6[d]	19.2[e]	46.5	8.2
MSIS-29					
Physical	21.0[c]	48.2[d]	67.4[e]	42.6	7.5
Psychological	27.7[c]	43.9[d]	68.8[e]	21.6	3.8

All *F* ratios were significant at p ≤ 0.01

[a] One way ANOVA of the HRQoL scales and the MS levels of disability classified using the Guys Neurological Disability Scale (GNDS)

[b] Reference scale for calculating relative validities is the Mental Health subscale (SF-36)

[c,d,e] Means within a row with different superscripts differ significantly (p ≤ 0.05, Duncan's Multiple Range Test)

SF-36= Medical Outcomes Survey Short Form – 36 Items

HAQUAMS= Hamburg Quality of Life Questionnaire in MS

MSIS-29= Multiple Sclerosis Impact Scale

HAQUAMS were quite sensitive to group differences, with four scales having relative

validity coefficients of 4.0 or greater, compared to the reference scale (SF-36 mental health

scale). As can be observed from the *post hoc* comparison, all scales of HAQUAMS and

MSIS-29 successfully discriminated each of the three disability groups (none, mild and

moderate. From the SF-36, only the physical function, bodily pain, general health and

vitality scale has significantly different scores for each of the three groups.

Current Ambulation Status

The ability of the HRQoL measures to discriminate between patients with MS,

classified on the level of ambulation are reported in Table 7. Sixty-five patients reported that

they were able to walk unaided, 32 patients indicated that they needed either unilateral or

bilateral support to walk, and 19 patients indicated that they were confined to a wheelchair

both indoors and outdoors. For the scales on all questionnaires, ordering mean scores tended

to follow the hypothesized order of better HRQoL scores in the group which could walk

unaided, with progressively lower scores in the groups requiring some support to help with

ambulation.

The results of the ANOVA indicated that the scores on the scales measuring physical

domain of all three questionnaires differed significantly between the three ambulation

groups: the SF-36 physical function scale ($F= 60.3$, $p < 0.01$); the HAQUAMS upper

mobility ($F= 40.0$, $p < 0.01$) and lower mobility ($F= 71.6$, $p < 0.01$) scales; and the MSIS

physical impact scale ($F= 52.9$, $p < 0.01$).

Table 7: Relationship between HRQoL Scores and Level of Ambulation (Concurrent Validity)

| Scale | Level of Ambulation | | | F-Ratio[a] | Relative Validity[b] |
	Walk (N=65)	Walk Aid (N=32)	Wheelchair (N=19)		
SF-36					
Physical Function	60.2^c	23.0^d	6.1^e	60.3†	35.5
Role-Physical	33.9^c	11.8^d	8.6^d	7.6†	4.5
Bodily Pain	64.7^c	46.2^d	45.1^d	7.8†	4.6
General Health	54.1^c	38.4^d	26.7^e	15.2†	8.9
Vitality	44.9^c	34.1^d	33.9^d	4.4*	2.6
Social Functioning	66.9^c	52.3^d	34.2^e	16.0†	9.4
Role-Emotional	50.8^c	44.8^c	29.8^c	1.7	1.0
Mental Health	66.2^c	59.0^c	57.9^c	1.7	1.0
HAQUAMS					
Fatigue	10.7^c	12.6$^{c,\,e}$	14.0^e	5.9†	3.5
Lower Mobility	10.4^c	16.6^d	22.3^e	71.6†	42.1
Upper Mobility	8.0^c	12.3^d	16.4^e	40.0†	23.5
Social Function	12.1^c	13.6$^{c,\,e}$	15.8^e	3.5*	2.1
Mood	18.3^c	24.9^d	27.2^d	16.6†	9.8
Total QoL	11.8^c	16.0^d	19.1^e	37.6†	22.1
MSIS-29					
Physical	27.5^c	54.1^d	74.3^e	52.9†	31.1
Psychological	34.5^c	49.4^d	61.7^d	9.6†	5.6

[†] Significant at $p \leq 0.01$
[*] Significant at $p \leq 0.05$
[a] One way ANOVA of the HRQoL scales and the level of ambulation classified using responses on question 7 of the Guys Neurological Disability Scale (GNDS)
[b] Reference scale for calculating relative validities is the Mental Health subscale (SF-36)
[c,d,e] Means within a row with different superscripts differ significantly ($p \leq 0.05$, Duncan's Multiple Range Test)
SF-36= Medical Outcomes Survey Short Form – 36 Items
HAQUAMS= Hamburg Quality of Life Questionnaire in MS
MSIS-29= Multiple Sclerosis Impact Scale

There was no significant differences between the three groups based on scores of the SF-36 mental health scale ($F= 1.7$, $p = 0.18$). However, the HAQUAMS mood scale ($F= 16.6$, $p < 0.01$) and MSIS-29 psychological impact scale ($F= 9.6$, $p < 0.01$) scores differed significantly. There was a significant difference in the scores of the HAQUAMS social scale ($F= 3.5$, $p < 0.05$), but this was not as significant as the difference observed for the SF-36 social function scale ($F= 16.0$, $p < 0.01$).

As would be expected, the sensitivity of the HRQoL scales to these known group differences was much higher for the scales assessing physical function (the SF-36 physical function, MSIS-29 physical impact scale and HAQUAMS upper & lower mobility scales) than for psychological scales (the SF-36 mental health, MSIS-29 psychological impact scale and HAQUAMS mood scales). The lower mobility scale of the HAQUAMS had the highest relative validity (Relative validity coefficient= 42.1) followed by the physical function scale of the SF-36 (Relative validity coefficient= 35.5) and finally the MSIS-29 physical impact scale (Relative validity coefficient= 31.1). The sensitivity of the overall QoL score of HAQUAMS was also quite high, as evidenced by a relative validity coefficient of 22.1.

Duncan's multiple range analysis illustrated that scales assessing physical domain for all three questionnaires displayed significant differences in their scores for each of the three ambulation groups. Other scales that displayed significant differences were: the general health and social function scales of the SF-36 and the overall QoL score of the HAQUAMS.

Responsiveness

Effect sizes (ES) and standardized response means (SRM) have been reported for two sub-groups classified based on the response to the global transition question. Effect size was calculated as the mean change score (difference between Time 1 and Time 2) divided by the

standard deviation of the Time 1 scores. Standardized response mean was calculated as the

mean change score divided by the standard deviation of the change score. Fifty-four of the

116 participants successfully completed the assessment at Time 2 and were included in the

calculation of the responsiveness indices.

Responsiveness indices (ES and SRM) for those patients whose global perception of

change was either "slightly worse" or "much worse" (N=20) compared to baseline (worse

sub-group) are shown in Table 8. In the worse sub-group, only the general health scale from

the SF-36 was found to have the appropriate direction for the change score and at least a

small change in scores (ES= 0.29; SRM=0.55). Appropriate direction of the change score

refers to a change score value with a negative sign for HAQUAMS and MSIS-29 scales and a

positive sign for the SF-36 scales. This difference in the expected sign or direction for these

measures exists because; a higher score indicates better quality of life on the SF-36 but

poorer quality of life or functioning on the HAQUAMS and MSIS-29. Hence, patients in the

worse sub-group are expected to have lower scores compared to baseline on the SF-36 scales

(indicating decreased functioning in the various SF-36 domains), but higher scores compared

to baseline on the HAQUAMS and MSIS-29 (indicating decreased functioning in the various

domains for these measures). Other scales of the SF-36 with appropriate sign for the change

score were: the bodily pain scale (+5.0); the vitality scale (+1.8); and the social functioning

scale (+0.6). Of these, only the bodily pain scale had slightly higher responsiveness indices

(ES= 0.19; SRM= 0.22). Four of the six scales of the HAQUAMS had negative change

scores, that is, change scores with the appropriate sign. These included fatigue (-0.4), lower

mobility (-0.8), social function (-0.7) and overall quality of life scales (-0.3).

Table 8: Responsiveness of the HRQoL measures for Those Who Reported Their Overall Condition Having Worsened Over the Last Three-Six Months

Instrument/Subscale	Time 1	Time 2	Change	Effect Size[†]	SRM[¶]
	Mean (SD)	Mean (SD)	Mean (SD)		
SF-36					
Physical Function	17.3 (17.7)	19.7 (20.9)	-2.1 (10.5)	0.12	0.20
Role-Physical	5.0 (10.3)	7.9 (23.7)	-2.6 (26.2)	0.25	0.10
Bodily Pain	49.1 (26.0)	44.1 (26.7)	**5.0 (22.5)**	0.19	0.22
General Health	35.3 (19.6)	29.6 (17.8)	**5.7 (10.4)**	0.29	0.55
Vitality	30.3 (18.8)	28.5 (18.5)	**1.8 (16.7)**	0.10	0.11
Social Functioning	49.4 (14.3)	48.8 (34.0)	**0.6 (25.2)**	0.04	0.02
Role-Emotional	30.0 (34.0)	33.3 (43.0)	-3.5 (42.9)	0.10	0.08
Mental Health	57.2 (23.3)	57.4 (18.4)	-0.2 (12.1)	0.01	0.02
HAQUAMS					
Fatigue	13.4 (3.6)	13.8 (3.0)	**-0.4 (2.6)**	0.11	0.15
Lower Mobility	18.1 (4.7)	18.9 (4.9)	**-0.8 (1.9)**	0.17	0.42
Upper Mobility	15.1 (4.3)	15.0 (4.8)	0.2 (2.6)	0.05	0.08
Social Function	14.7 (6.5)	15.4 (5.7)	**-0.7 (3.9)**	0.11	0.18
Mood	25.9 (6.3)	25.8 (6.6)	0.2 (5.9)	0.03	0.03
Total QOL	17.44 (3.7)	17.8 (4.0)	**-0.3 (2.1)**	0.08	0.14
MSIS-29					
Physical	60.7 (19.7)	57.5 (18.3)	3.2 (15.4)	0.16	0.21
Psychological	49.4 (19.9)	50.7 (20.4)	**-1.3 (10.8)**	0.07	0.12

[†] Mean change score divided by standard deviation of Time 1 scores
[¶] Standardized response mean= mean change scores divided by standard deviation of change scores
Note: Change scores that had a sign (direction) that was expected for that group have been bolded. Total N=20
SF-36= Medical Outcomes Survey Short Form – 36 Items
HAQUAMS= Hamburg Quality of Life Questionnaire in MS
MSIS-29= Multiple Sclerosis Impact Scale

For the MSIS-29, the psychological impact scale displayed a negative change score (-1.3). Of these scales, the HAQUAMS lower mobility scale with a SRM of 0.42, was much more responsive than all other scales (ES or SRM < 0.20).

Responsiveness for the thirty-four patients who responded as having gotten better compared to baseline has also been reported (see Table 9). None of the scales in the better sub-group had both: an appropriate direction for the change scores (i.e. change score with a positive sign) and a responsiveness index of at least 0.20. Appropriate direction for the change score refers to a change score value with a positive sign for HAQUAMS and MSIS-29 and a negative sign for the SF-36. This is because; a higher score indicates better quality of life on the SF-36 but poorer quality of life or functioning on the HAQUAMS and MSIS-29.

The scales for the PRO measures in the better sub-group are expected reflect an improvement relative to their scores at baseline. Based on this information, one would expect either the same or a lower score on the scales for the HAQUAMS and MSIS-29 at Time 2 compared to baseline. On the other hand, the same or a higher score would be expected on all scales of the SF-36 at follow-up to indicate some improvement in the HRQoL and its domains. Only the MSIS-29 displayed a change score with the appropriate sign (positive) for the better group for both its scales (physical and psychological impact scales). The mean change in the psychological impact scale was +3.0 with an effect size of 0.12 and SRM of 0.21, while the responsiveness for the physical impact scale was minimal (ES and SRM < 0.5). Change scores with appropriate signs were also observed for: the HAQUAMS fatigue and upper mobility scales (+0.1 and +0.3 respectively), and the SF-36 role-physical (-4.5), social function (-0.2) and physical function scales (-1.3).

Table 9: Responsiveness of the HRQoL Measures for Those Who Reported Their Overall Condition Having Gotten Better Over the Three-Six Month Time Period

Instrument/Subscale	Time 1 Mean (SD)	Time 2 Mean (SD)	Change Mean (SD)	Effect Size[†]	SRM[¶]
SF-36					
Physical Function	47.8 (30.5)	49.1 (29.4)	**-1.3 (11.9)**	0.04	0.11
Role-Physical	28.3 (37.1)	32.8 (38.4)	**-4.5 (34.7)**	0.14	0.15
Bodily Pain	61.0 (29.3)	60.1 (26.4)	0.9 (21.4)	0.01	0.01
General Health	49.7 (23.8)	49.1 (23.5)	0.6 (19.6)	0.14	0.17
Vitality	46.1 (20.5)	42.2 (22.1)	3.9 (17.9)	0.24	0.30
Social Functioning	66.9 (21.2)	67.1 (26.3)	**-0.2 (18.5)**	0.09	0.10
Role-Emotional	61.2 (44.1)	59.8 (44.0)	1.4 (41.4)	0.02	0.02
Mental Health	69.1 (22.3)	68.4 (23.7)	0.7 (19.5)	0.01	0.02
HAQUAMS					
Fatigue	11.2 (4.1)	12.6 (3.9)	**0.1 (2.1)**	0.03	0.05
Lower Mobility	11.9 (5.1)	12.1 (5.3)	-0.2 (2.8)	0.08	0.14
Upper Mobility	9.4 (3.9)	9.1 (3.5)	**0.3 (2.9)**	0.05	0.07
Social Function	12.1 (5.1)	12.3 (5.4)	-0.2 (3.7)	0.06	0.08
Mood	19.0 (7.5)	19.4 (8.3)	-0.4 (5.6)	0.17	0.26
Total QoL	12.1 (4.2)	13.1 (4.0)	-1.0 (2.0)	0.10	0.2
MSIS-29					
Physical	32.9 (22.1)	33.1 (19.4)	**0.6 (14.2)**	0.03	0.04
Psychological	36.8 (25.1)	32.7 (26.0)	**3.0 (14.2)**	0.12	0.21

[†] Mean change score divided by standard deviation of Time 1 scores
[¶] Standardized response mean= mean change scores divided by standard deviation of change scores
Note: Change scores that had a sign (direction of change) that was expected for that group have been bolded.
Total N=34
SF-36= Medical Outcomes Survey Short Form – 36 Items
HAQUAMS= Hamburg Quality of Life Questionnaire in MS
MSIS-29= Multiple Sclerosis Impact Scale

Responsiveness indices for all these scales were below 0.20.

Time for completion and patient opinion

The average time for completion of the SF-36 and HAQUAMS were 9.9 minutes and 9.5 minutes respectively (see Table 10). The MSIS-29 took the least amount of time to complete: 6.9 minutes. With respect to the length of the HRQoL questionnaires, 7% of the sample thought that the number of questions in HAQUAMS was "too many" compared to 8.9% for MSIS-29, and 11.7% for the SF-36. Overall, 88.7% of the patients thought that the length of HAQUAMS was just right; more than that for MSIS-29 (82.0%) and SF-36 (82.3%). A higher percentage of participants (90.4%) thought that the wording of the MSIS-29 was "mostly easy to understand", while this number was slightly lower for HAQUAMS (87.0%), and much lower for SF-36 (78.1%). A small proportion of participants reported that the wording was "mostly difficult to understand" for HAQUAMS (1.7%) and SF-36 (5.3%) but none for MSIS-29 (0.0%). The percentage of participants that thought that the content of the questionnaires was relevant to most of the problems faced in their day-to-day activities were 86.1% for MSIS-29, 81.7% for HAQUAMS, and 72.8% for the SF-36.

Although the mean time of completion was highest for HAQUAMS, a higher percentage of respondents indicated that the number of questions were just right (about 89%). This may imply that although HAQUAMS takes a slightly longer time to complete, its content is more relevant to patients with MS.

Table 10: Completion Time and Patient Opinion Regarding the HRQoL Measures

Variables	SF-36	HAQUAMS	MSIS-29
Time of completion in minutes: mean (SD)	9.9 (7.7)	9.5 (7.9)	6.9 (7.7)
Number of Questions[¶]			
Too many (%)	11.7	7.0	8.9
Too few (%)	6.3	4.4	8.9
Just Right (%)	82.0	88.7	82.3
Wording[¶]			
Mostly easy (%)	78.1	87.0	90.4
Mostly difficult (%)	5.3	1.7	-
No Opinion (%)	16.7	11.3	9.6
Relevance of content[¶]			
Mostly Yes (%)	72.8	81.7	86.1
Mostly No (%)	9.7	4.4	5.2
Not Sure (%)	17.5	14.0	8.7

[¶] Numbers corresponding with each option indicate the percentage of participants
SF-36= Medical Outcomes Survey Short Form – 36 Items
HAQUAMS= Hamburg Quality of Life Questionnaire in MS
MSIS-29= Multiple Sclerosis Impact Scale

Preliminary Analysis

Table 11 shows interrelationships between the investigated independent variables and the quality of life domains (as measured by the HAQUAMS). Interrelationships between interval variables were reported as Pearson's correlation coefficients while eta values were calculated to illustrate associations between nominal and interval variables. The significance level of each correlation was determined by the F test of the analysis of variance (ANOVA). Disability, depression, visual impairment and employment status displayed significant ($p <$ 0.01) correlations with all HRQoL domains such as overall quality of life, fatigue, upper and lower mobility, mood and social function.

As would be expected, disability was most strongly correlated with overall quality of life score (0.77), while gender, race and marital status had the weakest correlation with overall quality of life (0.01 to 0.03). Similarly, significant correlations were observed between overall quality of life score and visual impairment (-0.68, $p < 0.01$), depression (0.56, $p < 0.01$), employment status (0.47, $p < 0.01$), number of co-morbid conditions (0.27, $p < 0.01$), duration of disease (0.19, $p < 0.05$) and age (0.25, $p < 0.01$). The correlation between overall HRQoL measured by the HAQUAMS and visual impairment measured by the visual function questionnaire (VFQ) was negative, owing to differences in scoring. A higher score on the HAQUAMS indicates better quality of life but poorer visual function on the VFQ.

Where disability, visual impairment and employment status had a moderate to strong correlations with the mobility scales, other variables such as depression, age, duration of the disease and comorbid conditions also displayed significant ($p < 0.01$) but relatively weaker associations with these scales. Among these variables, depression had the highest correlation

Table 11: Bivariate Relationships (Correlations) Between Interval Predictor Variables and HRQoL Domains

	Total QoL	Fatigue	Upper	Lower	Mood	Social
Disability[¶]	0.77[†]	0.63[†]	0.65[†]	0.62[†]	0.60[†]	0.52[†]
Depression[¶]	0.56[†]	0.46[†]	0.29[†]	0.27[†]	0.60[†]	0.55[†]
Visual Impairment[¶]	-0.68[†]	-0.51[†]	-0.53[†]	-0.53[†]	-0.59[†]	-0.54[†]
Age[¶]	0.25[†]	0.16[#]	0.28[†]	0.35[†]	0.12	0.12
Duration of Disease[¶]	0.19[*]	0.12	0.22[*]	0.30[†]	0.08	0.04
Comorbid Conditions[¶]	0.27[†]	0.18[#]	0.23[*]	0.19[*]	0.18[#]	0.26[†]
Gender[‡]	0.02	0.20[*]	0.11	0.03	0.08	0.04
Race[‡]	0.03	0.05	0.09	0.01	0.04	0.12
Marital Status[‡]	0.01	0.04	0.08	0.09	0.07	0.06
Employment[‡]	0.47[†]	0.40[†]	0.43[†]	0.46[†]	0.34[†]	0.27[†]

[#] Significant at $p < 0.10$
[*] Significant at $p < 0.05$
[†] Significant at $p < 0.01$
[¶] The association between two interval variables was estimated with Pearson's correlation coefficient
[‡] The association between nominal and interval variables was estimated with the association measure Eta.
  The significance level of the correlation was determined by the F-test on the analysis of variance (ANOVA)
  QoL= Quality of life

with the HAQUAMS upper mobility score (0.29, $p < 0.01$), whereas age had the highest

correlation with the HAQUAMS lower mobility score (0.35, p < 0.01). Number of comorbid

conditions was found to be significantly correlated with the fatigue (0.18, p < 0.10), mood

(0.18, p < 0.10) and social functioning (0.35, p < 0.01) dimensions of HRQoL. None of the

demographic variables showed any significant correlations with any of the quality of life

dimensions. Gender had a significant but weak correlation with the fatigue scale (0.20, $p \leq$

0.05) but not with the other dimensions. The remaining demographic variables (marital

status and race) were not significantly correlated ($p > 0.05$) with any of the quality of life

domains including overall quality of life score.

Predictors of Overall Quality of life

The results of the hierarchical regression analysis, which identified demographic and

disease-related factors that were most strongly associated with overall HRQoL, are presented

in Table 12. Disability, depression, visual function and age were significantly associated

with poor HRQoL in relation to multiple sclerosis. Disability accounted for the greatest

increment of variance for HRQoL; with approximately 59% of the model being explained by

this variable. Higher scores on the GNDS (higher disability) were associated with higher

scores on the HAQUAMS (poorer quality of life). The results indicated that increase in

disability can lead to a significant decrease in HRQoL in patients with multiple sclerosis (β=

0.37, p $\leq$ 0.05).

In the second step [ΔR^2 0.04, F (2,113) = 97.12], whether depression explained any

variance in HRQoL was examined. The results showed that depression (β= 0.10, p < 0.05)

was also a significant predictor of quality of life. In the third step [ΔR^2 0.03, F=53.48],

Table 12: Hierarchical Regression Analysis to predict quality of life by disability, depression, demographic variables, duration of MS, other co-morbidities and visual impairment. (n=116)

	Step 1	Step 2	Step 3	Step 4	Step 6	Step 5	VIF$^{\pm}$
Block 1							
Disability	0.37†	0.31†	0.27†	0.29†	0.29†	0.23†	2.26
Block 2							
Depression	-	0.10†	0.10†	0.10†	0.10†	0.08†	1.46
Block 3							
Age	-	-	0.03	0.04*	0.04	0.05*	1.77
Employment Status	-	-	-0.99	-1.00	-1.01	-0.66	1.35
Block 4							
Comorbidity	-	-	-	-0.29	-0.29	-0.21	1.43
Block 5							
Duration¶	-	-	-	-	-0.01	-0.01	1.49
Block 6							
Visual Impairment	-	-	-	-		-0.07†	1.92
R^2	0.59	0.63	0.65	0.66	0.66	0.70	
ΔR^2	-	0.04	0.02	0.01	0.00	0.04	
F	160.44	97.12	51.55	42.36	34.99	35.19	

* Significant at $p < 0.05$
† Significant at $p < 0.01$
$\Delta R^2 = R^2$ change from previous step
$^{\pm}$ Variance Inflation Factor
¶ Duration of disease measured in Years
Dependent Variable: Quality of Life measured as overall quality of life score on the HAQUAMS
Independent Variables: Disability measured using Guys Neurological Disability Scale (GNDS); Visual Impairment measured using Visual Function Questionnaire (VFQ); Depression measured using Centers of Epidemiological Studies- Depression Scale

it was explored whether patient demographics would explain any changes in HRQoL scores.

Neither age nor employment was significantly associated with HRQoL scores. This was

followed by steps 4 and 5, whereby number of comorbid conditions and duration of disease

were added to the model. These variables were not significantly associated with HRQoL

scores comorbidity (β= -0.29, p = 0.10); duration (β= -0.01, p = 0.88) and both steps

collectively explained only 1% of the variance in the dependent variable. The last variable

that was added to the model was visual impairment (scores on the VFQ). Participants with a

high level of visual impairment (lower scores on the VFQ) reported significantly lower

HRQoL (higher scores on the HAQUAMS) (β= -0.07, p < 0.05). Visual impairment

explained an additional 4% variance in the HRQoL scores independent of disability and

depression [ΔR^2 0.04, F (7,108) = 35.19]. As presented in Table 11, predictors at all but one

step explained significantly more variance in the total HRQoL scores and the final model

explained 70% of the total variance in HRQoL. The variance inflation factors of all predictor

variables ranged from 1.35 to 2.26 and were less than the conventional cutoff of 4.0

indicating absence of any significant multicollinearity in the model.

Predictors of other Quality of Life Dimensions

Results of the separate multiple linear regression analyses to examine predictors for

each of the HRQoL dimensions are given in Table 13. The regression model of each

dimension had a different set of predictor variables. Independent variables for each model

were selected based on the strength of their correlation with that particular HRQoL

dimension (refer to Table 11). The depression variable was left out of the regression model

Table 13: Separate Multiple Linear Regression Analyses for Each of the Five Quality of Life Domains (HAQUAMS Sub-Scales)

Independent Variables	Fatigue		Upper Mobility		Lower Mobility		Mood		Social Function	
	β	SE	β	SE	β	SE	β	SE	β	SE
Disability	$0.20^{\dagger}$	0.05	$0.26^{\dagger}$	0.05	$0.27^{\dagger}$	0.07	$0.31^{\dagger}$	0.09	0.12	0.06
Depression	0.06^{*}	0.03	-0.04	0.04	-0.04	0.04	-	-	$0.16^{\dagger}$	0.04
Visual Impairment	-0.03	0.02	-0.06^{*}	0.03	-0.08^{*}	0.03	$-0.15^{\dagger}$	0.04	-0.08^{*}	0.03
Employment	-0.64	0.68	-1.36	0.83	-2.28^{*}	1.0	-0.45	1.38	0.61	0.99
Comorbid Conditions	-0.31	0.21	-0.18	0.25	-0.54	0.31	-0.15	0.40	0.32	0.28
Age	0.02	0.02	0.05	0.03	0.10^{*}	0.04	-	-	-	-
Duration of Disease	-	-	-0.01	0.05	0.04	0.06	-	-	-	-
Gender	-1.64^{*}	0.63	-	-	-	-	-	-	-	-

* Significant at $p < 0.05$
† Significant at $p < 0.01$
Missing values for beta coefficients and standard error indicate that the independent variable was not included in that particular model. Total N= 116.
β = Beta Coefficient
SE= Standard Error

for mood (measured by HAQUAMS), since both these scales measure the same underlying concept. Only variables that were significantly correlated with the dependent variable at an alpha level of 0.10 or less were included in the models.

Disability was the main determinant of fatigue (β= 0.20) followed by gender (β= -1.64) and depression (β= 0.06). With respect to gender, males with MS seem to have less fatigue compared to females. Visual impairment was not found to be a significant predictor of fatigue. However, it had a small but significant impact on mobility (β= -0.06 for upper mobility and β= -0.08 for lower mobility). The negative sign for the correlation was expected because a higher score indicates better visual functioning on the VFQ, but lower functioning on the HRQoL scales. Employment status (β= -2.28) and age (β= 0.10) were also found to be significant predictors of lower mobility. The negative β coefficient for the employment status indicates that those who are employed have lower scores on the HAQUAMS lower mobility scale, that is, they are more likely to have better mobility than those who are not employed. Similarly, it is possible that an increase in age will lead to lower scores on the HRQoL domains (β= 0.10). Number of comorbid conditions and duration of disease were not significantly related to mobility in patients with multiple sclerosis.

In addition to visual impairment (β= -0.08), only depression was found to significantly predict social function (β= 0.16). The main determinants of mood were disability (0.31) and visual impairment (β= -0.15). The β coefficients indicate one point increase in disability leads to a 0.31 point increase in the depression score. Similarly, a one point increase in VFQ scores leads to a 0.15 point decrease in the depression scale score. The negative correlation coefficient between VFQ and CES-D is due to the differences in

scoring. A higher score on the VFQ indicates better visual function but increased depression symptoms as measured by the CES-D. All models were significant at $p < 0.05$.

Regression Diagnostics for Phase I: Objectives 2 and 3

Variance inflation factors of independent variables were less than 2.5 for all Phase I regression models implying absence of any significant multicollinearity. Tests for normality of residuals (Shapiro-Wilk Test) and homogeneity of variance (White Test) were not significant at $p \leq 0.05$ (see Table 14), indicating that these assumptions were also met for all models.

Table 14: Tests of Normality and Homogeneity of Variances of Residuals for All Regression Models

Dependent Variable	W	p value	Chi-Sq	p value
Total Quality of Life	0.98	0.15	39.47	0.24
Fatigue	0.99	0.30	48.50	0.41
Upper Mobility	0.98	0.06	37.26	0.82
Lower Mobility	0.98	0.35	37.64	0.77
Mood	0.99	0.27	13.25	0.43
Social Function	0.98	0.24	19.14	0.45

W= Shapiro-Wilk Statistic for testing normality of the residuals
Chi-Sq= White test for homogeneity of variance of the residuals
Significance determined at $p \leq 0.05$
All dependent variables were measured using the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS)

Phase II

Response Rates and Physician Characteristics

   The mailing list from SK & A consisted of 6500 neurologists within the United States. Of these, a randomly selected sample of 2400 neurologists was mailed the final survey. The response rate was 4.6% after those who were ineligible or unreachable (i.e. those who had left the practice, had retired, or were not involved in the routine care of patients with MS) were deducted from the 2400 approached, as these were not true refusals (See Figure 2).

   One hundred and seven questionnaires were completed and returned by neurologists involved in the routine care of patients with MS. Table 15 depicts the key characteristics of these respondents. Males comprised 84% of the sample. Eighty-one percent of the neurologists had been practicing for at least ten years. There were a higher proportion of neurologists between the ages of 51 and 60 years (40.2%) compared to any other age group, and a majority of them were practicing in office based settings (83.2%). Only 15% of the respondents had participated in a MS-related clinical trial with a HRQoL component once in the past. There was an observable difference in the perceived usefulness of HRQoL information use among neurologists. The overall consensus was that HRQoL information can be advantageous (Mean: 5.3; SD: 1.0 on the facilitator scale) and that there were fewer drawbacks associated with using this information in the routine care of patients with MS (Mean: 2.9; SD: 1.0 on the barriers scale). Cronbach's alpha for the statements comprising the barrier (0.76) and facilitator (0.74) scales exceeded the minimum requirement of 0.70 indicating good internal consistency reliability.

Figure 2: Flow Chart Displaying Response to the Neurologist Survey

```
                  ┌──────────────────────────────────────────┐
                  │ Total number of neurologists in mailing list │
                  │                  6500                      │
                  └──────────────────────────────────────────┘
                                    │
             ┌──────────────────────┴──────────────────────┐
             │                                    ┌──────────────┐
             │                          ◄─────────│   4 Weeks    │
             │                          │         └──────────────┘
             ▼                          ▼
    ┌──────────────────┐       ┌──────────────────┐
    │   First mailing  │       │  Second mailing  │
    │ 2400 Neurologists│       │ 1800 Neurologists│
    └──────────────────┘       └──────────────────┘
             │                          │
             ▼                          ▼
  ┌────────────────────────┐  ┌────────────────────────┐
  │       80 Usable        │  │       26 Usable        │
  │ 51 Returned but Unusable│  │ 37 Returned but Unusable│
  │     22 Unreachable     │  │     10 Unreachable     │
  └────────────────────────┘  └────────────────────────┘
             └────────────┬─────────────┘
                          ▼
           ┌──────────────────────────────┐
           │         106 Usable           │
           │   88 Returned but Unusable   │
           │       32 Unreachable         │
           │                              │
           │      Response Rate:          │
           │                              │
           │            106               │
           │       ─────────────          │
           │       2400 − (88+32)         │
           │                              │
           │          = 4.6%              │
           └──────────────────────────────┘
```

$$\frac{106}{2400 - (88+32)} = 4.6\%$$
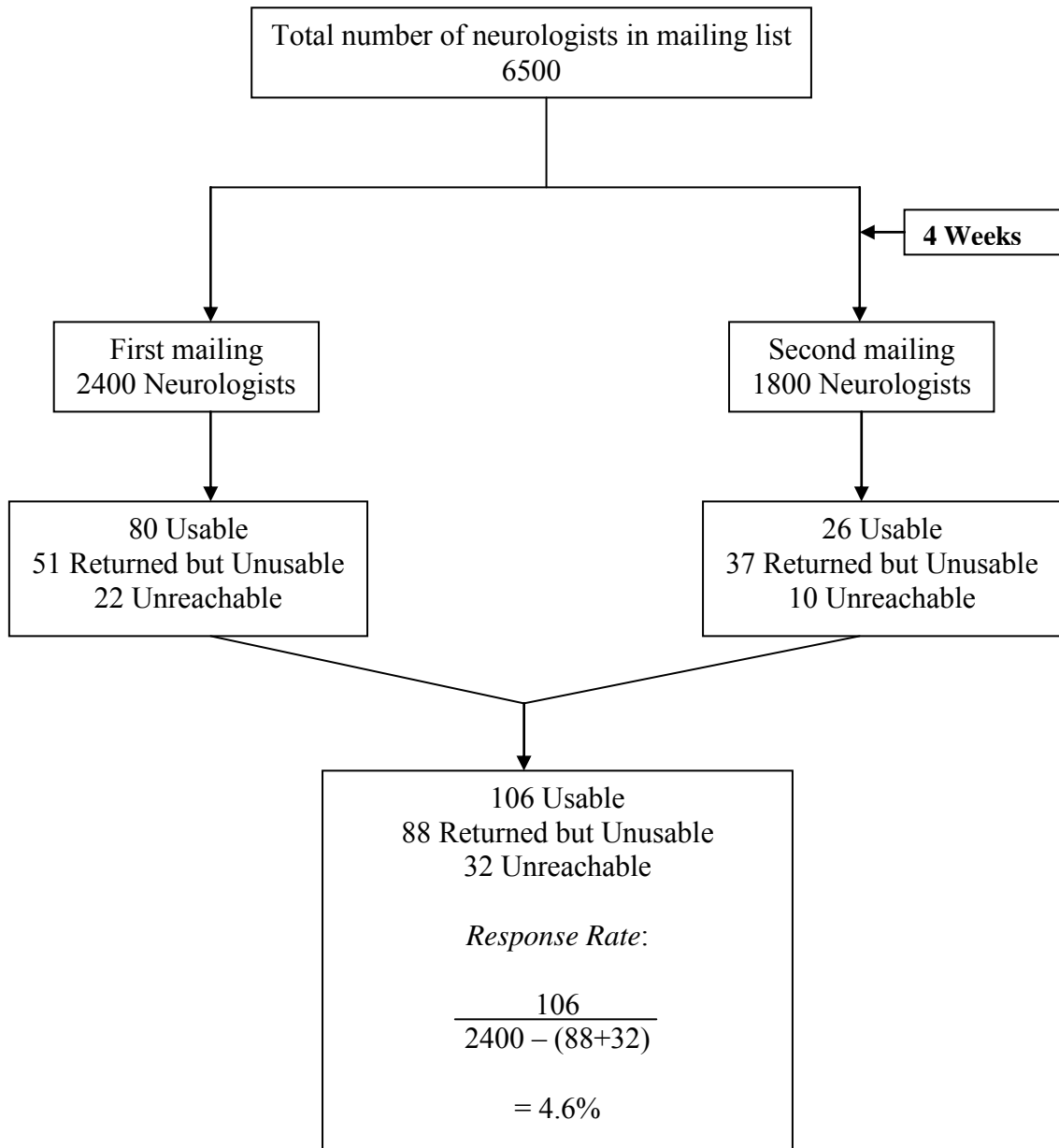
Table 15: Characteristics of the Responding Neurologists (Total N=107)

Variable	N (%)
Gender	
Male	90 (84.1)
Female	17 (15.9)
Age Group	
31 to 40 years	16 (15.0)
41 to 50 years	23 (21.5)
51 to 60 years	43 (40.2)
61 or older	25 (23.4)
Primary site of practice	
Hospital	3 (2.8)
University Hospital	15 (14.0)
Solo, Office Based	38 (35.5)
Group, Office Based	51 (47.7)
Participation in MS Clinical Trial	
Yes	16 (15.0)
No	91 (85.1)
Number of years as neurologist	
5 years or fewer	13 (12.2)
6 to 10 years	13 (12.2)
10 years or more	81 (75.7)
Stage of Change[†]	
Stage 0	24 (22.6)
Stage 1	45 (42.5)
Stage 2	20 (18.9)
Stage 3	11 (10.4)
Stages 4 & 5	6 (5.7)
Facilitator Scale Score	
Mean (SD)	5.3 (1.0)
Barrier Scale Score	
Mean (SD)	2.9 (1.0)
No. of patients seen per week	
Median (Range)	4 (1-150)

[†]Stage 0= unaware of any HRQoL questionnaires; Stage 1= aware of HRQoL questionnaires, but never thought about using them; Stage 2= thinking of using HRQoL questionnaires within the next 6 months; Stage 3= thinking of using HRQoL questionnaires within the next month; Stage 4= have been using HRQoL questionnaires for less than six months; Stage 5= been using HRQoL questionnaires for more than six months

The number of patients with MS seen per week by the neurologists ranged from 1 to 150 (Median= 4).

Classification Based on the Transtheoretical Model

The staging of HRQoL related behavior based on the Transtheoretical Model has also been reported (refer to Table 15). About 65% of the neurologists were either unaware of HRQoL questionnaires and their use, or had not thought about using formal standardized questionnaires in routine practice (Stages 0 and 1). Approximately 19% of the respondents were planning on using standardized HRQoL questionnaires in routine practice within the next six months (Stage 2) while about 10% of the respondents reported that they were planning on using such questionnaires within the next month (Stage 3). Only 6% indicated that they were currently using such questionnaires in the routine care of patients with MS (Stages 4 and 5).

Subgroup analyses of pre-contemplators (Stages 0 and 1) and contemplators (Stages 2 and 3) revealed significant differences between the two groups in terms of perceived barriers and facilitators to HRQoL assessment in patients with MS (see Table 16). As would be expected, the contemplator group such as those who were planning to use HRQoL information within at least the next six months, had higher scores on the facilitator scale [Mean (SD): 5.7 (1.0) vs. 5.2 (1.0), $p < 0.05$] and lower score on the barrier scale [Mean (SD): 2.5 (0.9) vs. 3.1 (1.0), $p < 0.01$] compared with that of the pre-contemplator group i.e. those who were unaware or had not thought of using HRQoL information.

Table 16: Differences Between Pre-Contemplators and Contemplators

Variable	Pre-Contemplators	Contemplators	p[*]
	Mean (SD)	Mean (SD)	
Importance of HRQoL information[†]	5.1 (1.5)	5.9 (1.1)	<0.01
Facilitator Scale Score	5.2 (1.0)	5.7 (1.0)	0.03
Barrier Scale Score	3.1 (1.0)	2.5 (0.9)	<0.01

[*] Independent sample *t-tests*
[†] Mean score on the following question from the neurologist survey: How important is it to collect HRQoL information in the routine care of patients with multiple sclerosis?
Note: Data excludes those who are currently using HRQoL information in routine practice. Total N=101. Pre-Contemplators included respondents classified under stages 0 & 1. Contemplators included respondents classified under Stages 2 & 3.
SD= Standard Deviation
HRQoL= Health Related Quality of Life

In other words, unlike the pre-contemplator group, contemplators perceived greater usefulness of HRQoL information and fewer disadvantages and/or problems associated with HRQoL assessment in the routine care of patients with MS. In terms of their degree of agreement with the following question: "How important is it to collect HRQoL information in the routine care of patients with multiple sclerosis?" the contemplator group (mean= 5.9; SD= 1.1) had significantly ($p < 0.05$) higher perceived importance of HRQoL assessment in MS compared to the pre-contemplator group (mean=5.1; SD= 1.5).

Comparison of HAQUAMS and MSIS-29

With respect to HAQUAMS and MSIS-29, the opinion of neurologists regarding: 1) the questionnaires' ability to provide any additional useful information compared to what is normally available; and 2) their ease of use from the perspective of the patients with MS, were compared using the Wilcoxon Sign Ranked test (see Table 17). There was a significant difference between the scores on the questions assessing additional usefulness ($p < 0.05$), as well in the perception of the length of the questionnaire ($p < 0.01$) from the patient's perspective for both questionnaires.

According to the neurologists, the HAQUAMS does a better job of providing additional useful information compared to what is available from conventional physical exams and clinical testing methods than does the MSIS-29 (Median: 6.0 vs. 5.0). However, the HAQUAMS was reported to be longer to complete as compared to the MSIS-29. There was no difference in the opinion of the neurologists regarding the way in which the questions for the two HRQoL measures were worded, as evidenced by the same median score (2.0) on

Table 17: Median Scores of Neurologists' Opinion About HAQUAMS and MSIS-29 Regarding their Usefulness and Ease of Use in Patients with MS

Opinion Questions	HAQUAMS[†]	MSIS-29[†]	p[*]
Additional useful information	6.0	5.0	0.02
Length	5.0	4.0	<0.01
Wording	2.0	2.0	0.10

[†]Median values for each opinion question
[*]p values for Wilcoxon Signed Rank Test
HAQUAMS= Hamburg Quality of Life Questionnaire in Multiple Sclerosis
MSIS-29= Multiple Sclerosis Impact Scale

that particular item. The median score of 2.0 indicated that in the neurologists' opinion, both

questionnaires comprised of questions which were relatively easy to understand.

Knowledge and Use of Specific HRQoL Questionnaires

Overall, utilization of any of the commonly used HRQoL questionnaires in MS

research listed in this survey was very low among responding neurologists (see Table 18).

Only six percent reported having used the Functional Assessment of Multiple Sclerosis

(FAMS) questionnaire in the past. Minimal use of the Medical Outcomes Survey Short

Form, Multiple Sclerosis Quality of Life-54, and the Multiple Sclerosis Quality of Life

Inventory was also reported (Range= 3.1% to 4.1%). With respect to knowledge about

existing HRQoL measures however, a much larger proportion of the neurologists reported

that they had heard of the HRQoL questionnaires included in this survey. More than 40% of

the respondents had heard of the Multiple Sclerosis Quality of Life – 54 as well as the

Multiple Sclerosis Quality of Inventory. Awareness about the other questionnaires ranged

from 25% to 37% among the responding neurologists with 12% reporting knowledge of other

questionnaires not referenced in the survey.

Table 18: Numbers and Percentages of Neurologists that Reported Having Used or Heard of MS-related HRQoL Questionnaires

Questionnaire	Used N (%)	Heard of N (%)
Medical Outcomes Survey Short Form (SF-36)	3 (3.1)	34 (34.7)
Multiple Sclerosis Quality of Life 54 (MSQoL-54)	4 (4.1)	43 (43.9)
Functional Assessment of Multiple Sclerosis (FAMS)	6 (6.1)	33 (33.7)
Multiple Sclerosis Quality of Life Inventory (MSQLI)	4 (4.1)	41 (41.9)
Multiple Sclerosis Impact Scale (MSIS-29)	1 (1.0)	31 (31.6)
Hamburg Quality of Life Questionnaire in MS (HAQUAMS)	1 (1.0)	37 (37.8)
Sickness Impact Profile (SIP)	1 (1.0)	25 (25.5)
Other	1 (1.0)	12 (12.2)

Predictors of the Neurologists' Intention to Use HRQoL Information

The results of the multiple linear regression model used to examine predictors of the neurologists intention to use HRQoL information are presented in Table 19. The primary independent variables included in this model were: attitude (measured by items 2 to 8 on the neurologist survey, see Appendix J); subjective norms (where referents were the American Academy of Neurology and Fellow Neurologists), and perceived behavioral control (measured by items 9 and 10 on the neurologist survey. See Appendix J). Other independent variables were gender (male vs. female), age-group, primary place of practice (hospital vs. office based), years in practice as a neurologist, number of MS patients seen per week and participation in a MS related clinical trial (yes vs. no).

Attitude was found to be a significant predictor of behavioral intention ($\beta = 0.03$, $p < 0.01$), where a positive attitude was associated with an increased intention to use HRQoL information. Number of years in practice as a neurologist ($\beta = -0.46$, $p = 0.03$) was significantly but inversely associated with the intention to use HRQoL information in the routine care of patients with MS. This means that neurologists who had been practicing for 10 years or more were less likely to show any intention of assessing HRQoL in patients with MS compared to those who had been practicing for fewer than 10 years. Subjective norms were also significantly associated with intention to assess HRQoL information ($\beta = 0.01$, $p = 0.05$). This indicates that positive social pressure (from referents such as the American Academy of Neurology and Fellow Neurologists) is associated with an increased likelihood of HRQoL assessment in the routine care of patients with MS. Among other variables, age-group had a slight tendency towards predicting behavioral intention ($\beta = 0.26$, $p = 0.06$).

Table 19: Factors Associated with the Intention to Use HRQoL Information in Routine Practice

Independent Variable	β Estimate	Std. Error	p	VIF
Attitude	**0.03**	**0.003**	**<0.01**	**1.14**
Years practice as neurologist	**-0.43**	**0.21**	**0.03**	**2.23**
Subjective Norms	**0.01**	**0.01**	**0.05**	**1.15**
Age group	0.26	0.14	0.06	2.04
Gender	-0.14	0.28	0.63	1.15
Place of practice	0.43	0.30	0.16	1.42
Behavioral control	0.14	0.10	0.20	1.09
Number of patients per week	0.01	0.01	0.42	1.35
Involved in MS-related trial	0.22	0.32	0.49	1.50

Note: Data from the original sample (N=106).
Independent variables: Attitude, subjective norms, behavioral control, gender, years of practice as neurologist, primary place of practice (hospital vs. office), age, number of MS patients seen per week and involvement in a MS clinical trial.
Dependent variable: Neurologists' intention to use HRQoL information.

None of the other independent variables in the model were found to be significant. The overall model was found to be significant ($F = 16.19$, $p < 0.01$) and explained almost 61% of the variation in the dependent variable (behavioral intention). The variance inflation factors for all independent variables were well within the acceptable limit of 4.0 (VIF < 2.5 for all variables), indicating absence of any significant multicollinearity within the model.

Regression Diagnostics for Phase II: Objective 4

The residuals for *behavioral intention*, which was the dependent variable, departed radically from normal distribution (Shapiro-Wilk $W = 0.96$, $p = 0.0016$). To deal with this problem, studentized residuals, which are a type of standardized residual, were examined to identify outliers. If a single observation is substantially different from all other observations (an outlier), it can make a large difference in the results the regression analysis. One observation with a studentized residual greater than -4.0 was dropped from the dataset in the interest of validity of the coefficients of the regression model.

The regression model was then rerun using data for 106 respondents (Refer to Table 19). None of the variance inflation factors exceeded 2.5, indicating that multicollinearity was not a problem with the data. Variance inflation factor was 2.23 for the variable years in practice as a neurologist and 2.04 for age group. Both these variables were retained in the final model since these values did not exceed the value of 4.0, which is a generally accepted limit for multicollinearity (Fisher JC et al., 1981). The residuals for the final model met the criteria of normality (Shapiro-Wilk $W = 0.98$, $p = 0.12$) as well as homogeneity of variance (*Chi Sq* $= 40.29$, $p = 0.86$)

Chapter 5: Discussion and Conclusions

The overall goal of this study was to investigate several research questions relevant to the area of health-related quality of life (HRQoL) in patients with multiple sclerosis (MS). Currently, there are several patient reported outcome (PRO) measures intended for use in patients with MS. However, there is no general consensus as to which measure is most suitable or appropriate to assess HRQoL in MS, especially in the routine clinical practice setting. One aim of the current study was to compare the psychometric properties, as well as neurologists' and patients' opinions regarding two PRO measures: the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS) and the Multiple Sclerosis Impact Scale (MSIS-29), with the intention of enabling evidence-based selection of PRO measures for use in the routine care of patients with MS.

Information obtained from such head-to-head comparisons can guide neurologists' choice of a PRO suitable for use in their routine clinical practice. An exhaustive comparison of the PRO measures which have been shown to be relevant to MS and have displayed desirable psychometric properties as evidenced by prior published studies (Gold et al., 2001; Hobart et al., 2001; Riazi et al., 2002) was performed. In the absence of a "gold standard" PRO measure in MS research, the Medical Outcomes Survey Short Form – 36 items (SF-36), which is a commonly used generic measure of MS-related HRQoL was used in this comparison.

In addition to addressing issues relating to HRQoL assessment, several research studies have been conducted whose main focus was to identify and examine the influence of several factors on the quality of life of patients with MS (Benedict et al., 2005; Amato et al.,

128

2001; Lobentanz et al., 2004; Wang et al., 2000). Disability and depression have been identified as primary determinants of HRQoL in patients with MS. Problems with visual functioning are also very common in MS. Visual impairment and its impact on HRQoL in MS had not been thoroughly studied, due to the absence of validated vision-related PRO measures in this population. However, research in this area has recently gained some attention in the last few years, following the validation of the Visual Function Questionnaire (VFQ) in a sample of patients with MS (Ma et al., 2002b; Balcer et al., 2000). Another aim of the current study was proposed in order to substantiate findings regarding the predictors of HRQoL and also investigate the influence of additional relevant variables such as visual impairment and chronic comorbid conditions such as heart disease, diabetes and arthritis, which had not been studied in the past.

Although commonly used in research and clinical trials, the utilization of HRQoL information in clinical practice has been limited. For the provision of optimum care to patients with MS, HRQoL assessment needs to transcend the realm of research into routine clinical practice. In order to do this however, it is necessary to identify current utilization, and areas that need to be targeted to facilitate the acceptance of HRQoL information by neurologists. Hence, a nationwide survey of neurologists was performed to provide empirical evidence of current practices regarding use of HRQoL information in patients with MS. In order to identify factors that have an influence on the intention to use such information in clinical practice, a framework of two health behavior theories was used. The Trans-Theoretical Model was used to categorize neurologists based on their stage of change regarding HRQoL information use. Additionally, the Theory of Planned Behavior was used in order to identify predictors of HRQoL intention (behavioral intention) in this population.

Phase I: Objective 1

Head-to-head Comparison of PRO Measures

Comparison of the PRO questionnaires (MSIS-29 and HAQUAMS) was performed on their psychometric properties and the opinions of patients and neurologists regarding their usefulness and ease of use. The first step for the psychometric comparison was to evaluate summated ratings scales, for example, HAQUAMS upper and lower mobility scales. This was done by determining the extent of missing data at the item level. A summated rating score cannot be estimated with the same degree of confidence if there is a large amount of missing data for a particular item. Missing responses might indicate problems with the wording of the response choices for those items. It also might indicate that respondents did not understand how to complete or provide the most suitable answer for that part of the questionnaire.

It can be observed from the findings of this study that one item on the lower mobility scale of the HAQUAMS had unusually high percentage of missing data. This item asked the respondents to estimate the distance that they could walk in metric units (meters). It was not surprising to encounter missing data for this question as respondents in the United States (US) may not be accustomed to using this system of measurement. The English language version of HAQUAMS was made available for the purpose of this study and hence no changes were made to maintain its validity. Correcting this issue however, may require replacement of the response choices with commonly used units of measuring length such as feet, yards or miles followed by a small scale validation study for use in patients in the US.

Item means and standard deviations were also examined for the two PRO measures. Item means are required to be approximately equivalent within a scale under traditional

130

Likert scaling criteria and were found to meet this criterion for both MSIS-29 and HAQUAMS. Item standard deviations should also be roughly equivalent; the rule of thumb being a standard deviation of around 1.0 for scales with five-choice response such as the HAQUAMS and MSIS-29 (Ware, Jr. & Gandek, 1998). The variances of the items within the scales for two PRO measures did not vary greatly and hence are consistent with this criterion. Further standardization of the items is probably not necessary as there is little to be gained by making such adjustments (Ware JE, Harris WJ, Gandek B, Rogers BW, & Reese PR, 1997)

Ideally, item-total correlations should be fairly high for items with their own corrected scale score. Items for all scales except for item 21 of the MSIS-29 (psychological impact scale: 0.12) were found to be stronger than the pre-determined correlation of 0.30. A low item-total correlation means the item is little correlated with the overall scale and the researcher should consider dropping it. Hence, the inclusion of item 21 of the MSIS-29 in calculating the psychological impact score needs to be re-assessed. Item-total correlations greater than 0.30 for all scales of HAQUAMS provide greater confidence that they are precisely measuring the underlying singular concept, thereby permitting comparison between two or more distinct groups of patients with MS.

Among scales measuring similar domains (physical and mental domains for each of the three measures), the HAQUAMS upper mobility scale displayed a somewhat high floor effect compared to the other physical function scales, although these were still well within the acceptable range of 20% (van der Putten, Hobart, Freeman, & Thompson, 1999). Floor effects displayed by this scale may represent its limited ability to discriminate between non-institutionalized samples of adults with MS based on self-reported upper physical

131

functioning. Floor and ceiling effects can also have an influence on responsiveness of the measures. The scale range for any measure must extend beyond the range of function (absence of floor or ceiling effects) of the patients for whom it will be used, or it will be incapable to demonstrating further improvement or deterioration between two or more time points. On the whole, HAQUAMS and MSIS-29 did not show any significant floor and ceiling effects. This may be partially due to the nature of the response sets to the questions, which are not limited to dichotomous answers. High floor and ceiling effects are observed for questions 4 and 5 of the SF-36, partly due to presence of 'yes/no' response options.

Pearson's *r* was calculated for physical and psychological domain scale scores of each instrument, and then correlations between them were analyzed using a multitrait-multimethod matrix. This well accepted method of evaluating convergence and divergence requires that at least two traits or constructs each be assessed by at least two disparate methods. Although the intercorrelations observed for the HAQUAMS mood scale with its upper and mobility scales were similar to what was reported by Gold and colleagues (2001), patterns of construct validity with respect to other PRO measures and quantitative tests of motor functions were inconsistent with their predictions. Divergent validity for the HAQUAMS mood scale would be supported if its correlation with MSIS-29 psychological and SF-36 mental health was higher than its correlation with MSIS-29 physical and SF-36 physical function. However, compared with the MSIS-29 psychological impact scale, the HAQUAMS mood scale had relatively a weaker relationship with the SF-36 mental health as well as with scores on the CES-D. Moreover, its associations with scores on the 9-Hole Peg Test and the Timed-25 Foot Walk Test (quantitative tests of motor function) were higher than that for the MSIS-29 psychological scale.

Interestingly, the correlation coefficient (0.71) between the HAQUAMS mood scale and the MSIS-29 physical impact scale (scales from *two different* instruments measuring different constructs) was almost the same as the correlation (0.70) between the physical and psychological impact scales of the MSIS-29 (two scales from *the same* instrument measuring different constructs). The intercorrelation between the MSIS-29 scales observed in this study (0.70) was much higher than what was reported previously (0.438) by McGuigan and colleagues (2004). One explanation may be that the shared features of the method of assessment could lead to the high correlation coefficient amongst MSIS-29 physical and psychological impact scales. However, the relatively large correlation coefficient between the HAQUAMS mood and MSIS-29 physical impact scales does not conform with the expectation that the multitrait-multimethod correlation should be lower compared to monotrait-multimethod correlations. These observations suggest relatively poor divergent validity of the mood scale of HAQAUMS, and to some extent the physical impact scale of the MSIS-29.

To gain a better understanding of where this anomaly arises, correlation coefficients between the HAQUAMS mood and MSIS-29 physical impact scales were calculated separately for the demographic variables. With respect to gender, this analysis revealed a higher correlation in males (0.81) compared with the females (0.66) implying an overlap in the mood and physical domains of these specific scales among community dwelling males with multiple sclerosis. Although the correlation was weaker among females, it was still at the upper extreme of acceptable limits (0.66 compared with the initial value of 0.71). With respect to other demographic variables, the correlation coefficients between the HAQUAMS mood and MSIS-29 physical impact scales were still quite high: 0.77 for those who were not

married; 0.69 for participants who were employed, and 0.67 for participants who were currently married. A comparatively low correlation between these scales was only seen for those who reported that they were currently unemployed (0.57). Poor construct validity may limit the legitimacy of the inferences that can be made regarding the underlying theoretical constructs for the HAQUAMS mood and MSIS-29 physical impact scales.

In summarizing this section on construct validity, it is important to consider the basic tenet of the multitrait-multimethod matrix that, "the pattern of relationships is more important than the absolute magnitude of the correlation coefficients". The correlations between the scores of the HAQUAMS mobility and MSIS-29 physical scales were significant and relatively large suggesting well-established convergence (monotrait-multimethod triangle for physical domain scales). These coefficients were also larger than most of the coefficient scores within the same instrument (multitrait-monomethod triangles) which provided evidence of divergence. Although the MSIS-29 physical impact scale had high correlation with the other mood scales, the overall pattern of correlations was consistent with the expectations of the multitrait-multimethod matrix. All of its correlations with the physical domains scales (0.76 and 0.82 with HAQUAMS mobility; -0.79 with SF-36 physical function scales) were consistently higher than multitrait-multimethod (-0.41 and 0.71) and multitrait-monomethod correlations (0.70) (pattern over magnitude). Negative correlations with SF-36 were due to differences in scoring for the two measures. A high score indicates better quality of life on the SF-36, but poor quality of life on the HAQUAMS.

The HAQUAMS mood on the other hand, failed to correlate as expected with other scales, thus violating the assumptions of the multitrait-multimethod matrix. The monotrait-multimethod correlations for this scale were not consistently higher than the multitrait-

monomethod or multitrait-multimethod triangles. This problem could either be a snag in the construct underlying one or all of these instruments, faults in the scales themselves or a combination of both. However, its abnormally high correlation with both self-report and clinical measures of physical domain implies that the problem lies with the HAQUAMS mood scale. The MSIS-29 appears to meet all the assumptions of the multitrait-multimethod matrix whereas the construct mismatch of the HAQUAMS mood scale implies poor construct validity and may need further evaluation in a U.S. population.

Concurrent and well as relative validity was examined for all measures included in this study against two external criteria variables: level of disability and ambulation. Relative validity analysis identifies those scales that contribute important distinctive information to each criterion variable. Based on the results of the relative validity analysis, the MSIS-29 physical impact scale was most strongly related to level of disability followed by the physical function scale of the SF-36 and the upper and lower mobility scales of HAQUAMS. Similar patterns were observed for the psychological domain scales with the MSIS-29 psychological impact scale performing slightly better that the HAQUAMS mood and SF-36 mental health scales. The overall HRQoL score on the HAQUAMS however, had the strongest relative validity to discriminate between levels of disability in this sample of patients with MS. HAQUAMS lower mobility scale had a much stronger relative validity coefficient with respect to the level of ambulation (second criterion variable), compared with the MSIS-29 physical impact and SF-36 physical function scales. Furthermore, relatively lower but still significant associations were also observed for the lower mobility and total quality of life score of the HAQUAMS. Thus relative validity analysis elucidates the superior sensitivity of

the mobility and overall quality of life score of the HAQUAMS to important clinical differences in level of disability and ambulation status in patients with multiple sclerosis.

A retrospective method was used to detect clinically important change over time by comparing change scores (baseline score minus follow up score) with an external criterion of change such as a transition question (Juniper, Guyatt, Willan, & Griffith, 1994). The change scores for all sub-scales of the three PRO measures were compared in this study. As would be expected in a non-institutionalized sample not undergoing an intervention or treatment (e.g. steroids), the responsiveness showed minimal effect sizes and standardized response means for both HAQUAMS and MSIS-29. One reason for this may be the fact that change is caused by natural progression over time rather than by treatment effect following a treatment (Norman, Stratford, & Regehr, 1997). Changes due to natural progression are generally expected to be very small and may be difficult to discern compared to immediate changes due to effect of say, a treatment. The responsiveness indices (effect size and standardized response mean) for scales of both measures that are important from the stand point of routine care such as overall quality of life scale of the HAQUAMS; physical and psychological impact scales of the MSIS-29, had insignificant effect sizes (less than 0.20). The results of the responsiveness indices however, need to be considered with care due to the small sample size used in this study.

Although past head-to-head comparisons of HRQoL measures have incorporated the standard criteria (data quality, scaling assumptions, validity, reliability and responsiveness), the present study also elicited patient and neurologist opinions regarding the usefulness of HAQUAMS and MSIS-29. Overall, the MSIS-29 was preferred by the patients in terms of ease of understanding, time for completion and relevance of content. These observations are

136

only generalizable the patients with MS included in this study and hence lack external validity. According to the results of the survey, neurologists believe that the HAQUAMS provides useful information, in addition to what can be obtained from conventional tests in MS, to a greater extent than the MSIS-29.

Recommending a PRO Measure for Use in Clinical Practice

In summary, this objective of the study extensively compared two PRO measures in MS. Each measure has attractive features which would lend itself to clinical practice as well as clinical trial settings. The results of this study support the evidence of the psychometric soundness of MSIS-29 as a measure of impact of MS on patients (Riazi et al., 2003; McGuigan et al., 2004; Hobart, Riazi, Lamping, Fitzpatrick, & Thompson, 2005). In addition it was found to be relevant from the patients standpoint, easy to score and concise. From this perspective, it would be practical to be incorporate this in the routine care of patients with MS.

However, MSIS-29 fails to address other aspects of the disease that may be relevant to patients with MS. In addition to having all the desirable properties of MSIS-29, HAQUAMS also emphasizes domains of fatigue and social complications that form part of the total burden experienced by patients with MS. Relative to the social function and vitality scales of the SF-36, the HAQUAMS social and fatigue scales displayed comparable criterion validity for level of disability. Both scales were also moderately correlated with their SF-36 counterparts (social scales: -0.43; fatigue and vitality: -0.58) indicating that they measured similar constructs. The negative correlation was observed because a higher score on the SF-36 indicates better quality of life but a poorer quality of life on the HAQUAMS and MSIS-

29. On an average, the HAQUAMS took less than ten minutes to complete and could be easily administered by members of a multidisciplinary team or junior medical staff. It could also be self-administered by the patients themselves in the waiting room, prior to be seen by the neurologist.

Based on these analyses no one measure emerged clearly or consistently better or worse than the other in terms of psychometric properties or neurologists' and patients' opinion. Hence, a recommendation of one particular PRO measure for use in MS-related clinical practice cannot be substantiated. This study conveys that HAQUAMS and MSIS-29 can both be effectively used in clinical practice, but seems unlikely that one measure will satisfy all the requirements deemed necessary by specific neurologists or practices. The choice of a quality of life measure ultimately rests on the clinician and may be indirectly related to their perception of the usefulness and intention to use such information in the routine care of MS patients.

Phase I: Objectives 2 and 3

Predictors of HRQoL in MS

As described earlier, assessment of HRQoL information is especially relevant to MS, which is linked with a broad spectrum of physical and social impairments. Several studies have found a significant influence of certain clinical variables on HRQoL in patients with MS. A substantial body of evidence has shown that impairment and disability has an independent but modest contribution to HRQoL in patients with MS. Other predictors that have been shown to have an influence on HRQoL are: course of MS, depression and fatigue. In the present study many of these variables were controlled for and for the first time an

attempt was made to investigate the influence of visual impairment and concomitant comorbid conditions (both self-reported).

Considering the research question posed (which factors have a unique contribution to HRQoL in patients with MS?), inspection of regression coefficients indicated that disability was the strongest significant and independent factor associated with HRQoL. The importance of disability in patients with MS is in agreement with other findings (Miller & Dishon, 2006; Benedict et al., 2005). Besides disability, we also found that depressed mood and increasing age were related to lower HRQoL. Finally, the results of this study demonstrated that visual impairment explained a significant amount of the variance in overall HRQoL and almost every HRQoL domain except for fatigue.

Interestingly, comorbid chronic conditions did not have a significant negative impact on overall HRQoL in patients with MS. Simple counts of comorbid conditions based on patient self-report were used to calculate comorbidity. Simple counts of comorbidities have been commonly used in HRQoL literature (Wensing, Vingerhoets, & Grol, 2001; Michelson, Bolund, & Brandberg, 2000; Cheng et al., 2003). The commonly used Charlson index of comorbidity was not considered for this study because of evidence of its inability to comprehensively explain variations in physical or mental aspects of HRQoL (Fortin et al., 2005a). Also, quality of life outcomes have been shown to correlate most strongly with self-reported comorbid conditions weighted by severity, followed by number of conditions by chart review and finally well-known comorbidity measured such as the Charlson Comorbidity Index (Bayliss, Ellis, & Steiner, 2005).

After accounting for the other predictors, visual impairment explained an additional 4% of the variance in overall HRQoL in the proposed model. The results of this study are

notable due to the fact that we measured disability using the Guys Neurological Disability Scale instead of the commonly used Expanded Disability Status Scale (EDSS). In contrast to the EDSS, the GNDS is capable of embracing a whole range of disabilities which can be encountered in the course of MS (Sharrack et al., 1999a). Thus, controlling for a wide range of other potential predictors provides us with a true representation of the impact that visual impairment can have on HRQoL in MS. The validity of these results is further strengthened by the fact that the visual function questionnaire (VFQ) has been established as a sensitive and useful tool in assessing visual function in patients with MS (Noble, Forooghian, Sproule, Westall, & O'Connor, 2006; Balcer et al., 2000; Ma et al., 2002a).

Seperate studies have suggested that HRQoL in MS is significantly affected by impairment and disability measured by the Expanded Disability Status Scale (Janardhan et al., 2000), cognitive impairment (Cutajar et al., 2000) and fatigue (Merkelbach, Sittinger, & Koenig, 2002b). Depression has been also shown to have a strong association with HRQoL in MS, independent of clinical course and disability (Provinciali, Ceravolo, Bartolini, Logullo, & Danni, 1999; Bakshi et al., 2000; Wang et al., 2000). The results of this study corroborated the prior evidence as disability (as measured by the GNDS) and depressive symptoms (as measured by the CES-D) both, had a strong and significant influence on HRQoL. Since patient and physician perceptions regarding these influential aspects of the disease (disability, depression, etc) differ, the results of the current study re-emphasize the need to recognize and evaluate them using PRO measures in routine care.

Importance of Visual Impairment to HRQoL in MS

The findings of this study regarding the role of visual impairment can have important implications in the routine care of patients with MS. Asymptomatic patients with MS, those who have no history of optic neuritis, subjective signs of visual impairment and normal visual acuity; may still have visual field defects that may not be detectable with conventional tests of visual acuity. Vidovic and colleagues (2005) reported that almost 58% of the symptom-free patients with MS had visual field defects, a finding similar to what was recorded by others in the past (Patterson & Heron, 1980). It has been suggested that these visual field defects, located in the peripheral areas of the field of vision, may evolve slowly and go unnoticed by patients with MS. Given the prevalence of visual impairment and the influence that it has on overall HRQoL, it may be necessary to routinely screen patients with MS using standard ophthalmic examination procedures or self-administered questionnaires such as the VFQ and others. A recent study has also published preliminary evidence of the ability of a supplementary questionnaire which increases its capacity of the VFQ to capture self-reported visual dysfunction in patients with MS (Raphael et al., 2006).

Phase II: Objective 1, 2, 3 and 4

Utilization of HRQoL Information in Routine Practice

Research paves the way for evidence-based selection of an appropriate measure of HRQoL, and identification of important variables that have a significant influence on HRQoL in patients with MS. However, in order to make effective use of such information, it is necessary that it is translated by practicing neurologists into the routine care of patients with MS. MS literature does not provide any evidence regarding the extent of the current use

of HRQoL questionnaires in routine clinical practice. Physicians in general, do not favor HRQoL assessment and this may be true for neurologists who are involved in the routine care of patients with MS.

Based on the Theory of Planned Behavior a hypothesis for exploration was developed: that neurologist's intention to use HRQoL information in patients with MS would be most influenced by their attitudes towards such information, their social norms and their perceived control over this behavior among other things. As hypothesized, neurologists' attitude towards HRQoL information in MS, strongly predicted their intention to use this information in routine practice. This suggests that interventions that strengthen or promote positive attitude towards HRQoL information may be effective in changing current practices. However, the mean score on the attitude scale [Mean (SD) = 61.7 (35.5); Range= -147 to +147] reflected a weak to moderate positive attitude in favor of assessing HRQoL in MS. Hence, programs that are created with the aim to promote acceptance of HRQoL assessment in practice, may not show significant improvements in neurologists' attitude. Such programs will need to have a rigorous study design and an evaluation strategy to detect changes in attitudes.

In accordance with the theory, normative beliefs - reflecting the neurologists' general perception of utilization of HRQoL information by their colleagues in MS and the stance of the American Academy of Neurology (AAN) - also predicted intention to use this information in practice. Although normative beliefs were strongly predictive of behavioral intention, the mean score on the subjective norm scale was very low [Mean (SD): 4.16 (1.3); Range= -42 to +42). In other words, the referents chosen for this study (AAN and other neurologists), seem to exert an influence on the behavioral intention of neurologists, but

these normative beliefs need to be strengthened. This indicates that support for HRQoL assessment in MS by professional organizations such as the AAN in the future, may increase use of such information among practicing neurologists. It is also possible that neurologists, who start incorporating HRQoL assessment in routine care of their patients with MS, may influence their colleagues follow suit. Perceived behavior control, that is, neurologists' perception of how much the behavior (HRQoL assessment) is under their control was not found to have a significant influence on intention.

Although neurologists expressed an interest in the topic and thought that HRQoL information was trustworthy, this aspect of the patients' perspective was far from being incorporated into everyday practice. Those who obtained quality of life information, did so in a relatively unstructured way as part of their clinical interview and only a minimal number of neurologists reported using HRQoL questionnaires routinely. Based on their responses and comments in the survey it appears that this could be because they are very busy and lack resources as well reimbursement for the extra time required to administer and score HRQoL questionnaires. Similar organizational problems including time, staff, resource constraints, as well as lack of reimbursement for services provided have been identified as major hurdles for physicians in provision of preventive care services in clinical practice (Carter, Belcher, & Inui, 1981).

This study also examined the relationship of the barriers and facilitators for HRQoL assessment to self-reported intention to assess such information in practice. In order to investigate this relationship, the barriers and facilitators scales were used as a proxy for decisional balance constructs. The decisional balance that a person feels may be thought of as a balance between the pros and the cons (barriers and facilitators in this study) associated

with the particular target behavior, which in this case is HRQoL assessment in clinical practice. According to those in the precontemplation stage may weigh in more heavily on the side of the cons toward a particular behavior. As individuals become conscious of the desire for change (contemplation stage), the decisional balance becomes less unipolar.

This study exhibited the expected decisional balance pattern in the sample of surveyed neurologists. Neurologists in the precontemplation group had a significantly higher score on the barrier scale and a significantly lower score on the facilitator scale compared to the contemplators. Thus, this study provides some evidence that changes in intention to assess HRQoL information may follow stages of change, which reflect a decisional balance between the barriers and facilitators of making such a change. Future research may be required to validate the proxy measure of decisional balance (barriers and facilitators scale). Improvements in this model may provide researchers with a framework that can be helpful in evaluating long term programs aimed at improving HRQoL acceptance by neurologists.

Improving HRQoL Acceptance among Neurologists

Based on these findings, certain important points come to light. Firstly, training efforts need to be targeted towards neurologists to facilitate assessment (administering and scoring of HRQoL questionnaires) as well as evaluating quality of life outcomes in patients with MS. Dealing with the issue of payment for the additional time required to assess HRQoL information can be problematic, since HRQoL assessment is not standardized in routine practice. One possible way to overcome this problem may be to establish a relative value-based payment system based upon Current Procedural Terminology (CPT) codes which has also been recently applied to the provision of medication therapy management

services by pharmacists (The Lewin Group, 2005). Although, one should keep in mind that such payment structures can only be brought into existence following the backing of relevant authorities (such as the American Academy of Neurology) and further legislative mandates for the incorporation of such information in the routine care of patients with MS.

Contrary to what has been documented regarding other specialists (Bezjak et al., 1998), a majority of the neurologists conveyed that they did not have problems in understanding how to use HRQoL information in the routine care of patients with MS, and did not think that scoring HRQoL questionnaires was difficult. Other explanations for the lack of utilization of HRQoL information in clinical practice may be that most of the neurologists, while considering the topic of HRQoL as very relevant and beneficial, seem unacquainted with available HRQoL instruments. Additionally, only a few of them actually had experience using HRQoL or any other PRO questionnaires. Lack of familiarity and comfort with HRQoL measurement may be one factor that hinders their use in daily practice.

Doctors are trained to obtain subjective information through clinical interviews. Using standardized HRQoL questionnaires to assist with treatment and monitoring is neither a standard component of medical training nor a familiar part of routine practice (Skevington, Day, Chisholm, & Trueman, 2005). Neurologists probably rely on their own clinical judgments, and are more acquainted with interpretation of a wide variety of clinical tests on a daily basis e.g. MRI scans. Hence, lack of use of HRQoL information may not be due to issues with the HRQoL questionnaires themselves, but may represent the hesitancy of neurologists to use unfamiliar techniques over the perceived assurance of familiar techniques. This may explain the finding that the intention to use HRQoL information was negatively associated with the number of years the respondent had been practicing as a neurologist.

Neurologists, who have been practicing for ten years or more, are less likely to show the behavioral intention compared to someone who had been practicing for fewer than ten years. It may be that neurologists who have been practicing for a long time may tend to adhere too strongly to their specific routine or beliefs and be less likely to be open to using relatively newer methods such as HRQoL questionnaires.

One suggestion that has been recommended to address this, is the incorporation and use of HRQoL measures during medical training leading to repeated exposure to these methods (Russak et al., 2003). Repeated use of health status and HRQoL questionnaires causes clinicians begin to instinctively make sense of the ranges over which scores can be expected and the meanings associated with the deviations from these values (Pincus & Wolfe, 2000; Wolfe & Pincus, 1991). Clinicians may also begin to comprehend the changes in scores reported across two or more visits using the patients as their own referents or controls. Initial (graduate) training in the use of HRQoL questionnaires would be able to provide the familiarity that may be necessary to facilitate their acceptance by neurologists and physicians in general.

This study provided evidence of the ease of administration (face-to-face and by mail) and scoring of recently developed questionnaires assessing functioning and HRQoL of patients with MS in an outpatient clinic. In a clinic setting, such questionnaires can be administered by health care professionals other than neurologists such as nurses, interns or even research assistants. Alternatively, the HRQoL and health status information may be collected by mail. The data collected can then be stored in a database on the clinic premises. Having access to such a database may allow neurologists to continually monitor their patients with MS without the need for frequent clinic visits, thus conserving time and resources.

Such questionnaires may also improve communication with patients and allow neurologists to understand aspects of the disease which are more relevant from the patient's perspective.

Limitations

Overall, Phase I (Objectives 1, 2 and 3) of this study was adequately powered and the sample size of 116 fell within the target range for all proposed analyses (testing concurrent validity and regression analyses to determine predictors of HRQoL and its domains). This sample size also met the recommendations of most statistical "rules of thumb" discussed earlier. However, the generalizability of the results will be somewhat limited because the sample was a convenience sample and included only regional patients with MS (mostly from West Virginia but also included some residents of Pennsylvania, Maryland and Ohio).

Item-scale and scale-domain structure of the questionnaires could have been tested to investigate some deviations observed in their psychometric properties such as, the high correlation coefficient between MSIS-29 physical impact and HAQUAMS mood scales as and the low item-total correlation for item 21 of MSIS-29. Testing the structure of the HRQoL questionnaires however, would require the utilization of statistical tests such as confirmatory factor analysis. A good general rule of thumb for factor analysis is a sample size of at least 300 (Tabachnick BG & Fidell LS, 1996b). The sample size of 116 in this study precluded the use of such techniques.

The course of MS for each patient, for example, whether the type of MS was Secondary Progressive, Primary Progressive, Relapsing Remitting, or Primary Relapsing, could not be identified due to unavailability of this information from many of the patient medical records. Course of MS has been shown to be a significant predictor of MS-related

HRQoL in the past and would have been a relevant variable to include in this study. Hence, the results of the regression analyses to identify predictors of HRQoL and its domains in this study may be subjected to omitted-variable bias.

Another limitation of this study was that time since last relapse was not assessed for patients who were included in the final sample. Exclusion of this variable may have implications for our findings. First, since the effects of a relapse can last for months or even a year, it is possible that some patients in our sample may not have completely recovered from a relapse that they had more than four weeks (inclusion criterion) prior to the first assessment. This may have affected their responses to the HRQoL questionnaires at the time of administration, as they were not at their true baseline state at that time. Second, differences may exist even between those who have completely recovered from a relapse. For example, someone who has completely recovered from a relapse three months ago may perceive their health status or quality of life differently than someone who completely recovered from a relapse more than two years ago.

Simple counts of comorbid conditions were used to calculate the comorbidity variable for the regression models (Phase 1, Objectives 2 and 3). One disadvantage of this approach was the reliance on a simple count of comorbid chronic conditions from a limited list of diseases, regardless of their severity. Also, the number and type of medical conditions may differ from those used elsewhere and limit the comparison of these results with other relevant studies. Future research that intends to adjust for comorbidity in relation to quality of life outcomes in MS can consider using other recommended multi-morbidity indices such as the Cumulative Illness Rating Scale (CIRS) and the Functional Comorbidity Index (FCI) (Fortin et al., 2006; Fortin et al., 2005b).

Responsiveness of the HRQoL measures was calculated using scores at baseline (Time 1) and follow-up (Time 2). In order to accurately calculate responsiveness, the time difference between the baseline and follow-up assessment is very important. This study was initially designed to determine responsiveness of the measures in the sample after three months. Hence, the follow-up assessment for each patient should have been made exactly three months following initial administration. However, due to difficulties encountered in scheduling patient visits exactly three months following baseline assessment, follow-up assessments were made during a three to six month time period following the baseline administration for each patient.

Only 54 of the 116 participants completed the assessments at Time 2 and the calculation of responsiveness was limited only to these participants. One reason for a low number of participants at follow-up was the short timeline for the study (March 1 to October 31, 2006). Since time to follow-up was decided to be at least three months following initial administration, the first follow-up assessment in the study period occurred after May 31, 2006. Similarly, follow-assessments were not done for anyone whose first administration was on or following August 1, 2006, because these assessments fell beyond the study period. Hence, follow-up data was collected only for those patients who had their first administration on or before July 31, 2006

A sample of 278 would be required in order to calculate responsiveness with a conservative effect size of 0.3 and a power level of 0.8. With respect to this estimation, the sample size for responsiveness analysis in this study was very small. The interpretation of the responsiveness should therefore be made with attention to the issues encountered with data collection and the small sample size. The responsiveness indices displayed no

significant change in the HRQoL of the patients with MS, irrespective of the direction (or sign) of the change score. However, the follow-up time was six months at the most and this may not have been sufficient to capture changes in non-institutionalized patients with MS. Longer follow-up periods ranging from 12 to 24 months would have been better able to capture such changes. A longer timeline can provide data that would not only allow for easy interpretation of responsiveness but also increase the overall sample size of the study.

Since this study relied exclusively on patient reported questionnaires, its conclusions may be affected by self-report or reporting bias. Self-report bias is inherent to the area of quality of life and involves an exaggeration or diminution of symptoms/functioning by the patients. Another type of reporting bias is called recall bias. Recall bias occurs when the way the respondent answers a question is affected not just by the correct answer, but also by the respondent's memory. Such a bias may have affected data regarding the year of diagnosis of MS (patient self-report). This is a limitation since the actual year of clinical diagnosis may have been different from what was reported by the patient. However, because of unavailability of such information in the patient medical records, the actual year of diagnosis could not be confirmed. It should be noted that prior to the first assessment, neurologists approached patients with MS and requested their participation in the study. Hence, it is possible that patient reports may have been influenced by their belief of how the treating neurologist may perceive their responses to the questionnaires in the study (similar to social desirability bias).

The findings of Phase II of this study are fairly generalizable since the respondents to the survey were a national sample of neurologists practicing in outpatient settings. One threat to the validity and generalizability of the results was a lower than usual response rate

(4.6%). This low response rate may have occurred due to absence of incentives provided to the neurologists. Monetary and non-monetary incentives can increase response rates among physicians and usually more impact when delivered with the initial questionnaire than when promised upon its return (Hopkins KD & Gullickson AR, 1992; Everett SA, Price JH, Bedell AW, & Telljohan Sk, 1997). Using lotteries has also been demonstrated as a cost-effective method to increase response rates among physicians in larger surveys (Baron, De Wals, & Milord, 2001). Lotteries involve a promise of an incentive (e.g. an opportunity to win a cash prize) in order to stimulate a better response rate.

A larger proportion of the sample (65%) reported that they were in the pre-contemplation stage (either unaware or not planning on using HRQoL information in practice). These respondents also indicated that it was less important to assess HRQoL information in patients with MS compared to contemplators. Based on these findings it may be that many neurologists may not assign sufficient importance to HRQoL assessment to warrant even completion of the HRQoL-related survey such as the one in this study. This could be a common trend amongst neurologists and another reason for lack of response.

In any case achieving a high response rate on physician surveys has been known to be a challenging task and physician response rates as low as 11% have been documented (Asch et al., 1997; Cummings, Savitz, & Konrad, 2001). The low response rate of this study may be incidental either to the length of survey (five pages plus two HRQoL questionnaires each) or to the target population i.e. neurologists. Differences may exist in the response rates of medical specialists (e.g. neurologists) compared to that of primary care physicians, and any such potential variations may still need further exploration. Response rates among neurologists may be improved by sending pre-screening cards asking whether they would be

151

willing to participate in an upcoming mail survey. The final survey instrument would then be sent only to those who respond positively to the pre-screening mailing in order to improve response rate.

The results of this study may also be susceptible to non-response bias (differences between responders and non-responders that may have an impact on the generalizability of the results). As a continuation of this study, follow-up letters will be mailed in order to collect non-response data from the neurologists in the sample. Another way to assess non-response bias could be to perform a telephone survey and determine whether there were any significant differences between those who returned the completed questionnaires and those who did not on variables such as age-group, gender, practice characteristics etc. This method would involve making a clinical appointment with the neurologist over the phone to collect this data and reimbursing them for their time. Such a non-response analysis can be performed in future surveys of neurologists. Other studies have assessed non-response bias, by comparing demographics of physicians based on their time of response. Late responders, that is, those that did not respond to the first mailing, were considered as proxies for non-responders. A review of these studies showed that minor differences were observed in medical practice variables (e.g. number of years in practice), while income, area and type of practice, gender and age on did not differ significantly among physicians (Kellerman & Herold, 2001).

Since information regarding HRQoL assessment is self-reported, results of this study may also be susceptible to social desirability bias. In some circumstances, respondents may be tempted to give the socially desirable response rather than describe what they actually think, believe, or do. This bias may have affected responses to questions that asked about the

intention to assess HRQoL information in clinical practice or the usefulness of such information in the routine care of patients with MS.

Considerations for Future Research

This study was the first of its kind to incorporate all psychometric properties as well as neurologist and patients' opinion regarding two currently relevant PRO measures in MS (MSIS-29 and HAQUAMS). Neither of the measures was found to be psychometrically superior to the other. However, it is clear that these measures are more suitable for use in MS compared to generic measures of HRQoL such as SF-36. The sample size for this study, although adequate to measure the psychometric properties of the measures, was modest. It is possible that stronger evidence of reliability, validity and item-level scaling success might have been found with a larger sample size and increased power. This study is one of the few that compared responsiveness for the PRO measures in a sample of non-institutionalized patients with MS. Although the analysis was not sufficiently powered to detect the changes in such patients, this study provides preliminary evidence of responsiveness of HAQUAMS and MSIS-29 and also insights into methodological problems that can be encountered when collecting data from non-institutionalized MS patients. Hence, further comparisons of these PRO measures should preferably be conducted as multi-site studies with a large and diverse (patients with varying levels of severity) population of patients with MS, in order to improve generalizability of the findings.

Incorporating HRQoL assessment in routine practice an as aid to clinical decision-making in MS patients is a logical follow up to the evidence that has been provided by this study using MS-related PRO measures. As can be observed from these findings, PRO

measures can not only be succinct, easy to score and administer but can also shed light on factors that are most relevant to non-institutionalized patients with MS for example, visual impairment. Pilot studies utilizing PRO measures (VFQ, GNDS) should be undertaken in the future to monitor critical factors affecting HRQoL (HAQUAMS) in patients with MS in routine clinical practice and this evidence should be corroborated with objective clinical tests (visual acuity, quantitative tests of motor function). In addition to known determinants of HRQoL the impact of other variables such as type of treatment should also be investigated. This is important because newer medications such as Tysabri (Natalizumab), a recombinant monoclonal antibody, may improve HRQoL in patients with MS not only due to patient-friendly dosing regimens (once a week administration) but also due to a different mechanism of action than that of conventional drugs (Interferons).

A shift of emphasis needs to take place with increased focus on practical applications of HRQoL questionnaires and their inclusion in clinical decision-making and policy decisions. Very few neurologists if any are utilizing even the most basic and standard instruments such as the SF-36. A larger push from professional organizations such as the American Academy of Neurology and the National Multiple Sclerosis Society is necessary to ensure that HRQoL questionnaires play a significant albeit an auxiliary role in the routine care of patients with MS.

References

Management of cataract in adults. Agency for Health Care Policy and Research (1993). *Clin.Pract.Guidel.Quick Ref.Guide Clin.,* 1-15.

Aaronson N (2002). Assessing health status and quality-of-life instruments: attributes and review criteria. *Qual.Life Res., 11,* 193-205.

Albrecht, G. (1996). Using subjective health assessments in practice and policy-making. *Health Care Anal., 4,* 284-292.

Amato, M. P., Ponziani, G., Rossi, F., Liedl, C. L., Stefanile, C., & Rossi, L. (2001). Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Mult.Scler., 7,* 340-344.

Arnold, A. C. (2005). Evolving management of optic neuritis and multiple sclerosis. *Am.J Ophthalmol., 139,* 1101-1108.

Asch, D. A., Jedrziewski, M. K., & Christakis, N. A. (1997). Response rates to mail surveys published in medical journals. *J Clin.Epidemiol., 50,* 1129-1136.

Avasarala, J. R., Cross, A. H., Clifford, D. B., Singer, B. A., Siegel, B. A., & Abbey, E. E. (2003). Rapid onset mitoxantrone-induced cardiotoxicity in secondary progressive multiple sclerosis. *Mult.Scler., 9,* 59-62.

Averbuch-Heller, L., Tusa, R. J., Fuhry, L., Rottach, K. G., Ganser, G. L., Heide, W. et al. (1997). A double-blind controlled study of gabapentin and baclofen as treatment for acquired nystagmus. *Ann.Neurol., 41,* 818-825.

Baker, G. A., Jacoby, A., Gorry, J., Doughty, J., & Ellina, V. (2005). Quality of life of people with epilepsy in Iran, the Gulf, and Near East. *Epilepsia, 46,* 132-140.

Bakshi, R., Shaikh, Z. A., Miletich, R. S., Czarnecki, D., Dmochowski, J., Henschel, K. et al. (2000). Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult.Scler., 6,* 181-185.

Balcer, L. J. (2001). Clinical outcome measures for research in multiple sclerosis. *J Neuroophthalmol., 21,* 296-301.

Balcer, L. J., Baier, M. L., Kunkle, A. M., Rudick, R. A., Weinstock-Guttman, B., Simonian, N. et al. (2000). Self-reported visual dysfunction in multiple sclerosis: results from the 25-Item National Eye Institute Visual Function Questionnaire (VFQ-25). *Mult.Scler., 6,* 382-385.

Barbotte, E., Guillemin, F., & Chau, N. (2001). Prevalence of impairments, disabilities, handicaps and quality of life in the general population: a review of recent literature. *Bull.World Health Organ, 79,* 1047-1055.

155

Baron, G., De Wals, P., & Milord, F. (2001). Cost-effectiveness of a lottery for increasing physicians' responses to a mail survey. *Eval.Health Prof., 24,* 47-52.

Bayliss, E. A., Ellis, J. L., & Steiner, J. F. (2005). Subjective assessments of comorbidity correlate with quality of life health outcomes: initial validation of a comorbidity assessment instrument. *Health Qual.Life Outcomes., 3:51.,* 51.

BECK, A. T., WARD, C. H., MENDELSON, M., MOCK, J., & ERBAUGH, J. (1961). An inventory for measuring depression. *Arch.Gen.Psychiatry, 4,* 561-571.

Beck, R. W., Cleary, P. A., Anderson, M. M., Jr., Keltner, J. L., Shults, W. T., Kaufman, D. I. et al. (1992). A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. *N.Engl.J Med., 326,* 581-588.

Belli, G., Tamburini, M., & Paci, E. (1994). What do Italian hospital physicians know about quality of life assessment in oncology? *Tumori, 80,* 24-27.

Benedict, R. H., Wahlig, E., Bakshi, R., Fishman, I., Munschauer, F., Zivadinov, R. et al. (2005). Predicting quality of life in multiple sclerosis: accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *J Neurol.Sci., 231,* 29-34.

Benito-Leon, J., Morales, J. M., & Rivera-Navarro, J. (2002). Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients. *Eur.J Neurol., 9,* 497-502.

Bennett, S. J., Oldridge, N. B., Eckert, G. J., Embree, J. L., Browning, S., Hou, N. et al. (2003). Comparison of quality of life measures in heart failure. *Nurs.Res., 52,* 207-216.

Bernth-Petersen, P. (1981). Visual functioning in cataract patients. Methods of measuring and results. *Acta Ophthalmol.(Copenh), 59,* 198-205.

Bessette, L., Sangha, O., Kuntz, K. M., Keller, R. B., Lew, R. A., Fossel, A. H. et al. (1998). Comparative responsiveness of generic versus disease-specific and weighted versus unweighted health status measures in carpal tunnel syndrome. *Med.Care, 36,* 491-502.

Bezjak, A., Ng, P., Skeel, R., Depetrillo, A. D., Comis, R., & Taylor, K. M. (2001). Oncologists' use of quality of life information: results of a survey of Eastern Cooperative Oncology Group physicians. *Qual.Life Res., 10,* 1-13.

Bezjak, A., Ng, P., Taylor, K., MacDonald, K., & Depetrillo, A. D. (1997). A preliminary survey of oncologists' perceptions of quality of life information. *Psychooncology., 6,* 107-113.

Bezjak, A., Taylor, K. M., Ng, P., MacDonald, K., & Depetrillo, A. D. (1998). Quality-of-life information and clinical practice: the oncologist's perspective. *Cancer Prev.Control, 2,* 230-235.

Bouchet, C., Guillemin, F., Paul-Dauphin, A., & Briancon, S. (2000). Selection of quality-of-life measures for a prevention trial: a psychometric analysis. *Control Clin.Trials, 21,* 30-43.

Bowling A & Windsor J (2001). Towards the good life: a population survey of dimensions of quality of life. *Journal of Happiness Studies, 2,* 55-81.

Brunet, D. G., Hopman, W. M., Singer, M. A., Edgar, C. M., & MacKenzie, T. A. (1996). Measurement of health-related quality of life in multiple sclerosis patients. *Can.J Neurol.Sci., 23,* 99-103.

Campbell DT & Fisk DW (1959). Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychol.Bull., 56,* 81-105.

CAMPBELL, D. T. & FISKE, D. W. (1959). Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychol.Bull., 56,* 81-105.

Carabellese, C., Appollonio, I., Rozzini, R., Bianchetti, A., Frisoni, G. B., Frattola, L. et al. (1993). Sensory impairment and quality of life in a community elderly population. *J Am.Geriatr.Soc., 41,* 401-407.

Carter, W. B., Belcher, D. W., & Inui, T. S. (1981). Implementing preventive care in clinical practice. II. Problems for managers, clinicians and patients. *Med.Care Rev., 38,* 195-216.

Cheng, L., Cumber, S., Dumas, C., Winter, R., Nguyen, K. M., & Nieman, L. Z. (2003). Health related quality of life in pregeriatric patients with chronic diseases at urban, public supported clinics. *Health Qual.Life Outcomes., 1,* 63.

Cohen & Cohen (1984). *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*. (Second ed.) Lawrence Erlbaum Associates.

Cohen J (1988). *Statistical Power Analysis for the Behavioral Sciences*. Lawrence Erlbaum Assoc Inc .

Cole, S. R., Beck, R. W., Moke, P. S., Gal, R. L., & Long, D. T. (2000). The National Eye Institute Visual Function Questionnaire: experience of the ONTT. Optic Neuritis Treatment Trial. *Invest Ophthalmol.Vis.Sci., 41,* 1017-1021.

Confavreux, C., Vukusic, S., Grimaud, J., & Moreau, T. (1999). Clinical progression and decision making process in multiple sclerosis. *Mult.Scler., 5,* 212-215.

Cooley, M. E., McCorkle, R., Knafl, G. J., Rimar, J., Barbieri, M. J., Davies, M. et al. (2005). Comparison of health-related quality of life questionnaires in ambulatory oncology. *Qual.Life Res., 14,* 1239-1249.

Correale, J., Rush, C., Amengual, A., & Goicochea, M. T. (2005). Mitoxantrone as rescue therapy in worsening relapsing-remitting MS patients receiving IFN-beta. *J Neuroimmunol., 162,* 173-183.

Cummings, S. M., Savitz, L. A., & Konrad, T. R. (2001). Reported response rates to mailed physician questionnaires. *Health Serv.Res., 35,* 1347-1355.

Cutajar, R., Ferriani, E., Scandellari, C., Sabattini, L., Trocino, C., Marchello, L. P. et al. (2000). Cognitive function and quality of life in multiple sclerosis patients. *J.Neurovirol., 6 Suppl 2,* S186-S190.

Cutter, G. R., Baier, M. L., Rudick, R. A., Cookfair, D. L., Fischer, J. S., Petkau, J. et al. (1999). Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain, 122 (Pt 5),* 871-882.

Dalton, C. M., Brex, P. A., Miszkiel, K. A., Hickman, S. J., MacManus, D. G., Plant, G. T. et al. (2002). Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. *Ann.Neurol., 52,* 47-53.

De Oliveira, M. A., Barbiere, A., Santos, L. A., Faresin, S. M., & Fernandes, A. L. (2005). Validation of a simplified quality-of-life questionnaire for socioeconomically deprived asthma patients. *J Asthma, 42,* 41-44.

Domingo-Salvany, A., Lamarca, R., Ferrer, M., Garcia-Aymerich, J., Alonso, J., Felez, M. et al. (2002). Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. *Am.J Respir.Crit Care Med., 166,* 680-685.

Drummond, M. F. (1987). Resource allocation decisions in health care: a role for quality of life assessments? *J Chronic.Dis., 40,* 605-619.

Edan, G., Morrissey, S., & Le Page, E. (2004). Rationale for the use of mitoxantrone in multiple sclerosis. *J Neurol.Sci., 223,* 35-39.

el Mallakh, R. S., Wright, J. C., Breen, K. J., & Lippmann, S. B. (1996). Clues to depression in primary care practice. *Postgrad.Med., 100,* 85-86.

Erdfelder, E. F. F. &. B. A. (1996). GPOWER: A general power analysis program. *Behavior Research Methods, Instruments, & Computers, 28,* 1-11.

Everett SA, Price JH, Bedell AW, & Telljohan Sk (1997). The Effect of a Monetary Incentive in Increasing the Return Rate of a Survey to Family Physicians. *Evaluation and Health Professions, 20,* 207-214.

Fayers PM & Machin D (2000). *Quality of Life: Assessment, Analysis, and Interpretation.* (1st ed.) London: John Wiley & Sons.

Fischer, J. S., LaRocca, N. G., Miller, D. M., Ritvo, P. G., Andrews, H., & Paty, D. (1999). Recent developments in the assessment of quality of life in multiple sclerosis (MS). *Mult.Scler., 5,* 251-259.

Fischer, J. S., Rudick, R. A., Cutter, G. R., & Reingold, S. C. (1999). The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Mult.Scler., 5,* 244-250.

Fisher JC & Mason RL (1981). The analysis of multicollinear data in criminology. In *Methods in Quantitative Criminology* (San Diego: Academic Press.

Fitzpatrick, R., Ziebland, S., Jenkinson, C., Mowat, A., & Mowat, A. (1993a). A comparison of the sensitivity to change of several health status instruments in rheumatoid arthritis. *J Rheumatol., 20,* 429-436.

Fitzpatrick, R., Ziebland, S., Jenkinson, C., Mowat, A., & Mowat, A. (1993b). Transition questions to assess outcomes in rheumatoid arthritis. *Br.J Rheumatol., 32,* 807-811.

Fortin, M., Bravo, G., Hudon, C., Lapointe, L., Almirall, J., Dubois, M. F. et al. (2006). Relationship between multimorbidity and health-related quality of life of patients in primary care. *Qual.Life Res., 15,* 83-91.

Fortin, M., Hudon, C., Dubois, M. F., Almirall, J., Lapointe, L., & Soubhi, H. (2005a). Comparative assessment of three different indices of multimorbidity for studies on health-related quality of life. *Health Qual.Life Outcomes., 3:74.,* 74.

Fox, R. J. & Cohen, J. A. (2001). Multiple sclerosis: the importance of early recognition and treatment. *Cleve.Clin.J Med., 68,* 157-171.

Freeman, J. A., Hobart, J. C., & Thompson, A. J. (2001). Does adding MS-specific items to a generic measure (the SF-36) improve measurement? *Neurology, 57,* 68-74.

Friedman, J. E., Zabriskie, J. B., Plank, C., Ablashi, D., Whitman, J., Shahan, B. et al. (2005). A randomized clinical trial of valacyclovir in multiple sclerosis. *Mult.Scler., 11,* 286-295.

Frohman, E. M., Brannon, K., Alexander, S., Sims, D., Phillips, J. T., O'Leary, S. et al. (2004). Disease modifying agent related skin reactions in multiple sclerosis: prevention, assessment, and management. *Mult.Scler., 10,* 302-307.

Fruehwald, S., Loeffler-Stastka, H., Eher, R., Saletu, B., & Baumhackl, U. (2001). Depression and quality of life in multiple sclerosis. *Acta Neurol.Scand., 104,* 257-261.

Galetta, S. L. & Markowitz, C. (2005). US FDA-approved disease-modifying treatments for multiple sclerosis: review of adverse effect profiles. *CNS.Drugs, 19,* 239-252.

Gold, S. M., Heesen, C., Schulz, H., Guder, U., Monch, A., Gbadamosi, J. et al. (2001). Disease specific quality of life instruments in multiple sclerosis: validation of the Hamburg Quality of Life Questionnaire in Multiple Sclerosis (HAQUAMS). *Mult.Scler., 7,* 119-130.

Gold, S. M., Schulz, H., Monch, A., Schulz, K. H., & Heesen, C. (2003). Cognitive impairment in multiple sclerosis does not affect reliability and validity of self-report health measures. *Mult.Scler., 9,* 404-410.

Goodkin, D. E., Hertsgaard, D., & Seminary, J. (1988). Upper extremity function in multiple sclerosis: improving assessment sensitivity with box-and-block and nine-hole peg tests. *Arch.Phys.Med.Rehabil., 69,* 850-854.

Gottberg, K., Gardulf, A., & Fredrikson, S. (2000). Interferon-beta treatment for patients with multiple sclerosis: the patients' perceptions of the side-effects. *Mult.Scler., 6,* 349-354.

Granger, C. V., Cotter, A. C., Hamilton, B. B., Fiedler, R. C., & Hens, M. M. (1990). Functional assessment scales: a study of persons with multiple sclerosis. *Arch.Phys.Med.Rehabil., 71,* 870-875.

Green SB (1991). How many subjects does it take to do a regression analysis? *Multivariate Behavioral Research, 26,* 499-510.

Greenfield, S. & Nelson, E. C. (1992). Recent developments and future issues in the use of health status assessment measures in clinical settings. *Med.Care, 30,* MS23-MS41.

Greenhalgh, J. & Meadows, K. (1999). The effectiveness of the use of patient-based measures of health in routine practice in improving the process and outcomes of patient care: a literature review. *J Eval.Clin.Pract., 5,* 401-416.

Gulick, E. E., Cook, S. D., & Troiano, R. (1993). Comparison of patient and staff assessment of MS patients' health status. *Acta Neurol.Scand., 88,* 87-93.

Guyatt, G., Walter, S., & Norman, G. (1987). Measuring change over time: assessing the usefulness of evaluative instruments. *J Chronic.Dis., 40,* 171-178.

Guyatt, G. H., Feeny, D. H., & Patrick, D. L. (1993). Measuring health-related quality of life. *Ann.Intern.Med., 118,* 622-629.

Guyatt, G. H., Veldhuyzen Van Zanten, S. J., Feeny, D. H., & Patrick, D. L. (1989). Measuring quality of life in clinical trials: a taxonomy and review. *CMAJ., 140,* 1441-1448.

Hagen, K. B., Smedstad, L. M., Uhlig, T., & Kvien, T. K. (1999). The responsiveness of health status measures in patients with rheumatoid arthritis: comparison of disease-specific and generic instruments. *J Rheumatol., 26,* 1474-1480.

Harper, R., Brazier, J. E., Waterhouse, J. C., Walters, S. J., Jones, N. M., & Howard, P. (1997). Comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. *Thorax, 52,* 879-887.

Hauser S (1994). Multiple sclerosis and other demyelinating diseases. In Isselbacher KJ & Martin JB (Eds.), *Harrison's Principles of Internal Medicine* (pp. 2289-2295). New York: McGraw-Hill.

Hayes, C. (1998). The use of patient based outcome measures in clinical decision making. *Community Dent.Health, 15,* 19-21.

Henriksson, F., Fredrikson, S., Masterman, T., & Jonsson, B. (2001). Costs, quality of life and disease severity in multiple sclerosis: a cross-sectional study in Sweden. *Eur.J Neurol., 8,* 27-35.

Hermann, B. P., Vickrey, B., Hays, R. D., Cramer, J., Devinsky, O., Meador, K. et al. (1996). A comparison of health-related quality of life in patients with epilepsy, diabetes and multiple sclerosis. *Epilepsy Res., 25,* 113-118.

Hersberger, K. E., Botomino, A., Mancini, M., & Bruppacher, R. (2006). Sequential screening for diabetes-evaluation of a campaign in Swiss community pharmacies. *Pharm.World Sci., 28,* 171-179.

Higginson, I. J. & Carr, A. J. (2001). Measuring quality of life: Using quality of life measures in the clinical setting. *BMJ, 322,* 1297-1300.

Hobart, J., Freeman, J., Lamping, D., Fitzpatrick, R., & Thompson, A. (2001). The SF-36 in multiple sclerosis: why basic assumptions must be tested. *J Neurol.Neurosurg.Psychiatry, 71,* 363-370.

Hobart, J., Lamping, D., Fitzpatrick, R., Riazi, A., & Thompson, A. (2001). The Multiple Sclerosis Impact Scale (MSIS-29): a new patient-based outcome measure. *Brain, 124,* 962-973.

Hobart, J. C., Riazi, A., Lamping, D. L., Fitzpatrick, R., & Thompson, A. J. (2004). Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome. *Health Technol.Assess., 8,* iii, 1-iii,48.

Hobart, J. C., Riazi, A., Lamping, D. L., Fitzpatrick, R., & Thompson, A. J. (2005). How responsive is the Multiple Sclerosis Impact Scale (MSIS-29)? A comparison with some other self report scales. *J.Neurol.Neurosurg.Psychiatry., 76,* 1539-1543.

Hogancamp, W. E., Rodriguez, M., & Weinshenker, B. G. (1997). The epidemiology of multiple sclerosis. *Mayo Clin.Proc., 72,* 871-878.

Holicky, R. & Charlifue, S. (1999). Ageing with spinal cord injury: the impact of spousal support. *Disabil.Rehabil., 21,* 250-257.

Honda, K. & Gorin, S. S. (2006). A model of stage of change to recommend colonoscopy among urban primary care physicians. *Health Psychol., 25,* 65-73.

Hoogervorst, E. L., Zwemmer, J. N., Jelles, B., Polman, C. H., & Uitdehaag, B. M. (2004). Multiple Sclerosis Impact Scale (MSIS-29): relation to established measures of impairment and disability. *Mult.Scler., 10,* 569-574.

Hopkins KD & Gullickson AR (1992). Response Rates in Survey Research: A Meta-Analysis of the Effects of Monetary Gratuities. *Journal of Experimental Education, 61,* 52-62.

Inafuku, H., Kasem Khan, M. A., Nagata, T., & Nonaka, S. (2004). Cutaneous ulcerations following subcutaneous interferon beta injection to a patient with multiple sclerosis. *J Dermatol., 31,* 671-677.

Izquierdo-Porrera, A. M., Gardner, A. W., Bradham, D. D., Montgomery, P. S., Sorkin, J. D., Powell, C. C. et al. (2005). Relationship between objective measures of peripheral arterial disease severity to self-reported quality of life in older adults with intermittent claudication. *J Vasc.Surg., 41,* 625-630.

Jacobs, D. A. & Galetta, S. L. (2004). Multiple sclerosis and the visual system. *Ophthalmol.Clin.North Am., 17,* 265-73, v.

Janardhan, V. & Bakshi, R. (2000). Quality of life and its relationship to brain lesions and atrophy on magnetic resonance images in 60 patients with multiple sclerosis. *Arch.Neurol., 57,* 1485-1491.

Janardhan, V. & Bakshi, R. (2002). Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol.Sci., 205,* 51-58.

Juniper, E. F., Guyatt, G. H., Willan, A., & Griffith, L. E. (1994). Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J.Clin.Epidemiol., 47,* 81-87.

Kauppinen, R., Sintonen, H., & Tukiainen, H. (1998). One-year economic evaluation of intensive vs conventional patient education and supervision for self-management of new asthmatic patients. *Respir.Med., 92,* 300-307.

Kazis, L. E., Anderson, J. J., & Meenan, R. F. (1989). Effect sizes for interpreting changes in health status. *Med.Care, 27,* S178-S189.

Keeffe, J. E., Lam, D., Cheung, A., Dinh, T., & McCarty, C. A. (1998). Impact of vision impairment on functioning. *Aust.N.Z.J Ophthalmol., 26 Suppl 1,* S16-S18.

Keller, S., Donner-Banzhoff, N., Kaluza, G., Baum, E., & Basler, H. D. (2000). Improving physician-delivered counseling in a primary care setting: lessons from a failed attempt. *Educ.Health (Abingdon.)., 13,* 387-397.

Kellerman, S. E. & Herold, J. (2001). Physician response to surveys. A review of the literature. *Am.J Prev.Med., 20,* 61-67.

Kenealy, P. M., Beaumont, J. G., Lintern, T. C., & Murrell, R. C. (2002). Autobiographical memory in advanced multiple sclerosis: assessment of episodic and personal semantic memory across three time spans. *J Int.Neuropsychol.Soc., 8,* 855-860.

Kirshner, B. & Guyatt, G. (1985). A methodological framework for assessing health indices. *J Chronic.Dis., 38,* 27-36.

Kohout, F. J., Berkman, L. F., Evans, D. A., & Cornoni-Huntley, J. (1993). Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. *J Aging Health, 5,* 179-193.

Kosinski, M., Keller, S. D., Hatoum, H. T., Kong, S. X., & Ware, J. E., Jr. (1999). The SF-36 Health Survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis: tests of data quality, scaling assumptions and score reliability. *Med.Care, 37,* MS10-MS22.

Kurtzke, J. F. (1955). A new scale for evaluating disability in multiple sclerosis. *Neurology, 5,* 580-583.

Langfitt, J. T. (1995). Comparison of the psychometric characteristics of three quality of life measures in intractable epilepsy. *Qual.Life Res., 4,* 101-114.

Lee, S. J., Joffe, S., Kim, H. T., Socie, G., Gilman, A. L., Wingard, J. R. et al. (2004). Physicians' attitudes about quality-of-life issues in hematopoietic stem cell transplantation. *Blood, 104,* 2194-2200.

Leibowitz, U. & Alter, M. (1968). Optic nerve involvement and diplopia as initial manifestations of multiple sclerosis. *Acta Neurol.Scand., 44,* 70-80.

Leuschen, M. P., Filipi, M., & Healey, K. (2004). A randomized open label study of pain medications (naproxen, acetaminophen and ibuprofen) for controlling side effects during initiation of IFN beta-1a therapy and during its ongoing use for relapsing-remitting multiple sclerosis. *Mult.Scler., 10,* 636-642.

Liang, M. H., Fossel, A. H., & Larson, M. G. (1990). Comparisons of five health status instruments for orthopedic evaluation. *Med.Care, 28,* 632-642.

Lobentanz, I. S., Asenbaum, S., Vass, K., Sauter, C., Klosch, G., Kollegger, H. et al. (2004). Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol.Scand., 110,* 6-13.

Logan-Club & Stacy, M. (1995). An open-labelled assessment of adverse effects associated with interferon 1-beta in the treatment of multiple sclerosis. *J Neurosci.Nurs., 27,* 344-347.

Ma, S. L., Shea, J. A., Galetta, S. L., Jacobs, D. A., Markowitz, C. E., Maguire, M. G. et al. (2002b). Self-reported visual dysfunction in multiple sclerosis: new data from the VFQ-25 and development of an MS-specific vision questionnaire. *Am.J.Ophthalmol., 133,* 686-692.

Ma, S. L., Shea, J. A., Galetta, S. L., Jacobs, D. A., Markowitz, C. E., Maguire, M. G. et al. (2002a). Self-reported visual dysfunction in multiple sclerosis: new data from the VFQ-25 and development of an MS-specific vision questionnaire. *Am.J.Ophthalmol., 133,* 686-692.

MacKenzie, C. R., Charlson, M. E., DiGioia, D., & Kelley, K. (1986). Can the Sickness Impact Profile measure change? An example of scale assessment. *J Chronic.Dis., 39,* 429-438.

Maguire, P., Walsh, S., Jeacock, J., & Kingston, R. (1999). Physical and psychological needs of patients dying from colo-rectal cancer. *Palliat.Med., 13,* 45-50.

Mangione, C. M., Lee, P. P., Gutierrez, P. R., Spritzer, K., Berry, S., & Hays, R. D. (2001). Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch.Ophthalmol., 119,* 1050-1058.

Mangione, C. M., Phillips, R. S., Seddon, J. M., Lawrence, M. G., Cook, E. F., Dailey, R. et al. (1992). Development of the 'Activities of Daily Vision Scale'. A measure of visual functional status. *Med.Care, 30,* 1111-1126.

Mao, H. F., Hsueh, I. P., Tang, P. F., Sheu, C. F., & Hsieh, C. L. (2002). Analysis and comparison of the psychometric properties of three balance measures for stroke patients. *Stroke, 33,* 1022-1027.

Massof, R. W. & Rubin, G. S. (2001). Visual function assessment questionnaires. *Surv.Ophthalmol., 45,* 531-548.

McDonald, W. I. & Barnes, D. (1992). The ocular manifestations of multiple sclerosis. 1. Abnormalities of the afferent visual system. *J Neurol.Neurosurg.Psychiatry, 55,* 747-752.

McDonald, W. I., Compston, A., Edan, G., Goodkin, D., Hartung, H. P., Lublin, F. D. et al. (2001). Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann.Neurol., 50,* 121-127.

McGuigan, C. & Hutchinson, M. (2004). The multiple sclerosis impact scale (MSIS-29) is a reliable and sensitive measure. *J Neurol.Neurosurg.Psychiatry, 75,* 266-269.

McHorney, C. A., Ware, J. E., Jr., Lu, J. F., & Sherbourne, C. D. (1994). The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med.Care, 32,* 40-66.

Meadows, K. A., Rogers, D., & Greene, T. (1998). Attitudes to the use of health outcome questionnaires in the routine care of patients with diabetes: a survey of general practitioners and practice nurses. *Br.J Gen.Pract., 48,* 1555-1559.

Merkelbach, S., Sittinger, H., & Koenig, J. (2002a). Is there a differential impact of fatigue and physical disability on quality of life in multiple sclerosis? *J Nerv.Ment.Dis., 190,* 388-393.

Meyer-Rosberg, K., Burckhardt, C. S., Huizar, K., Kvarnstrom, A., Nordfors, L. O., & Kristofferson, A. (2001). A comparison of the SF-36 and Nottingham Health Profile in patients with chronic neuropathic pain. *Eur.J Pain, 5,* 391-403.

Michelson, H., Bolund, C., & Brandberg, Y. (2000). Multiple chronic health problems are negatively associated with health related quality of life (HRQoL) irrespective of age. *Qual.Life Res., 9,* 1093-1104.

Miller, A. & Dishon, S. (2006). Health-related quality of life in multiple sclerosis: The impact of disability, gender and employment status. *Qual.Life Res., 15,* 259-271.

Miller, D. H., Thompson, A. J., Morrissey, S. P., MacManus, D. G., Moore, S. G., Kendall, B. E. et al. (1992). High dose steroids in acute relapses of multiple sclerosis: MRI evidence for a possible mechanism of therapeutic effect. *J Neurol.Neurosurg.Psychiatry, 55,* 450-453.

Miller, D. M., Rudick, R. A., Baier, M., Cutter, G., Doughtery, D. S., Weinstock-Guttman, B. et al. (2003). Factors that predict health-related quality of life in patients with relapsing-remitting multiple sclerosis. *Mult.Scler., 9,* 1-5.

Miller, D. M., Rudick, R. A., Cutter, G., Baier, M., & Fischer, J. S. (2000). Clinical significance of the multiple sclerosis functional composite: relationship to patient-reported quality of life. *Arch.Neurol., 57,* 1319-1324.

Millstein, S. G. (1996). Utility of the theories of reasoned action and planned behavior for predicting physician behavior: a prospective analysis. *Health Psychol., 15,* 398-402.

Mitchell, A. J., Benito-Leon, J., Gonzalez, J. M., & Rivera-Navarro, J. (2005). Quality of life and its assessment in multiple sclerosis: integrating physical and psychological components of wellbeing. *Lancet Neurol., 4,* 556-566.

Modrego, P. J., Pina, M. A., Simon, A., & Azuara, M. C. (2001). The interrelations between disability and quality of life in patients with multiple sclerosis in the area of Bajo Aragon, Spain: a geographically based survey. *Neurorehabil.Neural Repair, 15,* 69-73.

Moore, F., Wolfson, C., Alexandrov, L., & Lapierre, Y. (2004). Do general and multiple sclerosis-specific quality of life instruments differ? *Can.J Neurol.Sci., 31,* 64-71.

Morrow, D. G., Weiner, M., Deer, M. M., Young, J. M., Dunn, S., McGuire, P. et al. (2004). Patient-centered instructions for medications prescribed for the treatment of heart failure. *Am.J Geriatr.Pharmacother., 2,* 44-52.

Munari, L., Lovati, R., & Boiko, A. (2004). Therapy with glatiramer acetate for multiple sclerosis. *Cochrane.Database.Syst.Rev.,* CD004678.

Murphy, N., Confavreux, C., Haas, J., Konig, N., Roullet, E., Sailer, M. et al. (1998). Quality of life in multiple sclerosis in France, Germany, and the United Kingdom. Cost of Multiple Sclerosis Study Group. *J Neurol.Neurosurg.Psychiatry, 65,* 460-466.

National Institute for Clinical Excellence (2003a). Multiple sclerosis: Understanding NICE guidance - information for people with MS, their families and carers, and the public. NICE [On-line]. Available: http://www.nice.org.uk/page.aspx?o=94081

National Institute for Clinical Excellence (2003b). Multiple sclerosis: Understanding NICE guidance - information for people with MS, their families and carers, and the public. NICE [On-line]. Available: http://www.nice.org.uk/page.aspx?o=94081

Nelson, E., Wasson, J., Kirk, J., Keller, A., Clark, D., Dietrich, A. et al. (1987). Assessment of function in routine clinical practice: description of the COOP Chart method and preliminary findings. *J Chronic.Dis., 40 Suppl 1,* 55S-69S.

NICE (2003). Multiple sclerosis: Understanding NICE guidance - information for people with MS, their families and carers, and the public. NICE [On-line]. Available: http://www.nice.org.uk/page.aspx?o=94081

Nicholl, C. R., Lincoln, N. B., Francis, V. M., & Stephan, T. F. (2001). Assessing quality of life in people with multiple sclerosis. *Disabil.Rehabil., 23,* 597-603.

Noble, J., Forooghian, F., Sproule, M., Westall, C., & O'Connor, P. (2006). Utility of the National Eye Institute VFQ-25 questionnaire in a heterogeneous group of multiple sclerosis patients. *Am.J.Ophthalmol., 142,* 464-468.

Noonan, C. W., Kathman, S. J., & White, M. C. (2002). Prevalence estimates for MS in the United States and evidence of an increasing trend for women. *Neurology, 58,* 136-138.

Nordmann, J. P., Saraux, H., & Roullet, E. (1987). Contrast sensitivity in multiple sclerosis. A study in 35 patients with and without optic neuritis. *Ophthalmologica, 195,* 199-204.

Norman, G. R., Stratford, P., & Regehr, G. (1997). Methodological problems in the retrospective computation of responsiveness to change: the lesson of Cronbach. *J.Clin.Epidemiol., 50,* 869-879.

Nortvedt, M. W. & Riise, T. (2003). The use of quality of life measures in multiple sclerosis research. *Mult.Scler., 9,* 63-72.

Nortvedt, M. W., Riise, T., Myhr, K. M., Landtblom, A. M., Bakke, A., & Nyland, H. I. (2001). Reduced quality of life among multiple sclerosis patients with sexual disturbance and bladder dysfunction. *Mult.Scler., 7,* 231-235.

Nortvedt, M. W., Riise, T., Myhr, K. M., & Nyland, H. I. (1999). Quality of life in multiple sclerosis: measuring the disease effects more broadly. *Neurology, 53,* 1098-1103.

Nortvedt, M. W., Riise, T., Myhr, K. M., & Nyland, H. I. (2000). Performance of the SF-36, SF-12, and RAND-36 summary scales in a multiple sclerosis population. *Med.Care, 38,* 1022-1028.

Noseworthy, J. H., Vandervoort, M. K., Wong, C. J., & Ebers, G. C. (1990). Interrater variability with the Expanded Disability Status Scale (EDSS) and Functional Systems (FS) in a multiple sclerosis clinical trial. The Canadian Cooperation MS Study Group. *Neurology, 40,* 971-975.

Nunnnally JC (1978). *Psychometric Theory.* (2nd ed.) Mcgraw-Hill College.

Orme, J. G., Reis, J., & Herz, E. J. (1986). Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. *J Clin.Psychol., 42,* 28-33.

Ozakbas, S., Cagiran, I., Ormeci, B., & Idiman, E. (2004). Correlations between multiple sclerosis functional composite, expanded disability status scale and health-related quality of life during and after treatment of relapses in patients with multiple sclerosis. *J Neurol.Sci., 218,* 3-7.

Pandya, R., Metz, L., & Patten, S. B. (2005). Predictive value of the CES-D in detecting depression among candidates for disease-modifying multiple sclerosis treatment. *Psychosomatics, 46,* 131-134.

Panitch, H., Miller, A., Paty, D., & Weinshenker, B. (2004). Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. *Neurology, 63,* 1788-1795.

Park, E. R., DePue, J. D., Goldstein, M. G., Niaura, R., Harlow, L. L., Willey, C. et al. (2003). Assessing the transtheoretical model of change constructs for physicians counseling smokers. *Ann.Behav.Med., 25,* 120-126.

Patrick, D. L. & Deyo, R. A. (1989). Generic and disease-specific measures in assessing health status and quality of life. *Med.Care, 27,* S217-S232.

Patten, S. B., Fridhandler, S., Beck, C. A., & Metz, L. M. (2003). Depressive symptoms in a treated multiple sclerosis cohort. *Mult.Scler., 9,* 616-620.

Patterson, V. H. & Heron, J. R. (1980). Visual field abnormalities in multiple sclerosis. *J.Neurol.Neurosurg.Psychiatry., 43,* 205-209.

Patti, F., Amato, M. P., Filippi, M., Gallo, P., Trojano, M., & Comi, G. C. (2004a). A double blind, placebo-controlled, phase II, add-on study of cyclophosphamide (CTX) for 24

months in patients affected by multiple sclerosis on a background therapy with interferon-beta study denomination: CYCLIN. *J Neurol.Sci., 223,* 69-71.

Patti, F., Amato, M. P., Filippi, M., Gallo, P., Trojano, M., & Comi, G. C. (2004b). A double blind, placebo-controlled, phase II, add-on study of cyclophosphamide (CTX) for 24 months in patients affected by multiple sclerosis on a background therapy with interferon-beta study denomination: CYCLIN. *J Neurol.Sci., 223,* 69-71.

Patti, F., Cacopardo, M., Palermo, F., Ciancio, M. R., Lopes, R., Restivo, D. et al. (2003). Health-related quality of life and depression in an Italian sample of multiple sclerosis patients. *J Neurol.Sci., 211,* 55-62.

Paykel, E. S. & Priest, R. G. (1992). Recognition and management of depression in general practice: consensus statement. *BMJ, 305,* 1198-1202.

Pfennings, L., Cohen, L., Ader, H., Polman, C., Lankhorst, G., Smits, R. et al. (1999a). Exploring differences between subgroups of multiple sclerosis patients in health-related quality of life. *J Neurol., 246,* 587-591.

Pfennings, L., Cohen, L., Miller, D., Gerbaud, L., Vleugels, L., Freeman, J. et al. (1999b). Using the Short Form-36 with multiple sclerosis patients in five countries: a cross-cultural comparison. *Psychol.Rep., 85,* 19-31.

Pickard, A. S., Johnson, J. A., & Farris, K. B. (1999). The impact of pharmacist interventions on health-related quality of life. *Ann.Pharmacother., 33,* 1167-1172.

Pincus, T. & Wolfe, F. (2000). An infrastructure of patient questionnaires at each rheumatology visit: improving efficiency and documenting care. *J.Rheumatol., 27,* 2727-2730.

Poser, C. M., Paty, D. W., Scheinberg, L., McDonald, W. I., Davis, F. A., Ebers, G. C. et al. (1983). New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann.Neurol., 13,* 227-231.

Pozzilli, C., Marinelli, F., Romano, S., & Bagnato, F. (2004). Corticosteroids treatment. *J Neurol.Sci., 223,* 47-51.

Prasad, M., Rentz, A. M., & Revicki, D. A. (2003). The impact of treatment for gastro-oesophageal reflux disease on health-related quality of life: a literature review. *Pharmacoeconomics., 21,* 769-790.

Price, J. H., Jordan, T. R., & Dake, J. A. (2006). Obstetricians and gynecologists' perceptions and use of nicotine replacement therapy. *J.Community Health., 31,* 160-175.

Provinciali, L., Ceravolo, M. G., Bartolini, M., Logullo, F., & Danni, M. (1999). A multidimensional assessment of multiple sclerosis: relationships between disability domains. *Acta Neurol.Scand., 100,* 156-162.

Raphael, B. A., Galetta, K. M., Jacobs, D. A., Markowitz, C. E., Liu, G. T., Nano-Schiavi, M. L. et al. (2006). Validation and Test Characteristics of a 10-Item Neuro-Ophthalmic Supplement to the NEI-VFQ-25. *Am.J.Ophthalmol.,* ..

Raskin, A., Schulterbrandt, J., Reatig, N., & McKeon, J. J. (1969). Replication of factors of psychopathology in interview, ward behavior and self-report ratings of hospitalized depressives. *J Nerv.Ment.Dis., 148,* 87-98.

Rebergen, D., Hoenen, J., Heinemans, A., Bruinvels, D., Bakker, A., & van Mechelen, W. (2006). Adherence to mental health guidelines by Dutch occupational physicians. *Occup.Med.(Lond)., 56,* 461-468.

Riazi, A., Hobart, J. C., Lamping, D. L., Fitzpatrick, R., & Thompson, A. J. (2002). Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital based samples. *J Neurol.Neurosurg.Psychiatry, 73,* 701-704.

Riazi, A., Hobart, J. C., Lamping, D. L., Fitzpatrick, R., & Thompson, A. J. (2003). Evidence-based measurement in multiple sclerosis: the psychometric properties of the physical and psychological dimensions of three quality of life rating scales. *Mult.Scler., 9,* 411-419.

Richert, N. D., Ostuni, J. L., Bash, C. N., Leist, T. P., McFarland, H. F., & Frank, J. A. (2001). Interferon beta-1b and intravenous methylprednisolone promote lesion recovery in multiple sclerosis. *Mult.Scler., 7,* 49-58.

Rogerson RJ, Findlay AM, Coombes MG, & Morris A (1989). Indicators of Quality of Life. *Environment and Planning, 21,* 1655-1666.

Romberg, A., Virtanen, A., & Ruutiainen, J. (2005). Long-term exercise improves functional impairment but not quality of life in multiple sclerosis. *J Neurol., 252,* 839-845.

Rossier, P. & Wade, D. T. (2002). The Guy's Neurological Disability Scale in patients with multiple sclerosis: a clinical evaluation of its reliability and validity. *Clin.Rehabil., 16,* 75-95.

Rothwell, P. M., McDowell, Z., Wong, C. K., & Dorman, P. J. (1997). Doctors and patients don't agree: cross sectional study of patients' and doctors' perceptions and assessments of disability in multiple sclerosis. *BMJ, 314,* 1580-1583.

Rudick, R. A., Cutter, G., & Reingold, S. (2002). The multiple sclerosis functional composite: a new clinical outcome measure for multiple sderosis trials. *Mult.Scler., 8,* 359-365.

Rudick, R. A., Miller, D., Clough, J. D., Gragg, L. A., & Farmer, R. G. (1992). Quality of life in multiple sclerosis. Comparison with inflammatory bowel disease and rheumatoid arthritis. *Arch.Neurol., 49,* 1237-1242.

Russak, S. M., Sherbourne, C. D., Lubeck, D. P., Paulus, H. D., Chiou, C. F., Sengupta, N. et al. (2003). Validation of a rheumatoid arthritis health-related quality of life instrument, the CSHQ-RA. *Arthritis Rheum., 49,* 798-803.

Sadovnick, A. D., Dyment, D., & Ebers, G. C. (1997). Genetic epidemiology of multiple sclerosis. *Epidemiol.Rev., 19,* 99-106.

Schapiro RT, Baumhefner RW, & Tourtellotte WW (1997). Multiple Sclerosis: A Clinical Viewpoint To Management. In Raine CS, McFarland HF, & Tourtellotte WW (Eds.), *Multiple Sclerosis: Clinical and Pathogenetic Basis* (1st ed., pp. 391-420). London: Chapman & Hall.

Schor, E. L., Lerner, D. J., & Malspeis, S. (1995). Physicians' assessment of functional health status and well-being. The patient's perspective. *Arch.Intern.Med., 155,* 309-314.

Schulz, K. H., Gold, S. M., Witte, J., Bartsch, K., Lang, U. E., Hellweg, R. et al. (2004). Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. *J Neurol.Sci., 225,* 11-18.

Scrimshaw, S. V. & Maher, C. (2001). Responsiveness of visual analogue and McGill pain scale measures. *J Manipulative Physiol Ther., 24,* 501-504.

Sharrack, B. & Hughes, R. A. (1997). Reliability of distance estimation by doctors and patients: cross sectional study. *BMJ, 315,* 1652-1654.

Sharrack, B. & Hughes, R. A. (1999a). The Guy's Neurological Disability Scale (GNDS): a new disability measure for multiple sclerosis. *Mult.Scler., 5,* 223-233.

Sharrack, B., Hughes, R. A., Soudain, S., & Dunn, G. (1999b). The psychometric properties of clinical rating scales used in multiple sclerosis. *Brain, 122 (Pt 1),* 141-159.

Shinar, D., Gross, C. R., Price, T. R., Banko, M., Bolduc, P. L., & Robinson, R. G. (1986). Screening for depression in stroke patients: the reliability and validity of the Center for Epidemiologic Studies Depression Scale. *Stroke, 17,* 241-245.

Sipe, J. C., Knobler, R. L., Braheny, S. L., Rice, G. P., Panitch, H. S., & Oldstone, M. B. (1984). A neurologic rating scale (NRS) for use in multiple sclerosis. *Neurology, 34,* 1368-1372.

Skevington, S. M., Day, R., Chisholm, A., & Trueman, P. (2005). How much do doctors use quality of life information in primary care? Testing the trans-theoretical model of behaviour change. *Qual.Life Res., 14,* 911-922.

Solari, A. (2005). Role of health-related quality of life measures in the routine care of people with multiple sclerosis. *Health Qual.Life Outcomes., 3,* 16.

Solari, A. & Radice, D. (2001). Health status of people with multiple sclerosis: a community mail survey. *Neurol.Sci., 22,* 307-315.

Sorensen, T. L., Frederiksen, J. L., Bronnum-Hansen, H., & Petersen, H. C. (1999). Optic neuritis as onset manifestation of multiple sclerosis: a nationwide, long-term survey. *Neurology, 53,* 473-478.

Stangel, M. & Gold, R. (2005). Intravenous Immunoglobulins in MS. *Int.MS J, 12,* 5-10, 4.

Stanton, A. L. (1987). Determinants of adherence to medical regimens by hypertensive patients. *J Behav.Med., 10,* 377-394.

Steinberg, E. P., Tielsch, J. M., Schein, O. D., Javitt, J. C., Sharkey, P., Cassard, S. D. et al. (1994). The VF-14. An index of functional impairment in patients with cataract. *Arch.Ophthalmol., 112,* 630-638.

Stelmack, J. (2001). Quality of life of low-vision patients and outcomes of low-vision rehabilitation. *Optom.Vis.Sci., 78,* 335-342.

Stenager, E., Stenager, E. N., Knudsen, L., & Jensen, K. (1994). Multiple sclerosis: the impact on family and social life. *Acta Psychiatr.Belg., 94,* 165-174.

Stimson, G. V. (1974). Obeying doctor's orders: a view from the other side. *Soc.Sci.Med., 8,* 97-104.

Stratford, P. W., Binkley, F. M., & Riddle, D. L. (1996). Health status measures: strategies and analytic methods for assessing change scores. *Phys.Ther., 76,* 1109-1123.

Tabachnick BG & Fidell LS (1996b). *Using Multivariate Statistics*. (Third ed.) HarperCollins Publishers.

Tabachnick BG & Fidell LS (1996a). *Using Multivariate Statistics*. (Third ed.) HarperCollins Publishers.

Taylor, K. M., Macdonald, K. G., Bezjak, A., Ng, P., & Depetrillo, A. D. (1996). Physicians' perspective on quality of life: an exploratory study of oncologists. *Qual.Life Res., 5,* 5-14.

Teixeira-Salmela, L. F., Santiago, L., Lima, R. C., Lana, D. M., Camargos, F. F., & Cassiano, J. G. (2005). Functional performance and quality of life related to training and detraining of community-dwelling elderly. *Disabil.Rehabil., 27,* 1007-1012.

The Lewin Group (2005). Medication therapy management services: a critical review. *J.Am.Pharm.Assoc.(Wash.DC.)., 45,* 580-587.

Thompson AJ, Murray TJ, McDonald WI, & Polman C (2001). *Multiple Sclerosis: The Guide to Treatment and Management*. (5th ed.) Demos Medical Publishing.

Thompson, A. J., Montalban, X., Barkhof, F., Brochet, B., Filippi, M., Miller, D. H. et al. (2000). Diagnostic criteria for primary progressive multiple sclerosis: a position paper. *Ann.Neurol., 47,* 831-835.

USDHHS (1993). Management of cataract in adults. Agency for Health Care Policy and Research. *Clin.Pract.Guidel.Quick Ref.Guide Clin.,* 1-15.

Vahle, V. J., Andresen, E. M., & Hagglund, K. J. (2000). Depression measures in outcomes research. *Arch.Phys.Med.Rehabil., 81,* S53-S62.

van der Putten, J. J., Hobart, J. C., Freeman, J. A., & Thompson, A. J. (1999). Measuring change in disability after inpatient rehabilitation: comparison of the responsiveness of the Barthel index and the Functional Independence Measure. *J.Neurol.Neurosurg.Psychiatry., 66,* 480-484.

Verdier-Taillefer, M. H., Gourlet, V., Fuhrer, R., & Alperovitch, A. (2001). Psychometric properties of the Center for Epidemiologic Studies-Depression scale in multiple sclerosis. *Neuroepidemiology, 20,* 262-267.

Vickrey, B. G., Hays, R. D., Genovese, B. J., Myers, L. W., & Ellison, G. W. (1997). Comparison of a generic to disease-targeted health-related quality-of-life measures for multiple sclerosis. *J Clin.Epidemiol., 50,* 557-569.

Vickrey, B. G., Hays, R. D., Harooni, R., Myers, L. W., & Ellison, G. W. (1995). A health-related quality of life measure for multiple sclerosis. *Qual.Life Res., 4,* 187-206.

Wagner, A. K., Ehrenberg, B. L., Tran, T. A., Bungay, K. M., Cynn, D. J., & Rogers, W. H. (1997). Patient-based health status measurement in clinical practice: a study of its impact on epilepsy patients' care. *Qual.Life Res., 6,* 329-341.

Walters, S. J. & Campbell, M. J. (2004). The use of bootstrap methods for analysing Health-Related Quality of Life outcomes (particularly the SF-36). *Health Qual.Life Outcomes., 2,* 70.

Wang, J. L., Reimer, M. A., Metz, L. M., & Patten, S. B. (2000). Major depression and quality of life in individuals with multiple sclerosis. *Int.J Psychiatry Med., 30,* 309-317.

Ware JE, Harris WJ, Gandek B, Rogers BW, & Reese PR (1997). *MAP-R for Windows: Multitriat/Multi-item Analysis Program- Revised Users Guide*. Boston, MA.

Ware, J. E., Jr. & Gandek, B. (1998). Methods for testing data quality, scaling assumptions, and reliability: the IQOLA Project approach. International Quality of Life Assessment. *J.Clin.Epidemiol., 51,* 945-952.

Ware, J. E., Jr. & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med.Care, 30,* 473-483.

Warner, J. & Lessell, S. (1994). Neuro-ophthalmology of multiple sclerosis. *Clin.Neurosci., 2,* 180-188.

Weinshenker, B. G. (1995). The natural history of multiple sclerosis. *Neurol.Clin., 13,* 119-146.

Wensing, M., Vingerhoets, E., & Grol, R. (2001). Functional status, health problems, age and comorbidity in primary care patients. *Qual.Life Res., 10,* 141-148.

Whitaker JN & Mitchell GW (1997). Clinical Features of Multiple Sclerosis. In Raine CS, McFarland HF, & Tourtellotte WW (Eds.), *Multiple Sclerosis: Clinical and Pathogenetic Basis* (1st ed., pp. 3-19). London: Chapman & Hall Medical.

Williams JI, W.-D. S. (1989). Assessing quality of life: measures and utility. In Frederick Mosteller and Jennifer Falotico-Taylor (Ed.), *Quality of life and technology assessment* (Washington, D.C: National Academy Press.

Wolfe, F. & Pincus, T. (1991). Standard self-report questionnaires in routine clinical and research practice--an opportunity for patients and rheumatologists. *J.Rheumatol., 18,* 643-646.

Wood, P. H. (1980). Appreciating the consequences of disease: the international classification of impairments, disabilities, and handicaps. *WHO Chron., 34,* 376-380.

Zivadinov, R. (2005). Steroids and brain atrophy in multiple sclerosis. *J Neurol.Sci., 233,* 73-81.

List of Appendices

Appendix A: Patient Invitation Letter

Appendix B: Guys Neurological Disability Scale

Appendix C: Visual Function Questionnaire

Appendix D: Centers for Epidemiological Studies – Depression Scale

Appendix E: Additional Questions

Appendix F: Comorbidities

Appendix G: HRQoL Booklet

Appendix H: VFQ Items

Appendix I: Cover Letter for the Neurologist Survey

Appendix J: Neurologist Survey

Appendix A: Patient Invitation Letter

<div align="right">October, 2005</div>

Patient Name

Dear _____:

     The Departments of Neurology and the School of Pharmacy at West Virginia University, have come together to conduct a research study in the area of multiple sclerosis. You may be aware of the various symptoms of this condition which can have an impact on your quality of life. The objective of this study is to determine where the focus of care needs to be directed to enable us to ensure that you are receiving the best care possible for your multiple sclerosis and also identify ways to allow the neurologist to understand the issues which are most important from your perspective. I would like to encourage you to participate in this study during your next visit scheduled on the _____. Your participation will entail completion of a set of questionnaires and two non-invasive clinical tests. This study may provide useful information which will serve as a guide for your attending neurologist. Your input will be a source of tremendous help in providing general information which will be used by neurologists to help others who have your same health concerns.

     The information that you provide, when participating in the study, will be kept as confidential as legally possible and results will be presented only in an aggregate format.

     You do not have to answer every question in the questionnaire and participation in the study is completely voluntary. You may choose not to participate at any time; however, after you have provided the information, it will become anonymous and you will be unable to withdraw your data since there will be no way to identify individual information. If you choose not to participate, this will not jeopardize in any way your relationship with me or with the WVU neurology clinic.

     Please allow about forty-five minutes during your upcoming visit to participate in this study. You may answer the questions during the wait period before your consultation and complete the rest later. The study coordinators thank you in advance for your time and your contribution to a greater understanding of the health concerns of patients with multiple sclerosis. If you have any questions or need more information, please contact Vivek Pawar MS at (304) 685 7812 or Dr. Lesley-Ann Miller at (304) 293 0228.

Sincerely,

_____, MD
Department of _____

Appendix B: Guys Neurological Disability Scale

1. Cognitive disability:

A. Interview:

Do you have any problems with your memory or your ability to concentrate and work things out?

      ☐   yes   ☐   no

Do your family or friends think that you have such a problem?

      ☐   yes   ☐   no

If the answer to either question is 'yes':
Do you need help from other people for planning your normal daily affairs, handling money or making decisions?

      ☐   yes   ☐   no

If 'yes': (To the examiner)
Is the patient orientated in time, place and person?

      ☐   yes, fully
      ☐   yes, partially*
      ☐   no, totally disorientated*

*If the patient is not fully orientated, all their answers should be verified by the main carer(s) whose answers should take precedence.

B. Scoring:

0 – No cognitive problems.
1 – Cognitive problems not noticeable to family or friends.
2 – Cognitive problems noticeable to family or friends but not requiring help from others.
3 – Cognitive problems requiring help from others for normal daily affairs; patient is fully orientated in time, place and person.
4 – Cognitive problems requiring help from others for normal daily affairs; patient is not fully orientated.
5 – Patient is completely disorientated in time, place and person.

2. Mood disability:

A. Interview:

Have you been feeling anxious, irritable, depressed, or had any mood swings during the last month?
☐ yes ☐ no

Are you taking any medications for such problem
☐ yes ☐ no

If the answer to the first question is 'yes':
Has the problem affected your ability to do *any* of your usual daily activities such as work, house-work, or normal social activity with family and friends?
☐ yes ☐ no

If 'yes':
Has this problem been severe enough to prevent you from doing *all* your usual activities?
☐ yes ☐ no

Have you been admitted to hospital for treatment of your mood problem during the last month?
☐ yes ☐ no

B. Scoring:

0 – No mood problems
1 – Asymptomatic on current drug treatment.
2 – Mood problems present but not affecting the patient's ability to perform any of their usual daily activities.
3 – Mood problems affecting the patient's ability to perform some of their usual daily activities.
4 – Mood problems preventing the patients from doing all their usual daily activities.
5 – Mood problems requiring inpatient management.
X – Unknown (please score as the mean of the cognitive and fatigue disability scores rounded the nearest integer).

3. Visual disability:

A. Interview:

Do you have any problems with your vision that can't be corrected with ordinary glasses?
☐ yes ☐ no

If 'yes':
Can you read ordinary newspaper print (with ordinary glasses if worn, but not magnifying lenses)?
☐ yes ☐ no

If 'no':
Can you read large newspaper print?
☐ yes ☐ no

If 'no':
Can you count your fingers if you hold your hand out in front of you?
☐ yes ☐ no

If 'no':
Can you see your hand if you move it in front of you?
☐ yes ☐ no

B. Scoring:

0 – No visual problems.
1 – Visual problems (blurred vision, diplopia, scotomas) but patient is still able to read ordinary newspaper print.
2 – Unable to read ordinary newspaper print.
3 – Unable to read large newspaper print.
4 – Unable to count fingers if they hold their hand out in front of them.
5 – Unable to see hand movement if they move their hand in front of them.

4. *Speech and communication disability:*

A. Interview:

Do you have any problems with your speech?

☐ yes ☐ no

If 'yes':
Do you have to repeat yourself when speaking to your family or close friends?

☐ yes ☐ no

If 'yes':
Do you need to use sign language, or the help of your carer to make people understand you?

☐ yes ☐ no

If 'yes': (to the examiner)
Is the patient able to communicate effectively using these methods?

☐ yes ☐ no

B. Scoring:

0 – No speech problems.
1 – Speech problems which does not require the patient to repeat themselves when speaking to strangers.
2 – Speech problems which require the patient to repeat themselves when speaking to strangers.
3 – Speech problems which require the patient to repeat themselves when speaking to their family and close friends.
4 – Speech problems making speech difficult to understand; patient is able to communicate effectively by using sign language or the help of their carers.
5 – Speech problems making speech difficult to understand, patient is unable to communicate effectively by using sign language or the help of their carers.

5. *Swallowing disability:*

A. Interview:

Do you have to take care when swallowing solids or fluids?

☐ yes ☐ no

If 'yes':
Do you have to take care when swallowing with most meals?

☐ yes ☐ no

If 'yes':
Do you need a special diet such as soft or liquidated food to help with your swallowing?

☐ yes ☐ no

If 'yes':
Do you choke with most meals?

☐ yes ☐ no

If 'yes':
Do you have a feeding tube (nasogastric or gastrostomy tube)?

☐ yes ☐ no

B. Scoring:

0 – No swallowing problems.
1 – Needs to be careful when swallowing solids or liquids but not with most meals.
2 – Needs to be careful when swallowing solids or liquids with most meals; patient is able to eat food of normal consistency.
3 – Needs specially prepared food of modified consistency.
4 – Tendency to choke with most meals.
5 – Dysphagia requiring nasogastric or gastrostomy tube.

6. Upper limb disability:

A. Interview:

Do you have any problems with your hands or arms?
☐ yes ☐ no

If 'yes':
Do you have any difficulty in doing any of your zips *or* buttons?
☐ yes ☐ no

If 'yes':
Are you able to do *all* of your zips *and* buttons without help?
☐ yes ☐ no

Do you have any difficulty in tying a bow in laces or strings?
☐ yes ☐ no

If 'yes':
Are you able to tie a bow in laces or strings without help?
☐ yes ☐ no

Do you have any difficulty washing *and* brushing your hair?
☐ yes ☐ no

If 'yes':
Are you able to wash *and* brush your hair without help?
☐ yes ☐ no

Do you have any difficulty feeding yourself?
☐ yes ☐ no

If 'yes':
Are you able to feed yourself without help?
☐ yes ☐ no

If unable to do any of the functions listed:
Can you use your hands or arms for any other function?
☐ yes ☐ no

B. Scoring

0 – No upper limb problem.
1 – Problems in one or both arms, not affecting the ability to do any of the functions listed.
2 – Problems in one or both arms, affecting some but not preventing any of the functions listed.
3 – Problems in one or both arms, affecting all or preventing one or two of the functions listed.
4 – Problems in one or both arms preventing three or all of the functions listed.
5 – Unable to use either arm for any purposeful movements.

7. Lower limb disability:

A. Interview:

Do you have any problems with your walking?
☐ yes ☐ no

If 'yes':
Do you use a walking aid?
☐ yes ☐ no

If 'yes':
A. How do you *usually* get around outdoors?
☐ without aid
or ☐ with one stick or crutch *or* holding on to someone's arm
or ☐ with two sticks or crutches *or* one stick or crutch and holding on to someone's arm
or ☐ with a wheelchair

B. How do you *usually* get around indoors?
☐ without aid
or ☐ with one stick or crutch *or* holding on to someone's arm
or ☐ with two sticks or crutches *or* one stick or crutch and holding on to someone's arm
or ☐ with a wheelchair

If you use a wheelchair:
Can you stand and walk a few steps with help?
☐ yes ☐ no

B. Scoring

0 – Walking is not affected.
1 – Walking is affected but patient is able to walk independently.
2 – Usually uses unilateral support (single stick or crutch, one arm) to walk outdoors, but walks independently indoors.
3 – Usually uses bilateral support (two sticks or crutches, frame, or two arms) to walk outdoors, *or* unilateral support (single stick or crutch, or one arm) to walk indoors.
4 – Usually uses wheelchair to travel outdoors, *or* bilateral support (two sticks or crutches, frame, or two arms) to walk indoors.
5 – Usually uses a wheelchair indoors.

179

8. Bladder disablity

A. Interview:

Do you have any problems with your bladder?
□ yes   □ no

Are you taking any medications for such problems?
□ yes   □ no

If the answer to the first question is 'yes':
Do you have to rush to the toilet, go frequently, or have difficulty in starting to pass urine?
□ yes   □ no

Have you been incontinent in the last month?
□ yes   □ no

If 'yes':
Have you been incontinent in the last week?
□ yes   □ no

If 'yes':
Have you been incontinent every day?
□ yes   □ no

Do you use a catheter to empty your bladder?
□ yes   □ no

Do you need a permanent catheter in the bladder, or (*for men only*) do you use a sheath to collect your urine?
□ yes   □ no

B. Scoring:

0 – Normal bladder problems.
1 – Asymptomatic on current drug treatment.
2 – Urinary frequency, urgency, or hesitancy with no incontinence.
3 – Occasional urinary incontinence (once or more during the last month but not every week). *or* intermittent catheterisation without incontinence.
4 – Frequent urinary incontinence (once a week or more during the last month but not daily). *or* occasional urinary incontinence despite regular intermittent catheterisation.
5 – Daily urinary incontinence or permanent catheter (urethral/suprapubic) or penile sheath.

9. Bowel disability:

A. Interview:

Do you have any problems with your bowel movements?
□ yes   □ no

Are you no any medicines for such problems?
□ yes   □ no

If the answer to the first question is 'yes':
Do you suffer with constipation?
□ yes   □ no

If 'yes':
Do you need to take any laxatives or use suppositories for this?
□ yes   □ no

Do you usually use enemas?
□ yes   □ no

Do you usually evacuate your stools manually?
□ yes   □ no

Do you have to rush to the toilet to open your bowels?
□ yes   □ no

Have you had bowel accidents (been incontinent of faeces) in the last week?
□ yes   □ no
If 'yes':
Have you had bowel accidents every week?
□ yes   □ no

B. Scoring:

0 – No bowel problems.
1 – Asymptomatic on current drug treatment or constipation not requiring any treatment.
2 – Constipation requiring laxatives or suppositories *or* faecal urgency.
3 – Constipation requiring the use of enemas.
4 – Constipation requiring manual evacuation of stools *or* occasional faecal incontinence (once or more during the last month but not every week).
5 – Weekly faecal incontinence.

10. Sexual disabilities:

A. Interview:

The next set of questions relates to sexual function. Do you mind if I ask you about this?
- ☐ yes
- ☐ no
- ☐ not applicable (Celibate)

If the patient agrees:
Do you have any problems in relation to your sexual function?
- ☐ yes   ☐ no

If 'yes':
Do you suffer with lack of sexual interest?
- ☐ yes   ☐ no

Do you have any problems satisfying yourself or your sexual partner?
- ☐ yes   ☐ no

Is your sexual function affected by any physical problem such as altered genital sensation, pain, or spasms?
- ☐ yes   ☐ no

Do you have any problems with:
- (*for men*):   erection/ejaculation?
- (*for women*):   vaginal lubrication /orgasm?
- ☐ yes   ☐ no

If physical or sexual problems are present:
Do any of these difficulties totally prevent your sexual activities?
- ☐ yes   ☐ no

B. Scoring:

0 – Normal sexual functions *or* persons who are voluntarily celibate.
1 – Reduced sexual interest.
2 – Problems satisfying oneself or sexual partner.
3 – Physical problems interfering but not preventing sexual function.
4 – Autonomic problems interfering but not preventing sexual function.
5 – Physical or autonomic problems totally preventing sexual function.
X – Unknown (please score as the mean of the lower limb, bladder, and bowel disability scores rounded to the nearest integer).

11. Fatigue:

A. Interview:

Have you been feeling tired or getting tired easily during the last month?
- ☐ yes   ☐ no

If 'yes':
Have you been feeling tired most days?
- ☐ yes   ☐ no

Has this tiredness affected your ability to do *any* of your usual activities such as work, housework, or normal social activity with family and friends?
- ☐ yes   ☐ no

If 'yes':
Has this tiredness been severe enough to prevent you from doing *all* of your usual activities?
- ☐ yes   ☐ no

If 'yes':
Has the tiredness been severe enough to prevent you from doing *all* physical activities?
- ☐ yes   ☐ no

B. Scoring:

0 – Absent
1 – Occasional fatigue (present some days).
2 – Frequent fatigue (present most days).
3 – Fatigue affecting the patient's ability to perform some of their usual daily activities.
4 – Fatigue preventing the patient from doing all their usual daily activities.
5 – Fatigue preventing the patient from doing all their physical activities.
X – Unknown (please score as the mean of the cognitive and mood disability scores rounded to the nearest integer).

12. Other disabilities:

A. Interview:

Do you have other problems due to MS such as pain, spasms, or dizziness which have not been mentioned so far?

☐ yes   ☐ no

Are you taking any medicines for such problems?

☐ yes   ☐ no

If the answer to either question is 'yes':
Please name your worst problem: ....

Has this problem affected your ability to do *any* of your usual daily activities?

☐ yes   ☐ no

Has this problem been severe enough to prevent you from doing *all* your usual daily activities?

☐ yes   ☐ no

Have you been admitted to hospital for treatment of this problem?

☐ yes   ☐ no

B. Scoring:

0 – Absent.
1 – Asymptomatic on current drug treatment.
2 – Problems, present, but are not affecting the patient's ability to perform any of their usual daily activities.
3 – Problems affecting the patient's ability to perform some of their usual daily activities.
4 – Problems preventing the patient from doing all their usual daily activities.
5 – Problems requiring hospital admission for assessment or treatment.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. <u>In general,</u> would you say your overall <u>health</u> is*:

    (Circle One)

    READ CATEGORIES:

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is <u>excellent</u>, <u>good</u>, <u>fair</u>, <u>poor</u>, or <u>very</u> <u>poor</u> or are you <u>completely blind</u>?

    (Circle One)

    READ CATEGORIES:

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

---

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3.	How much of the time do you <u>worry</u> about your eyesight?

(Circle One)

READ CATEGORIES:

None of the time 1

A little of the time 2

Some of the time 3

Most of the time............................. 4

All of the time?.............................. 5

4.	How much <u>pain or discomfort</u> have you had <u>in and around your eyes</u> (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:

None...................................... 1

Mild....................................... 2

Moderate.............................. 3

Severe, or 4

Very severe?........................ 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5.	How much difficulty do you have <u>reading ordinary print in newspapers</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1

A little difficulty... 2

Moderate difficulty 3

Extreme difficulty 4

Stopped doing this because of your eyesight 5

Stopped doing this for other reasons or not
	interested in doing this 6

184

6. How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have <u>reading street signs or the names of stores</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have <u>going down steps, stairs, or curbs in dim light or at night</u>?

(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have <u>noticing objects off to the side while you are walking along</u>?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have <u>seeing how people react to things</u> you say?
(READ CATEGORIES AS NEEDED)

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. Because of your eyesight, how much difficulty do you have <u>picking out and matching your own clothes</u>?
   (READ CATEGORIES AS NEEDED)

   (Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have <u>visiting with people in their homes, at parties, or in restaurants</u> ?
   (READ CATEGORIES AS NEEDED)

   (Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have <u>going out to see movies, plays, or sports events</u>?
   (READ CATEGORIES AS NEEDED)

   (Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about <u>driving a car</u>. Are you <u>currently driving</u>, at least once in a while?

(Circle One)

Yes......................... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you <u>never</u> driven a car or have you <u>given up driving</u>?

(Circle One)

Never drove........ 1 *Skip To Part 3, Q 17*

Gave up............... 2

15b. IF GAVE UP DRIVING: Was that <u>mainly because of your eyesight</u>, <u>mainly for some other reason</u>, or because of <u>both your eyesight and other reasons</u>?

(Circle One)

Mainly eyesight..................................... 1 *Skip To Part 3, Q 17*

Mainly other reasons............................ 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons .... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have <u>driving during the daytime in familiar places</u>? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty..................................... 2
Moderate difficulty 3
Extreme difficulty 4

188

16. How much difficulty do you have <u>driving at night</u>? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you <u>all</u>, <u>most</u>, <u>some</u>, <u>a little</u>, or <u>none</u> of the time.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
17. <u>Do you accomplish less</u> than you would like because of your vision?	1	2	3	4	5
18. <u>Are you limited</u> in how long you can work or do other activities because of your vision?......................	1	2	3	4	5
19. How much does pain or discomfort <u>in or around your eyes</u>, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is <u>definitely true</u>, <u>mostly true</u>, <u>mostly false</u>, or <u>definitely false</u> for you or you are <u>not sure</u>.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I <u>stay home most of the time</u> because of my eyesight.	1	2	3	4	5
21. I feel <u>frustrated</u> a lot of the time because of my eyesight.	1	2	3	4	5
22. I have <u>much less control</u> over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to <u>rely too much on what other people tell me</u>...	1	2	3	4	5
24. I <u>need a lot of help</u> from others because of my eyesight.	1	2	3	4	5
25. I worry about <u>doing things that will embarrass myself or others</u>, because of my eyesight.	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

191

Appendix D: Centers for Epidemiological Studies – Depression Scale

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get "going."	☐	☐	☐	☐

The following section will ask some questions you and your multiple sclerosis. Please check or fill in the appropriate responses. Thank You!

1) What is your gender?
  ☐ Male
  ☐ Female

2) What is your age? _____ Years

3) What is your current marital status?
  ☐ Single, Never Married
  ☐ Married
  ☐ Separated
  ☐ Divorced
  ☐ Widowed
  ☐ A member of an unmarried couple

4) Which of the following would you say best describes your race?
  ☐ White
  ☐ African-American
  ☐ Hispanic
  ☐ Other

5) What is your current employment status?
  ☐ Employed
  ☐ Unemployed
  ☐ Unemployed due to multiple sclerosis

6) Please provide the year in which you were diagnosed with Multiple Sclerosis: _____

Please check if you have had or been treated for the following conditions in the past. If you have had a diagnosis or treatment for a condition not noted in the table, please describe under "<u>Other conditions not noted in the table</u>". If you have not had any diagnosis or treatments in the past, please check the box at the bottom of the page.

_____ Abnormal mammogram	_____ Ear/nose/throat trouble	_____ Kidney problem
_____ Abnormal PAP smear	_____ Eating disorder	_____ Learning disabilities
_____ Alcohol/other substance use	_____ Eye problems	_____ Measles/Mumps/Rubella
_____ Anemia	_____ Gout	_____ Mental health condition
_____ Arthritis/joint disease	_____ Diabetes	_____ Insomnia
_____ Asthma	_____ Head injury	_____ Mononucleosis
_____ Back problems	_____ Headaches	_____ Neck injury
_____ Bleeding trait	_____ Hearing loss	_____ Seizures
_____ Broken bones	_____ Heart disease	_____ Heart murmur
_____ Sinusitis	_____ Chicken pox	_____ Hepatitis
_____ Skin diseases	_____ Chronic cough	_____ High blood pressure
_____ Thyroid problem	_____ Congenital defect	_____ High cholesterol
_____ Dizziness or fainting spells	_____ Joint injuries	

_____ Cancer → Type _____

_____ Sexually transmitted disease → Type _____

_____ Ulcer / stomach or digestive problems

_____ Other _____

_____

☐ _I have not had any diagnosis or treatment in the past for any of the conditions noted above or any other conditions_

Appendix G: HRQoL Booklet

SECTION 1

- The following questions ask for your views about the impact of MS on your day-to-day life during the past two weeks

- For each statement, please circle the one number that best describes your situation

- Please answer all questions

In the past two weeks, how much has your MS limited your ability to ...	Not at all	A little	Mod-erately	Quite a bit	Extreme-ly
1. Do physically demanding tasks?	1	2	3	4	5
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4	5
3. Carry things?	1	2	3	4	5

In the past two weeks, how much have you been bothered by ...	Not at all	A little	Mod-erately	Quite a bit	Extreme-ly
4. Problems with your balance?	1	2	3	4	5
5. Difficulties moving about indoors?	1	2	3	4	5
6. Being clumsy?	1	2	3	4	5
7. Stiffness?	1	2	3	4	5
8. Heavy arms and/or legs?	1	2	3	4	5
9. Tremor of your arms or legs?	1	2	3	4	5
10. Spasms in your limbs?	1	2	3	4	5
11. Your body not doing what you want it to do?	1	2	3	4	5
12. Having to depend on others to do things for you?	1	2	3	4	5

In the <u>past two weeks,</u> how much have you been bothered by ...	Not at all	A little	Mod-erately	Quite a bit	Extreme-ly
13. Limitations in your social and leisure activities at home?	1	2	3	4	5
14. Being stuck at home more than you would like to be?	1	2	3	4	5
15. Difficulties using your hands in everyday tasks?	1	2	3	4	5
16. Having to cut down the amount of time you spent on work or other daily activities?	1	2	3	4	5
17. Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4	5
18. Taking longer to do things?	1	2	3	4	5
19. Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?	1	2	3	4	5
20. Needing to go to the toilet urgently?	1	2	3	4	5
21. Feeling unwell?	1	2	3	4	5
22. Problems sleeping?	1	2	3	4	5
23. Feeling mentally fatigued?	1	2	3	4	5
24. Worries related to your MS?	1	2	3	4	5
25. Feeling anxious or tense?	1	2	3	4	5
26. Feeling irritable, impatient, or short tempered?	1	2	3	4	5
27. Problems concentrating?	1	2	3	4	5
28. Lack of confidence?	1	2	3	4	5
29. Feeling depressed?	1	2	3	4	5

The following questions are regarding the section (Section 1) that you just completed.

1. Approximately how long did it take for you to complete this section? _____ minutes

2. What is your opinion regarding the number of questions in this section?

    ☐ The questions were too many
    ☐ The questions were too few
    ☐ The number of questions was just right

3. What is your opinion regarding the way the questions in this section were written?

    ☐ The questions were *mostly* easy to understand
    ☐ The questions were *mostly* difficult to understand
    ☐ No opinion

4. Do you feel that this section helped you express your opinion regarding most problems that you face in your day-to-day activities?

    ☐ Mostly Yes
    ☐ Mostly No
    ☐ Not Sure

SECTION 2

	much better	better	about the same	worse	much worse
1. Compared to <u>one year</u> ago, how would you rate your health in general now?	1	2	3	4	5
2. Compared to <u>4 weeks</u> ago, how would you rate your health in general?	1	2	3	4	5

3. What are your main complaints? *(Please mark not more than three according to their severity with 1, 2, 3 one indicating the worst problem)*

Difficulties in walking	....
Bladder control	....
Fatigue	....
Pain	....
Sensory disturbances	....
Coordination difficulties	....
Blurred /Double vision	....
Spasticity	....
Difficulties concentrating	....
Bad mood	....
Loneliness	....

Below is a list of complaints which may be of importance in MS. Please indicate how true each statement has been for you during the <u>past 7 days.</u>

Sensory symptoms	not at all	a little bit	somewhat	quite a bit	very much
4. I have pain.	1	2	3	4	5
5. Disturbed sensation affects me.	1	2	3	4	5

Fatigue / Thinking	not at all	a little bit	somewhat	quite a bit	very much
6. I have to rest during the day.	1	2	3	4	5
7. I have difficulties beginning or finishing things because I am tired.	1	2	3	4	5
8. I have difficulties learning new things.	1	2	3	4	5
9. I have difficulties remembering things.	1	2	3	4	5

198

Vision

	not at all	a little bit	somewhat	quite a bit	very much
10. I have disturbed vision while watching TV or reading.	1	2	3	4	5

Mobility / Lower Extremities

	not at all	a little bit	somewhat	quite a bit	very much
11. I have difficulties doing sports or running fast.	1	2	3	4	5
12. I have trouble getting around in public places.	1	2	3	4	5
13. I have trouble walking around at home.	1	2	3	4	5
14. I have difficulties standing.	1	2	3	4	5

15. I can walk:
    not at all
    up to 20 meters
    up to 100 meters
    up to 500 meters
    up to 1 kilometers
    .... kilometers

Mobility / Upper Extremities

	not at all	a little bit	somewhat	quite a bit	very much
16. I have difficulties writing.	1	2	3	4	5
17. I have trouble cleaning my home.	1	2	3	4	5
18. I have difficulties preparing a meal.	1	2	3	4	5
19. I have problems dressing and undressing.	1	2	3	4	5
20. I have difficulties eating.	1	2	3	4	5

Bladder / Bowel / Sexuality

	not at all	a little bit	somewhat	quite a bit	very much
21. I have trouble controlling my bladder.	1	2	3	4	5
22. I have trouble controlling my bowels.	1	2	3	4	5
23. I am satisfied with my sex life.	1	2	3	4	5

Social Function

	not at all	a little bit	somewhat	quite a bit	very much
24. I feel distant from my friends and my family.	1	2	3	4	5
25. I get support from friends or neighbours.	1	2	3	4	5
26. I get support from my family.	1	2	3	4	5
27. Communication about my illness is poor with my family.	1	2	3	4	5
28. My condition impairs my relationships to other people (friends, family)	1	2	3	4	5
29. I feel separated.	1	2	3	4	5

Mood

	not at all	a little bit	somewhat	quite a bit	very much
30. I am depressed about my condition.	1	2	3	4	5
31. I am scared because of my condition.	1	2	3	4	5
32. I feel useless.	1	2	3	4	5
33. I am losing hope about the fight against my illness.	1	2	3	4	5
34. I am content with my quality of life.	1	2	3	4	5
35. I can enjoy life.	1	2	3	4	5
36. I feel a sense of purpose in my life.	1	2	3	4	5
37. I am full of energy.	1	2	3	4	5

Handicap

38. How far does MS affect your ability to live a normal life?

(Mark 1 if MS does not affect your postion in life, your job or your family. Select 5 if MS makes you completely dependent and incapable of living a normal life)

not at all	a little bit	somewhat	quite a bit	very much
1	2	3	4	5

The following questions are regarding the section (Section 2) that you just completed.

1. Approximately how long did it take for you to complete this section? _____ minutes

2. What is your opinion regarding the number of questions in this section?

☐ The questions were too many
☐ The questions were too few
☐ The number of questions was just right

3. What is your opinion regarding the way the questions in this section were written?

☐ The questions were *mostly* easy to understand
☐ The questions were *mostly* difficult to understand
☐ No opinion

4. Do you feel that this section helped you express your opinion regarding most problems that you face in your day-to-day activities?

☐ Mostly Yes
☐ Mostly No
☐ Not Sure

SECTION 3

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)

   Excellent ☐
   Very Good ☐
   Good ☐
   Fair ☐
   Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)

   Much better than one year ago ☐
   Somewhat better now than one year ago ☐
   About the same as one year ago ☐
   Somewhat worse now than one year ago ☐
   Much worse now than one year ago ☐

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

Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a) **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b) **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c) Lifting or carrying groceries	1	2	3
3(d) Climbing **several** flights of stairs	1	2	3
3(e) Climbing **one** flight of stairs	1	2	3
3(f) Bending, kneeling, or stooping	1	2	3
3(g) Waling **more than a mile**	1	2	3
3(h) Walking **several blocks**	1	2	3
3(i) Walking **one block**	1	2	3
3(j) Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
   (Please circle one number on each line.)

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

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

	Yes	No
5(a) Cut down on the **amount of time** you spent on work or other activities	1	2
5(b) Accomplished less than you would like	1	2
5(c) Didn't do work or other activities as **carefully** as usual	1	2

6.	During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)
	Not at all ☐
	Slightly ☐
	Moderately ☐
	Quite a bit ☐
	Extremely ☐

7.	How much <u>physical</u> pain have you had during the <u>past 4 weeks</u>? (Please tick **one** box.)
	None ☐
	Very mild ☐
	Mild ☐
	Moderate ☐
	Severe ☐
	Very Severe ☐

8.	During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)
	Not at all ☐
	A little bit ☐
	Moderately ☐
	Quite a bit ☐
	Extremely ☐

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. Please give the one answer that is closest to the way you have been feeling for each item.

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

10.	During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)
	All of the time ☐
	Most of the time ☐
	Some of the time ☐
	A little of the time ☐
	None of the time ☐

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

(Please circle one number on each line.)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a) I seem to get sick a little easier than other people	1	2	3	4	5
11(b) I am as healthy as anybody I know	1	2	3	4	5
11(c) I expect my health to get worse	1	2	3	4	5
11(d) My health is excellent	1	2	3	4	5

Thank You!

The following questions are regarding the section (Section 3) that you just completed.

1. Approximately how long did it take for you to complete this section? _____ minutes

2. What is your opinion regarding the number of questions in this section?

    ☐ The questions were too many
    ☐ The questions were too few
    ☐ The number of questions was just right

3. What is your opinion regarding the way the questions in this section were written?

    ☐ The questions were *mostly* easy to understand
    ☐ The questions were *mostly* difficult to understand
    ☐ No opinion

4. Do you feel that this section helped you express your opinion regarding most problems that you face in your day-to-day activities?

    ☐ Mostly Yes
    ☐ Mostly No
    ☐ Not Sure

Table 3. Step 2: Averaging of Items to Generate VFQ-25 Sub-Scales

Scale	Number of items	Items to be averaged (after recoding per Table 2)
General Health	1	1
General Vision	1	2
Ocular Pain	2	4, 19
Near Activities	3	5, 6, 7
Distance Activities	3	8, 9, 14
Vision Specific:		
Social Functioning	2	11, 13
Mental Health	4	3, 21, 22, 25
Role Difficulties	2	17, 18
Dependency	3	20, 23, 24
Driving	3	15c, 16, 16a
Color Vision	1	12
Peripheral Vision	1	10

NEI-VFQ Scoring Algorithm – August 2002

Appendix I: Cover Letter for the Neurologist Survey

Dear Dr.

We are conducting a survey to determine neurologists' opinions regarding the use of health-related quality of life (HRQoL) information in the routine care of patients with multiple sclerosis (MS). We are also interested in your opinion regarding two HRQoL questionnaires designed for use in patients with MS (printed on colored paper) which have been included with this mailing.

It is our understanding that you may be involved in providing direct medical care to patients with MS in an outpatient setting. We are contacting a random sample from a nationwide selection of neurologists to ask them their views about HRQoL assessment in patients with MS, and whether or not they use HRQoL information in clinical practice.

Your input is essential for us to understand what neurologists feel about HRQoL assessment in patients with MS. Results from our study will allow us to identify the areas where efforts are needed to facilitate translation of HRQoL findings into usable information for clinical practice. Furthermore, your opinion regarding the specific enclosed questionnaires will aid in determining suitability of their use in the routine care of patients with MS.

It will only take a few minutes to complete the attached questionnaire and your responses will be kept as confidential as legally possible. On receiving your completed questionnaire, responses will be combined with responses from other neurologists and analyzed and the results of this study will be only reported in aggregate format. The survey is voluntary, however, we hope you will share your experiences and opinions about MS-related HRQoL information.

If you choose to participate, please mail the completed survey back to us in the self-addressed business reply envelope included alongside. This research is being conducted as part of a larger doctoral dissertation study in Pharmaceutical Sciences at West Virginia University. If you need any help completing this survey or have any questions, please contact Vivek Pawar at (304) 685-7812 or Lesley-Ann Miller, PhD at (304) 293-0228. Thank you in advance for providing this information.

Sincerely

_____   _____

Vivek Pawar, MS   Lesley-Ann Miller
Doctoral Candidate   Assistant Professor

Appendix J: Neurologist Survey

HEALTH-RELATED QUALITY OF LIFE ASSESSMENT IN PATIENTS WITH MULTIPLE SCLEROSIS (MS)
Neurologist Survey

Are you directly involved in the <u>routine care</u> of patients with multiple sclerosis?
   ☐ No **---** Please stop here and return this survey in the enclosed business reply envelope. *Thank you for your time.*
   ☐ Yes **---** Please continue with the next question

INSTRUCTIONS: Please spend a few minutes to look through the HRQoL questionnaire printed on the blue paper followed by the questionnaire printed on the yellow paper (enclosed) before you begin answering the questions.
We would like your <u>opinion regarding the enclosed HRQoL questionnaires</u>. Kindly CIRCLE (O) the desired response.

First, about the blue questionnaire…

a. Do you think that using the **blue questionnaire** in your patients with MS will provide additional useful information, compared to what you normally have available from conventional physical exams & clinical testing methods?

Mostly No			Not Sure			Mostly Yes
1	2	3	4	5	6	7

b. What do you think about the length of the **blue questionnaire**?

Too Short			Just Right			Too Long
1	2	3	4	5	6	7

c. From the perspective of patients with MS, what is your opinion regarding the way the questions are worded?

Mostly Easy to Understand			Not Sure			Mostly Difficult to Understand
1	2	3	4	5	6	7

Now, about the yellow questionnaire….

d. Do you think that using the **yellow questionnaire** in your patients with MS will provide additional useful information, compared to what you normally have available from conventional physical exams & clinical testing methods?

Mostly No			Not Sure			Mostly Yes
1	2	3	4	5	6	7

e. What do you think about the length of the **yellow questionnaire**?

Too Short			Just Right			Too Long
1	2	3	4	5	6	7

f. From the perspective of a patient with MS, what is your opinion regarding the way the questions are worded?

Mostly Easy to Understand			Not Sure			Mostly Difficult to Understand
1	2	3	4	5	6	7

INSTRUCTIONS: The following questions will ask your opinion regarding HRQoL assessment in routine care of patients with MS. Kindly CIRCLE (O) the desired response

1)   a. How important is it to collect HRQoL information in the routine care of patients with multiple sclerosis?

Not at all important   1   2   3   4   5   6   7   Very important

2)   a. HRQoL information may help address problems which the patients with MS will not bring up or think of

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Knowing about problems which patients with MS will not bring up or would not think of is…

Extremely Undesirable   1   2   3   4   5   6   7   Extremely Desirable

3)   a. Assessing HRQoL information will make the patients feel like I am concerned about their overall well-being

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. For patients with MS to feel that I am concerned about their overall well-being is

Extremely Undesirable   1   2   3   4   5   6   7   Extremely Desirable

4)   a. HRQoL information will help me understand the impact that MS is having on an individual's life

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Knowing what kind of impact MS is having on the life of my patient with MS is…

Extremely Undesirable   1   2   3   4   5   6   7   Extremely Desirable

5)   a. HRQoL information can provide subjective information about the patient over and above the information provided by standard objective tests

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Having a subjective assessment of my patient's condition in addition to standard objective tests is

Extremely Undesirable   1   2   3   4   5   6   7   Extremely Desirable

6)   a. HRQoL information can be used to monitor changes or responses to treatment in patients with MS

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Monitoring changes or responses to treatment using HRQoL information in patients with MS is

Extremely Undesirable   1   2   3   4   5   6   7   Extremely Desirable

7)   a. HRQoL information assessment in patients with MS can facilitate shared clinical decision making

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Making shared clinical decisions with MS patients is

Extremely Undesirable   1   2   3   4   5   6   7   Extremely Desirable

8)   a. Use of HRQoL questionnaires will lengthen the consultation   with the patient

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Lengthening consultation time with patients with MS to collect HRQoL information is…

Extremely Undesirable   1   2   3   4   5   6   7   Extremely Desirable

9)   a. I feel confident that I could assess HRQoL information from patients with MS if I wanted to

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Assessing HRQoL information from patients with MS is _____ for me

Easy   1   2   3   4   5   6   7   Difficult

10)   a. The decision whether or not to assess HRQoL information from patients with MS is beyond my control

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Whether I assess HRQoL information from patients with MS is entirely upto me

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

11)   a. The American Academy of Neurology recommends that I should assess HRQoL in patients with MS

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. What the American Academy of Neurology thinks regarding my decision about HRQoL assessment in patients with MS is important to me

Not at all   1   2   3   4   5   6   7   Very Much

12)   a. Other neurologists believe that HRQoL information should be assessed in patients with MS

Strongly Disagree   1   2   3   4   5   6   7   Strongly Agree

b. Doing what other neurologists believe regarding HRQoL assessment in patients with MS is important to me

Not at all   1   2   3   4   5   6   7   Very Much

I intend to assess HRQoL information from patients with MS

Strongly Disagree   *1*   *2*   *3*   *4*   *5*   *6*   *7*   ***Strongly Agree***

INSTRUCTIONS: The following questions will ask your opinion regarding HRQoL information in general. Kindly CIRCLE (O) the desired response

	Strongly Disagree			Not Sure			Strongly Agree
1) I do not understand how HRQoL information would be used in routine care of patients with MS	1	2	3	4	5	6	7
2) HRQoL information facilitates better communication with patients	1	2	3	4	5	6	7
3) HRQOL is not relevant to neurologists	1	2	3	4	5	6	7
4) HRQoL information allows for identification and prioritization of problems	1	2	3	4	5	6	7
5) There are no benefits of using HRQoL information in patients with MS	1	2	3	4	5	6	7
6) HRQoL information can be used to screen for hidden problems (e.g. psychological)	1	2	3	4	5	6	7
7) Scoring HRQoL questionnaires is difficult	1	2	3	4	5	6	7
8) HRQoL information requires too much resources or time	1	2	3	4	5	6	7
9) HRQoL information is not trustworthy	1	2	3	4	5	6	7
10) HRQoL information can be used to really treat the "whole" patient	1	2	3	4	5	6	7

Are there any other factors which influence your decision whether or not to use HRQoL information in patients with MS?

_____
_____
_____

INSTRUCTIONS: Please indicate whether you currently assess HRQoL information using formal standardized questionnaires in routine care of MS patients with MS? Kindly CHECK (✓) your response

☐ Yes   ☐ No

☐ I am thinking of using HRQoL questionnaires in my practice within the next month
☐ I am thinking of using HRQoL questionnaires in my practice within the next 6 months
☐ I am aware of HRQoL questionnaires, but have not thought about using them in my practice
☐ I am unaware of any HRQoL questionnaires and of how to use them in my practice

☐ I have been using HRQoL questionnaires in my practice for more than six months
☐ I have been using HRQoL questionnaires in my practice for less than six months

INSTRUCTIONS: Please indicate whether you have used in clinical practice or heard of the following HRQoL questionnaires. Kindly CHECK (✓) your response

	I have used	I have heard of
Medical Outcomes Survey Short Form (SF-36)	☒	☒
Multiple Sclerosis Quality of Life 54 (MSQOL-54)	☐	☐
Functional Assessment of Multiple Sclerosis (FAMS)	☒	☒
Multiple Sclerosis Quality of Life Inventory (MSQLI)	☐	☐
Multiple Sclerosis Impact Scale (MSIS-29)	☒	☒
Hamburg Quality of Life Assessment in Multiple Scleroris (HAQUAMS)	☐	☐
Sickness Impact Profile (SIP)	☒	☒
Other- _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _	☐	☐

INSTRUCTIONS: This section will ask information about you and your practice. Kindly CHECK (✓) your response

1. Please indicate your gender: ☐ Male   ☐ Female

2. Please indicate your age-group:

☐ 30 years or younger
☐ 31 to 40 years
☐ 41 to 50 years
☐ 51 to 60 years
☐ 61 years and older

3. Your primary practice site is:

☐ Hospital based   ☐ University-affiliated hospital   ☐ Solo, Office-based   ☐ Group, office based

☐ Others, Please Specify: _____

4. Approximately how many patients with MS do you personally see per week? _____ patients

5. Have you ever participated in a MS-related clinical trial with a HRQoL component? ☐ Yes   ☐ No

6. Please indicate the year in which you received your board certification in neurology: _____

7. How many years have you been in practice as a neurologist?

☐ Currently a resident
☐ 5 years or fewer
☐ 6-10 years
☐ 10 years or more

Additional comments regarding HRQoL assessment in patients with MS in clinical practice:
_____

_____
_____
THANK YOU FOR YOUR INPUT!
Kindly return this questionnaire to us in the enclosed business reply envelope.

Curriculum Vita

Vivek Pawar

1056 Van Voorhis Rd.
Apt K207
Morgantown, West Virginia 26505

E-Mail:vpawar@hsc.wvu.edu
Phone: (304) 685-7812
Fax: (304) 293-2529

ACADEMIC CREDENTIALS

West Virginia University (WVU)
2003 to Present
Department of Pharmaceutical Systems & Polic*y*
Degree: PhD in Health Outcomes Research. Expected graduation – December 2006
Dissertation in Progress: *"Health-Related Quality of Life in Multiple Sclerosis: Measurement, Predictors and Utilization in Routine Clinical Practice"*
Advisor: Dr. Lesley-Ann Miller

University of Louisiana at Monroe (ULM)
2001 to 2003
Department of Clinical & Administrative Sciences
Degree: MS in Pharmacy Administration
Field Study Title: *"Relationship between counseling/education services in patients with diabetes and certain physician characteristics using the National Ambulatory Medical Care Survey (NAMCS) database"*
Advisor: Dr. Joseph Feldhaus

University of Bombay
1997 to 2001
Bombay College of Pharmacy
Degree: BS in Pharmaceutical Sciences

RESEARCH EXPERIENCE

Community Health Initiatives, WVU
Jan 2006 to Present
Research Assistant
Responsibilities
Conducted extensive data management and statistical analysis using SAS ver. 9.0

Department of Pharmaceutical Systems & Policy, WVU
2005 to 2006
Research Assistant
Responsibilities
- Survey data collection and analysis
- Conducted focus groups and performed qualitative data analysis
- Performed large database analysis using West Virginia Medicaid administrative claims data
- Helped faculty with writing manuscripts for publication and grants for funding purposes

Center for Rural Emergency Medicine, WVU
2003 to 2004
Research Assistant:
Responsibilities
Performed literature searches, data analysis, survey development and submission of written reports

WORK
EXPERIENCE

School of Pharmacy Computer Laboratory, ULM
2001 to 2003
Graduate Assistant
Responsibilities
Provided computer-related support to Pharm. D students and managed inventory

Chemical, Industrial & Pharmaceutical Laboratories (Cipla) Ltd., Mumbai, India
1999
Summer Intern
Responsibilities
Internship experience involved practical training in Manufacturing & Quality Control and Quality Assurance departments

PUBLICATIONS

Pawar V, Smith MJ (2006). "Asthma-Related Health Care Utilization and Costs by African-Americans Enrolled in West Virginia Medicaid". *Respiratory Medicine* 100 (9): 1579-87

Mangone C, Tessaro I, Parker I, **Pawar V** (2006)**.** "Knowledge, Barriers and Predictors of Colorectal Cancer Screening in an Appalachian Church Population". *Preventing Chronic Disease* - In Press

Zizzi S, Goodrich D, Wu Y, Parker L, Rye S, **Pawar V***,* Mangone C and Tessaro I (2006). "Correlates of Physical Activity in a Community Sample of Adults in Appalachia". *Journal of Aging and Physical Activity* - In Press

Mody R, Kalsekar I, Kavookjian J, Iyer S, Rajagopalan R and **Pawar V** (2006). "Economic Impact of Cardiovascular Co-morbidity in Patients with Type 2 Diabetes". *Journal of Diabetes and Its Complications* - In Press

Jones DL, Kriska AM, Irrgang JJ, Lian Y, **Pawar V**, Crossett LS, Kwoh CK, Cauley JA (2006). "Physical Activity as a predictor of Long-term Physical Health Status after Total Knee Arthroplasty for Osteoarthritis". Abstract submitted to *Osteoarthritis Research Society International*

Tessaro I, Coughlin S, **Pawar V** (2006). "Colorectal Cancer Screening and Preventive Practices among Appalachian Men and Women with a Positive Family History". Submitted to *CDC* for initial review

Pawar V, Miller LA (2006). "Quality of Life in Multiple Sclerosis: Choosing a Suitable Measure". Manuscript in progress

Goodrich D, Tessaro I, **Pawar V** (2006). "Social Network Support, Church Integration & Support and Health Promoting Behaviors". Manuscript in progress

POSTER PRESENTATIONS

Pawar VS, Miller LA (2006). "Comparison of health-related quality of questionnaires in multiple sclerosis: A review". International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Meeting, Philadelphia, May 2006

Mody R, Kalsekar I, Kavookjian J, Iyer S, Rajagopalan R, **Pawar V** (2005). "Economic Impact of Cardiovascular Co-morbidity in Patients with Type 2 Diabetes". International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Meeting, Washington, D.C., May 2005. Abstract published in *Value in Health*, May 2005

Kavookjian J, Mody R, Iyer S, Rajagopalan R, Kalsekar I, **Pawar V** (2005). *"*Prevalence of Co-morbid conditions and concomitant medication use among Type 2 Diabetes patients in a State Medicaid population". International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Meeting, Washington, D.C., May 2005. Abstract published in *Value in Health*, May 2005

Pawar VS, Smith MJ (2004). "Asthma-Related Health Care Services Utilization by African-Americans in a Medicaid Population". International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Meeting, Washington, D.C., May 2004. *Best Poster Finalist Award*. Abstract published in *Value in Health* 2004; 7(3): 313

Pawar VS, Raval DH (2002). "Dietary Fat Intake and the Nutritional Aspects of Type 2 Diabetes: A Literature Review". Presented at the Southern Pharmacy Administration Conference, University of Louisiana at Monroe, Monroe, LA, 2002

RESEARCH PROJECTS

West Virginia Veteran Prostate Cancer Focus Groups: Plan for Examining Public Health Practices (2006)
Role: Conducted and transcribed focus groups and analyzed data using QSR*N6 software

A descriptive analysis of colorectal cancer-related health services utilization in the West Virginia Medicaid population (2005)
Submitted to the WVU Faculty Senate Award (Principal Investigator: Lesley-Ann Miller)
Role: Performed data cleaning, management and analysis. Helped in writing the final report

Building the West Virginia Collaborative Health Outcomes Research of Therapies and Services (CoHORTS) (2005)
Submitted to the Agency for Healthcare Research and Quality "Building Research and Infrastructure program (Principal Investigator: S. Suresh Madhavan)
Role: Assisted with research design for the research portion of the proposal

Cost-Effectiveness of Irbesartan in the treatment of ESRD among patients with Type 2 Diabetic Nephropathy (2005)
Decision Analysis class project, WVU School of Pharmacy

Developing a novel approach to rural emergency preparedness and injury prevention in a particularly vulnerable population and aim to enhance rural hospital emergency preparedness by providing accurate and timely information (2004)
<u>*Role*</u>*:* Performed literature reviews and assisted in constructing a survey to assess emergency
preparedness in a rural population

RELEVANT COURSES COMPLETED

Pharmacoepidemiology   Claims Data Analysis
Research Design and Data Analysis   Survey Research Methods
Pharmacoeconomics   Decision Analysis
Health Economics   Healthcare Finance
Introductory and Multivariate Statistics   Introductory Econometrics
Healthcare & Hospital Administration
Health Behavior and Health Education
Intro to Statistical Analysis Software (SAS)

COMPUTER SKILLS

Statistical Softwares: *SAS ver.9.0, SPSS ver. 11.0*
Decision Analysis: *DATA Treeage*
Productivity Programs: *Microsoft Office (Word, Excel and PowerPoint)*
Qualitative Data Analysis: *QSR*N6*
Database Management Systems: *Microsoft Access, FoxPro*
Reference Management Applications: *Reference Manager 10.0*

HONORS AND AFFILIATIONS

President, WVU-ISPOR student chapter (2005 – 2006)
Member, Rho Chi Honor Society (2004 – Present)
Secretary, WVU-ISPOR student chapter (2004 – 2005)
Best Poster Finalist Award, ISPOR 9th Annual International Meeting (2004)
Member, International Society for Pharmacoeconomics & Outcomes Research (ISPOR) (2003 – Present)

REFERENCES   Available upon request