The relationship between spasticity, quality of life and other neurological impairments in multiple sclerosis

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by

Kristijonas Milinis

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I. Abstract

Background: Previous research has shown that spasticity negatively affects physical functioning and health status, however information on its impact on overall quality of life (QOL) in multiple sclerosis (MS) is limited. Furthermore, qualitative studies indicate that spasticity may affect a number of MS-associated conditions such as fatigue, depression, anxiety, pain and sleep. However these relationships have not been examined in the quantitative studies.

Objectives: 1) To determine the effect of spasticity on overall QOL. 2) To investigate the relationships between spasticity and other neurological impairments associated with MS.

Methods: Demographic details were obtained and a questionnaire pack containing the World Health Organization Quality Of Life-BREF (WHOQOL-BREF), Leeds MS QOL scale (LMSQOL), World Health Organization Disability Assessment Schedule (WHODAS), Multiple Sclerosis Spasticity Scale-88 (MSSS-88), Numerical Rating Scale (NRS 0-10) for spasticity, Neurological Fatigue Index - MS (NFI-MS), Hospital Anxiety and Depression Scale (HADS), SF-Qualiveen for bladder dysfunction and Neuropathic Pain Scale (NPS) was given to patients at three UK neuroscience centres.

Results: 260 patients completed the questionnaire pack. 84.8% reported spasticity. 56.1% had moderate (NRS 4-6) or severe (NRS 7-10) spasticity. Patients with spasticity were more likely to be disabled, suffer from depression, have higher levels of fatigue and report more pain, bladder and sleep problems ($p<0.001$). An association between anxiety and spasticity was weak ($rho=0.2$, $p<0.05$). Older age, progressive type of MS, higher Extended Disability Status Scale (EDSS) score, unemployment were associated with increased severity of spasticity. Spasticity was found to be a significant predictor of WHOQOL-BREF physical health after adjusting for sociodemographic variables, anxiety, depression, fatigue, bladder dysfunction and pain. WHOQOL-BREF psychological health, social relationships, environment and LMSQOL were not predicted by spasticity after controlling for the same factors ($p>0.05$). Depression and fatigue were the strongest predictors of poor QOL, which is consistent with current literature.

Conclusions: Spasticity is very common in MS and is often severe and disabling. There is a strong association between spasticity and fatigue, depression, pain, sleep and bladder problems. The findings suggest that spasticity might directly and indirectly influence overall QOL.

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V. Abbreviations

AHC	Anterior horn cell
AS	Ashworth Scale
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CSF	Cerebrospinal fluid
DRT	Dorsal reticulospinal tract
EMG	Electromyography
EQ-5D	EuroQol - 5D
EDSS	Extended Disability Status Score
ET	Exercise training
FAMS	Functional Assessment in Multiple Sclerosis
FSS	Fatigue Severity Scale
GABA-B	Gamma-aminobutyric acid - B
HADS	Hospital Anxiety and Depression Scale
HRQOL	Health-related Quality of Life
HLA	Human Leukocyte Antigen
ICF	International Classification of Functioning, Disability and Health
IQR	Interquartile Range
ITB	Intrathecal baclofen
iTBS	intermittent Transcranial Magnetic Theta Burst Stimulation
LMQOL	Leeds Multiple Sclerosis Quality of Life scale
MAS	Modified Ashworth Scale
MFIS	Modified Fatigue Impact Scale
MHC	Major Histocompatibility Complex

MRI	Magnetic Resonance Imaging
MRT	Medial reticulospinal tract
MS	Multiple Sclerosis
MSQOL-54	Multiple Sclerosis Quality of Life - 54
MSSS-88	Multiple Sclerosis Spasticity Scale - 88
NARCOMS	North American Research Committee on Multiple Sclerosis
NFI-MS	Neurological Fatigue Index - Multiple Sclerosis
NHP	Nottingham Health Profile
NINDS	National Institute of Neurological Disorders and Stroke reflex scale
NPS	Neuropathic Pain Scale
PET-FDG	Positron Emission Topography - Fludeoxyglucose
PPMS	Primary Progressive Multiple Sclerosis
PRISM	Patient-Reported Impact of Spasticity
PS	Performance Scales
PSFS	Penn Spasm Frequency Scale
QOL	Quality of Life
REMS	Rapidly Evolving Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SCAT	Spinal Cord Assessment Tool
SCI	Spinal Cord Injury
SCI-SET	Spinal Cord Injury-Spasticity Evaluation Tool
SD	Standard Deviation
SF-12/36	Short Form - 12/36
SIP	Sickness Impact Profile

SPASM Support Programme for Assembly of a database for Spasticity Measurement

SPMS Secondary Progressive Multiple Sclerosis

SRSS Self-reported Spasticity Scale

SSQOL Stroke Specific Quality of Life

TONiC Trajectories of Outcome in Neurological Conditions

TS Tardieu Scale

UMN Upper Motor Neuron

VAS Visual analogue scale

VIF Variance inflation factor

WHO World Health Organisation

WHODAS 2.0 World Health Organisation Disability Assessment Schedule 2.0

WHOQOL-100 World Health Organisation Quality of life -100

WHOQOL-BREF World Health Organisation Quality of life - BREF

VI. Overview of the thesis

Chapter 1

An introductory chapter consists of three sections. In the first section, pathophysiology and measurement of spasticity is discussed. In the second section, a brief overview of multiple sclerosis is given with particular focus on spasticity in MS. In the third section, basic concepts and measurement issues of quality of life (QOL) are presented.

Chapter2

The second chapter of this thesis explores literature regarding the relationship between spasticity and QOL. Systematic review of the studies is presented here. Hypothesis and aims of the thesis are included as well.

Chapter 3

Methodology of the study is presented in chapter 3. Discussion of the recruitment process, inclusion and exclusion criteria and the rationale for the outcome measures is given. Description of the statistical analysis is also provided.

Chapter 4

Results are presented in chapter 4. Response rates, demographic characteristics and results from univariate and multiple regression analyses are presented.

Chapter 5

The last chapter discusses the findings of the study and revisits relevant literature. Limitations and strengths are discussed as well. The chapter ends the thesis with directions for future research.

Chapter 1- Introduction

1.1. Spasticity

1.1.1. Definition of Spasticity

Spasticity is a common neurological impairment (classified under 'Impairments' according to the International Classification of Functioning, Disability and Health (ICF)) in many chronic neurological disorders such as stroke, multiple sclerosis and spinal conditions (WHO, 2001). Despite it being a common problem it remains poorly defined (Malhotra, Pandyan, Day, Jones, & Hermens, 2009). This has been increasingly recognised as a major problem in research on spasticity (Pandyan et al., 2005). The lack of a precise definition hinders the development of valid measures of spasticity, which are fundamental for investigating pathophysiological mechanisms and assessing treatment outcomes (Pandyan et al., 2005). Due to its complex pathophysiology and diverse clinical features, defining spasticity has challenged researchers and clinicians for many years. The first attempts to define spasticity were made by Lance in 1980 (Lance, 1980). Lance defined spasticity as '"a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the UMN syndrome".

However, over the years it has been recognised that Lance's definition is too narrow to encompass a wide range of spasticity-associated phenomena (Burridge et al., 2005; Pandyan et al., 2005; Stevenson, 2010). A review by Pandyan et al. (2005) presented four arguments for why Lance's definition of spasticity may not be accurate: (1) There is insufficient evidence to suggest that spasticity results exclusively from increased tonic stretch reflex, and that other mechanisms such as alpha motor neurone hyperexcitability, increased transcortical reflexes and hyperactivity of group II spindle afferents may be involved, (2) Velocity dependency is not an exclusive property of spasticity, but can also be characteristic of visco-elastic structures (muscle, tendon, ligaments) (3) There is no evidence to suggest that phasic stretch reflex is related to increased resistance of passive muscle movement (4) Lastly, spasticity is no longer

considered to be purely motor disorder, as afferent input from cutaneous receptors and proprioreceptors contribute to muscle activity (Pandyan et al., 2005). In addition, Burridge et al. suggested that Lance's definition made no reference to the way spasticity manifests during active function, which may be more relevant to a patient experiencing it (Burridge et al., 2005). As a result, the Support Programme for Assembly of a database for Spasticity Measurement (SPASM) group proposed the most recent definition of spasticity describing it as 'disordered sensori-motor control, resulting from an upper motor neurone lesion, presenting as intermittent or sustained involuntary activation of muscles' (Pandyan et al., 2005).

Despite the efforts of SPASM group to introduce a standardised classification system of spasticity measurement, a systematic review by Malhotra et al. found that researchers continue to use different definitions of spasticity indicating that there is a widespread disagreement about the current understanding of spasticity and its measurement (Malhotra et al., 2009). In order to conceptualise what constitutes a meaningful measurement of spasticity, it is important to be familiar with the principles of normal muscle tone control and the pathophysiological mechanisms responsible for the development of spasticity.

1.1.2. Control of Muscle Tone

Pioneering work on control of muscle tone was carried out by Sherrington at the end of the 19th century (Sherrington, 1898, 1910). He discovered that muscle spindles, the small proprioceptive stretch receptors of the muscles, transmit information to the spinal cord regarding muscle length and rate of change of muscle length. The muscle spindles activate alpha motor neurones, via a monosynaptic reflex, which cause muscle contraction, a phenomenon known as a (myotatic) stretch reflex.

Two types of afferent fibres are responsible for relaying information from the muscle spindles to the spinal cord (Davidoff, 1992). When a muscle is stretched at a rapid rate, a short-latency reflex is initiated by the activation of Ia afferent sensory fibres. This type of reflex is velocity-dependent and is under control of gamma efferent fibres (fusimotor fibres) (Sheean & McGuire, 2009). In order to ensure smooth and

controlled muscle contraction, antagonist muscles are inhibited as a result of the stretch reflex arc, a process called reciprocal inhibition. Type II afferent fibres become activated independent of stretch velocity and are responsible for providing information regarding static muscle length and position (Dietz & Sinkjaer, 2007).

Another important component of muscle tone control is Golgi tendon organs. Located in the musculotendinous junction, Golgi tendon organs convey information via Ib afferent fibres to the spinal cord regarding the tension exerted by the muscle. Fine interplay between muscle spindles and Golgi tendons organs is responsible for normal muscle tone (Davidoff, 1992).

However, it is important to appreciate that both muscle stretch and Golgi tendon reflex arcs are under complex supraspinal and collateral neurone control, despite being simplistically described as mono- or oligosynaptic reflex systems (Davidoff, 1992). One group of specialised neurones are Renshaw cells, located in close proximity to anterior horn cells (AHCs). It has been shown that Renshaw cells become activated by collateral AHC branches and cause inhibition of AHCs and its synergists in order to limit and stabilise discharge frequency (recurrent inhibition) (Maltenfort, Heckman, & Rymer, 1998). In addition, inhibitory interneurons connected to Ia sensory fibre terminals exert, with the help of supraspinal stimulation, a constant inhibitory effect on AHCs. In reality, the interplay between these reflex arcs is extremely complex, hence current understanding of muscle tone control is still in the early stages.

1.1.3. Clinical features and pathophysiological correlates of spasticity

The upper motor neurone (UMN) syndrome is a collection of signs and symptoms that occurs as a result of an insult to UMNs anywhere along their course. Classically, the manifestations of UMNS are divided into positive and negative phenomena (table 1) (Sheean, 2002). Negative features of UMN damage include: motor weakness, fatigability, loss of dexterity and selective motor control and slowed movements. These features often precede the development of positive phenomena which are characterised by muscle overactivity. This manifests as tendon hyper-reflexia, clonus, the clasp-knife phenomenon, flexor and extensor spasms, the Babinski sign, spastic dystonia and

velocity-dependent hypertonia. Traditionally, only the latter was considered to be spasticity (Decq, Filipetti, & Lefaucheur, 2004; Stevenson, 2010).

Table 1. Classification of UMN-associated phenomena (Pandyan et al., 2005)

Positive features	**Negative Features**
Hyper-reflexia	Muscle weakness
Clonus	Loss of dexterity
Positive Babinski sign	Fatigability
Spasticity	
Flexor spasm	
Extensor spasm	
Mass reflex	
Co-contraction	
Spastic dystonia	

However, as these signs and symptoms usually occur together and are caused by the same insult to the UMN, the revised definition of spasticity proposed by SPASM consider all of the positive phenomena to represent different aspects of spasticity (Burridge et al., 2005; Pandyan et al., 2005). Although the pathophysiological mechanisms behind each of the aspects of spasticity may differ it has been recognised that this has little clinical relevance (Burridge et al., 2005).

Different features of spasticity can be grouped into three categories based on the pathophysiology and clinical manifestations (Sheean, 2002) (Table 2). A major factor contributing to the development of spasticity is an abnormal processing of the afferent inputs from the periphery such as muscle stretch, pain or cutaneous stimulation (Dietz & Sinkjaer, 2007). Clinical manifestation involves both the development of new reflexes and exaggeration of the existing ones. In a patient with spasticity, passive muscle stretching induces muscle contraction, called a tonic reflex, which constitutes a new

reflex (Sheean & McGuire, 2009). It is a velocity- (faster stretching causes more powerful contraction) and length (the shorter the muscle the easier to elicit contraction) dependent reflex. By definition, muscle hypertonicity should disappear once movement is stopped (Decq et al., 2004). This is an important feature which distinguishes spasticity from other disorders causing hypertonicity, such Parkinson's disease, where the limb stays rigid even after termination of movement. Intrinsic phasic spasticity encapsulates symptoms such as tendon hyper-reflexia and clonus, and is due to exaggeration of the phasic component of stretch reflex. The repetitive movement of the foot, as seen in clonus, is a result of the alternate stretching and unloading of the muscle spindles, which trigger a continuous phasic reflex (Stevenson, 2010). An exaggerated withdrawal reflex causes flexor and extensor spasms that are commonly observed in response to noxious cutaneous stimuli. In severe cases, a triple flexion reflex may occur, which is characterised by the simultaneous flexion of the hip, knee and ankle (Decq et al., 2004). A release of primitive cutaneous reflex, famously known as positive Babinski sign, often occurs and is the hallmark sign of a UMN lesion.

Table 2. Classification of clinical features and corresponding pathophysiological mechanisms of spasticity (Sheean, 2002)

Spinal reflexes	**Efferent drive**	**Disordered control of muscle movements**
Stretch Nociceptive Cutaneous	Spastic dystonia	Co-contraction

The second mechanism responsible for spastic dystonia is a continuous efferent discharge causing prolonged increase in muscle tone (Sheean, 2002). There is a sustained muscle contraction driven by efferent stimulation which is not dependent on sensory feedback. Clinically, this can be seen in patients with hemiparesis, who display flexion of the elbow and extension of the leg.

The third aspect of spasticity is a disordered voluntary motor control, known as co-contraction. Normally, contraction of the agonist muscle will simultaneously cause relaxation of the antagonist, this is known as a reciprocal inhibition. If UMNs are damaged, this reflex is dysfunctional which leads to simultaneous contraction of agonistic and antagonistic muscle groups. This is commonly seen in patients who experience spasms, characteristically occurring in response to body movements (Sheean & McGuire, 2009).

The manifestations of spasticity described above result from the damage to UMNs either at the spinal or supraspinal levels. UMNs exert inhibitory and excitatory effects on spinal reflexes, producing balanced control of muscle tone. Hence, if there is a loss of predominantly inhibitory fibres, a patient will develop more positive features of UMN syndrome and vice versa. Interestingly, in contrary to the previous understanding which supported that spasticity is predominantly caused by corticospinal tract dysfunction, it has been shown in animal models that pure corticospinal lesions produce weakness and loss of dexterity, but little spasticity (Mukherjee & Chakravarty, 2010). In contrast, dysfunction of the parapyramidal fibers, mainly the medial reticulospinal tract (MRT) and the dorsal reticulospinal tract (DRT), are critical in the development of spasticity (Mukherjee & Chakravarty, 2010; Sheean & McGuire, 2009). The DRT predominantly exerts an inhibitory effect on anterior horn cells and is under cortical control, whereas the MRT exerts excitatory effects and is independent from cortical activity. These tracts run in close proximity with the pyramidal tracts, hence lesions in the spinal cord may produce positive and negative phenomena depending on which tracts are affected. For instance, patients with complete spinal cord injuries exhibit markedly lower degrees of spasticity compared to patients with incomplete transection. This is likely to be a result of the incomplete damage primarily affecting the inhibitory tracts and sparing the excitatory ones (Sheean, 2002).

However, this only explains the pathophysiology of spasticity occurring secondary to the lesions affecting the spinal cord, but not the brainstem or the brain, such as in cases of stroke or traumatic brain injury. It has been observed that spasticity caused by lesions in UMNs at the supraspinal level is less prominent compared to spinal spasticity. This is explained by loss of cortical stimulation of the DRT causing unopposed excitatory stimulation of AHCs by the MRT (Sheean, 2002). As a result, lesions in the cortex or internal capsule will produce spasticity.

Clinical manifestations of spasticity, such as stiffness and reduced range of movement, are not necessarily a consequence of increased muscle tone secondary to increased muscle stretch reflex. Following an UMN lesion, changes in the visco-elastic properties of the muscle, soft tissues and tendons frequently occur in patients with spasticity (O'Dwyer & Ada, 1996). Accumulation of connective tissue, loss of sarcomeres and muscle atrophy may lead to reduced muscle compliance and contractures (Gracies, 2005). As a result, patients may develop increasing levels of stiffness and physical disability secondary to biomechanical changes and not solely due to alterations in the neural networks controlling muscle tone.

1.1.4. Mechanisms responsible for spasticity

Several mechanisms for development of spasticity have been suggested, however the pathophysiology remains to be incompletely understood. As previously mentioned, loss of supraspinal control which is mainly from the DRT is associated with increased sensitivity of AHCs. Other important changes include decreased Ib fibre inhibition and Renshaw cell inhibition (Gracies, 2005; Mayer, 1997; Mukherjee & Chakravarty, 2010; Sheean & McGuire, 2009). Although several studies attempted to show that muscle spindle sensitivity is up-regulated due to the increased gamma efferent drive, the results have not supported this (Burke, Gillies, & Lance, 1970; Mayer, 1997; Tardieu, Tardieu, Colbeau-Justin, & Bret, 1982). Disynaptic Ib inhibition has been found to be depressed with lesions in the brain, but not in the spinal cord (Decq et al., 2004). The H' response recruitment curves, also known as recurrent inhibition, are depressed in spasticity, however in up to 40% of patients the curve is identical to that of healthy

controls (Decq et al., 2004). Finally, intrinsic changes in the motor neurone also develop over time, characterised by abnormally prolonged plateau-like potentials that cause increased muscle contraction in response to synaptic inputs (Kiehn & Eken, 1997).

1.1.5. Measurement of spasticity

It is evident that spasticity is not a single entity, but has various manifestations with poorly understood underlying mechanisms. This explains why defining spasticity has been and still remains a challenge for many. While some may argue that defining spasticity may be of academic interest only, a meaningful measurement of spasticity is of great importance in clinical practice. Measurement of spasticity has proved equally difficult which is not surprising as the lack of a precise definition precludes any attempt of meaningful measurement.

There is a myriad of measures for spasticity that have been reported in the literature, reflecting the problematic nature of spasticity measurement (Burridge et al., 2005; Platz, Eickhof, Nuyens, & Vuadens, 2005; Priebe, Sherwood, Thornby, Kharas, & Markowski, 1996) (table 3). Since many of the tools to measure spasticity have been developed using Lance's definition there has been a focus on the assessment of muscle tone and passive range of movement (Burridge et al., 2005). However, it has been increasingly recognised that spasticity is a multidimensional problem and a measure of a single aspect of spasticity is not appropriate (Priebe et al., 1996).

Table 3. Classification of commonly used measurement tools for spasticity

Clinical	**Biomechanical**	**Electrophysiological**
Patient-reported measures	Goniometry assessment of range of motion	Electromyography
Visual Analogue Scale	Wartenburg pendulum test	H reflex
Numerical Rating Scale		T reflex
Penn Spasm Frequency Scale		H max/M max ratio
Spinal Cord Injury-Spasticity Evaluation Tool		
Patient-Reported Impact of Spasticity Measure		
Multiple Sclerosis Spasticity Scale - 88		
Self-Reported Scale for spasticity		
Clinician-administered measures		
Ashworth and Modified Ashworth Scales		
Tardieu Scale		
National Institute of Neurological Disorders and Stroke reflex scale		
Spinal Cord Assessment Tool		
Clonus Score		

Despite the variability in the methods for measuring spasticity, they can be generally grouped into three categories: clinical, biomechanical and electrophysiological (table 3). While clinical measures have high utility and are widely used in the clinical setting, the latter two require complicated equipment, hence their use is usually restricted to research purposes. It is beyond the scope of this chapter to review all of the methods for measuring spasticity, instead a brief overview of commonly used methods within each group is presented below.

1.1.5.1. Clinical methods

Clinical measures are the most commonly used methods in the assessment of

spasticity. They can be divided into clinician-rated and patient-rated. Research on functional movement in recent years has indicated that clinical signs of spasticity have little correlation with the functional aspects of spasticity (Dietz & Sinkjaer, 2007). For example, it has been shown that exaggerated tendon reflexes have little effect on active movement in patients with spasticity (Dietz & Sinkjaer, 2007). It is important to consider active function when assessing spasticity, since purely clinical signs and muscle resistance to passive stretch can be misleading when deciding on antispasticity therapy. For instance, without development of spastic muscle some patients with stroke would not be able to walk (Dietz & Sinkjaer, 2007).

It has been increasingly recognised that clinician-administered measures for spasticity are often inadequate and inappropriate. For example, the Ashworth scale, despite being the most widely used measure for spasticity, has been recently questioned due to concerns over its validity, reliability and responsiveness (Fleuren et al., 2010; Pandyan et al., 1999; Pandyan, Price, Barnes, & Johnson, 2003; Platz et al., 2005). Moreover, studies have shown that findings on examination performed by a clinician do not always correlate with the severity and even location of spasticity reported by the patients (Lechner, Frotzler, & Eser, 2006; Priebe et al., 1996; Skold, Levi, & Seiger, 1999). Because the Ashworth scale only measures muscle resistance to passive stretch, it has been suggested that it does not measure other aspects of spasticity that are important to a patient (Burridge et al., 2005; Lechner et al., 2006; Platz et al., 2005; Priebe et al., 1996). For example, it is not possible to assess spasticity-related spasms, pain or interference with active function using the Ashworth scale alone.

It has been argued that spasticity is a complex and multidimensional problem and only the person experiencing spasticity can reliably judge its severity (Kirshblum, 1999; Priebe et al., 1996; Skold, 2000). As a result, recently there has been a growing interest in developing tools that measure spasticity from the patient's perspective across a variety of neurological conditions, so as to help clinicians understand and adequately treat spasticity-related symptoms. The use of patient-reported measures for spasticity is also becoming a standard practice in randomised controlled trials evaluating anti-

spasticity therapies, as shown by several recent studies (Adams & Hicks, 2011; Boviatsis, Kouyialis, Korfias, & Sakas, 2005; Schyns, Paul, Finlay, Ferguson, & Noble, 2009). Despite the considerable number of studies investigating self-reported measures of spasticity, little agreement exists on their place in current clinical practice and research. Numerous systematic reviews have evaluated various tools for spasticity assessment including biomechanical, electrophysiological and clinician assessed, however patient-reported measures for spasticity have received little attention (Burridge et al., 2005; Hinderer & Gupta, 1996; Hsieh, Wolfe, Miller, & Curt, 2008; Platz et al., 2005)

A systematic literature review identified seven self-reported spasticity scales. The scales can be grouped into those measuring severity of spasticity: Visual Analogue Scale (VAS)/ Numerical Rating Scale (NRS) and Penn Spasm Frequency Scale (PSFS); those measuring impact of spasticity: Spinal Cord Injury-Spasticity Evaluation Tool (SCI-SET), Performance Scales Spasticity (PSS), Patient-Reported Impact of Spasticity Measure (PRISM) and Self-Reported Scale for Spasticity (SRSS); or both: Multiple Sclerosis Spasticity Scale - 88 (MSSS-88). In the paragraphs below, a description of the scales and their psychometric properties such as utility, validity and reliability are discussed.

1.1.5.1.1. Patient-reported measures for spasticity

1.1.5.1.1.1. Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS)

Even though the Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS) have been introduced to grade spasticity fairly recently (Farrar, Troxel, Stott, Duncombe, & Jensen, 2008; Lechner et al., 2006; Skold et al., 1999), they have been widely used in the studies on pain, patient satisfaction and quality of life (Farrar, Berlin, & Strom, 2003; Farrar, Young, LaMoreaux, Werth, & Poole, 2001). VAS is a simple way of assessing spasticity by asking the patient to rate the degree of spasticity on a 100mm graphical scale which is normally graded from 0 (no spasticity) to 100 (worst possible spasticity) in reference to a certain time frame (present, previous hour, 24 hours etc.) or activity i.e. post-intervention. NRS is slightly different in the sense that it is an 11-point numerical response scale (range 0-10).

Several studies have shown that VAS/NRS has robust psychometric properties

(Anwar & Barnes, 2009; Farrar et al., 2008; Skold et al., 1999). Evidence on test-retest reliability and construct validity of NRS was presented in a study by Anwar et al. (n=35) (Anwar & Barnes, 2009). NRS was found to have little variability between two sequential visits and correlated moderately with the Ashworth scale (r=0.46) and to a lesser but significant degree with Tardieu scale (r=0.4).

VAS and NRS have also been shown to have high responsiveness (Farrar et al., 2008; Skold et al., 1999). Skold et al. in a study on SCI patients demonstrated that VAS was more likely to detect a change after intervention compared to clinical assessment using the Ashworth scales (Skold et al., 1999). Similarly, Farrah et al. in a post hoc analysis of a randomised controlled trial on MS patients found that NRS had higher responsiveness than the Ashworth scale and PSFS (Farrar et al., 2008). The authors anchored NRS scores on patients' global impression of change (PGIC) and defined clinically important difference (CID) and minimal clinically important difference (MCID) for NRS spasticity as 29.5% and 18% respectively.

VAS/NRS has high clinical utility due to its simplicity and ease of administration. Validation of VAS/NRS across different neurological conditions could provide a simple and convenient comparison measure. It is noteworthy that VAS/NRS intends to measure the severity of spasticity, however it cannot differentiate between the underlying disease mechanisms. This is important since biomechanical changes in the muscle can mimic neurogenic spasticity, but these would not respond to antispasticity therapies. Unfortunately, this is a common flaw of most clinical measures for spasticity. In addition, other symptoms such as pain occurring simultaneously with spasticity might influence the VAS score thus confounding the result (Farrar et al., 2008). However, spasticity related pain is often the most troubling symptom reported by patients, therefore measuring sensory symptoms associated with spasticity might be considered equally important (Lechner et al., 2006; Skold et al., 1999).

1.1.5.1.1.2. Penn Spasm Frequency Scale (PSFS)

PSFS is a five point scale which is used by the patient to rate frequency of spasms. 0 represents 'no spasms' and 4 represents 'spontaneous spasms occurring

more than ten times per hour' (Penn et al., 1989). The scale was later modified by Priebe et al. who added a second component to assess severity of spasms and interference with function (Priebe et al., 1996). The second component is completed only if a respondent affirms the first part. PSFS measure is simple, quick and easy to complete for a patient and does not require specialised equipment.

Although it was initially developed for patients with spinal spasticity resulting from MS or SCI, PSFS has also been used in studies on stroke and traumatic brain injury (Meythaler, Guin-Renfroe, Brunner, & Hadley, 2001). Despite this widespread use little is known about the psychometric properties of PSFS (Hsieh et al., 2008). Two studies that evaluated the correlation between PSFS and clinical methods (patellar tap, ankle clonus, Achilles reflex) and the Ashworth scale showed poor to moderate correlation (Lechner et al., 2006; Priebe et al., 1996). Consequently, Priebe et al. questioned whether PSFS is a poor tool that inadequately measures spasticity or whether the Ashworth scale does not represent the elements of spasticity that are important to a patient (Priebe et al., 1996). A similar study by Lechner et al. (n=47) investigated the validity of PSFS and found that if a patient is asked to rate their spasticity at 'present', PSFS scores correlate with the Ashworth scale much more strongly than the scores of 'general' spasticity reported by a patient (Lechner et al., 2006). The authors suggested that the PSFS and clinical examination represent different dimensions of spasticity and that severity of general spasticity cannot be adequately assessed with clinician administered methods alone. Moreover, spasticity fluctuates greatly over time and a single clinical measure can only produce a point-in-time estimate of its severity (Skold, 2000).

Lastly, Benz et al. in a study on Spinal Cord Assessment Tool (SCAT) compared PSFS and SCAT scores showing that only presence of clonus strongly correlated with self-reported spasms, while flexor and extensor spasms did not, indicating that clonus might play an important role in a patient's perception of severity of the spasms (Benz, Hornby, Bode, Scheidt, & Schmit, 2005).

Despite its prevalent use in clinical practice, no studies have established its reliability. In addition, PSFS has been shown to be less responsive than NRS by Farrah et al. (Farrar et al., 2008). As discussed above, in terms of content validity, PSFS only

measures one aspect of spasticity, thus it should not be used as a sole measurement of spasticity. Moreover, it is crucial to specify the timeframe since spasms vary throughout the day and change in frequency and intensity in response to activities. Although Priebe et al. reported the preliminary use of interference with function subscale, no further validation has been found in the literature (Priebe et al., 1996).

1.1.5.1.1.3. Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET)

The complex effects of spasticity on the function may not be captured by scales measuring severity of spasticity such as VAS or frequency of spasms (PSFS) (Hsieh et al., 2008; Skold et al., 1999). As a result, Adams et al. developed a Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET), a 35-item, 7-day recall questionnaire which aims to assess the impact of spasticity in patients with chronic SCI (Adams, Ginis, & Hicks, 2007). The tool covers various aspects of daily life that may be affected by spasticity ranging from mobility to social functioning. Since spasticity may also have positive effects on mobility and posture, the authors employed a bidirectional response scale (-3 – extremely problematic, +3-extremely helpful) (Mahoney et al., 2007). This feature of the tool allows the identification of aspects of spasticity that are positive and negative. The SCI-SET was shown to have excellent internal consistency (alpha=0.9), test-retest reliability (ICC=0.91) and construct validity as measured by self-reported severity, self-reported spasticity impact and PSFS.

Three interventional studies were performed that administered the SCI-SET as an outcome measure of spasticity, however only one study by Kumru et al. showed significant improvement in scores on SCI-SET after repetitive transcranial magnetic stimulation in patients with SCI (Adams & Hicks, 2011; Boutilier, Sawatzky, Grant, Wiefelspuett, & Finlayson, 2012; Kumru et al., 2010).The designers of the SCI-SET reported that a 7-day recall period might lead to inability of the tool to capture short term effects of an intervention, thus responsiveness still remains to be elucidated. Another limitation of the tool is that some patients might attribute difficulty to perform certain tasks to unrelated physical impairment, and not necessarily spasticity.

1.1.5.1.1.4. Patient-Reported Impact of Spasticity Measure (PRISM)

Another tool that measures the impact of spasticity was developed by Cook et al. in war veterans with SCI (Cook et al., 2007). It is a multidimensional construct containing 41-items that represent seven subscales which include: 'Social Avoidance/Anxiety, Psychological Agitation, Daily Activities, Need for Assistance/Positioning, Need for Intervention, and Social Embarrassment'. To take into account varied effects of spasticity on patient's life the PRISM scale also includes one item which refers to how much positively or negatively patients feel they are affected by spasticity.

The tool demonstrates good reliability in terms of internal consistency (Cronbach's α =0.74. to 0.96) and reproducibility (intra-class correlation co-efficient = 0.82 to 0.91). Construct validity has only been partially validated by comparing PRISM scores with self-reports of severity of the spasms and interference with function. It is noteworthy, that only 'daily activities' and 'need for intervention' subscales of PRISM significantly correlated with PSFS interference with function scale. To date no studies compared PRISM with clinical methods since authors argued that the scale measures the impact of spasticity rather than the symptom itself. Westerkam et al. showed significant negative correlations of 3 PRISM subscales (daily activities, positive impact and need for assistance/positioning) with Life Situation Questionnaire-Revised (Westerkam, Saunders, & Krause, 2011). Since PRISM was developed in a highly specific population of war veterans, applicability in a different population affected by SCI is uncertain.

1.1.5.1.1.5. Multiple Sclerosis Spasticity Scale – 88 (MSSS-88)

Although studies report that spasticity affects around 85% of MS patients very few tools have been developed to target spasticity assessment in MS patients (Berger, 2013). This niche in clinical research on outcome measures in MS was filled by the development of MSSS-88 by Hobart et al. (Hobart et al., 2006). MSSS-88 is a patient-reported, interval-level outcome measure for spasticity in MS that is based on Rasch measurement principles (Hobart et al., 2006). It is an 88-item scale that covers 8 components which address symptoms and the physical and psychosocial impact of

spasticity. Each of the eight scales showed good fit statistics and high person separation index (>0.92) supporting good reliability and validity. Moderate correlations with MS Impact Scale - 29, SF-36, Functional Assessment of MS and self-report of spasticity confirmed convergent validity of the MSSS-88.

The three physical subscales were reported to have larger floor effects than other scales indicating the need to expand the content of these subscales. The major advantage of MSSS-88 over existing spasticity scales is its interval properties compared to ordinal scales like SCI-SET or PRISM. Three clinical trials employed MSSS-88 as an outcome measure in addition to clinical methods (Mori et al., 2011; Schyns et al., 2009; Sosnoff, Motl, Snook, & Wynn, 2009). Two out of three trials demonstrated better responsiveness of the scale compared to Ashworth. Schyns et al. found that vibration therapy resulted in reduced scores on the spasm subscale on MSSS-88 with no change in the Ashworth scale (Schyns et al., 2009). Similarly, significant reductions on MSSS-88 walking and pain/discomfort subscales were noted in response to 4-week unloaded exercise, while there was no improvement on the Ashworth scale (Sosnoff et al., 2009).

1.1.5.1.1.6. Performance Scales Spasticity subscale

Performance scales have been developed and used by the North American Research Committee for Multiple sclerosis (NARCOMS) to assess disability in MS based on patient self-reports (Marrie & Goldman, 2007; Schwartz, Vollmer, & Lee, 1999). The scale covers eight domains, one of which is spasticity. The subscale for spasticity is a single item 6-point response scale that measures the impact of spasticity on the daily activities: 0='normal' (no symptoms of spasticity), 5='total' (everyday, spasticity problems prevent me from doing many of my daily activities). Schwartz et al. reported high test-retest reliability for the spasticity subscale (0.76) and internal consistency for overall PS (alpha=0.89) (Schwartz, Bode, & Vollmer, 2012). Convergent validity has only been partially validated by Marie et al. against Timed 25 Foot Walk (0.78) (Marrie & Goldman, 2007). Additional evidence of validity of the scale was obtained in a study by Rizzo et al. where the scale was shown to closely correlate with SF-36, Patient-Determined Disease Steps (PDDS) and the remaining Performance scales (Rizzo,

Hadjimichael, Preiningerova, & Vollmer, 2004). In the same study patients receiving intrathecal baclofen reported less spasticity compared to oral antispasticity drugs.

1.1.5.1.1.7. Self-Report Spasticity Scale (SRSS)

SRSS was recently developed by Barker et al. in stroke patients to assess the severity of spasticity (Barker, Horton, Kent, & Tennant, 2013). The authors aimed to develop a tool that is simple, quick and acceptable to use in everyday clinical practice and community follow-up. SRSS consists of 8 items representing 6 domains of spasticity: pain, spasms, fatigue, restricted movement, loss of balance and altered appearance. The scale was subjected to Rasch analysis which showed absence of multidimensionality, good fit to the model and high reliability (r=0.701). Circumferential evidence on the convergent validity was achieved from comparisons with Barthel Index (r=-0.652) and London Handicap Scale (r=-0.658), however no other tools for assessing spasticity were employed. Currently, SFSS has been validated only in stroke patients and more research is needed to determine whether the scale could be adopted in other conditions. There is some concern whether the scale measures spasticity or other phenomena such as paresis or arthritis. If further research proves it is a valid tool for spasticity, SRSS can be widely used as a quick and easy-to-administer tool in clinical practice.

1.1.5.1.2. Clinician-administered measures for spasticity

1.1.5.1.2.1. Tonic Spasticity

The Ashworth Scale (AS) is the most widely used measure for spasticity and was originally developed as an outcome measure for antispasticity treatment in multiple sclerosis (Ashworth, 1964). The AS measures muscle resistance to passive stretch on a 5-point scale (0-no increase in tone, 4-a limb is rigid in flexion or extension). The Modified Ashworth Scale (MAS) was designed by Bohanon and Smith to increase sensitivity to change by adding 1+ as most of the patients were rated at the lower end (Bohannon & Smith, 1987).

Despite being the most commonly used measure for spasticity, the AS has many flaws. As far as face validity is concerned, the AS measures muscle tone to passive

stretch, which is only one aspect of the current spasticity definition. Indeed, Skold et al. found that only 60% of patients reporting spasticity are detected to have spasticity based on clinical methods alone (Skold et al., 1999). This is not surprising since the AS measures spasticity only in the flexors and extensors of the limbs and the rest of the body areas such as thorax, neck and jaw are not examined (Lechner et al., 2006; Skold, 2000). Furthermore, Burridge et al. on behalf of the SPASM group argued that AS should not be considered as a valid and gold standard tool since AS measures spasticity during passive motion, while in fact problems during active motion are more relevant to the patient (Burridge et al., 2005). The Ashworth Scale correlates poorly with other clinical manifestations of spasticity such as hypereflexia and clonus, which begs the question whether the Ashworth scale can measure the reflexogenic nature of spasticity (Platz et al., 2005). Lastly, a number of studies reported low inter-rater and intra-rater reliability, hence discouraging its use in assessment of spasticity (Fleuren et al., 2010; Pandyan et al., 1999). Despite the flaws of AS, the tool has high clinical utility, as it is quick and easy to administer and does not require specialised equipment.

Another method to assess muscle tone is by using the Tardieu Scale (TS). The TS differs from the AS since the examiner applies three different velocities of passive stretch (Tardieu, Shentoub, & Delarue, 1954). The quality of the muscle reaction at specified velocities and the angle at which the muscle reaction occurs was shown to differentiate between neurogenic and biomechanical muscle resistance (Patrick & Ada, 2006). Due to the scarcity of research on TS, a review by Haugh et al. concluded that validity and reliability of the scale has not been determined so far (Haugh, Pandyan, & Johnson, 2006).

1.1.5.1.2.2. Phasic spasticity

Several grading systems have been proposed to quantify reflex responses. The National Institute of Neurological Disorders and Stroke (NINDS) myotatic reflex scale, which uses a grading system ranging from 0-absent reflex to 4-enhanced reflex plus clonus has been shown to have moderate to substantial inter-rater reliability (Litvan et al., 1996). The Spinal Cord Assessment Tool (SCAT), developed by Benz et al. in spinal

cord patients, assesses reflexes, clonus and flexor and extensor spasms (Benz et al., 2005). It was shown to have good concurrent reliability when compared to EMG, however no studies have evaluated the reliability so far (Platz et al., 2005).

1.1.5.2. Biomechanical and Electrophysiological methods

Alternatives to subjective clinical measurements of spasticity are objective laboratory methods, namely biomechanical and electrophysiological. Although they may provide important information for research purposes, these methods are costly, time consuming and require specialised equipment and training (Burridge et al., 2005). In addition, these measures have been shown to correlate poorly with clinical methods such as PSFS and VAS (Voerman et al., 2009; Voerman, Gregoric, & Hermens, 2005).

Biomechanical methods offer an objective way of quantifying velocity-dependent muscle resistance to passive stretch by use of dynamometer or pendulum tests (Biering-Sorensen, Nielsen, & Klinge, 2006). Both methods require electro-goniometers or computerised software, which hinders their widespread use. The advantage of biomechanical methods is that they can distinguish between neurogenic and visco-elastic causes of spasticity and objectively assess the degree of resistance, which eliminates measurer's bias (Biering-Sorensen et al., 2006).

Electromyography (EMG) has been used either in conjunction with biomechanical methods or alone in the assessment of spasticity (Biering-Sorensen et al., 2006). It is noteworthy that spasticity assessment with EMG has to be undertaken with some stimulation, either electrical (H-reflex) or mechanical (tendon tap (T-reflex)). Spontaneous EMG activity is only seen during muscle spasm (Biering-Sorensen et al., 2006). Hyper-excitability of the stretch reflex in spasticity is characterised by an increase in the H max/ M max ratio, because of exaggerated response of the H reflex and the absence of inhibition associated with relaxation (Decq et al., 2004). EMG has been an invaluable tool in studying the pathophysiology of spasticity, however its use as a measurement for spasticity has some important limitations (Voerman et al., 2005). Firstly, the size of responses heavily depends on muscle mass, subcutaneous fat and skin resistance, hence it is not possible to reliably compare the readings across patients

(Biering-Sorensen et al., 2006). Secondly, EMG responses such as H-reflex or T-reflex vary greatly across healthy individuals. Lastly, no correlation has been observed between MAS and EMG in patients with spasticity, however this could also be due to the flaws of clinical measurement (Voerman et al., 2009; Voerman et al., 2005)

1.1.6. Conclusions

The literature on the definition of spasticity and its measurement remains conflicting. Inconsistent and sometimes completely opposite findings and views among researchers and clinicians highlight the ongoing interest in this subject and this is unlikely to end in the near future. In the words of Stokic, editor of Clinical Neurophysiology: 'the truth [about spasticity] is still in the eye of the beholder' (Stokic, 2010).

Whatever the underlying pathophysiology of spasticity might be, it is a serious complication of UMN damage that carries a significant burden for patients and their carers. Spasticity is a recognised impairment in a number of adult conditions which affect the central nervous system including stroke, multiple sclerosis, spinal cord injury, motor neurone disease and traumatic brain injury. Spasticity is a particularly common and troublesome impairment in patients with multiple sclerosis (MS), affecting up to 84% of patients (Rizzo et al., 2004). In the next section, a general overview of MS is presented with a particular emphasis on MS-related spasticity.

1.2. Multiple Sclerosis

1.2.1. Overview

Multiple Sclerosis (MS) is a neurodegenerative disease characterised by chronic inflammation, demyelination and degeneration of the central nervous system (Olek, 2002). At the initial stage of the disease neuroinflammation is transient producing paroxysmal attacks followed by remyelination and recovery, hence the relapsing-remitting nature of MS (Compston & Coles, 2008). However, in the majority of patients remyelination is not durable and progressive fibrosis and degeneration of the central nervous system occurs (Weinshenker et al., 1989). In the last couple of decades, there has been a rapid increase in the development of disease-modifying therapies (DMTs) with a view to control the course of the disease. Although the DMTs have been shown to be effective in reducing relapses, their effectiveness in preventing disability and delaying transition to secondary progressive disease is limited (Derwenskus, 2011; Goodin et al., 2002). As the disease progresses neurological impairments and disability become increasingly common, affecting patient functioning, ability to perform activities of daily living (ADL) and quality of life (QOL) (Zwibel, 2009). Consequently, in order to minimise the impact of MS on QOL a regular comprehensive assessment and management of consequences of the disease remains central to the care of MS patients.

1.2.2. Historical perspective

The first descriptions of a demyelinating disorder were documented by the famous French neurologist Jean Martin Charcot in 1868 (Charcot, 1868a). He described the correlation between clinical and pathological features of the illness in patients with intermittent neurological symptoms. At histological examination he noted the presence of plaques, axonal demyelination and inflammatory cell infiltration and suggested the term '*sclérose en plaques disseminée," (Charcot, 1868b).* Since then, a number of discoveries have been made which greatly contributed to better understanding of the pathophysiology of MS. The utilisation of experimental autoimmune encephalomyelitis has led to the widely accepted notion of an autoimmune basis of MS (Rivers, Sprunt, & Berry, 1933). This was later supported by Elvin Kabat, who discovered oligonoclonal bands (Kabat, Glusman, & Knaub, 1948). Following this, findings from twin studies and

viral infections associated with development of MS led to the hypothesis that MS occurs in genetically susceptible individuals after exposure to an environmental agent (Kurtzke, 1993; Levin et al., 2003; Myrianthopoulos & Mackay, 1960). Lastly, in more recent years advancements in biotechnology and neuroimaging have led to the discovery of a number of disease modifying therapies and successful application of MRI in the diagnosis and management of MS.

1.2.3. Epidemiology and aetiological factors

MS is the most common demyelinating disease of the central nervous system affecting 126 669 people (203 in 100000) in the United Kingdom (Mackenzie, Morant, Bloomfield, MacDonald, & O'Riordan, 2014). The peak age of onset for MS is 40 in women and 45 in men (Mackenzie et al., 2014). Relapsing remitting MS has an earlier age of onset (25-29) compared to primary progressive (35-39). Female to male ratio is 2:1, which is also characteristic of other autoimmune disorders (Olek, 2002).

Incidence and prevalence of MS varies greatly geographically. Highest prevalence is seen in countries with temperate climates such as North America, Northern Europe, New Zealand and South Eastern Australia (Kurtzke, 1993). The geographical variation may be explained by environmental factors, latitude and racial differences with white races being more commonly affected than Asian and African (Elian, Nightingale, & Dean, 1990; Marrie, 2004). MS prevalence appears to increase going south to north in the northern hemisphere, and the reverse is true for the southern hemisphere (Hammond et al., 1987; Simpson, Blizzard, Otahal, Van der Mei, & Taylor, 2011). To exemplify such a distinct trend, MS prevalence is higher in Scotland compared to England (Mackenzie et al., 2014).

A number of environmental exposures have been postulated, however no single agent has been identified to be causative so far (Marrie, 2004). Infection, vaccinations, occupational exposures, stress, smoking and sunlight have been reported to be associated, however the evidence is contradicting (Ascherio & Munger, 2007; Ebers, 2008; Marrie, 2004). Reduced sunlight exposure has the strongest supporting evidence (Ascherio & Munger, 2007). It was speculated that the geographical variation of MS may

be explained by vitamin D deficiency, which is common in countries with a temperate climate (Ascherio & Munger, 2007; Marrie, 2004). In addition, vitamin D has been shown to have antinflammatory properties (Krishnan & Feldman, 2011). Findings from migration studies also support the hypothesis of environmental agents triggering MS (Alter et al., 1962; Hammond, English, & McLeod, 2000). It has been found that migration from a low incidence area to a high incidence area before puberty leads to the individual adopting the higher risk for MS of the new area, but this seems not to be true if migration occurs after puberty (Hammond et al., 2000).

1.2.4. Pathogenesis

The aetiology of MS is unknown, however it is believed that the disease develops in genetically susceptible individuals in the presence of environmental triggers (Compston & Coles, 2008). There is a 1-5% risk of developing MS if a parent or a sibling has the disease, with 25% concordance among monozygotic twins (Robertson, Clayton, Fraser, Deans, & Compston, 1996). Genetic studies have identified HLA alleles on chromosome 6, namely DR15 and DQ6, which were shown to be associated with increased risk of MS, particularly in northern Europeans (Marrosu et al., 1992; Olerup & Hillert, 1991). The HLA genes have been suggested to play an important role in determining whether T cells recognise antigenicity towards myelin proteins (Mohme et al., 2013).

Studies on experimental encephalomyelitis have established a central role of T cells in the pathogenesis of inflammation, demyelination and plaque formation (Fletcher, Lalor, Sweeney, Tubridy, & Mills, 2010). It is known that CD4 T cells are activated by local glial and dendritic cells presenting autoantigens via MHC class II system (Fletcher et al., 2010). Subsequently, CD4 T cells transform into Th1 cells. Activated Th1 cells disrupt the myelin, release other antigens, attract nonspecific inflammatory cells and antimyelin-forming B cells by secreting various cytokines such as interferon-gamma and TNF-a (Hafler, 2004). The presence of oligoclonal bands points towards B cell involvement in the pathogenesis of MS. The reasons for CD4 T cell reactivity to antigens in the central nervous system are not known, however environmental triggers have

been suggested (Ebers, 2008; Marrie, 2004). Epstein-Barr virus has been implicated to activate CD4 T cells via molecular mimicry (Lang et al., 2002). Lang et al. identified that basic myelin protein is identical to proteins found on Epstein-Barr virus (EBV) (Lang et al., 2002). In addition, B cells found in demyelinating plaques have been shown to be EBV positive (Serafini et al., 2007).

The pathologic hallmarks of MS are demyelinating plaques within the white matter containing inflammatory infiltrates (Inglese, 2006). The recurrent attacks of inflammation eventually lead to scarring and gliosis. Repeated attempts at remyelination cause oligodendrocyte loss contributing to the progressive impairment (Hafler, 2004). Aside from demyelination, neuroaxonal damage is thought to be central in causing permanent neurological deficits (Trapp, Ransohoff, & Rudick, 1999). Various mechanisms involving inflammation, free radicals and nitric oxide have been implicated in axonal loss (Bjartmar, Wujek, & Trapp, 2003).

1.2.5. Clinical features

Depending on the location of inflammation within the CNS, presentation in MS can vary greatly. The majority of patients present with a clinically isolated syndrome (CIS) characterised by acute or subacute onset of neurological deficit lasting for a few weeks and followed by complete or near complete recovery (D. H. Miller, Chard, & Ciccarelli, 2012). The resolution of symptoms appears to be a result of decreasing inflammation and oedema, rather than remyelination, which might not occur despite the absence of symptoms (Achiron & Barak, 2000). McAlpine reported that the most common presenting symptoms were limb weakness (40%), optic neuritis (22%), paraesthesia (21%), diplopia (12%), vertigo (5%) and disturbance of bladder control (5%) (McAlpine, 1972). Very few symptoms are specific to MS, which include Lhermitte's symptom (an electrical feeling running down the spine triggered by neck flexion) and Uthoff's phenomena (temporary worsening of the symptoms with an increase of core body temperature). As the disease advances, symptoms of fatigue, depression, spasticity and cognitive dysfunction predominate the clinical picture and substantially contribute to MS-related disability (Zwibel, 2009).

1.2.6. Diagnosis

Due to the variable nature of presentation, diagnosis of MS can be challenging. To aid this the McDonald diagnostic criteria for MS have been developed, with the most recent corrections made in 2010 (Polman et al., 2011) (table 4). According to the McDonald criteria the diagnosis requires objective evidence of lesions disseminated in time and space, i.e. more than one clinical attack with more than one area of CNS affected. In the majority of cases diagnosis can be made on clinical grounds alone, however when diagnosis is ambiguous MRI imaging may help to identify the lesions in space and time. MS-characteristic lesions include periventricular, juxtacortical, infratentorial and within the spinal cord on T2 MRI scan which may or may not be gadolinium-enhancing. Occurrence of new lesions on T2 sequence at any point in time during follow-up constitutes dissemination in time. Supportive investigations include CSF for oligonoclonal bands and visual evoked potentials, usually performed in the less common cases of insidious neurological progression. MRI identifies abnormality in the brain or spinal cord in over 95% of patients with MS, however presence of MRI lesions alone (radiologically isolated syndrome) should not lead to a diagnosis of MS, as non-specific changes in the brain are common, particularly in patients over 50.

Table 4**.** The 2010 McDonald criteria for diagnosis of MS (Polman et al., 2011)

Clinical presentation	**Additional data needed for MS diagnosis**
≥2 attacks; objective clinical evidence of ≥2 lesions or 1 lesion with reasonable history of a prior attack	none
≥2 attacks; objective clinical evidence of 1 lesion	Dissemination in space: -≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or await for another clinical attack implicating a different CNS location
1 attack; objective clinical evidence of ≥2 lesions	Dissemination in time: simultaneous presence of asymptomatic gadolinium enhancing and non-enhancing lesions; or a new T2 and/or gadolinium enhancing lesion at any point of follow up; or await for a second clinical attack
1 attack; objective clinical evidence of 1 (clinically isolated syndrome)	Requires evidence on dissemination in both space and time(as above)
Insidious neurological progression (suggestive of PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following: 1. ≥1 T2 lesions in MS-typical regions of CNS 2. ≥2 lesions in the spinal cord 3. Positive CSF (oligonoclonal bands and/or elevated IgG index)

1.2.7. Clinical Course

No biochemical or radiological markers have been identified so far to classify different types of MS, hence clinical course remains the only way of defining the disease type. There are four main distinct stages of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). The likelihood of having a second attack after CIS, hence diagnosis of MS, increases substantially in the presence of MRI lesions at the first

presentation (D. H. Miller et al., 2012). Estimated risk of MS if MRI is abnormal is as high as 80%, while only less than 20% of patients with normal MRI will develop MS. Other factors associated with a decreased risk of developing MS are optic neuritis, sensory symptoms and negative oligonoclonal bands (D. H. Miller et al., 2012). Of those who develop MS, 85% experience relapsing-remitting disease with recurrent attacks of neurological deficits followed by complete or near complete recovery over the course of a few weeks. A relapse by definition is a neurological deterioration or a new symptom occurrence lasting for more than 24 hours and is preceded by a relapse free period of 30 days in the absence of fever or other systemic disease, which would otherwise unmask subclinical features of MS (Inglese, 2006). Although the relapses occur erratically, they usually do not exceed 1.5 occurrences per year (Inusah et al., 2010) . However, after 25 years of disease activity the majority of patients eventually convert to SPMS, which is characterised by incomplete recovery and progressive, accumulative neurological impairment (Confavreux, Vukusic, Moreau, & Adeleine, 2000).

A substantial minority (approximately 15%) of patients present with primary progressive MS, characterised by progressive insidious neurological impairment with predominant spinal involvement (Thompson et al., 1997). It often presents a diagnostic challenge to the clinicians and requires extensive investigations including neuroimaging and CSF laboratory studies. PPMS is associated with later age of onset, equal male to female ration, lower lesion load and fewer gadolinium-enhancing lesions (D. H. Miller & Leary, 2007). Since PPMS is thought to be driven by neurodegenerative processes, rather than inflammatory, patients with PPMS typically do not respond to disease modifying drugs and rapidly progress to high levels of disability (D. H. Miller & Leary, 2007). In less than 5%, patients present with features of primary progressive MS with superimposed relapses, a type known as progressive-relapsing MS (Tullman, Oshinsky, Lublin, & Cutter, 2004).

Other less common types are benign and malignant MS. The use of term ‘benign MS’ has been somewhat controversial and misleading. It is defined as minimal or no disability, equivalent of EDSS ≤ 3, 10 years after disease onset (Glad, Nyland, & Myhr, 2006). However, it is has been increasingly recognised that patients with a benign form

of MS, although not physically disabled, often suffer from fatigue, depression and cognitive impairment, which can negatively affect QOL and employment status (Glad, Aarseth, Nyland, Riise, & Myhr, 2010). Rarely, MS may follow a malignant course causing severe disability in multiple neurological systems or death within a short period of time (Lublin & Reingold, 1996).

1.2.8. Prognosis

The course of MS is variable. Although MS is rarely fatal, as the disease progresses it is almost invariably associated with increased levels of disability and reduced quality of life (Wynia, van Wijlen, Middel, Reijneveld, & Meilof, 2012). Fifty percent of patients will require a walking aid within 15 years of disease activity (Tremlett, Zhao, Rieckmann, & Hutchinson, 2010). Death ensues approximately after 30 years of disease and is a result of increased risk of skin, chest and bladder infections secondary to severe neurological disability (Compston & Coles, 2008). Factors associated with disease progression are: male, older age, motor symptoms, frequent relapse and incomplete remissions (Tremlett et al., 2010) .

1.2.9. Spasticity in multiple sclerosis

Data regarding prevalence and impact of MS-related spasticity is scarce. Several patient surveys estimated that spasticity affects approximately 64% -84% of the MS population (MS Society Symptom Management Survey, 1997; Rizzo et al., 2004). However, a survey exploring opinions of healthcare professionals regarding MS-related spasticity showed that neurologists believe that less than a half of their patients have spasticity (Collongues & Vermersch, 2013). The NARCOMs survey involving more than 20000 participants found that 16% of the respondents had no spasticity, 31% minimal, 19% mild (occasional), 17% moderate (frequently affects activities), 13% severe (need to modify daily activities) and 4% total (prevents daily activities) (Rizzo et al., 2004). The data from the MS Symptom Management Survey showed that muscle spasms and muscle stiffness are among the most troublesome and common symptoms together with fatigue, pain and bladder problems (MS Society Symptom Management Survey, 1997).

Spasticity may cause pain, reduce ability to walk and interfere with personal hygiene (Paisley, Beard, Hunn, & Wight, 2002; Stevenson, 2010; Thompson, Jarrett, Lockley, Marsden, & Stevenson, 2005). Indeed it is spasticity, not weakness, that has been shown to be associated with increased levels of disability in MS patients (Barnes, Kent, Semlyen, & McMullen, 2003).

Several studies investigated the costs and societal burden of MS-related spasticity (Arroyo, Vila, & Clissold, 2011; Oreja-Guevara, 2011; Svensson, Borg, & Nilsson, 2014). Svensson et al. reported results from a patient survey on costs related to MS spasticity in a Swedish population (Svensson et al., 2014). Total annual cost per patient was estimated to be 114393 Euros. Interestingly, direct medical costs accounted only for 7% of this total and direct non-medical costs related to personal assistance, housing and informal care accounted for more than 60%. In addition, health care costs in patients with severe spasticity were found to be 2.4 times higher compared to those with mild spasticity. It is noteworthy that the costs of antispasticity therapy and rehabilitation services were minimal, accounting for only 3% of direct medical costs while disease-modifying therapies were responsible for 56%. The review by Berger et al. on the current management practices of MS related spasticity indicated that more effort should be made to improve the provision of adequate antispasticity treatment (Berger, 2013).

A large cross-sectional '6E' study in Spain (n=2029) found that a significantly larger proportion of patients with MS spasticity compared to those without spasticity required carer support (16.3% vs. 4%), used rehabilitation services (10.6% vs. 40.8%) and required special MS disability subsidies (59.6% vs. 26.5%) (Oreja-Guevara, 2011). A Spanish twin study '5E' retrospectively reviewed medical records of up to 3 years of patients with MS spasticity resistant to two or more medications in order to determine the natural evolution of spasticity in this patient cohort (Arroyo et al., 2011). The study showed that patients with resistant spasticity continued to progress to more severe stages in the period of 2.1 years despite treatment with antispasticity medication. More than a third of patients were wheelchair-bound and only 18% were in employment. These data suggest that spasticity is associated with a significant health care burden,

primarily through reduced capacity to work, use of social services and reliance on informal care from family and friends.

1.2.9.1. Spasticity and its relationship with other MS impairments

There is limited evidence regarding the relationship between spasticity and other clinical features commonly associated with MS such as pain, fatigue, sleep problems, urinary dysfunction, anxiety, depression etc. Based on the data from the healthcare professionals survey regarding spasticity management in MS, neurologists felt that mobility impairment, rigidity, pain, bladder dysfunction, spasms and sleep disorders were the most disabling symptoms associated with spasticity (Collongues & Vermersch, 2013).

Similar preliminary findings were reported from the patient survey in Spain (Oreja-Guevara, 2011). Oreja – Guevara et al. in the '5E' study (n=2029) found that patients with spasticity had significantly more sleep problems (50.9% $p<0.001$) than patients without spasticity (26.1%). However authors did not indicate what measures were used to quantify sleep disturbance, nor was a definition for patients with or without spasticity provided. In the same study urinary disturbance was found to be more common in patients with spasticity (70%) compared to those without (29.2%, $p<0.05$). In a cross-sectional German study MOVE 1 (n=414) around half of the MS patients with spasticity reported symptoms of pain, bladder dysfunction and fatigue (Flachenecker, Henze, & Zettl, 2014). No symptom-specific scales were used, except for fatigue, which was assessed using Wurzburg Fatigue inventory in MS (WEIMus). However authors did not compare fatigue levels across the groups of increasing spasticity, hence limited information can be derived from this study.

The findings from the above studies suggest that there might be an association between spasticity and other factors, however studies failed to administer appropriate measures for spasticity and other neurological impairments. There is insufficient data to assume that relationships existing between spasticity and other clinical features are causal. It is possible that unrelated symptoms occur with an increasing incidence as MS progresses, and spasticity might represent a marker of the severity of the disease.

1.2.9.2. Management of spasticity

Adequate management of spasticity is fundamental in order to maximise mobility and avoid associated complications. Early treatment measures are important in preventing a self-perpetuating cycle of worsening spasticity, which affects mobility and increases pain, which in turn can amplify spasticity (Stevenson, 2010). Spasticity may lead to very serious, but preventable complications such as contractures, pressure ulcers and spinal deformities that can have a significant impact on patient's life (Kheder & Nair, 2012).

A wide variety of antispasticity therapies have been described in the literature, ranging from oral medication used in the early stages of the disease to botulinum toxin injections and surgical techniques in patients who are severely affected. However overall effectiveness of antispasticity therapies remains limited (Paisley et al., 2002). A Cochrane systematic review of oral antispasticity agents in MS concluded that clinical benefit of these agents is small and the tolerability is low (e.g. muscle weakness, drowsiness, nausea and liver toxicity) (Shakespeare, Boggild, & Young, 2003). Hence, despite a wide array of antispasticity medications available on the market, spasticity remains a challenge for many healthcare professionals.

The management of spasticity is problematic requiring close co-operation between the physicians and patients in order to achieve the best results (Thompson et al., 2005). However, this is often difficult, with evidence from large patient surveys in North America and Europe indicating low satisfaction with antispasticity treatment both from patient and healthcare professional perspectives (Flachenecker et al., 2014; Rizzo et al., 2004). In a German study (MOVE1) 41.3% of patients were not satisfied or partially dissatisfied with the treatment. In addition, patients with more severe spasticity were more likely to be dissatisfied with the treatment than patients with mild spasticity (Flachenecker et al., 2014). Equally, more than 40% healthcare professionals feel dissatisfied with antispasticity interventions in MS (Collongues & Vermersch, 2013).

There is also some evidence to suggest that management practices vary greatly and are often suboptimal. In a study by Barnes et al. (n=68) the investigators evaluated the adequacy of MS spasticity management in a random sample of MS in

Newcastle Upon Tyne (Barnes et al., 2003). The study confirmed that spasticity is poorly managed as more than half of the sample had moderate to severe spasticity. In addition, the authors also reported that in more than 50% of the patients dose adjustments of oral antispasticity agents needed to be made. This is in line with findings of MOVE1 study, which reported that 61%, 37% and 16% of patients with mild, moderate and severe spasticity respectively did not receive antispasticity therapy (Flachenecker et al., 2014). In addition, a healthcare professional survey revealed that a quarter of neurologists do not regularly monitor spasticity symptoms (Collongues & Vermersch, 2013). Similar findings were obtained from the MS Society survey on spasticity management indicating that spasticity management in the UK needs improvements in order to meet patient needs (MS Society Symptom Management Survey, 1997). 56% of the patients claimed they had never seen a rehabilitation specialist and 60% had never been seen by an MS specialist nurse.

The first step in the management of spasticity is setting goals which should be agreed between a patient and management team. Goal attainment scale is commonly used to measure the success of an intervention (Kheder & Nair, 2012). Examples of spasticity management goals are the relief of discomfort, improved sitting, standing and walking, facilitated activities of daily living, reduced burden of care, improved body image and self-esteem and prevention of complications mentioned earlier (Stevenson, 2010). On the other hand, not every patient with spasticity requires aggressive treatment, especially when spasticity is not associated with functional limitations or pain and discomfort (Dietz & Sinkjaer, 2007). Spasticity can be beneficial for posture and transfers and may reduce leg dependent oedema and risk of deep vein thrombosis (Haselkorn et al., 2005). The following paragraphs describe the management options of spasticity.

1.2.9.2.1. Identification of triggers

A number of triggers for spasticity have been reported by patients (Phadke, Balasubramanian, Ismail, & Boulias, 2013). Common factors exacerbating spasticity include: urinary infection, pain, pressure ulcers, infection, ingrown toenail, constipation

and urinary calculi. Patient and carer education about how to recognise and report these aggravating factors is an important part of spasticity management (Kheder & Nair, 2012).

1.2.9.2.2. Non-pharmacological interventions

Rehabilitation is the backbone of spasticity management and should always be employed alongside other therapies (Kesselring & Beer, 2005). However, a recent Cochrane review reported that there is limited evidence on efficacy of non-pharmacological interventions to treat MS-related spasticity (Amatya, Khan, La Mantia, Demetrios, & Wade, 2013). Passive muscle stretching may help prevent and treat contractures, improve mobility and posture, however its benefit is of questionable importance (Katalinic, Harvey, & Herbert, 2011). Exercise, particularly cycling and using a treadmill, is suggested to improve overall strength and function in patients with spasticity, however its effect on directly reducing spasticity is not well established (Ada, Dorsch, & Canning, 2006). Correct posture is crucial in preventing secondary complications; standing exercises and proper positioning can prevent the occurrence of contractures, reduce spasticity, and improve bladder function, bowel function and overall well-being (Stevenson, 2010). Whole body vibration therapy, transcranial magnetic stimulation, transcutaneous electrical nerve stimulation and electromagnetic therapy have been reported but remain only experimental (Amatya et al., 2013).

1.2.9.2.3. Antispasticity agents

A variety of medications exist to treat spasticity, however their effectiveness is low and side effects are common. Several systematic reviews emphasised conceptual difficulties with measurement of spasticity, hence assessing the effectiveness of antispasticity agents remains a serious issue in clinical trials (Paisley et al., 2002; Shakespeare et al., 2003). Although there is some evidence to suggest that antispasticity agents reduce muscle tone as measured by the Ashworth Scale, their effect on physical functioning is questionable (Paisley et al., 2002).

Every effort should be made to identify the most effective drug on an individual basis (Kheder & Nair, 2012). Multiple medications should be attempted if a single agent

therapy fails. Centrally acting agents include gamma-aminobutyric acid-B (GABA-B) receptor agonists (baclofen, diazepam), a2-receptor agonists (tinazidine) and cannabinoids. Drugs acting peripherally are botulinum toxin and dantrolene. Most commonly used agents according to the Spanish patient survey '5E' are baclofen (75.5%), tizanidine (37.3%), benzodiazepines (31.9%), gabapentin (15.7%), botulinum toxin (12.7%), cannabinoids (11.3%) and others (4.4%) (Oreja-Guevara, 2011).

Baclofen is the most widely used oral antispasticity agent. It reduces motor neurone activity by stimulating GABA-B receptors. Baclofen has been shown to be effective in reducing spasticity compared to placebo, however side effects are common which include weakness, dizziness and drowsiness. Previous reviews have not found any difference between baclofen and diazepam in relieving spasticity, however diazepam was associated with a worse side effect profile (Paisley et al., 2002; Shakespeare et al., 2003).

Another class of antispasticity agents acting as GABA-B agonists are benzodiazepines. Benzodiazepines can be effective in treating spasticity, particularly if sleep problems are prominent, however its use is limited for day time symptoms due to drowsiness and sensorimotor slowing.

GABAergic agents, such as gabapentin and pregabalin, have been shown to have some effectiveness in reducing spasticity (L. J. Bradley & Kirker, 2008). Although initially developed as anti-convulsants, serendipitous observations have shown that they might reduce spasticity in MS patients. Both drugs are less effective in reducing spasticity compared to baclofen and diazepam, however they can be useful if pain and discomfort associated with spasticity are the prominent symptoms.

Tizanidine is a centrally acting a2-receptor agonist which inhibits excitatory spinal neurones and reduces muscle tone. Careful tapering of tinazidine should be performed as it can precipitate adrenergic crisis. There is strong evidence in favour of tizanidine over placebo in the short term reduction of spasticity, however its long term effects are less clear (Eyssette, Rohmer, Serratrice, Warter, & Boisson, 1988; C. Smith, Birnbaum, Carter, Greenstein, & Lublin, 1994).

There is growing evidence to support the use of cannabinoids in treating

spasticity and other symptoms of MS (Leussink et al., 2012); the mechanism of action by which cannabinoids reduce spasticity is currently unknown. A meta-analysis of three randomised controlled trials investigated the effects of nabiximols (cannabinoid agent) as an add-on therapy in patients who failed on standard oral antispasticy agents (Wade, Collin, Stott, & Duncombe, 2010). The authors concluded that nabiximols produces significant benefit compared to placebo and is well tolerated. However, the use of cannabinoids is limited due to concerns over their long term cognitive and behavioural effects.

Botulinum toxin, which blocks acetylcholine release, is particularly useful for managing focal spasticity, such as adduction spasticity of the legs (Kesselring & Beer, 2005). Injections of botulinum toxin into the selected muscle with the help of EMG or ultrasound can achieve relief of spasticity for 3-4 months. Post injection physiotherapy and splinting can maximise the effects of botulinum toxin injections.

1.2.9.2.4. Surgical therapies

Oral baclofen has very low bioavailability, hence its effects on the central nervous system are minimal. Intrathecal baclofen (ITB) bypasses this problem by delivering high doses of baclofen directly into the central nervous system without causing baclofen-associated side effects. ITB should be considered in patients who fail on two oral antispasticity agents and those with predominant lower limb spasticity (Erwin et al., 2011). A successful trial of ITB warrants pump implantation in such patients (Kheder & Nair, 2012). Regular follow up appointments are needed to refill the pump and to detect pump-related complications such a failure, infection and cerebrospinal fluid leakage.

Surgical peripheral neurectomy and chemical neurolysis using phenol injections are useful in cases where spasticity affects large, powerful muscles groups such as thigh adductors. This technique may achieve relief for many months, however spasticity may recur as a result of sprouting of new nerve endings.

A radical surgical technique which can be used to treat spasticity is selective dorsal rhizotomy. Transection of sensory nerves decreases Ib sensory gamma afferent input to the spinal cord which in turn reduces motor neurone excitation. However, the

invasive nature of dorsal rhizotomy limits its use to only few selected cases.

1.2.10. Conclusions

Multiple sclerosis is a demyelinating disorder of the CNS, which is associated with severe disability and a number of neurological symptoms. Spasticity is one of the most commonly occurring impairments in MS and has been shown to be associated with significant disease burden. Management of spasticity is difficult, since current therapies have limited effectiveness. Because of the chronic nature of the disease and the widespread impact MS can have on patients' lives, there has been a growing interest in understanding quality of life (QOL) in MS. In the following section of this chapter, an overview of the concepts and measurement of QOL is presented with the focus on QOL determinants in MS.

1.3. Quality of Life

1.3.1. Overview and Historical Perspective

Quality of life (QOL) is a relatively new concept in the health care setting, which has been extensively studied only in the last three decades. However, the roots of QOL concepts date back as far as ancient Greece. Aristotle described 'happiness' as 'a certain kind of virtuous activity of the soul, happiness was a God-given blessing, therefore a happy man lives well and does well' (Zhan, 1992).

It was not until mid-20th century before measurement of QOL was introduced into medical practice. As one of the pioneers of QOL assessment, Karnofsky devised a scale with the emphasis on physical function and performance status of the patient (Karnofsky & Burchenal, 1949). Karnofsky's Performance Status scale was an innovative measure of disease outcome compared to the conventional focus on prognosis and disease progression (Zhan, 1992). Later, Katz et al. developed an Index of Activities of Daily Living which not only assessed physical function, but also addressed the implications of physical function on everyday activities (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963). It is evident that the first attempts to measure patients' QOL were primarily focused on physical aspects of life. Over the years it was recognised that this biomedical model of QOL is far from sufficient to explain its complex underpinning concepts, and that social and mental aspects are equally important contributors to QOL (1995).

QOL is recognised to be a fundamental part of current health care across the world and is relevant to everyone at all stages of life (Bakas et al., 2012). Albrecht and Fitzpatrick have identified four uses of QOL assessment in health care (Albrecht GL, 1994). It is used (1) for planning and assessment of care for individual patients (2) as an outcome measure in clinical trials and medical research (3) for health needs assessment of populations (4) for resource allocation. Currently, the US Food and Drug Agency and European Medicines Agency strongly encourage the utilisation of QOL measures in the assessment of new therapies (Baumstarck et al., 2013b). And this trend is also observed in MS research: 118 clinical trials have reported the use of QOL measures by the end of 2012 (Baumstarck et al., 2013b). QOL research has however

been challenged with a number of issues despite its widespread use in clinical practice, health care assessment and policy making. These issues range from basic conceptual frameworks to practicalities of measurement and their clinical application (Ferrans, 2007; Ferrans et al., 2005; Rapkin & Schwartz, 2004; 1996). This section presents an overview of the basic concepts of QOL, issues in QOL measurement and its relevance to MS.

1.3.2. Definitions and concepts

QOL is a complex and multidimensional construct for which many definitions have been proposed (table 5) (Carr & Higginson, 2001). It is also not uncommon to find authors of scientific articles avoiding defining QOL; this has been illustrated by a systematic review which found that 16 out of 68 papers on QOL models failed to provide a definition (Taillefer, Dupuis, Roberge, & LeMay, 2003). The lack of a universally agreed definition presents serious methodological concerns in QOL research. At the basic level of understanding, QOL could be conceptualised as a combination of all sources of satisfaction (including positive anticipation) minus threats (including negative anticipation) (Mitchell, Benito-León, González, & Rivera-Navarro, 2005). The World Health Organisation defines QOL as 'The perception by individuals of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns.' (WHO, 1996). Three core prerequisites are embedded in the WHO definition: (1) assessment of QOL is subjective and individualised, (2) QOL is a multidimensional construct, (3) involves individuals' perception of both negative and positive dimensions.

Table 5**.** Definitions of QOL (Carr & Higginson, 2001)

'The extent to which hopes and ambitions are marched by experience'
'The perception by individuals of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns'
'Appraisal of one's current state against some ideal'
'The things people regard as important in their lives'

Despite increasing efforts to reach a consensus on a standard definition of QOL, a

number of other terms have been used interchangeably which adds additional confusion to the literature concerning QOL research. The most cited examples include life satisfaction, well-being, happiness, health status and living conditions (Haas, 1999). Health-related QOL (HRQOL) is a particularly commonly used term and although used interchangeably with QOL it connotes a different meaning. QOL is determined by health-related factors (physical, functional and mental well-being) and non-health-related factors (social support, environment, jobs, family, spirituality, etc.) (Ferrans et al., 2005). In contrast, HRQOL is a narrower concept viewed generally from the medical perspective (Rudick & Miller, 2008). It is concerned with aspects of QOL that are directly related or affected by the presence of disease or treatment. As Schipper suggests 'HRQOL is the functional effect of an illness and its consequent therapy upon a patient as perceived by the patient' (Schipper, Clinch, & Olweny, 1996). Despite these apparent differences, the distinction between HRQOL, health status and QOL is often blurred and the terms are used interchangeably in the literature (C. Bradley, 2001).

1.3.3. QOL domains

Although there is a belief that QOL is unidimensional, by far a greater number of advocates support the idea that QOL is a multidimensional construct, requiring assessment of multiple domains (Guyatt, Veldhuyzen Van Zanten, Feeny, & Patrick, 1989; Pagano & Gotay, 2006; Rejeski & Mihalko, 2001; Torrance, 1986). Again, as there is no consensus on the definition of QOL, it is also not clear which domains should be included in the assessment of QOL. In the early 1990s, Ferrans suggested the taxonomy of the conceptualisations of QOL and grouped it into 6 domains:(1) normal life, (2) social utility, (3) happiness/affect, (4) satisfaction with life, (5) achievement of personal goals, and (6) natural capacities (Ferrans, 1990). A number of different QOL domains such as work, civic rights, personal development have been since reported to be important aspects of QOL (Cummins, 1996; Meeberg, 1993; Shalock, 1996; Wilson & Cleary, 1995). In 1995, WHO QOL group set out to develop a cross-culturally valid QOL measure based on the data from 15 centres around the world (WHO, 1995). The group developed two measures, WHOQOL-100 and WHOQOL-BREF (26 item version), which

assess QOL across 6 dimensions: physical, environment, social relationships, psychological, spiritual, and level of independence. The WHOQOL-100 has been shown to be a valid measure across different countries and cultures in a number of conditions (WHO, 1998b). However, despite extensive collaboration of a large number of experts, WHO QOL Assessment has been criticised for having no justification of the choice of domains and omitting some of the domains such as material well-being or productivity/employment (Hagerty et al., 2001).

No single list of QOL domains is exhaustive due to the individual nature of QOL. As a result, individualised QOL models have been suggested as exemplified by the Schedule for the Evaluation of Individualised Quality of Life (SEIQOL) (McGee, O'Boyle, Hickey, O'Malley, & Joyce, 1991). The patient is asked to identify five areas of their life and rate them using visual analogue scales. In the direct weighting version, the patient also rates the relative importance of each domain in the context of overall QOL. This gives a unique insight into how the important aspects of QOL, as determined by a patient, are affected by a disease or treatment. However, the use of individualised QOL instruments has been limited due to lack of standardisation and concerns that it measures individual domains of QOL rather than overall QOL (Moons, Marquet, Budts, & De Geest, 2004).

1.3.4. Models of QOL

The multidimensional nature and varied use of terms of QOL has led to the development of a great number of conceptual models of QOL (Bakas et al., 2012). A model, also referred to as a conceptual framework, is a schematic representation of theory explaining underlying phenomena and in this case QOL is represented by depicting interrelationships among concepts. A systematic review in 2004 identified three most commonly used models of QOL in the literature: Wilson and Cleary, Ferrans and colleagues, and World Health Organization International Classification of Functioning, Disability, and Health (WHO ICF) (Bakas et al., 2012). All of the models (described below) have a similar notion in that they are based on biomedical and psychosocial grounds.

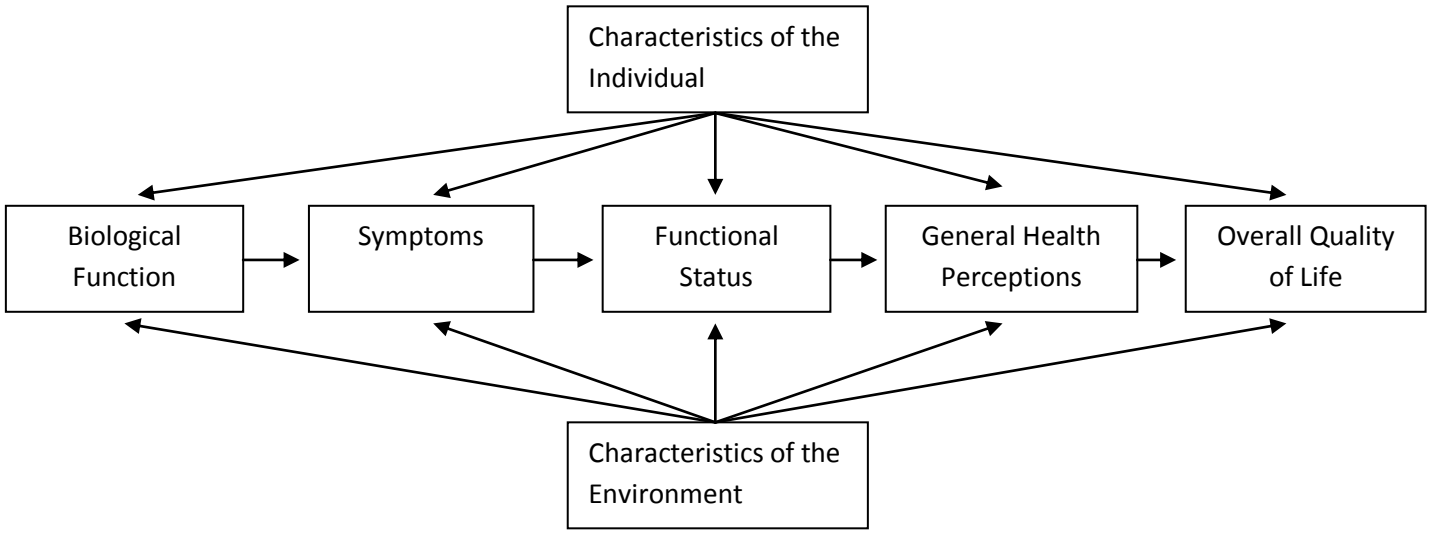
1.3.4.1. Wilson and Cleary QOL model

One of the first taxonomies of conceptualisations of QOL was proposed by Wilson and Cleary in 1995 (Wilson & Cleary, 1995). The model served as a basis for the majority of QOL models that were developed in a number of conditions. Wilson and Cleary structured the outcomes moving along the continuum of increasing complexity starting with biological parameters to symptomatology, functionality, general health perceptions and finally overall QOL. Authors suggested that each domain is related to the others and may also have reciprocal relationships. In addition, individual and environmental factors may influence the outcomes at any stage, affecting overall QOL, however authors did not define these two factors. Health status and QOL were used interchangeably in the model, which are now accepted to be conceptually distinct.

1.3.4.2. Ferrans QOL model

Wilson and Cleary's work formed the basis of the model devised by Ferrans and colleagues (Ferrans et al., 2005). The authors retained the five major domains, but simplified the model by removing the non-medical factors and the labels in arrows depicting the relationships (figure 3). Precise definitions for individual and environmental factors were suggested in the model. The authors further improved the theoretical background regarding the main concepts of the model. Ferrans et al. suggested examples of measurement tools and indicated that causal and reciprocal relationships may exist between the domains, but did not specify. In a systematic review of HRQOL models, Bakas et al. recommended the use of Ferrans and colleagues' model as a guide for researchers formulating and testing hypothesis due to its clarity, improved definitions and sound theoretical basis (Bakas et al., 2012).

Figure 1. Ferrans QOL model(Ferrans, Zerwic, Wilbur, & Larson, 2005)



1.3.4.3. World Health Organisation health/QOL model

World Health Organization International Classification of Functioning, Disability, and Health (WHO ICF) developed a universal model of health and health states for use across different cultures and disciplines (2001). The primary focus of WHO ICF is on health and related psychosocial aspects, which contrasts to an earlier WHO model proposed in 1980 focusing on impairment, disability and handicap (1980). WHO ICF conceptualised HRQOL as a person's perception of health and health-related domains of well-being, hence the model focuses on health rather than overall QOL. It was suggested that WHO ICF serves more as a classification framework of health, disease and functioning, rather than a guide for hypothesis generation in QOL research (Bakas et al., 2012).

1.3.5. QOL and response shift

Another important property of QOL is that it is a dynamic concept rather than a static phenomena (Rapkin & Schwartz, 2004); a patient's experience of a disease changes their expectations, hence their QOL changes too. The term 'response shift' has been introduced to describe the idea that the reference, by which people judge their QOL, changes as the disease progresses (Carr, Gibson, & Robinson, 2001). As a result, QOL constantly changes over time and is under the influence of a number of factors

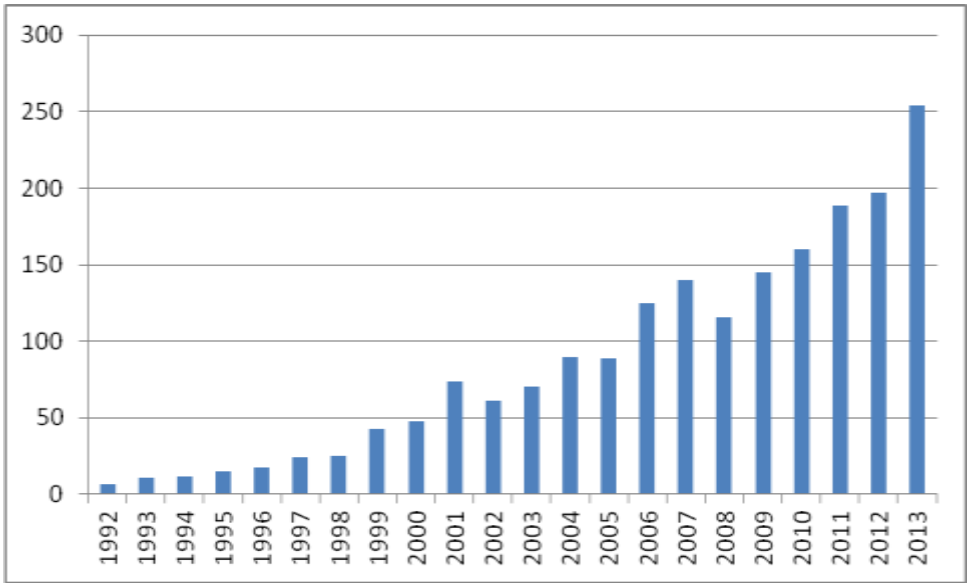
(Carr et al., 2001). For example, even in the clinical trial where QOL is measured at equal intervals, differences in patient's responses are very likely to be observed since the study participants follow individual disease trajectories (Rapkin & Schwartz, 2004). Hence QOL response shift could be understood as epiphenomenon: individual's rating of QOL can respond to treatment, disease progression and other life events in an atypical way, i.e. statistically different from the expected value hypothesised by an observer. The following driving forces of response shift are: (1) catalyst (e.g. diagnosis of disease), (2) antecedents (i.e. personal characteristics of the individual such as personality and expectations, (3) mechanisms (i.e. means of dealing with the impact of the disease, such as coping and adaptation abilities) (Burns, Graham, Rose, & Simmons, 2012). The implication of 'response shift' is particularly relevant in assessment of an intervention. The concern is that because of the 'response shift' it might be impossible to ascertain whether QOL instrument measures the attribute of interest (i.e. QOL) or the change of internal standards (Burns et al., 2012).

1.3.6. QOL in MS

QOL has been extensively studied in patients with MS (Baumstarck et al., 2013b; Benito-Leon, Morales, Rivera-Navarro, & Mitchell, 2003; D. M. Miller & Allen, 2010; Mitchell et al., 2005). Although QOL research is a relatively new field in MS with first papers appearing in the literature in the early 1990s, it has been a subject of intense scientific research ever since (Rudick, Miller, Clough, Gragg, & Farmer, 1992; Solari, 2005). This exponentially increasing interest is not without justification (figure 4). Due to the progressive and disabling nature of the disease, QOL in MS can be substantially reduced. Indeed, studies that compared QOL across a number of chronic conditions found that QOL in MS was worse than in inflammatory bowel disease, rheumatoid arthritis, psychotic disorders, epilepsy and diabetes (Chopra, Herrman, & Kennedy, 2008; Hermann et al., 1996; Rudick et al., 1992). Benito-Leon et al.'s review on QOL in MS suggested five reasons why MS patients have particularly poor QOL: (1) MS causes a myriad of disabling neurological and neuropsychiatric impairments, which can have detrimental effect on virtually all aspects of daily living (2) patients with MS

are diagnosed at a young age, thus MS impacts the most productive years and is a source of anticipation of future disability (3) MS course is unpredictable and patients lose sense of control over their lives (4) there is currently no cure for MS (5) established treatments show little success, carry risks and are often inaccessible due to health inequalities (Benito-Leon et al., 2003). In the absence of curative therapies, maximising QOL is the ultimate goal in the management of MS patients. In order to achieve this, it is important to understand what factors are influential to QOL in MS.

Figure 2. A number of publications per year on quality of life in multiple sclerosis in the Pubmed database.



1.3.6.1. Determinants of QOL in MS

Research has found that agreement is poor between patients and clinicians upon which factors influence QOL (Janse et al., 2004). Health care professionals often focus on physical aspects of patient care while patients prioritise psychological and social aspects (Rothwell, McDowell, Wong, & Dorman, 1997). This is also supported by findings in studies showing poor concordance between physical functioning and overall QOL (Ford, Gerry, Johnson, & Tennant, 2001; Rothwell et al., 1997). For example, in a study on progressive MS patients (n=29) O'Connor et al. found no correlations between overall QOL and EDSS, Multiple Sclerosis Functional Composite score and MRI lesion

load (O'Connor, Lee, Ng, Narayana, & Wolinsky, 2001). These observations have led to the belief that factors other than physical ones must heavily influence overall QOL.

1.3.6.1.1. Neuropsychiatric dysfunction and mental health

Psychiatric disturbances have consistently been found to be one of the strongest predictors of QOL in MS (Mitchell et al., 2005). In a study by O'Connor et al. mentioned above, while no correlation was found between physical measures and QOL, emotional well-being and mental health were strongly related to overall QOL scores (O'Connor et al., 2001). Depression affects around half of patients with MS and has been found to negatively influence QOL (Amato, Ponziani, Rossi, et al., 2001; Chwastiak et al., 2002; Goksel Karatepe et al., 2011; Jones et al., 2012). Mitchell et al. suggested several ways by which depression affects QOL: (1) depression diminishes motivation, interest and concordance thus retarding physical performance, (2) depression occurs when all of the coping resources have been exhausted, thus is a good marker of deeper underlying problems, (3) patients with depression have a 'distorted' view of the world, thus their appraisal of QOL might make it look worse than it actually is (Mitchell et al., 2005).

Anxiety has also been identified as a risk factor for reduced QOL (Fruehwald, Loeffler-Stastka, Eher, Saletu, & Baumhackl, 2001). High levels of anxiety and psychological distress have been found to affect up to 40% of newly diagnosed patients (Janssens, van Doorn, de Boer, van der Meche, et al., 2003). A particularly troubling aspect of anxiety are fears of disease progression and disability (Mitchell et al., 2005). Kern et al. demonstrated that sub-syndromal psychiatric disturbances such as interpersonal sensitivity, paranoid ideation and obsessive-compulsiveness are particularly common and are associated with lower QOL irrespective of disability (Kern et al., 2009). In addition, psychiatric symptoms may also influence the way patients perceive the impact of neurological dysfunction. Janssens et al. found that depression and anxiety are important mediators of the impact of disability on QOL (Janssens, van Doorn, de Boer, Kalkers, et al., 2003). The study found that EDSS scores were significantly associated with reduced mental and physical domains of SF-36, however

after adjustment for anxiety and depression disability was not found to be a significant predictor for mental health and general health scales.

Cognitive dysfunction is becoming an increasingly recognised complication of MS and has been linked to reduced QOL. The estimated prevalence of cognitive impairment in the MS population is 45-65% (Amato, Ponziani, Siracusa, & Sorbi, 2001; Rao, Leo, Bernardin, & Unverzagt, 1991). Cutajar et al. reported significant correlation between memory impairment, executive function and QOL (Cutajar et al., 2000). Benedict et al. showed that cognitive impairment is a significant predictor of QOL even after controlling for depression (Benito-Leon, Morales, & Rivera-Navarro, 2002). However, the relationship between QOL and cognitive impairment is not linear. Kenealy et al. demonstrated that patients with severe cognition dysfunction and autobiographical memory impairment have significantly better QOL than less severely affected individuals (Kenealy, Beaumont, Lintern, & Murrell, 2000). The authors suggested that the lack of insight is the most likely explanation for such observations.

1.3.6.1.2. Psychosocial factors

Factors that may be less clinically evident, such as coping and self-efficacy, have also been identified to be playing important roles in determining patient's perception of their QOL (McCabe, Stokes, & McDonald, 2009; Motl, McAuley, Snook, & Gliottoni, 2009). Self-efficacy is a concept that describes an individual's belief in their ability to overcome challenges using innate abilities. Chronic progressive disorders such as MS pose an increasing number of challenges as the disease worsens, hence maintaining high levels of self-efficacy is crucially important. Self-efficacious individuals show greater improvements on physical and mental domains of QOL in response to treatment (Motl et al., 2009). Similarly, different coping styles have been shown to be important predictors of QOL (McCabe et al., 2009). For example, wishful thinking has been shown to be a strong predictor of poor QOL (McCabe & McKern, 2002). From the clinical perspective, identifying coping strategies and subjecting patients to psychological interventions, such as group therapy, can have positive effects on overall QOL (Tesar, Baumhackl, Kopp, & Gunther, 2003).

A person's abilities to cope and maintain high levels of self-efficacy are constantly under the influence of their environment, family, friends, health professionals etc. Hence, social support is a vital mediator of many of the factors that influence QOL (Fong, Finlayson, & Peacock, 2006). Indeed, an individual may enter a self-perpetuating cycle of poor social support leading to loss of coping and self-efficacy abilities, which in turn can increase social isolation and stigma. As a result, maintaining social networks through employment, education and hobbies is an imperative aspect of good QOL in patients with MS (Mitchell et al., 2005).

1.3.6.1.3. Neurological impairments

Physical symptoms and disability have been shown to reduce QOL in MS, but are weaker predictors of QOL compared to the neuropsychiatric and psychosocial factors described in the paragraphs above (Amato, Ponziani, Rossi, et al., 2001; Janssens, van Doorn, de Boer, Kalkers, et al., 2003). The most commonly reported symptoms in a population survey (n=2265) included: fatigue (96%), balance and dizziness (92%), loss of mobility (91%), sensory problems (88%), bladder problems (87%), loss of memory and concentration (87%), spasticity (85%), vision problems (82%), pain (81%), bowel problems (74%), sexual dysfunction (70%), tremor (68%), speech and swallowing problems (68%) (Hemmett, Holmes, Barnes, & Russell, 2004). Despite the high prevalence of these symptoms and impairments, little is known about their effects on QOL. Since the majority of these symptoms coexist and are related to advancing levels of disability, it is difficult to ascertain their individual contribution in determining QOL. A common limitation of a number of studies is that only one or two impairments are accounted for in the regression analyses with QOL as a dependent factor, hence not addressing all of the possible contributors (Wynia, Middel, van Dijk, De Keyser, & Reijneveld, 2008).

A number of studies have identified fatigue to be a significant predictive factor for a wide range of QOL domains after adjusting for confounders, such as disability and depression (Zwibel, 2009). Sleep disturbance has been found to be twice as common in patients with MS compared to the general population (62% vs. 32%) and have been

shown to be an independent predictor of QOL as measured by SF-36 (Lobentanz et al., 2004). Pain is another important symptom of MS. MS-related pain can be musculoskeletal or central neuropathic in origin or may be related to spasms and trigeminal neuralgia (Khan & Pallant, 2007). Presence of pain has been linked to lower QOL, depression, sleep disturbance and work problems (Kalia & O'Connor, 2005).

Nortvedt et al. also reported that bowel, bladder and sexual dysfunction are associated with lower QOL (Nortvedt et al., 2001). Importantly, the authors emphasised that these problems are very common even at lower levels of disability (53%, n=6, EDSS<4).

Although physical symptoms and impairments are less predictive of overall QOL compared to other factors such as coping, self-efficacy and depression, they are an important part of the MS patient's life due to their high prevalence and interference with function (Zwibel, 2009). In the absence of curative treatment, symptomatic management forms the basis of care for patients with MS. Finally, both physical and psychosocial factors influence QOL and may interact with each other, hence a biopsychosocial approach in the management of patients with MS should be employed.

1.3.7. Effect of disease-modifying therapies on QOL in MS

A number of clinical trials have evaluated disease-modifying therapies (DMT) using QOL measures (Benito-Leon et al., 2003). Until recent years, QOL instruments were either not employed in clinical trials or used only as secondary outcome measures (Benito-Leon et al., 2002). This has changed with the arrival of costly new therapies. QOL measures have played an important part in proving the cost-effectiveness of DMTs, this provides essential evidence for healthcare-related agencies such as the National Institute of Health and Clinical Excellence (NICE) in approving the use of new therapies.

The results from studies investigating the effect of DMTs on QOL have been conflicting. A systematic review by Rudick et al. (2008) concluded that because of the differences in methodologies, rigor, interventions and study samples, drawing conclusions about the effect of DMTs on QOL was not possible (Rudick & Miller, 2008). Overall, the studies have reported improvement in QOL scores, however not always

with statistical significance. The strongest evidence for improving QOL in MS has been found in studies assessing the effectiveness of natalizumab. Two randomised placebo controlled trials (Natalizumab Safety and Efficacy in Relapsing-Remitting MS (AFFIRM) and Safety and Efficacy of Natalizumab in Comnination with Interferon-β-1 in Patients with Relapsing Remitting MS (SENTINEL)) showed significant improvements in physical and mental components on SF-36 irrespective of disease activity (Polman et al., 2006; Rudick et al., 2006).

Less conclusive results have been reported in studies on interferon-β and glatiramer acetate therapies. The outcomes of these studies were greatly varied reporting significant improvements, no improvement at all, and even negative effects on QOL (Rudick & Miller, 2008).

1.3.8. Measuring QOL in MS

'When you can measure what you are speaking about and express it in numbers, you know something about it – but when you cannot measure it in numbers your knowledge is of a meagre and unsatisfactory kind – it may be the beginning of knowledge but you have scarcely, in your thought, advanced to the stage of science whatever the matter may be' (Lord Kevin)

Until recently, the mainstay outcome measures in MS research and clinical practice were based on laboratory tests, imaging, neurological examination and disability scores such as EDSS. Although these measures provide important information concerning patients' disability status, disease activity and the likelihood of disease progression, limited information regarding impact of the disease on QOL can be obtain using these measures alone. For example, the EDSS is heavily weighted towards mobility and walking ability, but does not reflect many other important aspects of disease severity such as pain or vitality (Hemmett et al., 2004). Indeed, studies have shown that severity of disease is a poor predictor of QOL (Nortvedt, Riise, Myhr, & Nyland, 1999; O'Connor et al., 2001). Norveldt et al. compared SF-36 scores with EDSS and found that only physical functioning, social functioning and general health showed significant correlations, while the other QOL domains did not (Nortvedt et al., 1999). In

addition to this, QOL measures may also help predict the rate of progression to disability irrespective of EDSS scores and MRI lesion load at baseline (Nortvedt, Riise, Myhr, & Nyland, 2000). Hence, QOL measures not only provide invaluable information about the impact of MS in a way that neurological examination and disability measures do not, but they may also serve as a predictor of disease progression.

There are two general approaches to HRQOL assessment: health profiles and utility assessment (D. M. Miller & Allen, 2010). Health profiles, also known as health status measures, are multidimensional constructs, which consist of several subscales and are based on psychometric techniques. These are self-reported measures that are commonly used in clinical trials and clinical practice. Examples include SF-36 and MS Impact Scale-29 (MSIS-29). In comparison, utility measures are generic tools that are based on economic and decision theory and are reported as a summary score. EuroQol tools are examples of utility measures. They are useful in policy making and health care provision in assessing the costs and benefits of a medical intervention (Kattan, 2003). At the individual level they aid patients in making choices between treatments in light of profound costs and side effects.

As a result of the wealth of research on QOL in MS a wide range of QOL measures have been developed. Two broad types of QOL measures exist: generic and specific. Generic tools refer to QOL measures that have been designed to assess QOL in any disease. They are useful in making standardised comparisons across conditions which can provide important information for developing health policies and service provision. Disease-specific QOL measures by definition are designed for use in a specific condition. They are intended to capture more subtle disease-specific aspects of QOL, which otherwise might not be reflected in generic tools. Disease-specific tools may be more reliable than generic tools, particularly when assessing clinical interventions which target specific aspects of the disease (Baumstarck et al., 2013a; Benito-Leon et al., 2003; D. M. Miller & Allen, 2010; Rudick & Miller, 2008).

Table 6 contains the list of commonly used generic and disease-specific QOL tools in MS. By far the most widely used generic tool in the MS population is Short Form – 36 (SF-36). It is considered to be a measure of health status, rather than overall QOL

and has been validated in a number of conditions (Ware & Sherbourne, 1992). Several limitations of using SF-36 in MS have been reported, which include poor responsiveness, large floor and ceiling effects and problems with using summary scores (Hobart, Freeman, Lamping, Fitzpatrick, & Thompson, 2001). To address the weakness of the generic measures, a number of MS-specific QOL tools have been developed (table 6). One such example is MSQOL-54, which contains 18 MS-specific items added to SF-36 (Vickrey, Hays, Harooni, Myers, & Ellison, 1995). More detailed description of QOL measures in MS is given in chapter 2.

Table 6**.** Generic and MS-specific QOL instruments (Benito-Leon et al., 2003)

Generic	**MS-Specific**
Nottingham Health Profile	MSQOL-54
Sickness Impact Profile	Disability and Impact Profile
SF-36/SF-12	Functional Assessment of MS
Farmer Quality of Life Index	Hamburg QOL Questionnaire in MS
EuroQoL	Leeds MS QOL
Functional Status Questionnaire	MS Impact Scale
	QOL Index -MS version
	Performance Scales

1.3.9. Psychometric properties of QOL assessment

Validity refers to what extent a tool measures what it intends to measure. Hence, for a QOL measure to be valid it should be grounded on a sound conceptual basis and meet the robustness of the following psychometric criteria: reliability, internal and external validity and responsiveness.

Reliability or internal consistency refers to what extent the set of items from the same domain are consistent in measuring the trait. The reliability coefficient is expressed as Cronbach's alpha, which should be higher than 0.7 in order for a measure to have sufficient reliability (Reynaldo & Santos, 1999). Test-retest reliability is another

property of the measure, which refers to what extent the responses of the scores remain consistent over a period of time. This requires a collection of data at baseline and usually after 2-4 weeks in order to calculate the degree to which the scores correlate, using Spearman's rho or Pearson's correlation coefficients.

There are two properties of internal validity that should be taken into account when evaluating the validity of a measure. First, content validity is a non-statistical assessment of a measure involving critical analysis of the questionnaire contents. It addresses issues such as whether all of the themes of the domain are measured by the items and whether the items represent correct themes. Second, construct validity is a statistical analysis which examines the extent to which the theoretical framework of the questionnaire measures what it proposes to measure. Although there are many different statistical methods to investigate this, the underlying notion is the same which involves analysis of the relationships between responses to different items (Baumstarck et al., 2013a). Examples include exploratory and confirmatory factor analyses, Rasch method and computation of correlation coefficients.

The extent to which two measures show agreement is called external validity. Convergent (also concurrent) validity refers to the relationship between different domains of the measure or other previously validated measure. When the questionnaire scores are compared with established 'gold standard' measures, such as clinical parameters, it is referred to as criterion validity. However, very often in QOL research there is no established 'gold standard' measure.

Lastly, the responsiveness refers to measure's ability in detecting a change of a trait under investigation, in this case person's QOL. This is particularly important in clinical trials evaluating therapeutic efficacy. Despite the abundance of QOL measures in MS there is limited data on responsiveness of these measures (Baumstarck et al., 2013a).

1.3.10. Practical Considerations and Barriers of QOL assessments

Despite the fact that patient-reported outcome measures of QOL provide invaluable information when assessing treatment effectiveness and disease impact, a

significant proportion of clinicians are reluctant to employ QOL instruments in day-to-day practice (Solari, 2005). The barriers include: sceptical attitudes of clinicians toward QOL measurements, the lack of guidelines on interpreting clinically meaningful change and the absence of theoretical consensus regarding the definition of QOL (D. M. Miller & Allen, 2010). Practicalities of administering, processing, scoring, storing and retrieving data from QOL tools are also significant barriers to their acceptability in the already multifaceted clinical care of MS patients (Solari, 2005). While research has shown that length of the questionnaires seems not to be a burden for patients with MS, the complexities in structure of domains and scoring systems often discourage physicians from using them. Indeed, one survey on renal transplant physicians found that 55% would be willing to use QOL tools if they were more user-friendly (Lee et al., 2004).

Despite this, QOL assessment helps clinicians to detect the disease aspects that would otherwise go unrecognised, provides a means of evaluating treatment effectiveness and facilitates physician-patient co-operation, therefore it is fundamental to ensure the widespread use of QOL assessment by improving its acceptability (Bandari, Vollmer, Khatri, & Tyry, 2010; Solari, 2005). Recent developments in technology and measurement science have led to innovative ways of administering QOL tools using computerised adaptive testing (CAT) (D. M. Miller & Allen, 2010). Questions of increasing difficulty are posed to respondents based on the item-response theory. This allows assessment of QOL with a high degree of precision using a minimum number of questions, which scores are automatically computed by the software. It is predicted that such developments in patient-reported outcome measures will help to incorporate more widely QOL assessment in care of MS patients (D. M. Miller & Allen, 2010).

1.3.11. Conclusions

In conclusion, QOL research is a rapidly evolving area of health and social sciences. QOL measurement plays a vital role in the assessment of health services and clinical interventions and guides policy makers in resource allocation. Nevertheless, there are a number of challenges that QOL research is faced with. The lack of a precise

definition, differences in conceptual frameworks and disagreement on how QOL should be assessed may hinder the future progress in QOL research in MS.

Assessing QOL in patients with MS forms a fundamental part of today's clinical practice. QOL measures provide important information about the impact of disease, which might otherwise be overlooked using traditional outcome measures such as EDSS. QOL assessment is particularly important in MS as there is a considerable body of evidence to suggest that MS is associated with significant reduction across a wide range of QOL domains. Recognising that both physical and psychosocial factors may affect QOL is important in order to address these issues and improve QOL.

Spasticity is a common and disabling symptom in MS. Up to 85% of MS patients report symptoms of spasticity; management can be extremely challenging for health professionals and frustrating for patients. Although much is known about the impact of spasticity on disability and physical functioning, little literature exists on its effects on QOL despite spasticity being a more prevalent symptom compared to pain, vision, bladder, bowel and sexual problems in MS. In this chapter, the importance of QOL assessment in health care and understanding what factors influence self-perceived QOL was discussed. In the following chapter a systematic review discusses the evidence on the relationship between spasticity and QOL.

Chapter 2 - Literature Review

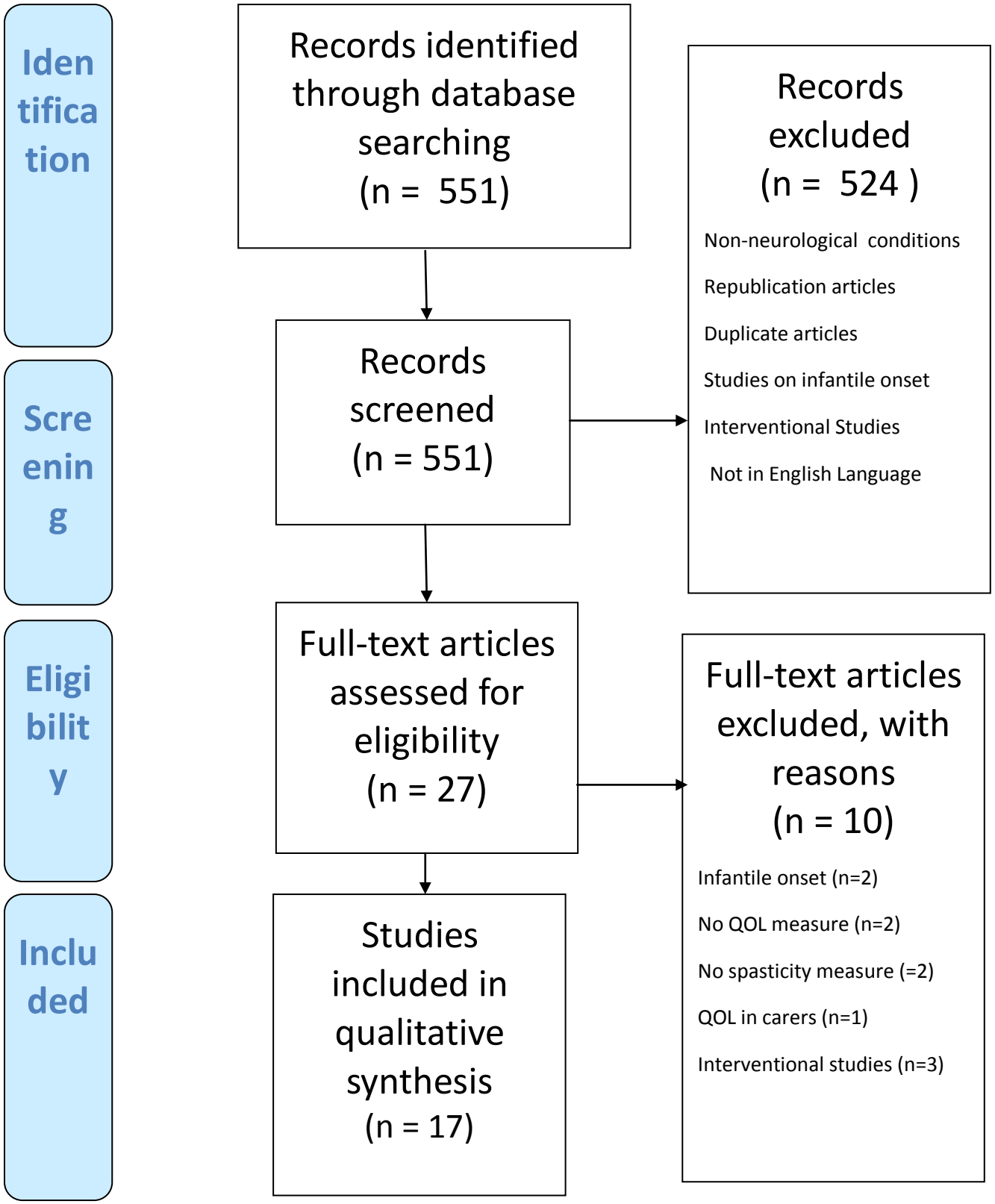
2.1. Introduction

Previous studies have emphasised that spasticity can adversely affect physical functioning in MS (discussed in Chapter 1), however few studies have investigated the effects of spasticity on QOL. The aim of this chapter is to systematically review the literature concerning the relationship between spasticity and QOL. Any adult neurological condition which may be characterised by presence of spasticity will be reviewed. Special attention will be paid to MS-related spasticity and its effects on QOL.

2.2. Methods

MEDLINE (1950 to 3 December 2013), CINAHL (1981 to 3 December 2013), Embase (1980 to December 2013) and PsychINFO (1950 to 3 December 2013) databases were searched for papers investigating the effects of spasticity on quality of life (see appendix 1 for detailed search strategy). Search terms included 'spast*' and 'quality of life'. Inclusion criteria restricted selection of articles to those on adults with acquired neurological conditions (age>18 years), reporting both spasticity and QOL outcome measures and published in English. Studies on patients with infantile onset spasticity (less than 2 years), such as cerebral palsy, were excluded. Interventional trials investigating the effects of antispasticity agents which employed QOL tools as outcome measures were excluded from the review. Finally, the reference lists of the selected articles were reviewed to identify additional studies.

Figure 3. Literature search methodology



2.3. Results

The search identified 551 articles. After excluding duplicates and applying inclusion criteria, 17 articles were selected for review. Most studies were cross-sectional or prospective (table 7). Although any neurological condition of adults met eligibility criteria, studies were only found in three chronic neurological conditions, specifically multiple sclerosis (MS) (n=5), stroke (n=6), and spinal cord injury (SCI) (n=6).

2.3.1. Spasticity Assessment Tools

Ashworth and modified Ashworth scales (MAS), which were used in 6 studies (35%). Six studies (35%) employed patient reported measures for spasticity. Visual analogue scales (VAS) and Numerical Rating Scales (NRS) were used in four studies. Westerkam et al. used a self-administered tool for assessing spasticity in patients with spinal cord injury called the Patient Reported Impact of Spasticity Measure (PRISM) (Westerkam et al., 2011). Two studies concurrently administered MAS and NRS (Arroyo, Massana, & Vila, 2013; Flachenecker et al., 2014). Rizzo et al. grouped patients into increasing degrees of spasticity severity using the Performance Scale Spasticity Subscale (Rizzo et al., 2004). In the remainder of the studies (n=7) spasticity assessment tools were not specified and spasticity was reported as present or absent.

Table 7**.** Summary of the studies

Number of studies	**Type of study**	**Conditions**	**QOL measures**	**Spasticity measures**	**Studies that found significant effect of spasticity on HRQOL**
17	Cross-sectional (13) Longitudinal (4)	Stroke (6) MS (5) SCI (6)	SF-36/12 (8) EQ-5D – (5) WHOQOL-BREF (1) SIP (1) NHP (1) MSQoL-54 (1) NRS (2) VAS (1) SSQOL (1)	Ashworth scale/MAS (6) NRS/VAS (4) PRISM (1) Performance Scales (1) Unspecified (7)	Stroke -2 (33%) MS - 5 (100%) SCI -5 (83%)

2.3.2. Quality of Life Assessment tools

A variety of QOL measures were employed in the studies. Most of the studies (n=15, 88.2%) administered health-related quality of life (HRQOL) measures. The three most widely used measures of HRQOL were Short Form-36 (SF-36), Short Form-12 (SF-12) and EuroQol-5D (EQ-5D). SF-36 and SF-12 assess health status across eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) (Ware & Sherbourne, 1992). Each dimension is rated between 0 and 100, with higher scores representing better HRQOL. Scores below 50 are interpreted as worse HRQOL compared to an age-matched general population. Summary scores for physical and mental components are derived from the eight domain scores.

Five studies administered EQ-5D, a commonly used health utility measure. EQ-5D is a preference-based questionnaire which consists of a visual analogue scale (VAS) and a 5-dimension questionnaire which measures mobility, usual activities, self-care, pain/discomfort and anxiety/depression (Rabin & de Charro, 2001).

The remainder of general QOL tools included the Sickness Impact Profile (SIP), Nottingham Health Profile (NHP), numerical rating scale (NRS)/visual analogue scale (VAS) and World Health Organisation Quality of Life – BREF (WHOQOL-BREF). The SIP assesses functional status across 6 domains which are grouped under physical, mental and social dimensions (Bergner, Bobbitt, Carter, & Gilson, 1981). The NHP comprises of 38 items assessing health status across 6 dimensions: physical mobility, pain, social isolation, emotional reactions, energy, and sleep (O'Brien, Banner, Gibson, & Yacoub, 1988). The WHOQOL-BREF consists of 26 items, which represent four broad domains of QOL (physical health, psychological well-being, social relationships and satisfaction with environment) (WHO, 1998a). It is considered a more global measure of QOL as it addresses the non-health related aspects such as social roles, relationships, spirituality, self-perceived well-being and satisfaction with life (Huang, Wu, & Frangakis, 2006).

Two studies administered disease-specific tools. The Multiple Sclerosis Quality of Life-54 (MSQoL-54) questionnaire was developed to measure HRQOL in MS. MSQoL-54 is based on SF-36 and contains additional MS-specific items on bowel, bladder, cognitive function and health distress (Vickrey et al., 1995). The Stroke Specific Quality of Life (SSQOL) questionnaire consists of 49 items that examine 12 domains of HRQOL including energy, family roles, language, mobility, mood, personality, self-care, social roles, thinking, vision, upper-extremity function and work productivity (Williams, Weinberger, Harris, Clark, & Biller, 1999).

2.3.3. Spasticity and Quality of Life in Multiple Sclerosis

Five cross-sectional studies investigated the relationship between spasticity and HRQOL in MS, all of which found spasticity to be associated with lower HRQOL (Table 8). The two largest studies, conducted in North America, estimated spasticity either through patient grading using Performance Scales spasticity subscale or by unspecified

questions in a telephone interview and found that patients with spasticity had considerably worse scores on physical components measured by SF-36/SF-12 and only slightly worse scores on the mental component (Rizzo et al., 2004; Wu, Minden, Hoaglin, Hadden, & Frankel, 2007) (table 9). Multicentre cross-sectional studies in Europe (Spain, Germany, Sweden) reported that increasing levels of spasticity (measured by self-reported NRS) were associated with parallel decrease in scores on SF-12, EQ-5D and MSQoL-54 (Arroyo et al., 2013; Flachenecker et al., 2014; Svensson et al., 2014). Arroyo et al. (n=419) reported that spasticity, assessed by either MAS and NRS, affected certain aspects of HRQOL, namely general health, physical functioning, physical role and vitality as measured by SF-36 (Arroyo et al., 2013).

Table 8**.** Summary of the studies investigating effects of spasticity on QOL in MS.

Author	Design	Sample	Spasticity tool	QOL measure	Comments
Rizzo et al. (2004), USA	Cross-sectional	n=20969, NARCOMS registry. 4 groups of patients with increasing degrees of spasticity. Demographic factors associated with severe spasticity were: older age, male, education, unemployed, longer period since diagnosis.	Performance Scales (spasticity subscale)	SF-36	Patients without spasticity scored 47.4 on PCS ad 52.1 on PCS. Patients with severe-total spasticity scored 28.7 on PCS and 45.8 on MCS.
Arroyo et al. (2013), Spain	Cross-sectional	n=419, multicentre study. Mean age 46.4 (SD 11), 62.4% female, 71% on antispasticty treatment, 43.9 % SP, 42.1%RR. Sociodemographic factors associated with severe spasticity: aged between 45-65, longer course of MS, secondary progressive, urinary dysfunction, living alone.	NRS – patient MAS	SF-12	Compared to general population PCS and MCS scores were 31 (9.3) and 45.4 (12). Correlation between spasticity and QOL weak to moderate (r=-0.2 to -0.5). Patients with lower QOL scores were older, no education, SP, confined to bed, urinary dysfunction
Flachenecker et al. (2013), Germany	Cross-sectional	n=414, multicentre. Mean age 48.6 (9.6), 64.3% female, 44.7% RR, 44.4% SP, median EDSS score 5.5, disability worsened with spasticity severity,	NRS- patient NRS-physician	EQ-5D MSQoL-54	Patients with mild spasticity scored 0.6 (0.2) on EQ-5D, while patients with severe spasticity 0.3 (0.3). Similar trends on MSQoL-54. Patients with spasticity were more disabled, had more fatigue, sleep dysfunction and pain.

Svensson et al. (2014), Sweden	Cross-sectional	n=105, 68%female, mean age 58 (11), MS duration 24 (12), 64% SP, Average NRS score 4.	NRS- patient	EQ-5D	QOL scores expressed as QALY and VAS. Patients with mild spasticity scored 0.54 (0.3) and 58.4 (20.6) respectively. Patients with severe spasticity scored 0.37 (0.4) and 49.9 (22.3).
Wu et al.(2007), USA	Cross-sectional	n=2109, data collected computer assisted telephone interview, 77% female, 38% age 45-55	Unspecified	SF-12	PCS scores significantly lower in spasticity group 32.10 (0.29) than without spasticity 43.01 (0.43). MCS scores are lower in spasticity group 47.85 (0.34) than without spasticity 50.56 (0.39).

Several clinical factors were found to increase the likelihood of experiencing severe spasticity in MS (Arroyo et al., 2013; Rizzo et al., 2004). These included older age, longer duration of MS, secondary progressive type of MS, pain, fatigue, sleep problems, urinary dysfunction and increasing disability. However, none of the studies accounted for these confounders when comparing HRQOL scores. Only one study by Svensson et al. (n=105), assessing the costs and HRQOL in MS-related spasticity, reported spasticity to be a significant predictor of EQ-5D scores irrespective of Expanded Disability Status Scale (EDSS) scores using linear regression analysis (Svensson et al., 2014).

Table 9. Effects of spasticity on physical and mental domains in MS.

	Sample size	Condition	Cohorts	Physical	Mental Component	Measure
Rizzo et al.	20969	MS	Severe/Total spasticity	28.7	45.8	SF-36
			No spasticity	47.4	52.1	
Wu et al.	2109	MS	Spasticity	32.1	47.85	SF-12
			No spasticity	43.1	50.56	
Flachenecker et al.	419	MS	Mild	54.9	59.6	MSQoL-54
			Severe	39.5	48.7	

2.3.4. Spasticity and Quality of Life in Spinal Cord Injury

Five cross-sectional studies and one longitudinal prospective study reported the effects of spasticity on QOL in adults who have suffered a spinal cord injury (SCI) (table 10). Spasticity was found to be associated with significantly worse physical components, but not always with mental domains. Westgren et al. (n=320) found all of the domains on SF-36 to be significantly lower in patients with spasticity compared to the rest of the cohort (Westgren & Levi, 1998). However, only patients who rated their spasticity as 'problematic' were included in the spasticity group (n=33) (Westgren & Levi, 1998). Post et al. (n=318) reported that patients with spasms scored significantly lower on physical and social, but not mental domains on SIP (Post, de Witte, van Asbeck, van Dijk, & Schrijvers, 1998). Vogel et al. in a study on adults with paediatric-onset SCI found SF-12 scores to be significantly lower in patients with spasticity (Vogel, Krajci, & Anderson, 2002). Singh et al. (n=50) in a study on QOL determinants at 6 months post-injury found spasticity was associated with significantly lower QOL (VAS)

(Singh, Dhankar, & Rohilla, 2008). All of the studies reported that other impairments experienced by the patients including bladder, bowel, pain and respiratory problems were significantly associated with worse HRQOL.

Table 10**.** Summary of the studies investigating effects of spasticity on QOL in SCI.

Author	Design	Sample	Spasticity tool	QOL measure	Comments
Westgren et al.(1998), Sweden	Cross-sectional	n=353, mean age 42, 261 male, 124 tetraplegic, 176 paraplegic.	Unspecified	SF-36	33 patients defined as problematic spasticity compared against the rest of the cohort. Scores were significantly lower in all the domains. Younger age at injury unemployment, bladder problems , bowel problems were associated with significantly lower scores.
Westerkam et al. (2011), USA	Cross-sectional	n=1549, mean age 45.1, average age at injury 32.5,	PRISM NRS	Life Situation Questionnaire-Revised NRS QOL	Regression analysis showed spasticity was associated with home, vocational, global satisfaction and overall QOL.
Noonan et al. (2008), USA	Cross-sectional	n=70, age at injury 45(18), age at follow up 51 (18), female 19%	Unspecified	SF-36 NRS overall QOL (from QLQ-C30)	Stepwise regression analysis showed spasticity is not a significant predictor of SF-36 scores after adjusting for confounders such as motor impairment, bladder, bowel and sexual dysfunction.
Post et al. (1998), Netherlands	Cross-sectional	n=318, mean age 39.4 (12.5), mean time after injury 3.6 (1.9) years,	Unspecified	SIP Life Satisfaction Questionnaire	Spasms were associated significantly lower physical and social domains and life satisfaction, but not psychological domain. Other significant factors were pain, respiratory problems, urinary tract infections, but these were not accounted.
Vogel et al. (2002), USA	Cross-sectional	n=216, mean age 29, mean age at injury 14, patients with paediatric-onset SCI	Unspecified	SF-12 Satisfaction with Life Scale	Spasticity was associated with lower SF-12 scores but not with life satisfaction. Pressure sores and UTI were associated with lower HRQOL and life satisfaction.
Singh et al. (2007), India	Longitudinal prospective (6 months)	n=50, mean age at injury 34.23(15), mean age 37 (15), Male 36%	Unspecified	VAS	60%reported spasticity. It was significantly associated with lower QOL score. Bowel, urinary problems and pain also significantly lowered QOL. No adjustments to confounders were made.

Two studies examined the relationship between spasticity, associated symptoms and QOL. In a large study (n=1549) by Westerkam et al. spasticity was a significant predictor of overall QOL (measured by NRS) and life satisfaction (home, vocational, global satisfaction measured by Life Situation Questionnaire) after adjusting for sociodemographic variables (age, sex, marital status, employment and time since diagnosis) (Westerkam et al., 2011). In a study by Noonan et al. (n=70), although spasticity was a significant predictor of physical component scores (SF-36) after adjusting for sociodemographic confounders, spasticity became an insignificant predictor once other confounders (bowel, bladder, sexual dysfunction and motor impairment) were taken into account (Noonan, Kopec, Zhang, & Dvorak, 2008).

2.3.5. Spasticity and Quality of Life in Stroke

Six studies (4 longitudinal, 2 cross-sectional) reported conflicting results on the relationship between spasticity and QOL in stroke survivors. In a large study (n=460) by Gillard et al., the investigators measured HRQOL at 3 months, 1 year and 2 years after stroke using SF-12, EQ-5D, and SSQOL (Gillard, 2005). Gillard et al. reported that patients with spasticity scored consistently lower on all the three outcome measures at every follow-up. Similar findings were reported in a study of 211 patients by Urban et al. (Urban et al., 2010). Patients with spasticity had significantly lower EQ-5D scores compared to the cohort without spasticity at 6 months after stroke (Urban et al., 2010). In addition, patients with spasticity had worse Barthel Index scores, indicating greater problems with activities of daily living.

Four studies found no significant relationship between spasticity and QOL. Wissel et al. (n=103) found that stroke survivors with spasticity (measured with MAS) had significantly lower scores on EQ-5D immediately after stroke (6 days), but not at 16 weeks of follow up (60.3 vs. 80.6, p=0.07), although disability levels measured by Barthel Index were significantly worse in the spasticity group at both baseline and follow up (Wissel et al., 2010). Welmer et al. (n=66) reported that patients with post-stroke spasticity (n=13) had significantly worse scores on the physical functioning

subscale of SF-36, but not on the remainder of the subscales (Welmer, von Arbin, Widen Holmqvist, & Sommerfeld, 2006). Dajpratham et al. in a multicentre cross-sectional study (n=327) in Thailand found no difference on WHOQOL-BREF scores (Dajpratham, Kuptniratsaikul, Kovindha, Kuptniratsaikul, & Dejnuntarat, 2009). Similarly, Ones et al. (n=88) found no significant correlation between NHP scores and spasticity (r=-0.12, p>0.05) (Ones, Yilmaz, Cetinkaya, & Caglar, 2005).

Table 11**.** Summary of the studies investigating effect of spasticity on QOL in stroke

Author	Design	Sample	Spasticity tool	QOL tool	Comments
Wissel et al. (2010), Germany	Longitudinal Prospective (16 weeks)	n=103, mean age 69 (35-96), female 38%, 86% ischaemic stroke	MAS	EQ-5D	24.35% developed spasticity at baseline. Patients with spasticity scored significantly lower on EQ-5D than patients without spasticity. At 16 weeks 21.4 % had spasticity, no significant effect on HRQOL.
Urban et al. (2010), Germany	Longitudinal prospective (6 months)	n=211, mean age 68(13), male 62%	MAS	EQ-5D	75 patients developed spasticity. EQ-5D was significantly lower in patients with spasticity compared to cohort without spasticity (53.6 vs 80,p<0.001). Patients with spasticity had lower Barthel scores.
Welmer et al.(2006), Sweden	Longitudinal Prospective (3, 18 month follow up)	n=66, 13 developed spasticity,	MAS	SF-36	Only physical functioning scores were significantly lower in spasticity cohort. Spasticity group also had higher levels of disability measured by Barthel.
Dajpratham et al. (2009), Thailand	Cross-sectional	n=327, mean age 62.2 (12), 193 males, spasticity 41.6%.	MAS	WHOQOL-BREF	No difference across QOL scores was found between patients with spasticity and without spasticity.
Gillard et al.(2012), USA	Longitudinal prospective (3 months, 1year and 2 years)	n=460, mean age 66, 49% female,	Unspecified	SF-12 EQ-5D SSQOL	Significantly lower scores in all 3 QOL measures in 54 patients with spasticity compared to controls.
Ones et al. (2005), Turkey	Cross-sectional	n=88, mean age 62.9(11.4), male 56.8%, proportion of patients with spasticity not reported	Ashworth scale	NHP	No correlation was found between spasticity and QOL (r=-0.12, p>0.05)

2.4. Discussion

This review presented the current evidence on the relationship between spasticity and QOL in three neurological conditions: MS, SCI and stroke. Although generalisation of the results should be interpreted with caution due to different methodologies, study designs, outcome measures and participants, it appears that spasticity is associated with lower HRQOL.

Physical components of HRQOL were more affected by increasing levels of spasticity compared to mental components. This is in keeping with previous studies on spasticity and its effects on physical functioning and disability, and supports the contention that these HRQOL measures reflect health status (Arroyo et al., 2011; Oreja-Guevara, 2011; Sommerfeld, Eek, Svensson, Holmqvist, & von Arbin, 2004). Several studies reported mental components of SF-12 and SF-36 to be negatively correlated with spasticity, which illustrates a relationship between increasing spasticity and worsened psychological well-being (Gillard, 2005; Post et al., 1998; Wu et al., 2007).

Wider implications of spasticity on family, work and social functioning are less clear. Studies that administered more global measures of QOL such as WHOQOL-BREF, rather than measures of health status, found no significant relationship between spasticity and QOL (Dajpratham et al., 2009; Noonan et al., 2008). In a qualitative study on SCI patients with spasticity, Mahoney et al. found that subjects adjust to having spasticity and learn how to control it (Mahoney et al., 2007). Some subjects utilised spasticity to counteract the weakness and improve posture and transfers. These observations may explain a lack of impact of spasticity on overall QOL in the selected studies. However, the results from two qualitative studies on spasticity in MS indicated that spasticity has detrimental effects on a variety of aspects of life, and not exclusively physical health (Morley, Tod, Cramp, & Mawson, 2013; Nicolson & Anderson, 2001). Morley et al. performed semi-structured interviews with 12 patients with MS-related spasticity and found that spasticity adversely affected not only physical aspects of health, but also relationships, self-esteem, employment, goal-setting and future planning. Some subjects reported that spasticity contributed to anxiety and depression.

Unpredictability of spasticity was found to cause embarrassment and loss of sense of control of subjects' lives. Similar observations were reported by Nicolson et al. in a qualitative study, which involved three focus groups consisting of patients with MS-related spasticity. The authors confirmed that spasticity can have deleterious effects on patients' social roles, mental health and physical function. Future studies are needed to investigate broader effects of spasticity in multiple sclerosis using quantitative methods to test hypotheses generated in the qualitative studies.

The relationship between spasticity and HRQOL appears to be weakest in the stroke population, with only two out of six studies reporting significant difference (Gillard, 2005; Urban et al., 2010). Although the results should be interpreted with caution due to variable methodology and sample sizes, it could be hypothesised that spasticity does not have a major impact on HRQOL in stroke patients, and other factors may play a more important role.

2.4.1. Weaknesses of the studies

The major limitation of the studies is the failure to control for confounding factors. Studies on MS reported that spasticity is commonly associated with various sociodemographic variables (age, employment status, education, living alone) and disease-related variables (longer course of duration, secondary progressive MS, higher EDSS score, pain, bladder dysfunction, sleep problems, fatigue) (Arroyo et al., 2013; Flachenecker et al., 2014; Rizzo et al., 2004). Unfortunately, only one study accounted for EDSS score, and found that spasticity is a significant predictor of HRQOL irrespective of the levels of disability (Svensson et al., 2014).

Two studies on SCI patients found that spasticity was a predictor of HRQOL after accounting for sociodemographic variables and time since injury (Noonan et al., 2008; Westerkam et al., 2011). However, once other SCI-associated conditions were taken into account (pain, bowel, sexual dysfunction and motor impairment), spasticity was found to be an insignificant predictor of HRQOL. Although the authors concluded that spasticity is not a significant determinant of HRQOL, it may be that spasticity might indirectly influence HRQOL as it may worsen symptoms of pain, interfere with sexual

function and cause more disability. In addition, the authors did not administer specific measures for these variables, but used dichotomous values instead (presence/absence of a symptom). The interrelationships between different variables would need further confirmation using appropriate measures by employing more sophisticated statistical techniques such as structural equation modelling.

2.4.2. Conceptual issues in QOL assessment

Fifteen out of seventeen studies in this review used health status measures including SF-12, SF-36, SIP and utility measure EQ-5D, all of which are heavily weighted towards physical functioning. Not surprisingly, all of these measures correlated closely with spasticity as expected from the data on studies investigating the effects of spasticity on disability (Arroyo et al., 2011; Lundstrom, Terent, & Borg, 2008; Sommerfeld et al., 2004).

It is important to make a distinction between HRQOL and overall QOL, a subject briefly discussed in Chapter 1, Quality of Life section. HRQOL is a narrower entity of global QOL, which only encompasses the domains that are directly affected by disease or treatment (Schipper et al., 1996). As a result, HRQOL excludes other aspects of life such as cultural, political or societal (Ferrans et al., 2005). However, Ferrans et al. argued that in patients with chronic conditions virtually every aspect of life can be affected, hence the concept of HRQOL is insufficient to address all potential effects of a condition (Ferrans, 2007; Ferrans et al., 2005).

It is noteworthy that measures such as SF-36 and SIP, although employed to measure QOL in the selected studies, have been shown to measure different constructs of QOL (Huang et al., 2006; K. W. Smith, Avis, & Assmann, 1999). For example, a large study (n=11,440) by Huang et al. investigated the psychometric properties of the SF-36 and WHOQOL-BREF and concluded that the SF-36 measures HRQOL whereas WHOQOL-BREF measures global QOL (Huang et al., 2006). The findings are consistent with widely accepted models of QOL, such as Wilson and Cleary and Ferrans, in which SF-36 is a measure of health perception and not overall QOL (Ferrans et al., 2005; Wilson & Cleary, 1995). To avoid the conceptual confusion, the authors of the proposed models

urged researchers to clearly define their study outcomes, however the terms QOL and HRQOL were used interchangeably in the published studies and none of the studies explicitly provided the definition of QOL.

As discussed in Chapter 1, the relationship between self-perceived QOL and health status is not straightforward, i.e. a person with poor health might not necessarily report poor QOL, and equally not all persons with excellent health have good QOL. In a study of 493 patients with cancer, Covinsky et al. found that 43% of the most severely disabled rated their global QOL as good or better, while a significant 15% of those with the best physical function rated their QOL as fair or poor (Covinsky et al., 1999). Smith et al. performed path analysis on 12 studies that employed health status and overall QOL measures and found that health status is influenced more by physical functioning, while overall QOL by emotional well-being (K. W. Smith et al., 1999). It is evident that measures of health status and overall QOL are distinct and measure different constructs.

Ferrans et al. argued that the dis-concordance between health perception and overall QOL is explained by the interaction of life satisfaction and individual and environmental factors (Ferrans, 2007). Since a person's evaluation of QOL is based on the system of internal standards which are under the influence of individual and environmental factors, self-perception of QOL might differ independently from health status. However, from the studies reviewed here it is impossible to conclude how spasticity affects overall QOL, since health status measures, rather than overall QOL tools, were employed.

Only two studies employed a disease-specific measure of HRQOL (Stroke Specific Quality of Life and MSQoL-54). Generic QOL instruments are useful for comparing QOL across different conditions, but they might be insensitive to minor changes in specific conditions (Baumstarck et al., 2012; Benito-Leon et al., 2003). For example, there is some evidence to suggest that SF-36 might not be appropriate in the MS population, due to its significant floor and ceiling effect (Hobart et al., 2001). Disease specific measures of QOL are generally accepted as more advantageous

because they enable researchers to capture subtle and unique effects of a particular condition on QOL, which otherwise might be overlooked by generic measures (Benito-Leon et al., 2003). There is a possibility that some of the studies failed to find a correlation between spasticity and QOL because of the limitations of using generic scales rather than disease specific scales.

2.4.3. Problems with spasticity assessment

Seven studies did not specify the measures of spasticity, and reported only its presence or absence. Clearly, there is a wide spectrum of severity of spasticity, hence dichotomous categorisation of spasticity might not be valid. For instance, Westgren et al. classed patients to have spasticity only if they reported it to be 'problematic', which only comprised 10% of the subjects, while estimated prevalence of spasticity in SCI is ~50% (Singh et al., 2008; Westgren & Levi, 1998).

The Ashworth scale was the most commonly employed measure for spasticity (6 studies). However, as discussed in Chapter 1 there is a growing body of evidence to disregard it as a valid tool for assessment of spasticity (Burridge et al., 2005; Fleuren et al., 2010; Pandyan et al., 1999). Hence, the relationship between spasticity and QOL needs to be re-examined using appropriate measures for spasticity.

2.4.4. Limitations of the review

The main limitation of this review is that only observational studies, mostly cross-sectional in nature, were included. Consequently, it is impossible to determine a causal relationship between spasticity and QOL. In addition, outcome measures for spasticity and QOL reported in the studies were frequently inadequate as both of these concepts are complex and multifaceted.

Another limitation of the review is that only limited data could be extracted from the studies. For instance, only three out of seven studies that used SF-36 reported the individual domain scores. For future work, reporting individual subscale scores would provide better insight into which areas of QOL are most affected by spasticity.

Lastly, a meta-analysis was not possible for this review because of different methodologies, participants and outcome measures.

2.5. Conclusions

Spasticity appears to be an important factor in determining HRQOL in MS and SCI, but is less significant in the stroke population. Physical components are more affected by spasticity than mental domains. It is currently not known whether spasticity affects QOL directly or mediates via associated conditions such as fatigue, depression, anxiety, pain etc. Based on the findings of the studies, no clear conclusions could be made regarding effects of spasticity on overall QOL, since the studies employed health status measures. In conclusion, due to the methodological flaws regarding both spasticity and QOL assessment, the relationship between spasticity and QOL requires further investigation.

Chapter 3 - Methodology

3.1. Hypotheses

1. Spasticity is associated with worse overall QOL.

2. There is a positive relationship between spasticity and the following MS-associated conditions: pain, bladder, sleep, fatigue, disability, anxiety and depression.

3.2. Aims

To achieve the answers to the above hypotheses, this thesis aims to**:**

1. To investigate the relationship between spasticity and overall QOL using patient-reported outcome measures for spasticity (MS Spasticity Scale-88) and two QOL measures: overall QOL measure (WHOQOL-BREF) and MS-specific measure (Leeds MS QoL Scale)

2. To determine whether spasticity is an independent predictor of QOL after adjusting for confounding factors using multiple linear regression model.

3. To investigate the relationship between spasticity and pain, bladder, sleep, fatigue, disability, anxiety and depression using robust patient-reported measures.

3.3. Overview and study design

The present study forms a pilot phase of the larger study entitled 'Trajectories of Outcome in Neurological Conditions (TONiC)'. TONiC is a UK based multicentre observational study investigating the factors influential to QOL in MS and motor neurone disease. Brief descriptions of qualitative, cross-sectional and longitudinal stages of the TONiC study are given below.

3.4. Study phases

3.4.1. Phase 1 – Qualitative stage

A total of 78 participants took part in the focus groups and interviews. 8 focus group sessions were carried out to identify the main themes underpinning the concepts of QOL in MS. Following this, in-depth, semi-structured interviews were conducted by a

PhD student (HA) using an inductive approach. In an inductive approach, the themes obtained from the interview are data driven, which means that themes are not fitted into pre-existing theoretical models, but coded based on the data (Boyatzis, 1998). 43 participants (mean age 52 yrs (range 20-75 yrs), 16 males (37%), EDSS range 0-9.5, illness duration 15 years (range = 5months – 45 years)) took part in this study phase, representing 4 different types of MS: 14 RRMS, 13 PPMS, 14 SPMS and 5 REMS. The aim of phase 1 was to explore the factors expressed by participants as being influential to their QOL.

In preparation for the qualitative stage of the study, a literature search was performed to identify the scales that measure these factors. A preliminary version of the questionnaire pack was piloted on 11 participants through a process of cognitive debrief. Patients were given 2 weeks to fill out the questionnaires and were contacted by the research assistants (NR, CP) to give feedback on the content, layout, appropriateness and length. The feedback from the patients led to a number of revisions and the finalised pack was produced to be used for phase 3.

3.4.2. Phase 2 – Documentation of demographic information

The aim of phase 2 of the study was to record the demographic information of the participants. The following parameters were documented:

1. Age and sex
2. Date of diagnosis
3. Type of MS
    - Relapsing-remitting MS
    - Secondary progressive MS
    - Primary progressive MS
    - Rapidly evolving MS – 2 or more disabling relapses in 1 year (if MRI has been repeated it should show 1 or more gadolinium enhancing lesions on the brain or a significant increase in T2 lesion load as compared with previous recent MRI)
4. Disease-modifying therapy

5. Contact preference (email, phone call, post)
6. Clinician-rated prediction of patient's QOL over the next year (1-improve, 2-stay stable, 3-worse, 4 – no opinion)
7. Patient's preference for method of completion (postal or online questionnaire).

The rationale for recording this information was to identify the factors associated with an increased likelihood of withdrawal from the study, thus addressing the problem of selection bias.

3.4.3. Phase 3 – Questionnaire Administration

The main centre for recruitment was the Walton NHS Foundation Trust. Two other sites (Royal Preston Hospital and Salford Royal Hospital) also took part in the pilot of phase 3. During this phase, questionnaires were administered to the patients that had given phase 2 and 3 consents. The data obtained from the pilot study was used for the statistical analysis in this thesis.

3.4.4. Phase 4 – Longitudinal Phase

Participants diagnosed with MS <1 year will be invited to participate in phase 4 of the study. Patients taking part in the longitudinal phase will receive the questionnaire pack at 6 months following the first questionnaire and then yearly for the next 5 years. In order to address the burden of a large volume of questionnaires, a shortened version of the pack will be administered to the prospective cohort. This will be achieved through item reduction of the newly designed scales using Rasch analysis of the data collected during the pilot phase. The aim of the longitudinal study is to assess the change of various parameters over time and investigate their impact on overall QOL.

3.5. Ethical approval

Ethical approval was granted in full by the National Research Ethics Service Northwest committee in November 2011 (reference no 11/NW/0743). Local Research and Development approval was obtained from the Walton NHS foundation Trust. The study was conducted in accordance with the substantial amendment 4, which was approved in November 2013 after final modifications were made to the questionnaire packs before administration.

3.6. Study Population

Patients with a diagnosis of MS that fulfilled McDonald or Poser diagnostic criteria were invited to take part in the study.

3.6.1. Principal Inclusion Criteria

1. Diagnosis of MS.
2. Adults
3. Capable of answering questionnaires with or without assistance.
4. Capable of providing informed consent.
5. Patients diagnosed >1 year ago were included in the cross-sectional phase of the study (phase 3). For longitudinal study (phase 4) patients were recruited only if the diagnosis was made <1 year.

3.6.2. Principal Exclusion Criteria:

1. Patients that have not fulfilled McDonald or Poser diagnostic criteria (e.g. clinically isolated syndrome)
2. Patients with other demyelinating disorders of the CNS (e.g. neuromyelitis optica)
3. Concomitant serious medical or psychiatric condition
4. Not capable of informed consent
5. Not capable of answering the questionnaires (severe cognitive impairment, language barriers)

3.7. Patient Recruitment Procedure

Patient recruitment was commenced in Jan 2012 at the Walton NHS Foundation Trust. The patients were approached by a healthcare professional (neurologist, nurse, physiotherapist) or one of the members of the TONiC research team (NR, HA, CR, KM) in the outpatient clinics.

As part of the recruitment process, patients were given a short overview of the rationale, aims and risks of the study supplemented with a patient information leaflet (PIL). To ensure that the patients do not feel pressured to take part in the study, all potential subjects were given a minimum of 15 minutes to decide whether they are

willing to participate in the study. The consenting procedure took place in a quiet room in the outpatient department or clinical trials unit to ensure patient privacy. The recruiting person assisted with any questions or queries that a patient might have. If a patient was not able to give written consent, one witness was required to countersign a consent form stating that they had witnessed the participant's non-written consent.

In instances where a patient was not able to consent for phase 3 (e.g. time constraints, needing more information), a recruiting person gave a PIL with the consent forms and a pre-paid envelope to take back home. Similarly, if a patient's carer was not present at the time of recruitment, a PIL together with the consent forms and a pre-paid envelope was given to the patient. The researcher offered a 2-week follow-up contact by phone, letter, or email according to patient preference, in order to answer any queries that the patient or his/her carer might have had.

If a patient expressed an interest in taking part in the study either through other members of staff or by directly contacting the research team, the consent forms together with the pre-paid envelope would be posted to the patient.

First post-out of the questionnaires was administered to 186 participants in December 2013. Out of 250 patients that had been consented during the period between 2012 -2013 December, only the patients with the diagnosis >1 year and who expressed a preference for postal questionnaire completion received a questionnaire pack. Together with the questionnaire pack a cover letter, news letter and Christmas greeting were included. Participants who had not consented for phase 3 or whose carers had not consented, were posted a phase 3 PIL together with the consent form and a carer PIL with the consent form accordingly.

Four to five weeks after the initial post-out the non-respondents were contacted by phone, email or letter (based on the preferred choice of contact on the phase 2 database) by one of the researchers (KM and HA) to inquire if any assistance was needed for completing the questionnaire and if they are still willing to participate. If a patient decided to withdraw, a researcher would thank politely, reassure about their right to decline, remind them that they are welcome to join the study in the future if they change their mind and ask if they mind returning the blank questionnaire in order

to minimise the costs of the study. If a patient only partially completed the questionnaire, he or she would be asked if the research team could use the incomplete questionnaire for some parts of the statistical analysis. The clinical care team would be informed not to re-approach patients who have previously declined.

Following the initial post-out and follow-up of the non-respondents it was apparent that some participants were challenged by the large volume of the questionnaire. Consequently, during the remaining recruitment period, a consenting person would show a paper copy of the questionnaire to a potential participant and explain the reasons for the lengthy format. In addition, a patient would be informed that, although it is preferred that the entire questionnaire is completed in a single attempt or within one day, the questionnaire may also be completed in stages. It was agreed within the research team that it was unrealistic to expect the patients to complete questionnaires in a single attempt due to the high prevalence of impairments in the MS population, such as difficulties with concentration and fatigue.

In order to meet the target of 250 completed questionnaires by the end of March, so that Rasch analysis could reduce the number of items in preparation for the longitudinal phase, the recruitment was intensified by inviting all of the consultant neurologists, MS nurses and MS therapists to offer an opportunity for the patients to take part in the TONiC study. In addition, MS patients attending inpatient day treatment ward for natalizumab infusions were invited to take part in the study by the researcher (KM). Patients were allowed to complete the questionnaire pack while waiting for the clinic appointment or receiving treatment and then return it to the clinical or research staff on the same day.

3.8. Data entry, processing and 10% check

Demographic data was uploaded online on the phase 2 database. Although an analogous phase 3 database was planned to be designed for entry of the questionnaire data, due to unforeseen IT problems the completion date for the online phase 3 database was postponed. An alternative method for entering preliminary data was sought using the Filemaker Pro 12 software. A 10% data check was performed before

exporting the data in into Excel format.

3.9. Measures used in the Questionnaire Pack

The pack contained 31 questionnaires (table 12). The scales consisted of previously validated measures and newly developed tools that had not been validated in MS. A detailed description of scales relevant to this thesis is given below.

Table 12**.** Questionnaires used in TONiC

Relevant to this study	**Not relevant to this study**
MSSS-88	MS - Coping
NRS spasticity	EuroQol-5D
Hospital Anxiety and Depression Scale	Herth Hope Index
Neurological Fatigue Index - MS	Multiple Sclerosis Vision Questionnaire
WHOQOL-BREF	London Handicap Scale
Leeds MS QOL	MS Impact Scale
Neuropathic Pain Scale	Medical Outcome Study Sleep Scale
SF-Qualiveen	MS Self-efficacy Scale
WHO Disability Assessment Schedule 2.0	Social Withdrawal Scale in MS
	COPE scale
	Epworth Sleepiness Scale
	Rosenberg Self-Esteem Scale
	Stigma Scale for Chronic Illness
	General Self-Efficacy Scale
	Peen State Worry Questionnaire
	Multidimensional Health Locus of Control Scale
	MS Work Instability Scale
	MS Intimacy and Sexuality Questionnaire
	Neurological Hopelessness Scale
	Leeds Spasticity Scale
	NRS (pain, coping, disability, QOL, fatigue, hopelessness)
	Health Economics Questionnaire

3.9.1. Spasticity measures

Two patient-reported measures were used in the assessment of spasticity: the numerical rating scale 11 (NRS11) and MS Spasticity Scale-88 (MSSS-88) (three subscales: pain/discomfort, spasms, stiffness). Detailed psychometric characteristics of the scales are provided in Chapter 1, under the spasticity section.

3.9.1.1. Justification for choosing patient-reported measures for spasticity

Measurement of spasticity has been the subject of intense debate and controversy for many years and unfortunately as of today there is no single perfect measure for spasticity (Burridge et al., 2005; Pandyan et al., 2005). The reasons for choosing patient-reported outcome measures are many. Firstly, as discussed in chapter 1, clinician ratings of spasticity poorly correspond to patient reports (Lechner et al., 2006; Priebe et al., 1996; Skold et al., 1999). Spasticity may vary throughout the day or week and is under the influence of many factors that are often clinically silent (Skold, 2000). Hence, single measurement of spasticity performed by a clinician might inadequately represent the overall severity of spasticity and can often be undetectable (Lechner et al., 2006; Skold, 2000). Secondly, although previous similar studies employed the Ashworth Scale, there is growing evidence suggesting low reliability and poor validity of this measure (Fleuren et al., 2010; Pandyan et al., 1999). Lastly, biomechanical and electrophysiological studies were considered to be inappropriate and impractical for use in this large scale, population-based study.

In contrast, self-assessment of spasticity is much more information-rich, since patients themselves experience spasticity. In addition, patient-reported measures for spasticity are easy to administer in population surveys, such as the TONiC study. It has been increasingly recognised that assessment of a single aspect of spasticity, such as tonic or phasic spasticity alone, is not adequate. As a result, three subscales of the MSSS-88 assessing stiffness, spasms and pain and discomfort were included in the questionnaire pack.

In addition to MSSS-88, the numerical rating scale for spasticity was used. NRS has been shown to be a reliable and valid measure of spasticity in previous studies (Arroyo et al., 2013; Barnes et al., 2003; Farrar et al., 2008). In the present study,

patients were asked to rate their spasticity over the preceding 2 weeks. Some studies used a 24h period, however because of the length of the questionnaire pack and time references for other measures, (e.g. fatigue) 2 weeks was felt to be the most appropriate time frame (Arroyo et al., 2013; Svensson et al., 2014). Spasticity was explained to patients as 'stiffness, tightness, cramps and spasms in muscles'. NRS was used to stratify the study sample into four groups based on the severity of spasticity: 0 - none, 1-3 - mild, 4-6 moderate, 7-10 severe (Arroyo et al., 2013; Flachenecker et al., 2014; Svensson et al., 2014). Lastly, data regarding spasticity obtained using NRS would allow standardised comparisons with other neurological conditions, such as MND, in the future.

3.9.2. QOL measures

Two QOL measures were chosen: a generic tool, WHOQOL-BREF, and an MS-specific, Leeds Multiple Sclerosis Quality of Life scale (LMSQoL). The measures were selected on the basis that they both measure overall QOL, in contrast to previous studies, which administered health status measures (Arroyo et al., 2013; Flachenecker et al., 2014; Ford, Gerry, Johnson, et al., 2001; Huang et al., 2006; Wu et al., 2007). As discussed in chapter 1, QOL assessment is complex and there is lack of agreement on which measures are best to use in the MS population. There is a notion that general QOL instruments may be less sensitive than disease-specific ones, therefore both measures were included in this study. In addition, there is no overall WHOQOL-BREF score, while LMSQOL allows calculation of the total QOL score. With the view of future studies investigating QOL in other neurological conditions, generic QOL measures would enable comparisons to be made across different conditions.

3.9.2.1. LMSQoL

LMSQoL is an 8-item instrument that was developed in a community-based sample with MS (Ford, Gerry, Tennant, et al., 2001). The developers' aim was to design an instrument that measures overall QoL and not merely the aspects of impairment, disability and handicap- a feature of many previous health status or HRQOL measures, such as MSQOL-54 and Functional Assessment in Multiple Sclerosis (FAMS) (Cella et al.,

1996; Vickrey et al., 1995). The eight items of the scale address: tiredness, loneliness, energy, worries about health, family relationships, appearance, attitudes of other people, and the future. All of the items are rated on the four-point Likert Scale (0-not at all; - sometimes; 2-quite often; 3 - most of the time).

The scale was shown to meet the requirements of unidimensionality using psychometric Rasch analaysis, have high internal consistency (Cronbach's a=0.86), good reliability (test-retest Spearman's rank=0.85) and good external validity (General Well Being Index, Spearman's rank=0.83). The scale was shown to measure different construct to health status, by having low correlation with SF-36 physical functioning subscale (rank=0.35).

Further validation of the LMSQoL scale was undertaken on a sample of 69 Turkish patients, which showed the scale to be valid and reliable in the Turkish language (Akbiyik et al., 2009). More evidence on the validity and responsiveness of the LMSQoL was generated in a post-hoc analysis of the transcutaneous electrical nerve stimulation trial for back pain in 100 patients with MS (Nicholl, Hobart, Cramp, & Lowe-Strong, 2005). The scale was shown to be responsive to treatment (effect size: 0.34) and have moderate internal consistency (Cronbach's a=0.71). Convergent validity was examined using MSQOL-54, which showed moderate correlations with emotional health subscales (-0.38 to -0.65) and physical health subscales (-0.27 to -0.5), except for physical function subscale which was statistically non-significant. The findings are in line with the results obtained by Ford et al. in the scale development study described above (Ford, Gerry, Tennant, et al., 2001). High responsiveness was also supported in a multicentre, observational study (n=197) examining the effects of glatiramer acetate on QOL using LMSQOL, which improved significantly after treatment (Jongen et al., 2010).

3.9.2.2. WHOQOL-BREF

In the early 1990s, the WHOQOL group recognised a lack of conceptual agreement of QOL and its standardised measurement (1995). In particular, it was emphasised that the existing 'QOL' measures were focused on disability and health aspects, and were not measuring QOL per se (1995, 1996). In order to address these

problems, an international collaborative initiative, the WHO QOL group, was set up which proposed a definition of QOL (described in Chapter 1) and set out to develop a QOL instrument, which would reflect the WHO definition of QOL. WHOQOL – 100 assessment was developed in 15 field centres simultaneously across the globe, covering 24 facets of QOL (1998b). It was recognised that in some circumstances the lengthy format of WHOQOL-100 was not appropriate, and a shortened version, the WHOQOL-BREF was designed (1998a). The WHOQOL-BREF retained all 24 facets with a single item representing each facet and included an additional 2 items addressing overall QOL and general health.

WHOQOL-BREF consists of 4 domains: physical health (7 items), psychological (6 items), social relationships (3 items) and environment (8 items). Domain scores are scaled in a positive direction, i.e. higher scores denote better QOL. The mean score of the facets within each domain is used to calculate domain score. In order to make the scores comparable with WHOQOL-100, the mean scores are multiplied by 4.

WHOQOL-BREF was shown to have good internal consistency (Cronbach's alpha range 0.66 to 0.86), excellent discriminative validity between ill and healthy subjects and good test-retest reliability (Pearson's correlation 0.66 to 0.87) (1998a). Confirmatory factor analysis showed acceptable fit to the model (0.901 Comparative Fit Index) when 4 domain solution was applied. Multiple regression analysis confirmed a significant contribution of each of the domains to overall QOL (>60% variance explained for each domain) (1998a).

Despite the large scale of the WHOQOL project and robustness of the WHOQOL-BREF, comparatively very few papers reported the use of WHOQOL-BREF in studies on MS. A literature search (February 2014) using WHOQOL AND multiple sclerosis produced only 11 hits on the MEDLINE search engine. Out of 11 studies, only 2 reported psychometric properties of WHOQOL-BREF in the MS population (Ozakbas, Akdede, Kosehasanogullari, Aksan, & Idiman, 2007; Wynia et al., 2008). The study by Chopra et al. compared MSQOL-54 and WHOQOL-BREF in 112 patients at two time points: at relapse and at 1 month later. MSQOL-54 showed better responsiveness and better correlation with EDSS (r=0.54 vs. r= 0.13) (Chopra et al., 2008). The correlation

between two instruments was low (r=0.17). The authors suggested that MSQOL-54 may be more favourable to assess QOL in both remission and relapse. Another study by Wynia et al. investigated the effects of MS-related disabilities (Multiple Sclerosis Impact Profile) on QOL using two measures: SF-12 and WHOQOL-BREF (Wynia et al., 2008). Regression analyses revealed that SF-12 was only sensitive to changes in physical disabilities, while WHOQOL-BREF scores were also significantly influenced by psychosocial variables. The authors concluded that the WHOQOL-BREF provides a more comprehensive assessment of QOL than SF-12.

In conclusion, the WHOQOL-BREF is a measure of overall QOL that has been developed and validated in large populations of people with and without conditions. It has been shown to have highly robust psychometric properties, however there has been a paucity of application of the WHOQOL-BREF in the MS population and this needs further examination.

3.9.3. Measures for fatigue, pain, depression, anxiety, bladder dysfunction and disability

Literature search identified a number of impairments that may confound the relationship between spasticity and QOL (Arroyo et al., 2013; Oreja-Guevara, 2011; Rizzo et al., 2004). These included fatigue, pain, depression, anxiety, bladder dysfunction and disability. Although bowel problems can often be seen in patients with spasticity, a measure of bowel function was not included for several reasons. Firstly, there is no validated measure of bowel dysfunction for MS in the literature. Secondly, the qualitative stage (phase 1) of the TONiC study did not identify bowel dysfunction to be influential to patients' QOL in MS. Thirdly, previous similar studies on spasticity, QOL and related impairments did not identify correlations between spasticity and bowel dysfunction (Arroyo et al., 2013; Oreja-Guevara, 2011; Rizzo et al., 2004). Finally, bladder and bowel dysfunction are known to be intimately related, therefore accounting for bladder dysfunction in the regression models will provide a proxy assessment of bowel dysfunction.

3.9.3.1. Fatigue – NFI-MS

Neurological fatigue index for multiple sclerosis (NFI-MS) is a self-report measure for fatigue which was developed and validated in a large sample (n=635) of patients with MS (Mills, Young, Pallant, & Tennant, 2010a). The items were derived from qualitative work with MS patients, which were then tested against strict assumptions of Rasch measurement model.

NFI-MS consists of 23 items and covers 4 domains: physical (8 items), cognitive (4 items), diurnal sleep (6 items) and nocturnal sleep (5 items). The summary scale (10 items) is derived from adding up physical (8 items) and cognitive subscale scores (2 items). All of the subscales were shown to fit to the Rasch model and met the requirement of unidimensionality. Test-retest analysis confirmed good reliability of the subscales (Spearman's correlation 0.796 to 0.864, Wilcoxon Signed Rank <0.05). Physical and cognitive scales showed better external validity (assessed by Modified Fatigue Impact Scale, VAS Fatigue, Fatigue Severity score (Spearman rank 0.58 to 0.71)) than diurnal and nocturnal sleep subscales (0.43 to 0.51).

The main advantage of NFI-MS compared to the previous scales assessing fatigue, such as Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS), is that raw scores can be converted to linear measurements. In addition, given fit to the Rasch model, summation of raw scores gives sufficient statistic of ordinal level of fatigue, hence it can be conveniently administered in clinical practice.

3.9.3.2. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) was developed by Zigmond and Snaith in 1983 with the aim to aid rapid detection and quantification of the two most common mood disorders: depression and anxiety (Zigmond & Snaith, 1983). Somatic manifestations of depression and anxiety were not included in the scale, in order to reduce false positives as a result of physical symptoms related to the underlying somatic disorder. The HADS contains 14 items with 4 response options (0-3).

The scale has been shown to have good internal consistency (Cronbach alpha 0.8-0.93) and high short term (<2 weeks) reliability (r>.80) (Herrmann, 1997). High

correlation of both subscales with the observer assessment support external validity of the scale (Herrmann, 1997).

Several studies employed HADS in the assessment of depression and anxiety in the MS population (Honarmand & Feinstein, 2009; Janssens, van Doorn, de Boer, Kalkers, et al., 2003; Janssens, van Doorn, de Boer, van der Meche, et al., 2003; Jones et al., 2012). Honarmand et al. examined psychometric performance of HADS in the MS sample (n=140), reporting high sensitivity and specificity of the depression subscale (Honarmand & Feinstein, 2009). A score of ≥8 was suggested to be the most optimal cut-off point both for anxiety and depression. The anxiety subscale was shown to be a reliable measure only in patients diagnosed with generalised anxiety disorder, but not with other anxiety-related conditions.

3.9.3.3. Disability - World Health Organisation Disability Assessment Schedule 2.0

WHODAS 2.0 is a disability assessment instrument which is based on the conceptual framework of the International Classification of Functioning, Disability and Health (ICF) (WHO, 2001). WHO defines disability as: '"a difficulty in functioning at the body, person, or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors" (WHO, 1980).

WHODAS 2.0 contains 36 items rated on the 5-point scale (1-no difficulty, 5-extreme or cannot do) and measures disability across 6 life domains: understanding and communicating (6 items), getting around (5 items), self-care (4 items), getting along with others (5 items), life activities (8 items), and participation in society (8 items) (Üstün, 2010). The instrument allows calculation of the global disability score (0-no disability, 100-worst disability) and the individual domain scores. SPSS syntax was obtained from the WHO website to calculate 'item-response theory' based scores for global and individual domains.

WHODAS 2.0 was developed and validated cross-culturally across 19 countries involving large study populations (Garin et al., 2010; Üstün, 2010). The scale has robust 7-factor structure with good internal consistency across all subscales (Cronbach's apha

0.79-0.96) and excellent retest reliability (r=0.98). External validity was supported by high correlation with other measures of disability and health, including SF-12, London Handicap Scale, WHOQOL-100 and Functional Independence Measure.

3.9.3.4. Bladder - SF-Qualiveen

SF-Qualiveen was developed based on the original 30-item Qualiveen questionnaire, which assess a broad range of urinary symptoms in neurological disorders, including incontinence, urgency and voiding problems (Bonniaud, Bryant, Parratte, Gallien, & Guyatt, 2006; Bonniaud, Bryant, Parratte, & Guyatt, 2008). SF-Qualiveen contains 8-items rated on 5-point response scale and covers 4 domains (2 items per domain): bother with limitations, frequency of limitations, fears and feelings. The scale was shown to have high correlation with original version of Qualiveen (r=0.7-0.92), however correlations with clinical history and symptoms was generally low (r=0.26=0.65). Internal consistency was high (0.83-0.9).

3.9.3.5. Neuropathic Pain Scale

The Neuropathic Pain Scale (NPS) was designed to assess qualitative and quantitative aspects of neuropathic pain (Galer & Jensen, 1997). The NPS was originally developed in patients with peripheral nerve conditions (diabetes, post-herpetic neuralgia), but since then has been validated in central causes of neuropathic pain, such as MS (Rog, Nurmikko, Friede, & Young, 2007).

The NPS consists of 11 items which are rated on a 10-point Likert Scale and address a broad range of pain experiences. 8 items interrogate different qualities of pain, including "Sharp," "Hot," "Dull," "Cold," "Sensitive," "Itchy," "Deep," and "Surface.". The remaining three items assess global severity of pain, temporality of pain and unpleasantness.

The scale has been shown to have acceptable internal consistency (Cronbach's alpha 0.78) and external validity (SF-12 bodily pain r=-0.49, Short Form McGill Pain Questionnaire r=0.63) (Rog et al., 2007). Short-term reliability of the scale was supported by moderate test-retest correlation (r=0.71).

3.10. Data Analysis

Statistical analysis of the data was carried out using Statistical Package for Social Sciences (SPSS) 20.0. Selected item reversal was performed before calculating total and domain scores. Missing data analysis at the item level showed less than 5% missing data. Conversion and summation of the item scores was performed in accordance with the guidance provided by the authors of the scales, i.e. computation of the WHOQOL-BREF and WHODAS 2.0 scores was done using SPSS syntax obtained from the WHO website. Reliability of the measures was assessed using Cronbach's alpha. A value greater than 0.7 was considered to be acceptable (Reynaldo & Santos, 1999).

For purposes of descriptive statistics, normally distributed data was presented as means, standard deviations and ranges. Frequency counts and percentages were used to present the results on categorical data. Assessment of normality of the data distribution was based on Q-Q plots, histograms, Kolmogorov-Smirnov test and Shapiro-Wilkinson test. Medians and interquartile ranges were used to describe not normally distributed data.

Depending on the type of data appropriate tests were used to detect statistically significant differences across four severity groups of spasticity. Letters in the brackets indicate what test was performed when reporting the results. One-way ANOVA (F) was used to assess normally distributed variables across three or more groups. Student t test (t) was used to compare two groups with normally distributed variables. The remaining comparisons were performed utilising non-parametric tests including Mann-Whitney U (U) for two groups and Kruskal-Wallis (H) for more than two groups. Chi – square test (χ^2) was employed to compare the differences across the groups with categorical variables. When less than five counts were observed, Fisher's exact test was used instead to determine statistical significance.

Spearman's rank correlation was use to describe the associations between spasticity and other variables (QOL, disability, fatigue, etc.). Differences in means and medians, were deemed statistically significant if p value was <0.05. Spearman's rank values were defined as follows: negligible ($r<0.2$), weak ($r=0.2$-0.39), moderate ($r=0.4$-0.59), high (0.6-0.79), very high (≥ 0.8) (Armitage, 1994). α value of <0.05 was

considered to represent statistically significant correlation. Bonferroni correction was used for multiple comparisons across the groups. For post-hoc ANOVA analysis, Tukey's HSD test was used to determine statistically significant differences.

3.10.1 Multiple regression analysis

The contribution of spasticity and other clinical and sociodemographic variables to predicting QOL was assessed using multiple regression analysis. Although questionnaire data which is based on the Likert-type scales is considered ordinal and not suitable for parametric testing, an assumption of linearity may be made with larger sample, multiple items and more than 5 point Likert-type response options (Baggaley & Hull, 1983; Carifio, 2007). For future studies, ideally the raw scores should be transformed to the interval-level data using the Rasch method (Rasch, 1960).

Several assumptions were sought and tested before accepting the validity of the regression models (Field, 2005):

1. Normal distribution of the dependent variables. The assumptions were tested visually using histograms and Q-Q plots, and statistically employing Komogorov-Smirnov test and Shapiro-Wilkinson test. However, with larger samples > 50 these are likely to be significant, hence these were only considered supplemental to visual plots.

2. Linear relationship between predictor and outcome variables. The linearity of the relationships was explored using scatter plots.

3. Homoscedasticity of the predictor variables. This implies that that the residuals at each level of the predictors should have the same variance. The assumption was tested using scatter plots of the standardised residuals.

4. Normally distributed errors. The residuals of the model are random, therefore they should be normally distributed with the mean of 0. This assumption was tested by examining distribution of the residuals using histogram.

5. Independent errors. The regression model assumes that the residuals should be uncorrelated. Durbin-Watson test is used to test the assumption. A value of 2 means that the residuals are uncorrelated (Field, 2005). Although there is no agreed cut off

points, values more than 1 and less than 3 are considered to be acceptable.

6. Multicollinearity. If more than one predictor is used, there should be no perfect correlation between them (Pearson's correlation >0.8 or >0.9) (Field, 2005). The correlations are tested by performing correlation matrix of the predictor variables. In addition, variance inflation factor (VIF) and tolerance statistic are used to investigate multicollinearity (Field, 2005). The average VIF value should be below 4 and the tolerance statistic above 0.2.

7. Outliers. Unusual cases were identify using 'case diagnostics' option on SPSS and were subsequently interrogated. It is expected that 5% of cases will be outliers which is consistent with 2 standard deviations. None of the regression analyses exceeded 5% limit.

Chapter 4 - Results

4.1. Missing data analysis

Less than 5% of missing data at the item level was detected. Missing values of the summary scores are shown in table 13. There were more missing data in the WHODAS domains compared to the remaining scales. Specific instructions regarding the process of dealing with missing values were followed and are summarised in appendix 2. There were no significant differences between subjects with and without missing values regarding age, sex, disease duration, type of MS and employment status.

Table 13. Missing data from the total or domain scores

Measure	Number of patients	Percentage
MSSS-88 stiffness	2	0.4
MSSS-88 pain and discomfort	2	0.4
MSSS-88 spasms	2	0.4
SF- Qualiveen	2	0.8
NFI-MS	0	0
HADS-A	3	1.2
HADS-D	3	1.2
WHOQOL-Physical	1	0.4
WHOQOL-Psychological	2	0.8
WHOQOL-Social relationships	3	1.2
WHOQOL-Environment	1	0.4
LMSQOL	8	3.2
WHODAS-communication	7	2.7
WHODAS-getting around	10	3.8
WHODAS-self-care	3	1.2
WHODAS-getting along	3	1.2
WHODAS-life activities	8	3.1
WHODAS-participation	10	3.8
NPS	3	1.2

4.2. Reliability of the scales

Cronbach's alpha was calculated to assess the reliability of the measures. Cronbach's alpha values of the scales and subscales are presented in table 14. Good internal consistency was confirmed across all the measures with values higher than 0.7.

WHOQOL-BREF social relationships domain had a borderline Cronbach's alpha (0.7), which is consistent with the findings from the previous studies (WHO, 1998a).

Table 14. Internal consistency of the measures

Measure	Cronbach's alpha	No of items
MSSS-88 stiffness	0.96	12
MSSS-88 pain and discomfort	0.95	9
MSSS-88 spasms	0.96	14
SF-Qualiveen	0.94	8
NFI-MS physical	0.94	8
NFI-MS cognitive	0.87	4
NFI-MS abnormal sleep	0.81	5
NFI-MS overall fatigue	0.94	10
HADS-A	0.87	7
HADS-D	0.79	7
WHOQOL-Physical	0.83	7
WHOQOL-Psychological	0.83	6
WHOQOL-Social relationships	0.71	3
WHOQOL-Environment	0.82	8
LMSQOL	0.80	8
WHODAS	0.98	36
NPS	0.94	10

4.3. Response rates

186 questionnaires were administered during the initial mail out in December 2013 to the participants who had previously given phase 2 and/or phase 3 consent. After having made the follow up calls to the non-responders, a total of 122 (65.6%) patients returned completed questionnaires packs.

During the period between 6 January 2014 and 17 March 2014 190 participants were recruited and given the questionnaires packs in the clinics. 103 (54.3%) questionnaires were returned following the reminder calls to the non-responders. A total of 225 completed questionnaires were received at the Walton centre (225/376, 59.8% response rate). Together with 25 questionnaires from Preston and 10

questionnaires from Salford, a total of 260 participants were included in the data analysis.

4.4. Sociodemographic characteristics

Sociodemograpahic information of the sample is summarised in the Table 15. Mean age of the participants was 50.8 years (SD 11.8, range 22-76). 178 (63.5%) were female, with male to female ratio 1:2.2. Majority of the patients had relapsing-remitting MS (122, 46.9%), followed by secondary progressive (66, 25.4%), rapidly evolving (40, 15.4%) and primary progressive MS (28, 10.8%). Median duration of the disease was 10 years (range 1-47). Only 32 patients (12.3%) had had a relapse in the preceding year. The sample included a broad range of disability levels. 101 (38.8%) patients had EDSS score below 4, 122 (46.8%) had EDSS score 4.5-6.5 and the rest of the sample (36, 13.8%) were classed as EDSS 7-9.5.

Only 57 (21.9%) participants were in full time and 36 (13.8%) in part time employment. A third of the whole sample were retired due to medical reasons. Majority of the subjects were married or cohabiting (185, 71%). Less than a fifth of patients were single or separated (42, 16.2%). A small minority were divorced (18, 6.9%) or widowed (11, 4.2%).

Table 15**.** Sociodemographic characteristics of the sample

Characteristics	
Total sample	n=260
Age	
Mean (SD)	50.8 (11.8)
Range	22-76
Sex (%)	
Female	178 (68.4)
Male	81 (31.2)
Unknown	1 (0.0)
MS type (%)	
Relapsing-remitting	122 (46.9)
Rapidly evolving	40 (15.4)

Secondary progressive	66 (25.4)
Primary progressive	28 (10.8)
Unknown	4 (0.02)
Duration of disease (years)	
Median (IQR)	10 (15)
Mean (SD)	13.1 (9.6)
Range	1-47
1 or more relapse in the last year (%)	32 (12.3%)
EDSS score (%)	
0-4	101 (38.8)
4.5-6.5	122 (46.8)
7.0-7.5	12 (4.6)
8.0-9.5	24 (9.2)
Unknown	1 (0.0)
Employment status (%)	
Full time employment	57 (21.9)
Medically retired	76 (29.2)
Unemployed	17 (6.5)
Part-time	36 (13.8)
Retired	47 (18.1)
Not working for other reasons	23 (8.8)
Unknown	4 (0.02)
Marital Status (%)	
Single/separated	42 (16.2)
Married/cohabiting	185 (71.2)
Divorced	18 (6.9)
Widowed	11 (4.2)
Unknown	4 (0.02)
Centre (%)	
Walton centre	225 (86.5)
Preston	25 (9.6)
Salford	10 (3.8)

SD: standard deviation, IQR: interquartile range

4.5. Sociodemographic characteristics of non-responders

Sociodemographic information of the sample was compared with the non-responders to identity the sources of selection bias. Table 16 summarises demographic characteristics of the non-responders. There were no significant differences between the groups regarding sex, disease duration, MS type and EDSS score ($p>0.05$). The

non-responders were younger (mean age 47.6, SD 12.1), which was statistically significant (p=0.006).

Table 16. Sociodemographic characteristics of the non-responders

Characteristic		p value
Sample	151	
Age		
Mean (SD)	47.6 (12.1)	p = 0.006
Female, %	66.2	p=0.126
Duration		
Mean (SD)	12.0 (10.4)	p = 0.088
MS type, %		p = 0.146
Relapsing-remitting	44.7	
Rapidly evolving	24.7	
Secondary progressive	20.7	
Primary progressive	10.0	
EDSS score, %		p=0.746
0-4	43.0	
4.5-6.5	42.2	
7.0-7.5	6.0	
8.0-9.5	8.6	

Note: p values <0.05 indicate statistically significant difference between responders and non-responders

4.6. Spasticity characteristics

Spasticity was assessed using NRS and MSSS-88 three physical subscales (stiffness, pain and discomfort, spasms). The following values of the NRS spasticity were used to categorise patients into 4 groups according to increasing levels of severity: none (0), mild (1-3), moderate (4-6), severe (7-10) (Arroyo et al., 2013; Flachenecker et al., 2014; Svensson et al., 2014). The mean of the NRS spasticity of the overall sample was 4.3 (SD 3.0) (table 17). Majority of the patients had at least some

degree of spasticity (219, 84.8%) with nearly a third of patients reporting severe spasticity (76, 29.2%).

Table 17. NRS spasticity and MSSS-88 scores

Spasticity characteristics	
NRS spasticity (n=257)	
No (NRS <1) (%)	41 (15.8)
Mild (NRS 1-3) (%)	70 (26.9)
Moderate (4-6) (%)	70 (26.9)
Severe (7-10) (%)	76 (29.2)
NRS total mean (SD)	4.3 (3.0)
MSSS-88 (n=257)	
Stiffness (median, min-max)	25 (12-48)
Pain and discomfort (median, min-max)	17 (9-36)
Spasms (median, IQR)	21 (14-56)

239 patients completed three subscales of MSSS-88. The patients were instructed not to complete the questionnaire if they did not experience spasticity in order to relieve participant's burden. However, there was some discrepancy when comparing MSSS-88 completion rate with the NRS spasticity results, as 41 patients scored 0 on the NRS, while only 21 patients did not complete MSSS-88. This is most probably as a result of failure to read the instructions, with patients without spasticity completing the questionnaire. Minimal values for each of three MSSS-88 subscales were assigned to those 21 persons who did not complete the questionnaire in order to retain these subjects in the analysis. The results of MSSS-88 subscales are shown in table 17.

4.7. Spasticity in relation to sociodemographic and disease parameters

Several clinical and sociodemographic variables were found to be associated with increased severity of spasticity (table 18). Older age was significantly associated with higher degrees of spasticity ($F(3) = 5.3$, $p=0.001$). Patients with severe spasticity were

more likely to have a progressive type of MS (χ^2 = 33.4, p<0.001). No difference was observed between SPMS and PPMS (p=1.0). Interestingly, duration of MS appeared not to have a significant effect on spasticity levels (H (3) = 4.5, p=0.213). Since PPMS could have confounded the results, duration of disease was compared after excluding PPMS patients, however no statistical significance was observed (H (3) = 4.24, p=0.229). Patients diagnosed within 4 years had a similar degree of spasticity (4.1, SD 2.7) when compared to those with over 20 years of disease activity (4.9, SD 2.8, p=0.86).

Spasticity increased in parallel to worsening disability (χ^2 =56.3, p<0.001). However, less than a third (27.6%) of patients with severe spasticity had EDSS score >6.5, with a majority of patients experiencing moderate or severe spasticity at lower levels of disability. More patient with severe spasticity had a relapse were in the preceding year, however this was not statistically significant (χ^2 = 1.66, p=0.657). Severity of spasticity did not significantly differ between RRMS and REMS (U=2.56, 0.364). There were no significant differences in sex across the spasticity groups (p=0.326). Patients were less likely to be employed as spasticity levels increased, with only 21.3% of participants with severe spasticity in full or part time employment.

Table 18**.** Spasticity in relation to sociodemographic and MS characteristics

	Spasticity				
	None	**Mild**	**Moderate**	**Severe**	p value
Age (mean, CI)	45.5 (42.0-49.3)	49.9 (47.1-52.5)	51.4 (48.8-54-4)	54.26 (51.9-56-7)	0.001
Sex (female %)	70.7	72.5	72.9	60.5	0.326
MS type (progressive %)	14.6	19.1	44.9	57.3	0.001
Duration of MS (median, IQR)	9 (11)	9 (14)	10.5 (18)	12.5 (16)	0.216
Relapse in the last 12 months (%)	4 (11.4)	10 (18.2)	8 (21.1)	7 (21.9)	0.657
Disabled (EDSS>6.5) (%)	2.4	5.8	14.3	27.6	<0.001
In employment (%)	61.0	41.2	31.9	21.3	<0.001

4.8. Quality of Life profile of the sample

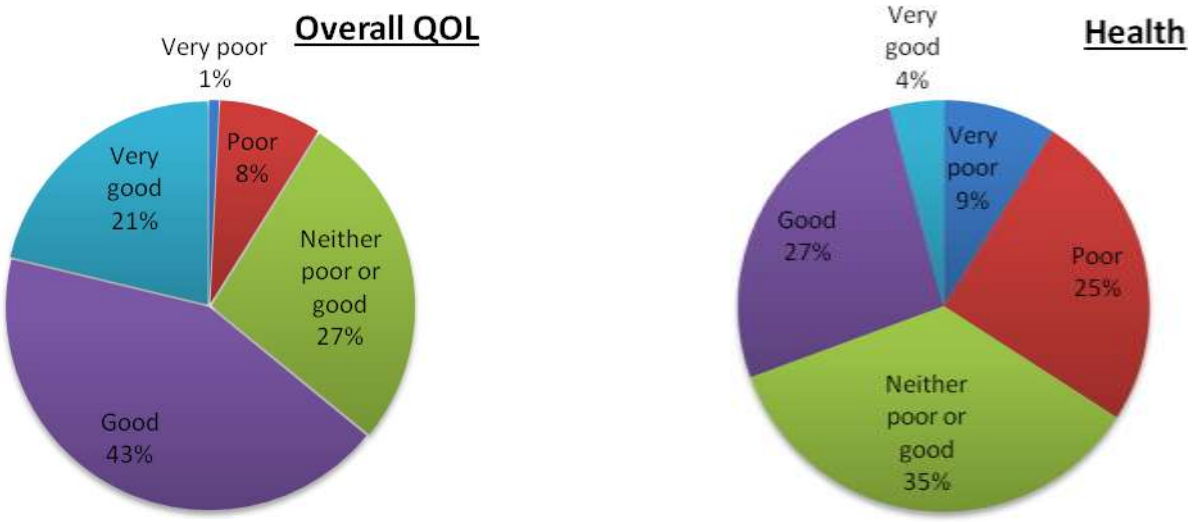
QOL was assessed by two measures: the LMSQOL and WHOQOL-BREF. Table 19 summarises QOL scores of an overall sample. The mean score on the LMSQOL scale was 10.0 (SD 4.6) with scores ranging from 1 (better QOL) to 22 (worse QOL). The WHOQOL-BREF raw scores were transformed on a 4-20 scale. All domain scores are scaled in positive direction (higher score indicates better QOL). Mean scores were 13.8 (SD 3.2) on the physical domain, 14.1 (SD 2.8) on the psychological domain, 14.5 (SD 3.3) on the social relationships domain and 15.0 (SD 2.5) on the environment domain.

Table 19**.** QOL scores of the sample

QOL instrument	**Score**
LMSQOL	
Mean (SD, min-max)	10.0 (4.6, 1-22)
WHOQOL-BREF (SD, min-max)	
Physical	13.8 (3.2, 6.3-20)
Psychological	14.1 (2.8, 5.33-20)
Social relationships	14.5 (3.3, 4-20)
Environment	15.0 (2.5, 8-20)

Figure 6 shows how patients rated their QOL and health. Majority of the patients reported their QOL as good (111, 42.9%), with only 23 participants (8.9%) rating QOL as poor or very poor. In contrast, patients rated their health worse, with more than a third (88, 34.1%) reporting as being dissatisfied or very dissatisfied with their health. Only 11 patients (4.3%) were very satisfied with their health.

Figure 4. WHOQOL-BREF quality of life and health ratings



4.8.1. Quality of life in relation to sociodemographic and disease characteristics

Several sociodemographic and clinical parameters were examined in relation to the LMSQOL scores and four domains of the WHOQOL-BREF (table 20). Age was found to be an insignificant factor on both measures, except for physical domain of the WHQOL-BREF ($F(3) = 6.2$, $p<0.001$), with older patients reporting worse physical health. There were no significant differences in QOL scores across both sexes, except for social relationships domain with females reporting better QOL ($t(254) = 2.6$, $p=0.01$). Disability, measured by EDSS, was strongly associated with worse QOL across all the domains on the WHOQOL-BREF and LMSQOL. However, the relationship between disability and QOL was not linear (figure 7). While there was a significant difference in LMSQOL scores between mild (EDSS 0-4, median 9.0) and moderate disability (EDSS 4.5-6.5, median 11.0) ($H(3) = 12.1$, $p=0.007$), no statistical significance was observed using pairwise comparisons between mild or moderate disability and most disabled group (EDSS 8-9.5) ($H(3) = -1.0$, $p=1.0$). Similar observations were found in relation to the WHOQOL-BREF domains, except for physical domain (patients with higher EDSS grade had consistently lower scores on the physical domain).

While there was no statistical difference in LMSQOL scores between different MS types (p=0.498), QOL was worse across all of the WHOQOL-BREF domains in progressive types of MS compared to relapsing remitting or rapidly evolving MS (p<0.001). There was no statistical difference between SPMS and PPMS groups (p=0.95). Longer duration of MS was associated with only marginally lower QOL scores on the both measures, which was not statistically significant (p>0.05). Patients in full or part time employment had significantly higher scores compared to unemployed or retired (LMSQOL t (247) = 2.134, p=0.33). Marital status was found to be significant only in relation to the WHOQOL-BREF Social relationships and Environment domains (Social relationships t (251) = 2.89, p=0.004, Environment t (253) = 2.35, p=0.019).

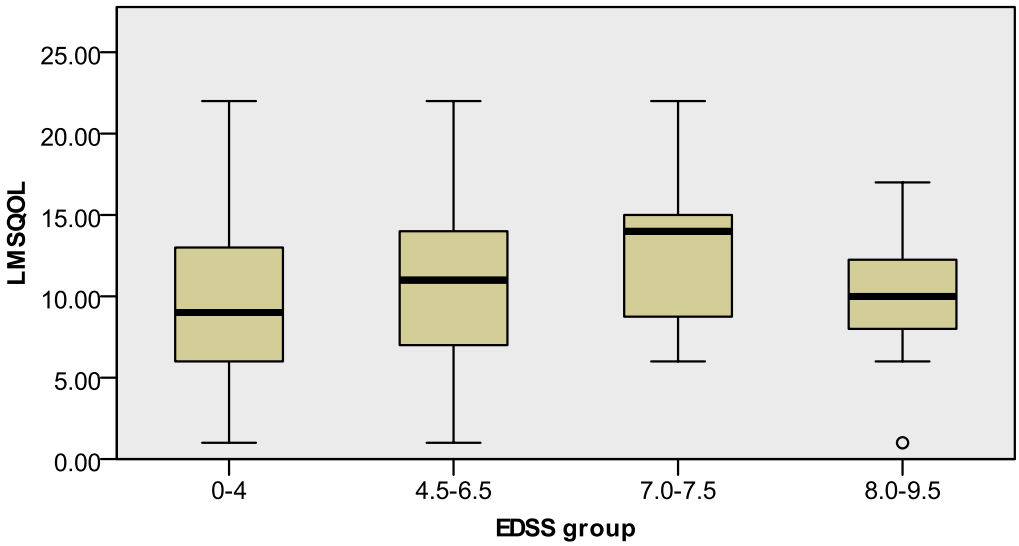
Table 20**.** QOL in relation to sociodemographic and disease parameters

	LMSQOL	**WHOQOL Physical**	**WHOQOL Psychological**	**WHOQOL Social relationships**	**WHOQOL Environment**
Age (n), mean (SD)					
22-42 (59)	10.2 (5.2)	14.1 (3.4)*	14.2 (3.2)	14.9 (3.4)	15.0 (2.6)
43-51 (63)	9.8 (4.8)	13.7 (3.2)*	14.3 (2.8)	15.0 (3.5)	15. 0 (2.8)
52-59 (70)	10.1 (4.5)	12.8 (3.1)*	13.9 (2.9)	14.3 (3.3)	15.1 (2.5)
over 60 (70)	9.6 (3.9)	11.9 (2.6)*	13.8 (2.3)	13.9 (3.1)	14. 9 (2.1)
Sex (n)					
Male (81)	10 (5.1)	13.2 (3.1)	14.2 (2.8)	13.7 (3.3)*	14.7 (2.6)
Female (177)	10 (4.0)	13.1 (3.2)	14.0 (2.8)	14.9 (3.3)*	15.1 (2.5)
EDSS (n), median (IQR)					
0-4 (97)	9.0 (7)***	15.4 (4.3) ***	15.3 (3.7) ***	16 (3.3) ***	16 (3.1) ***
4.5-6.5 (118)	11 (7) ***	12.0 (4.6) ***	13.8 (4) ***	14.7 (4.0) ***	15 (4.0) ***
7.0-7.5 (12)	14 (6) ***	10.5 (4.5) ***	12.6 (5.7) ***	13.3 (4.5) ***	13 (3.9) ***
8-9.5 (22)	10 (4) ***	11.4 (3.5) ***	12.7 (3.0) ***	14.0 (4.7) ***	14.5 (2.1) ***

MS type					
RR (122)	9.7 (4.8)	14.0 (3.2)***	14.7 (4)**	16 (4)***	16. 0 (4)**
RE (40)	9.5 (5.2)	14.2 (3.2)***	15.3 (4.3)**	16 (2.7)***	15.3 (3.4)**
PP (27)	10.3 (4.5)	11.8 (2.6)***	12.7 (4)**	13.3 (4)***	15.0 (3.5)**
SP (66)	10.7 (3.9)	11.5 (2.5)***	13.3 (3.3)**	13.3 (4.3)***	14.8 (2.5)**
Duration					
1-4 (54)	10.1 (4.8)	13.9 (3.3)	15.3 (4)	14.5 (3.5)	15.3 (2.5)
5-9 (65)	10.5 (4.7)	13.3 (3.3)	14.5 (3.3)	14.8 (3.0)	14.6 (2.5)
10-19 (71)	9.8 (4.8)	13.1 (3.4)	14.7 (4.7)	14.6 (3.6)	15.1 (2.8)
20 plus (67)	10.0 (4.2)	12.4 (2.8)	13.7 (3.3)	14.3 (3.2)	15.0 (2.2)
In Employment					
Yes (93)	9.2 (4.5)*	15.1 (2.8) ***	15.0 (2.8) ***	15.2 (2.8)*	15.6 (2.3)**
No (162)	10.5 (4.6)*	12.0 (2.8) ***	13.6 (2.5) ***	14.2 (3.5)*	14.7 (2.6)**
Married					
Yes (185)	9.86 (4.4)	13.2 (3.1)	14.3 (2.8)	14.3 (2.7)**	15.2 (2.5)*
No (71)	10.47 (5.1)	12.9 (3.6)	13.6 (2.9)	13.6 (2.9)**	14.4 (2.5)*

*p <0.05, **p<0.01, ***P <0.001

Figure 5. LMSQOL scores compared across EDSS groups



4.8.2. Spasticity and QOL

Table 21 shows the comparisons of QOL scores using one-way ANOVA across four spasticity groups. The LMSQOL scores were significantly higher (worse QOL) in patients with increasing severity levels of spasticity (F (3) = 7.9, p<0.001). Post-hoc

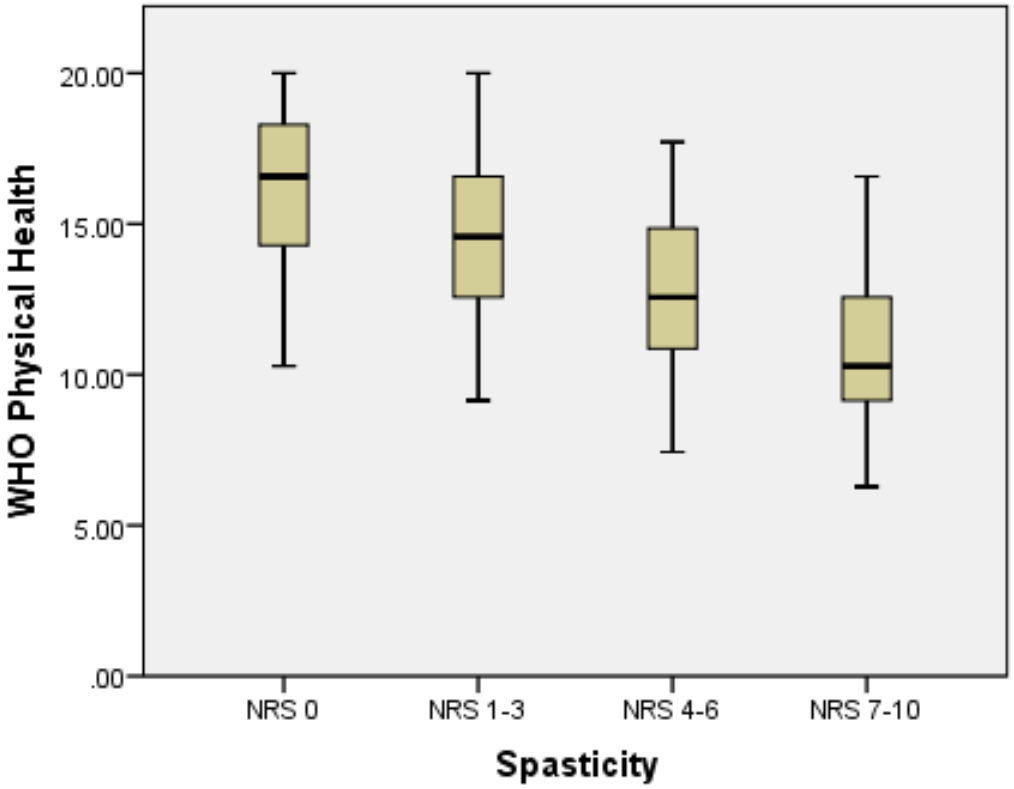
comparisons using Tukey's HSD test showed that significant differences were found between none or mild spasticity and severe spasticity, but not between other groups.

Table 21**.** Spasticity and QOL

	Spasticity				
	None	**Mild**	**Moderate**	**Severe**	p value
LMSQOL (mean, SD)	8.32 (4.3)	8.94 (4.5)	10.13 (4.6)	11.92 (4.2)	<0.001
WHOQOL – BREF (mean, SD)					
Physical	16.0 (2.7)	14.4 (2.8)	12.5 (2.7)	11.0 (2.4)	<0.001
Psychological	15.4 (2.7)	15.1 (2.3)	13.7 (2.7)	12.9 (2.7)	<0.001
Social relationships	15.2 (3.2)	15.6 (3.0)	14.3 (3.3)	13.5 (3.4)	<0.001
Environment	16.6 (2.3)	15.9 (2.4)	14.6 (2.5)	13.8 (2.0)	<0.001

Similar trends were observed on the WHOQOL-BREF domains. Increasing severity of spasticity had the most pronounced effect on the Physical domain scores ($F(3) = 41.1$, $p<0.001$). Post-hoc tests revealed that physical domain scores decreased significantly (worse QOL) at every stage of advancing spasticity. There were significant differences across all groups, except between none or mild spasticity on Psychological domain ($F(3) = 13.0$, $p<0.001$). Social relationships domain scores were significantly different between none or mild and severe spasticity ($F(3) = 5.9$, $p=0.001$). Environment domain scores worsened as spasticity increased ($F(3) = 16.3$, $p<0.001$). However, post-hoc Tukey's HSD showed that there appeared to be only a significant difference between NRS 0-3 and NRS 4-10 groups on the Environment domain.

Figure 6. WHQOL Physical Health in relation to spasticity



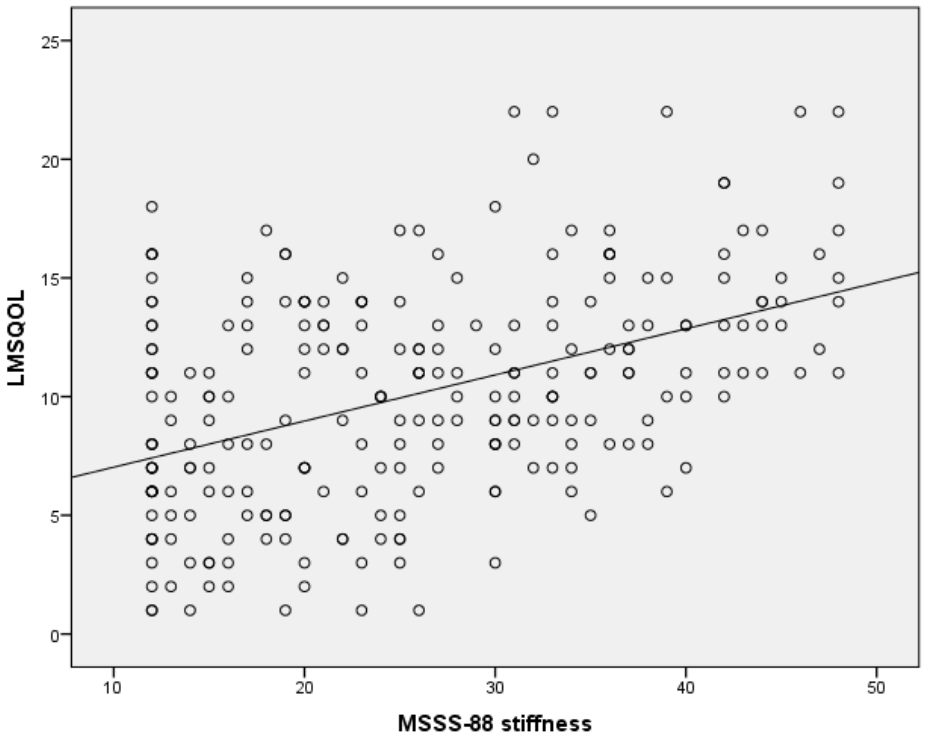
Spearman's rank correlations were carried out to investigate the relationship between three MSSS-88 subscales and QOL (table 22). Statistically significant correlations ($p<0.001$) were found between all MSSS-88 subscales and the LMSQOL and WHOQOL-BREF domains. Pain and discomfort subscale of the MSSS-88 correlated particularly strongly with both QOL measures ($r = -0.3$ - -0.7, $p<0.001$). Overall, spasticity correlated less well with the LMSQOL compared to the WHOQOL-BREF domains. Spasticity was found to be strongly associated with physical, psychological and environment domains, but less so with social relationships domain.

Table 22**.** Spearman's rank correlation (*r)* between spasticity and QOL

	Stiffness	**Pain and discomfort**	**Spasms**
LMSQOL	0.42	0.40	0.36
WHOQOL-BREF			
Physical	-0.64	-0.70	-0.61
Psychological	-0.48	-0.47	-0.43
Social relationships	-0.31	-0.30	-0.31
Environment	-0.45	-0.45	-0.44

p<0.001

Figure 7. Linear relationship between LMSQOL and MSSS-88 stiffness subscale



4.9. Disability profile of the sample

Disability was assessed with the WHODAS 2.0. The scores were transformed on a 0-100 scale. Higher scores indicating higher degree of disability. Since majority of the patients were not in employment, domain scores regarding work were not calculated. Table 23 shows the means, standard deviation and ranges of WHODAS domain scores. Mean score of overall WHODAS 2.0 was 33.81 (SD 22.2, range 0-89.7). Domains with the highest scores were 'Getting around' (mean 48.1, SD 31.4) and 'Life activities' (mean 52.23, SD 33.2).

Table 23**.** WHODAS 2.0 domain scores of the sample

n=234	**Mean (SD)**	**min-max**
Communication	24.42 (23.5)	0-95
Getting around	48.71 (31.4)	0-100
Self-care	26.20 (29.6)	0-100
Getting along with people	22.57 (16.7)	0-91.7
Life activities	52.23 (33.2)	0-100
Participation in society	33.22 (24.1)	0-100
Total disability	33.81 (22.2)	0-89.7

4.9.1. Spasticity and Disability

Spasticity was found to be closely related to disability. Table 24 shows comparisons of the total WHODAS 2.0 scores across the spasticity groups. Pairwise comparison between the groups showed that disability levels were significantly higher in patients with increasing spasticity (H (3) = 84.63, p<0.001). Disability was worse but not statistically significantly different between none and mild spasticity (p=0.266).

Table 24**.** Disability in relation to spasticity

	Spasticity				
	None	**Mild**	**Moderate**	**Severe**	p value
Total WHODAS 2.0 Score (median, IQR)	10.87 (17.4)	20.1 (25.5)	37.37 (26.6)	50.51 (30.4)	<0.001

Moderate to high correlations were observed between spasticity and individual domains of WHODAS 2.0 (r=0.43-0.71, p<0.001). As expected, the correlations were lower between spasticity and 'Understanding and Communicating' and 'Getting along with people' domains (r=0.43-0.49). Physical domains regarding self care, mobility and participation in society showed strongest correlations with spasticity (r=0.54-0.71).

Table 25. Spearman's rank correlations (*r)* between spasticity and disability

	Stiffness	**Pain and discomfort**	**Spasms**
WHODAS 2.0			
Understanding and Communication	0.43	0.49	0.46
Getting around	0.71	0.66	0.65
Self-care	0.61	0.58	0.59
Getting along with people	0.47	0.48	0.45
Life activities	0.57	0.54	0.52
Participation in the society	0.60	0.55	0.54
Overall disability	0.70	0.68	0.68

p<0.001

4.10. Depression and Anxiety

Mood disorder was measured using the Hospital Anxiety and Depression Scale (HADS). Cut-off point of ≥8 was applied for both anxiety and depression scales (Honarmand & Feinstein, 2009). Mean depression score (HADS-D) was 5.6 (SD 3.7). Almost a third (74. 28.5%) of the total sample had depression (HADS-D ≥8). Mean anxiety score was 7.1 (4.0) and 111 (42.7%) had a score of ≥8 on the HADS-A.

4.10.1. Depression in relation to sociodemographic and clinical characteristics

Several demographic and MS related variables were compared between patients with (n=74) and without depression (n=182) (table 26). No difference in age of the participants was found between the two groups (t (253) = -0.301, p =0.764). Male to female ratio was similar in both groups (69.8% vs. 66.2% female, χ^2 (1) = 0.311, p=0.656). Patients with advanced EDSS (>6.5) were more likely to be depressed,

however this was not statistically different (χ^2 (1) =1.34, p=0.247). Progressive disease course was found to be significantly associated with depression (χ^2 (1) = 7.2, p=0.008). There was no significant difference in duration of disease between patients with and without depression (U = 6771.5, p = 0.809). Significantly smaller proportion of patients in the depression group were in employment (20.5%) compared to depression-free group (42%) (χ^2 = (1) = 10.6, p=0.001).

Table 26**.** Comparison of sociodemographic and disease characteristics between depressed and depression-free groups

	Depression	**No depression**	p value
Age (mean, SD)	51. 1 (12.0)	50.6 (11.7)	0.764
Sex (female %)	49 (66.2)	127 (69.8)	0.656
Progressive (%)	36 (49.5)	57 (31.5)	0.008
Duration (median, IQR)	11 (14)	10 (15)	0.809
EDSS >6.5 (%)	13 (17.6)	22 (12.1)	0.247
In Employment (%)	16 (20.5)	76 (42)	0.001

4.10.2. Anxiety and its relation to sociodemographic and clinical characteristics

Only younger age was found to be significantly associated with anxiety (t (253) = 2.05, p=0.046), while no significant differences were found across other clinical and sociodemographic parameters including sex (χ^2 (1)= 0.035, p=0.852), EDDS score (χ^2 (1)=0.004, p=0.949), progressive type (χ^2 (1)=1.923, p=166), employment (χ^2 (1)=0.093, p=0.76) and disease duration (U = 7252, p=0.215) (table 27).

Table 27**.** Comparison of sociodemographic and disease characteristics between anxiety and anxiety-free groups

	Anxiety	**No anxiety**	p value
Age (mean, SD)	49.1 (11.8)	52.1 (11.8)	0.046
Sex (female %)	77 (69.4)	99 (68.3)	0.852
Progressive (%)	35 (31.8)	58 (40.3)	0.166
Duration (median, IQR)	10 (12)	11 (16)	0.215
EDSS >6.5 (%)	15 (13.5)	20 (13.8)	0.949
In Employment (%)	40 (37)	51 (35.2)	0.76

4.10.3. Spasticity and its relation to depression and anxiety

Cases of depression and anxiety were compared across four spasticity groups (table 28). There was a significantly larger proportion of patients with depression at more severe levels of spasticity (17.1% in none vs. 45.3% in severe spasticity, χ^2 (3) = 19.888, p<0.001). Modest correlations were detected between three MSSS-88 subscales and HADS-D (r=0.38-0.43, p<0.01) (table 29).

Table 28**.** Cases of depression and anxiety in spasticity groups

	Spasticity				
	None	**Mild**	**Moderate**	**Severe**	p value
Depression (%)	7 (17.1)	10 (14.5)	21 (30.4)	34 (45.3)	<0.001
Anxiety (%)	15 (36.6)	28 (40.1)	27 (39.1)	39 (52.0)	0.289

In contrast, only weak correlations were found between MSSS-88 subscales and HADS-A (r=0.22-0.25) (table 29). There was no statistical difference in number of anxiety cases across spasticity groups, although there was a positive trend between increasing spasticity and higher prevalence of anxiety (χ^2 (3) = 3.754, p = 0.289).

Table 29**.** Spearman's rank correlation (*r)* between spasticity and QOL

	Stiffness	**Pain and discomfort**	**Spasms**
Depression	0.43	0.42	0.38
Anxiety	0.22	0.25	0.23

p<0.01

4.11. Spasticity and Fatigue

Three subscales of the NFI-MS were used in the assessment of fatigue and abnormal sleep. The mean score of the overall fatigue was 19.6 (SD 6.8, range 0-30). Table 30 shows the comparisons of fatigue levels across four spasticity groups. There was a significant increase in the overall fatigue scores as the levels of spasticity increased (H (3) = 52.03, p<0.001). Pairwise comparisons with adjusted p-values showed that there was no significant difference between none and mild spasticity (p=0.2) as well as moderate and severe spasticity (p=0.942). Similar trend was observed in relation to physical fatigue subscale (H (3) = 52.3, p<0.001). One-way ANOVA showed that cognitive fatigue was also significantly affected by spasticity (F (3) = 116.9, p < 0.001). Post hoc Tukey HSD showed that there was no statistically significant difference between none and mild spasticity (p=0.07) and moderate and severe spasticity (p=0.789). It appears that presence of spasticity in determining fatigue is less significant at mild and extreme levels of spasticity.

Table 30**.** Spasticity and fatigue (NFI-MS)

	Spasticity				
	None	**Mild**	**Moderate**	**Severe**	p value
Overall fatigue (median, IQR)	16.0 (9)	17 (9)	21 (9)	23 (7)	<0.001
Physical (median, IQR)	13 (8)	15 (9)	17 (7)	19 (7)	<0.001
Cognitive fatigue (mean, SD)	4.2 (3.1)	5.6 (3.1)	7.0 (3.1)	7.4 (2.8)	<0.001
Abnormal nocturnal sleep (mean, SD)	7.1 (3.1)	7.9 (3.7)	8.9 (2.9)	9.71 (2.8)	<0.001

Abnormal nocturnal sleep was also found to be affected by increasing levels of spasticity ($F(3) = 78.88$, $p<0.001$). Post hoc analysis showed slightly different trends in comparison to physical and cognitive fatigue. Patients with no spasticity had significantly less abnormal nocturnal sleep compared to moderate ($p=0.017$) and severe spasticity ($p<0.001$), but not mild spasticity ($p=0.56$). There was no significant difference between mild and moderate spasticity, but there was a significant difference between mild and severe spasticity ($p=0.003$).

Table 31 shows Spearman's rank correlations between three MSSS-88 subscales and the NFI-MS domains. Moderate correlations were found between spasticity and overall, physical and cognitive fatigue ($p<0.001$). Pain and discomfort subscale had higher correlations with NFI-MS than other two MSSS-88 subscales. Spasticity was found to correlate more closely with physical fatigue ($r=0.51$-0.61) compared to cognitive fatigue ($r=0.41$-0.5). Weakest correlations were observed between abnormal nocturnal sleep and spasticity ($r=0.35$-0.47).

Table 31**.** Spearman's rank correlation (*r)* between spasticity and fatigue

	Stiffness	**Pain and discomfort**	**Spasms**
NFI – MS - overall	0.51	0.61	0.52
NFI – MS - physical	0.52	0.61	0.52
NFI – MS- cognitive	0.41	0.5	0.42
NFI-MS – abnormal nocturnal sleep	0.35	0.47	0.4

$p<0.01$

4.12. Spasticity and Pain

Neuropathic Pain Scale (NPS) was used to assess the severity, type and range of pain experiences in patients with MS. Fifty participants reported no pain and were instructed not to complete the questionnaire. In order to include these participants in the analysis, the score of 0 was assigned to each NPS subscale. Total mean NPS score was 29 (SD 24.8, range 0-100) (table 32). Data on the temporality of pain was available only for 160 subjects (a total of 100 patients excluded). 50 patients selected more than one option with regards to temporality of pain, which precluded using the data according to the instructions. Constant background pain with breakthrough pain was the most common type of pain experienced by MS patients (84, 52.5%). More than a third experienced occasional pain (59, 36.9%), while 10.6% had constant pain.

Table 32**.** Pain characteristics on NPS scale

(n=258)	**Mean**	**SD**	**Range**
Intensity	3.4	3.1	0-10
Sharp	3.1	3.2	0-10
Burning	2.6	3.2	0-10
Dull	3.5	3.1	0-10
Cold	2.1	2.9	0-10
Sensitive	2.5	3.1	0-10
Itchy	1.9	2.9	0-10
Unpleasant	3.8	3.2	0-10
Deep	3.6	3.4	0-10
Surface	3.1	3.1	0-10
Total	29.7	24.8	0-100

When total NPS scores were compared across four spasticity groups, there was a significant trend of increasing pain prevalence in parallel to worsening spasticity (H (3) = 52.25, p<0.001) (table 33). Pairwise comparisons showed significant differences in pain levels in all groups, except between moderate and severe spasticity (p=0.14) as well as moderate and mild spasticity (p=0.125)

Table 33**.** Total NPS scores compared across spasticity groups

	Spasticity				
	None	**Mild**	**Moderate**	**Severe**	p value
NPS total (median, IQR)	0 (20)	22 (34)	27 (34)	47 (33)	<0.001

Table 34 shows the Spearman's rank correlations between different types of pain and MSSS-88 spasticity subscales. There was a moderate correlation between spasticity and total NPS score (r=0.53-0.6, p<0.001). Highest correlations were observed between spasticity and 'intense', 'sharp', 'dull', 'unpleasant' and 'deep' pain (r=0.41-

0.62). The correlations were weak to modest between spasticity and superficial or allodynic pain ('burning', 'cold', 'sensitive', 'itchy' and surface') (r=0.33-0.45, p<0.001). As expected, pain and discomfort subscale correlated better with NPS than stiffness or spasms subscales (r=0.6 (pain and discomfort) vs. r=0.53 (stiffness) and r=0.53 (spasms)).

Table 34**.** Spearman rank correlation s between spasticity and NPS domains

n=(256)	**Stiffness**	**Pain and discomfort**	**Spasms**
Intensity	0.52	0.60	0.53
Sharp	0.51	0.57	0.49
Burning	0.38	0.47	0.38
Dull	0.44	0.52	0.46
Cold	0.38	0.39	0.39
Sensitive	0.38	0.42	0.39
Itchy	0.33	0.36	0.34
Unpleasant	0.49	0.57	0.46
Deep	0.51	0.58	0.51
Surface	0.41	0.49	0.39
Total	0.53	0.60	0.53

p<0.01

4.13. Spasticity and bladder dysfunction

Bladder dysfunction and its impact was assessed by the SF-Qualiveen. The mean score of the total SF-Qualiveen was 1.25 (IQR 2). Table 35 shows the severity of the overall bladder dysfunction in relation to worsening spasticity. It was found that patients with more severe spasticity had significantly more bladder problems (higher SF-Qualiveen score) (H (3) = 33.23, p < 0.001). Pairwise comparisons with adjusted values showed that there was no statistically significant difference between mild spasticity and none (p=1.0) or moderate spasticity (p=0.364). In contrast, at more severe levels of spasticity the SF-Qualiveen scores were significantly higher in patients with severe spasticity compared to moderate spasticity (median 2.38 (IQR 2.1) vs. median 1.25 (IQR 1.76), p=0.045).

Table 35**.** Bladder dysfunction and spasticity

	Spasticity				
	None	**Mild**	**Moderate**	**Severe**	p value
Total Bladder (median, IQR)	0.63 (1.25)	0.75 (1.63)	1.25 (1.75)	2.38 (2.1)	<0.001

Correlations between four domains (bother with limitations, fear, feelings and frequency limitations) of SF-Qualiveen and MSSS-88 subscales were performed (table 36). Modest (r=0.35-0.45), but statistically significant (p<0.01) correlations were observed across all the domains.

Table 36**.** Spearman's rank correlation between spasticity and bladder dysfunction

	Stiffness	**Pain and discomfort**	**Spasms**
Bother with limitations	0.44	0.42	0.39
Fears	0.38	0.40	0.41
Feelings	0.42	0.40	0.39
Frequency limitations	0.39	0.35	0.38
Overall	0.45	0.44	0.44

p<0.01

4.14. Regression Analysis

The results above show that spasticity is associated with reduced QOL on both measures (the LMSQOL and WHQOL-BREF). However, as postulated in the hypothesis of this thesis, spasticity was also found to be related to other sociodemographic (age, employment) and clinical variables (depression, anxiety, fatigue, pain, bladder dysfunction, disability). These factors may also have influential role to QOL in patients with MS. To investigate an independent contribution of spasticity towards QOL, hierarchical multiple regression analysis was employed. Before inserting predictors into

the final regression models, a series of univariate regression analyses were performed to identify any significant predictors of QOL.

4.14.1. Univariate regression analysis

All of the dependent variables were considered to be normally distributed, except for WHQOL-BREF psychological health and social relationships domains. Log and square transformations were attempted but normality parameters did not improve. Not normally distributed data was unlikely to affect the regression analysis due to the large sample size (n=260). According to the central limit theorem, the distribution of the means of the samples in the population is normal, therefore even if the distribution of the given sample is not normal, assumptions of normally distributed data can be made if the sample size is >40 (Ghasemi & Zahediasl, 2012).

Individual sociodemographic variables and clinical parameters were tested using univariate regression analysis in predicting QOL. Each set of predictors was analysed in relation to five outcome variables: four domains of the WHOQOL-BREF and LMSQOL. The results of the univariate analyses regarding adjusted R^2 values, betas, standard errors, and standardised β coefficients are reported in appendix 3. Predictors with p value below 0.05 were considered to be significant and were included in the multiple regression analysis. All of the independent variables were significant across the both measures, except for sociodemographic predictors, which varied depending on the measure and domain. Table 37 shows the variables found to be significant in relation to the LMSQOL and the individual domains of the WHOQOL-BREF.

Table 37. Variables found to be significant predictors of QOL in univariate regression analysis

	WHOQOL-BREF Physical health	WHOQOL-BREF Psychological health	WHOQOL-BREF Social relationships	WHOQOL-BREF Environment	LMSQOL
Sociodemographic and disease parameters					
Age	+		+		
Sex			+		
Marital status			+	+	
Employment	+	+	+	+	+
Type of MS	+	+	+	+	
Duration	+				
Associated conditions					
Anxiety	+	+	+	+	+
Depression	+	+	+	+	+
Bladder dysfunction	+	+	+	+	+
Fatigue	+	+	+	+	+
Pain	+	+	+	+	+
Spasticity	+	+	+	+	+
Disability	+	+	+	+	+

4.14.2. Hierarchical multiple regression analysis

Predictors of QOL found to be significant in the univariate regression analyses were included in the multiple regression models. Independent variables were inserted into the models in four steps:

1. Step 1 - Sociodemographic variables

2. Step 2 - Associated conditions- depression, anxiety, bladder dysfunction, fatigue, pain

3. Step 3 - Spasticity

4. Step 4 - Disability

At each step of the analysis, the assumptions of the regression model (described in the Methodology Chapter) were checked and were deemed to be valid. Since MSSS-88 subscales had very high intercorrelations (r=0.84-0.89) which would adversely affect multicollinearity, only one subscale (MSSS-88 muscle stiffness) was included in the analysis. Five multiple regression analyses were carried out, which results are described below in relation to the individual domains of the WHOQOL-BREF and LMSQOL.

4.15. Results of multiple regression analysis

4.15.1 WHOQOL-BREF Physical Health

The final model (step 4) accounted for 74.3% variance of the WHOQOL-BREF Physical Health domain (adjusted R^2 = 0.743, F (11, 210) = 58.95, $p<0.001$) (table 38). Addition of spasticity (step 3) produced a significant change in R^2 value (R^2change 0.013, p=0.01). Spasticity was a significant predictor of QOL after adjusting for sociodemographic variables and associated conditions (β=-0.16, p=0.001). Insertion of disability in to the model (step 4) improved the R^2 value (R^2 change 0.019, $p<0.001$), however spasticity became an insignificant predictor (β=-0.08, p=0.117). Employment (β=0.11, p=0.015), depression (β=-0.15, p=0.006), fatigue (β=-0.29, $p<0.001$), pain (β=-0.18, $p<0.001$) and disability (β=-0.28, $p<0.001$) remained significant predictors of QOL in the final model.

Table 38. Hierarchical multiple regression analysis with WHOQOL-BREF Physical health as a dependent variable

	Step 1			**Step 2**			**Step 3**			**Step 4**		
	Adjusted R^2 0.249* **		**R^2 change 0.263*** **	**Adjusted R^2 0.711*** **		**R^2 change 0.46*** **	**Adjusted R^2 0.724*** **		**R^2 change 0.013** **	**Adjusted R^2 0.743*** **		**R^2 change 0.019*** **
	B	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**
Sociodemographic and disease parameters												
Age	0.001	0.02	0.01	-0.02	0.01	-0.06	-0.02	0.01	-0.07	-0.03	0.01	-0.09
Type (relapsing)	1.8	0.48	0.25***	0.54	0.31	-0.08	0.30	0.32	0.04	-0.01	0.31	-0.001
Duration	0.03	0.03	0.09	-0.01	0.02	-0.03	-0.01	0.02	-0.03	-0.001	0.02	-0.003
Employment	2.68	0.44	0.41***	1.03	0.29	0.15***	0.88	0.29	0.13**	0.69	0.28	0.12*
Associated conditions												
Anxiety				-0.05	0.04	-0.07	-0.05	0.04	-0.07	-0.04	0.04	-0.05
Depression				-0.20	0.05	-0.23***	-0.19	0.05	-0.22***	-0.13	0.05	-0.15**
Bladder dysfunction				-0.12	0.13	-0.04	-0.06	0.12	-0.02	-0.06	0.12	-0.02
Fatigue				-0.17	0.02	-0.37***	-0.16	0.02	-0.35***	-0.13	0.02	-0.29***
Pain				-0.03	0.01	-0.25***	-0.03	0.01	-0.19***	-0.02	0.01	-0.18***
Spasticity							-0.05	0.02	-0.16**	-0.03	0.02	-0.08
Disability										-0.04	0.01	-0.28***

p<0.05*, p<0.01**,p< 0.001***

4.15.2. WHOQOL-BREF Psychological Health

The final model accounted for 66.8% variance of the WHOQOL-BREF Psychological Health domain (adjusted R^2=0.668, F (9, 219) = 50.49, p<0.001) (Table 39). Addition of spasticity (step 3) did not improve the R^2 value (R^2 change=0.002, p=0.208) and spasticity was not a significant predictor of QOL after adjusting for sociodemographic variables and associated conditions (β=-0.02, p=0.208). Addition of disability into the final model produced a significant change in R^2 value (R^2 change = 0.011, p=0.008). Anxiety (β=-0.13, p<0.04), depression (β=-0.48, p<0.001), fatigue (β=-0.14, p=0.01) and disability (β=-0.21, p=0.008 were predictive of psychological health. Sociodemographic variables were only significant at step 1 (R^2=0.066, F (2, 19) = 9.49, p<0.001).

Table 39. Hierarchical multiple regression analysis with WHOQOL-BREF Psychological health as a dependent variable

	Step 1			**Step 2**			**Step 3**			**Step 4**		
	Adjusted R^2 0.066* **		**R^2 change 0.073*** **	**Adjusted R^2 0.632*** **		**R^2 change 0.567*** **	**Adjusted R^2 0.633*** **		**R^2 change 0.002**	**Adjusted R^2 0.668*** **		**R^2 change 0.011** **
	B	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**
Sociodemographic and disease parameters												
Type (relapsing)	0.77	0.38	0.13*	0.02	0.27	0.01	-0.003	0.23	0.00	-0.22	0.29	-0.04
Employment	1.11	0.38	0.19**	-0.08	0.26	-0.01	-0.12	0.26	-0.02	-0.25	0.27	-0.04
Associated conditions												
Anxiety				-0.1	0.04	-0.15**	-0.11	0.04	-0.16**	-0.08	0.04	-0.11*
Depression				-0.36	0.04	-0.47***	-0.36	0.05	-0.46***	-0.36	0.05	-0.48***
Bladder dysfunction				-0.29	0.12	-0.12*	-0.26	0.12	-0.11*	-0.13	0.12	-0.05
Fatigue				-0.09	0.02	-0.21***	-0.08	0.02	-0.20***	-0.06	0.02	-0.14*
Pain				-0.01	0.01	-0.07	-0.01	0.01	-0.05	-0.004	0.01	-0.03
Spasticity							-0.02	0.02	-0.06	-0.003	0.02	0.01
Disability										-0.03	0.01	0.21**

p<0.05*, p<0.01**, p< 0.001***

4.15.3. WHOQOL-BREF Social Relationships

Step 2 of the analysis produced the most optimal model, however only 35.5% of variance of the WHOQOL-BREF Social Relationships domain was explained (adjusted R^2=0.355, F (10, 209) = 13.08, p<0.001) (table 40). Addition of spasticity or disability did not produce a significant change in R^2 value (Step3 R^2 change = 0.000, p=0.697, step 4 R^2 change= 0.002, p=0.456). Being married (β=0.15, p=0.005) and having relapsing type of MS (β=0.14, p=0.047) were significantly predictive of better QOL. In addition, anxiety (β=-0.21, p=0.004), depression (β=-0.29, p<0.001) and pain (β=-0.14, p=0.016) were consistently predictive of worse QOL.

Table 40. Hierarchical multiple regression analysis with WHOQOL-BREF Social relationships as a dependent variable

	Step 1			**Step 2**			**Step 3**			**Step 4**		
	Adjusted R^2 0.084* **		**R^2 change 0.103*** **	**Adjusted R^2 0.355*** **		**R^2 change 0.249*** **	**Adjusted R^2 0.353*** **		**R^2 change 0.000**	**Adjusted R^2 0.351*** **		**R^2 change 0.002**
	B	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**
Sociodemographic and disease parameters												
Age	-0.01	0.02	-0.05	-0.03	0.02	-0.09	-0.03	0.02	-0.10	-0.03	0.02	-0.10
Sex	0.74	0.50	0.10	0.73	0.40	0.10	0.80	0.40	0.10	0.61	0.43	0.08
Married	1.18	0.45	0.16*	1.10	0.40	0.15**	1.13	0.40	0.16**	1.30	0.41	0.18**
Type (relapsing)	1.26	0.50	0.19*	0.94	0.47	0.14*	0.93	0.49	0.14	0.94	0.53	0.13
Employment	0.38	0.47	0.06	-0.53	0.43	-0.08	-0.53	0.44	-0.08	-0.62	0.46	-0.09
Associated conditions												
Anxiety				-0.17	0.06	-0.21**	-0.17	0.06	-0.21**	-0.13	0.06	-0.16*
Depression				-0.26	0.07	-0.29***	-0.26	0.07	-0.30***	-0.31	0.08	-0.35***
Bladder dysfunction				-0.10	0.18	-0.04	-0.09	0.19	-0.03	0.03	0.20	0.01
Fatigue				0.01	0.03	0.02	0.01	0.03	0.02	0.03	0.04	0.06
Pain				-0.02	0.01	-0.14*	-0.02	0.01	-0.14*	-0.02	0.01	-0.11
Spasticity							0.001	0.02	0.004	-0.002	0.03	-0.01
Disability										-0.01	0.02	-0.08

p<0.05*, p<0.01**, p< 0.001***

4.15.4. WHOQOL-BREF Environment

49.8% variance of the WHOQOL-BREF Environment domain was explained by the model produced at step 4 (adjusted R^2= 0.498, F (10, 210) = 22.71, p<0.001) (table 41). Spasticity was found to be an insignificant predictor of QOL after adjusting for sociodemographic variables and associated conditions (β=-0.129, p<0.067). The strongest predictors of QOL were disability (β=-0.36, p<0.001), depression (β=-0.17, p=0.024), bladder dysfunction (β=-0.17, p=0.008) and pain (β=-0.12, p=0.044). Anxiety (β=-0.13, p=0.04) and fatigue (β=-0.13, p=0.046) and being married (β=0.11, p=0.03) were significant predictors before adjusting for disability.

Table 41. Hierarchical multiple regression analysis with WHOQOL-BREF Environment as a dependent variable

	Step 1			**Step 2**			**Step 3**			**Step 4**		
	Adjusted R^2 0.061* **		**R^2 change 0.073*** **	**Adjusted R^2 0.448*** **		**R^2 change 0.391**	**Adjusted R^2 0.457*** **		**R^2 change 0.006**	**Adjusted R^2 0.498*** **		**R^2 change 0.033*** **
	B	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**
Sociodemographic and disease parameters												
Married	0.78	0.34	0.14*	0.67	0.27	0.12*	0.58	0.27	0.11*	0.58	0.27	0.11
Type (relapsing)	0.70	0.34	0.14*	0.20	0.29	0.004	-0.04	0.30	-0.01	-0.34	0.31	-0.07
Employment	0.72	0.34	0.14*	-0.23	0.28	-0.05	-0.30	0.28	-0.06	-0.54	0.29	-0.11
Associated conditions												
Anxiety				-0.08	0.04	-0.13*	-0.08	0.04	-0.13*	-0.07	0.04	-0.11
Depression				-0.16	0.05	-0.24**	-0.15	0.05	-0.22**	-0.11	0.05	-0.17*
Bladder dysfunction				-0.56	0.13	-0.26***	-0.53	0.13	-0.25***	-0.35	0.13	-0.17**
Fatigue				-0.05	0.02	-0.14*	-0.05	0.02	-0.13*	-0.01	0.02	-0.03
Pain				-0.02	0.01	-0.16**	-0.01	0.01	-0.13*	-0.01	0.01	-0.12*
Spasticity							-0.03	0.02	-0.11	-0.01	0.02	-0.02
Disability										-0.04	0.01	-0.36***

p<0.05*, p<0.01**, p< 0.001***

4.15.5. LMSQOL

The model produced at step 2 of the analysis accounted for 57% variance of the LMSQOL scores (adjusted R^2=0.57, F (6, 233) = 52.79, p<0.005) (table 42). Addition of spasticity and disability did not significantly improve model variance parameters (step 3 R^2 change =0.002, p=0.267, step 4 R^2 change = 0.006, p<0.07). Neither spasticity (β=0.05, p=0.327), nor disability (β=0.15, p=0.07) were significant predictors after adjusting for sociodemographic parameters and associated conditions. Strongest predictors of poor QOL (higher LMSQOL score) were depression (β=0.37, 0<0.001) followed by anxiety (β=0.24, p<0.001), fatigue (β=0.22, p<0.001) and pain (β=0.12, p=0.015).

Table 42. Hierarchical multiple regression analysis with LMSQOL as a dependent variable.

	Step 1			**Step 2**			**Step 3**			**Step 4**		
	Adjusted R^2 0.017*		**R^2 change 0.024***	**Adjusted R^2 0.565*** **		**R^2 change 0.555*** **	**Adjusted R^2 0.578*** **		**R^2 change 0.002**	**Adjusted R^2 0.582*** **		**R^2 change 0.006**
	B	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**	**B**	**SE**	**β**
Sociodemographic and disease parameters												
Employment	-1.37	0.60	-0.14*	0.79	0.50	0.08	0.84	0.46	0.09	1.0	0.48	0.10
Associated conditions												
Anxiety				0.27	0.06	0.24***	0.27	0.06	0.25***	0.26	0.07	0.23***
Depression				0.46	0.08	0.37***	0.44	0.08	0.37***	0.42	0.09	0.34***
Bladder dysfunction				0.27	0.20	0.07	0.24	0.21	0.06	0.02	0.23	0.01
Fatigue				0.14	0.04	0.22***	0.14	0.04	0.21***	0.11	0.04	0.16**
Pain				0.02	0.01	0.12*	0.02	0.01	0.10	0.02	0.01	0.10
Spasticity							0.03	0.03	0.05	0.01	0.03	0.02
Disability										0.03	0.02	0.15

p<0.05*, p<0.01**, p< 0.001***

Chapter 5 - Discussion

5.1. Overview

A cross-sectional questionnaire-based study was carried out in the UK to investigate the relationship between spasticity, QOL and other neurological impairments in MS. Although several studies have been conducted in this field, a number of methodological limitations regarding both spasticity and QOL measurement were identified. The present study attempted to address these weaknesses to increase the validity of the findings. Firstly, to avoid the conceptual confusion regarding QOL, the study operated on a definition of QOL proposed by WHO (WHO, 1995). To fulfil the requirement of this definition, two instruments, WHOQOL-BREF and LMSQOL, which measure overall QOL and not merely health status, were chosen. Secondly, literature review found that measurement of spasticity is complex, multidimensional and clinician-administered measures do not reflect patients' experience. To address these issues a robust multidimensional MS-specific measure for spasticity, MSSS-88, was employed alongside NRS. Lastly, the present study acknowledged that many factors may influence QOL, therefore the relationship between QOL and spasticity was controlled for other neurological impairments and sociodemographic variables. The study findings are discussed in the paragraphs below.

5.2. Prevalence and severity of spasticity

The study confirmed high prevalence of spasticity in the MS population. As many as 84.8% reported some degree of spasticity, with almost a third of patients (29.2%) suffering from severe spasticity. Despite the fact that most of the patients recruited to the study attended tertiary centres for neurology, which provide specialised rehabilitation services for spasticity, prevalence and severity of spasticity was found to be similar to previous population surveys in MS (Arroyo et al., 2013; Flachenecker et al., 2014; Rizzo et al., 2004). This highlights the problematic nature of spasticity and limited efficacy of current treatments (Paisley et al., 2002; Shakespeare et al., 2003). This has important implications for healthcare costs and the overall burden of MS. Previous studies have shown that MS-related spasticity is associated with significant healthcare

utilisation (Schapiro, 2014; Svensson et al., 2014; Tyry, Salter, Largent, & Marrie, 2014). Patients with spasticity were more likely to attend emergency department, be hospitalised, require appointments with a neurologist, MS nurse and physiotherapist and rely on a professional caregiver support (Schapiro, 2014; Tyry et al., 2014).

A significant proportion (29.2%) of MS patients was found to have severe spasticity, for which management can be particularly problematic. Arroyo et al. found that patients who did not respond to two antispasticity agents progressed to more severe degrees of spasticity over the course of 3 years (Arroyo et al., 2011). Up to a third of patients became wheelchair bound and less than a fifth were still in employment. The findings from this study also show a sharp decline in proportion of patients in employment as severity of spasticity increases. 21.3% of patients with severe spasticity were in full or part time employment compared to 61% with no spasticity. Svensson et al. in a study on 105 patients with MS investigated the costs related to spasticity and reported that reduced capacity to work and care giver burden were the biggest contributors to societal costs related to MS-associated spasticity (Svensson et al., 2014). Hence, maximising mobility and administering adequate treatment is imperative to prevent loss of productivity of MS patients. However, in a review on spasticity management practices in Europe, Berger emphasised that only 3% of overall healthcare costs in MS are related to rehabilitation services and antispasticity agents (Berger, 2013). As a result, increasing provision of these services may have a significant impact on reducing burden of spasticity in MS.

5.3. Spasticity and sociodemographic and disease characteristics

Several important sociodemographic and disease parameters were found to be related to severity of spasticity. As expected, patients with higher EDSS were found to have more severe spasticity. However, it is important to acknowledge that less than a third of patients with severe spasticity had EDSS >6.5, with the majority of patients experiencing moderate or severe spasticity at lower levels of disability. This highlights the importance of using measures that specifically assess spasticity in MS, and not simply disability (Flachenecker et al., 2014). In addition, several studies found that the

impact of spasticity on healthcare utilisation is significant even after accounting for disability (Schapiro, 2014; Svensson et al., 2014; Tyry et al., 2014). Interestingly, although patients with severe spasticity had longer duration of disease, this was not found to be statistically significant (p=0.213). This was thought to be confounded by PPMS, however no statistical significance was observed even after excluding patients with PPMS. This may suggest that location of CNS lesions, rather than duration of disease may be more important for development of spasticity. Of note, patients diagnosed with MS within 4 years were found to have similar degree of spasticity when compared to patients diagnosed >20 years (NRS 4.1 and 4.9 respectively, p=0.89). 85% of those with recent diagnosis (<4 years) reported some degree of spasticity with 15.2% of patients having severe spasticity. The findings highlight that even very early in the course of MS spasticity is a common impairment and may need early intervention.

Progressive type of MS was associated with significantly higher levels of spasticity. However, no difference was observed in spasticity levels between rapidly evolving and relapsing remitting MS. This contrasts to the findings from the NARCOMS study by Rizzo et al. (Rizzo et al., 2004). Authors reported that a relapse in the last 6 months and worsening MS (determined by a patient as worse MS symptoms compared to a year before) were significantly associated with severe spasticity. In this study, the majority of patients diagnosed with rapidly evolving MS were recruited from the day treatment unit. It is likely that these patients had well-controlled MS as a result of regular infusions of natalizumab, preventing development of spasticity. Similar to the findings from the study mentioned above, patients with severe spasticity were more likely to have had a relapse in the last 12 months, however because of small numbers no statistical significance was detected (p=0.657).

5.4. Relationship between spasticity and QOL

The main aim of this study was to determine the relationship between spasticity and QOL in MS. Previous studies reported that spasticity is associated with worse health status and physical functioning, however effects of spasticity on overall

QOL have not been explored so far (Arroyo et al., 2013; Flachenecker et al., 2014; Rizzo et al., 2004; Svensson et al., 2014; Wu et al., 2007). In order to achieve this, two measures of overall QOL were administered: WHOQOL-BREF and LMSQOL. The above QOL measures were selected for three reasons. Firstly, using a generic QOL measure such as the WHOQOL-BREF, would allow comparisons about the impact of spasticity on QOL across other neurological conditions which are also characterised by spasticity. Secondly, the LMSQOL was employed as an MS-specific QOL measure, which might be more sensitive to subtle changes in QOL than generic QOL measures (Bandari et al., 2010; Benito-Leon et al., 2002; D. M. Miller & Allen, 2010). Lastly, since the WHOQOL-BREF provides scores only for individual domains, the LMSQOL was used for calculating a global QOL score.

The study found a significant linear relationship of worsening QOL as severity of spasticity increased, this was true across both measures. The findings support previous observations regarding significant negative effects of spasticity on health status, physical function and activities of daily living in MS (Arroyo et al., 2013; Flachenecker et al., 2014; Rizzo et al., 2004). The study also provides first insight into the strong negative relationship between spasticity and overall QOL. The LMSQOL scores were significantly higher (worse QOL) in patients with severe spasticity compared to no or mild spasticity ($p<0.001$). In accordance with previous research, the physical health domain of the WHOQOL-BREF was particularly strongly related to worsening spasticity (rho -0.61--0.7), with significant differences in domain scores across all four spasticity groups ($p<0.001$).

Spasticity was also found to be associated with significantly worse scores on the non-physical domains of the WHOQOL-BREF including psychological health, social relationships and environment. This provides important information about broader implications of spasticity in MS, which are not simply related to physical disability. The psychosocial effects of spasticity in MS have only been previously explored in qualitative studies (Bhimani, McAlpine, & Henly, 2012; Morley et al., 2013; Nicolson & Anderson, 2001). The studies found that spasticity can have deleterious effects on patients'

psychological health and social roles. Patients reported that spasticity affected their relationships, employment and future planning. Anxiety, depression, low self-esteem and locus of control were all reported to be affected by spasticity. The present study has taken these observations from qualitative to quantitative stages. The findings closely accord with the studies reported by Nicolson et al. and Morley et al. supporting wide-ranging effects of spasticity on overall QOL in MS (Morley et al., 2013; Nicolson & Anderson, 2001).

A number of sociodemographic and clinical parameters have been shown to affect QOL, which may confound the relationship between spasticity and QOL (Benito-Leon et al., 2002; Mitchell et al., 2005; Rudick & Miller, 2008). In this study, increasing age, disability, progressive type of MS, unemployment and being unmarried were shown to be associated with worse QOL. Furthermore, univariate analyses identified several MS-associated conditions to be significantly predictive of worse QOL, which included fatigue, pain, bladder dysfunction, anxiety and depression. These findings confirm previous observations regarding predictors of QOL in MS (Ford, Gerry, Johnson, et al., 2001; Janssens, van Doorn, de Boer, van der Meche, et al., 2003; Lobentanz et al., 2004; Wynia et al., 2008). The question arises whether QOL is diminished as a result of spasticity or other conditions listed above. To address this issue hierarchical multiple regression was employed. Five regression models were constructed corresponding with five dependent variables: four domains of the WHOQOL-BREF and one for LMSQOL.

Table 43. Summary of multivariable regression analyses

	Physical Health				Psychological Health				Social relationships				Environment				LMSQOL			
Steps	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Standardised Beta coefficients	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**	**β**
1) Sociodemographic and disease parameters[a]																				
Age	0.01	-0.06	-0.07	-0.09					-0.05	-0.09	-0.10	-0.10								
Sex									0.10	0.10	0.10	0.08								
Marital status									**0.16**	**0.15**	**0.16**	**0.18**	**0.14**	**0.12**	**0.11**	0.11				
Type (relapsing)	**0.25**	-0.08	0.04	-0.01	**0.13**	0.01	0.01	-0.04	**0.19**	**0.14**	0.14	0.13	**0.14**	0.01	-0.01	-0.07				
Duration	0.09	-0.03	-0.03	-0.01																
Employment	**0.41**	**0.15**	**0.13**	**0.12**	**0.19**	-0.01	-0.02	-0.04	0.06	-0.08	-0.08	-0.09	**0.14**	-0.05	-0.06	-0.11	**-0.14**	0.08	0.09	0.1
2) Neurological impairments																				
Anxiety		-0.07	-0.07	-0.05		**-0.15**	**-0.16**	**-0.11**		**-0.21**	**-0.21**	**-0.21**		**-0.13**	**-0.13**	-0.11		**0.24**	**0.25**	**0.23**
Depression		**-0.23**	**-0.22**	**-0.15**		**-0.47**	**-0.46**	**-0.48**		**-0.29**	**-0.30**	**-0.30**		**-0.24**	**-0.22**	**-0.17**		**0.37**	**0.37**	**0.34**
Bladder dysfunction		-0.04	-0.02	-0.02		**-0.12**	**-0.11**	-0.05		-0.04	-0.03	-0.03		**-0.26**	**-0.25**	**-0.17**		0.07	0.06	0.01
Fatigue		**-0.37**	**-0.35**	**-0.29**		**-0.21**	**-0.20**	**-0.14**		0.02	0.02	0.02		**-0.14**	**-0.13**	-0.03		**0.22**	**0.21**	**0.16**
Pain		**-0.25**	**-0.19**	**-0.18**		-0.07	-0.05	-0.03		**-0.14**	**-0.14**	-0.14		**-0.16**	**-0.13**	**-0.12**		**0.12**	0.10	0.10
3) Spasticity			**-0.16**	-0.08			-0.06	0.01			-0.01	-0.01			-0.11	0.01			0.01	0.02
4) Disability				**-0.28**				**-0.21**				-0.08				**0.36**				0.15
Model performance (adjusted R^2)	**0.249**	**0.711**	**0.724**	**0.743***	**0.066**	**0.632**	**0.633**	**0.668***	**0.084**	**0.355***	**0.353**	**0.351**	**0.061**	**0.448**	**0.457**	**0.498***	**0.017**	**0.565***	**0.578**	**0.582**
R^2 change	**0.263**	**0.46**	**0.013**	**0.019**	**0.073**	**0.567**	0.002	**0.011**	**0.103**	**0.249**	0.001	0.002	**0.073**	**0.391**	0.006	**0.033**	**0.024**	**0.555**	0.002	0.006

[a] *Not all of the sociodemographic variables were significant in univariate analyses. Blank rows correspond with those variables that were not entered into the multivariable regression models*

**The model with the most optimal performance*

Note: the bold indicates significant values (p<0.05)

Spasticity was found to be a significant predictor of WHOQOL-BREF physical health domain after accounting for sociodemographic variables and associated conditions. However, once disability was added to the model spasticity became insignificant. It could be hypothesised that spasticity mediates most of its effects on physical health via disability, however this needs to be further investigated using more advanced statistical techniques such as structural equation modelling (further discussed under limitations). For the remaining dependent variables (LMSQOL and WHOQOL-BREF psychological health, social relationships, environment domains) spasticity was not found to be significantly predictive of worse QOL. This raises a second question: if spasticity is not an independent predictor of QOL, could it mediate its effects via other conditions? Alternatively, could it be that spasticity is not an important factor in determining overall QOL in MS and the previous observations are as a result of confounders such as depression, fatigue etc.? Studies investigating QOL in MS have previously reported that physical impairments were weaker predictors of QOL compared to psychological and social factors (Amato, Ponziani, Rossi, et al., 2001; Ford, Gerry, Johnson, et al., 2001; Lobentanz et al., 2004). On the other hand, it is not known how spasticity is related to other variables, which are strong predictors of QOL in MS such as depression. It maybe that spasticity may affect mood or social relationships, which could in turn reduce QOL. To investigate this, the relationships between spasticity and fatigue, sleep, pain, bladder dysfunction, anxiety and depression were sought and the findings are discussed below.

5.5. Relationship between spasticity and other neurological impairments

5.5.1. Depression and anxiety

There is paucity of research investigating the relationship between spasticity and mood disorders, such as depression and anxiety, which are particularly common in MS (Chwastiak et al., 2002). Three qualitative studies found that spasticity had important implications to emotional and psychological well-being in MS (Bhimani et al., 2012; Morley et al., 2013; Nicolson & Anderson, 2001). Some patients reported feeling depressed as a result of pain and physical limitations related to spasticity, others

experience anxiety caused by unpredictability of spasticity-related spasms and uncertainty regarding future progression. To date, no quantative studies examined the relationship between spasticity and mood disorders using instruments that specifically assess depression and anxiety in MS. Two studies reported that spasticity was associated with only marginal reductions in mental health components on SF-36 (Arroyo et al., 2013; Rizzo et al., 2004). Flachenecker et al. found no difference on EQ-5D anxiety and depression subscale scores between mild, moderate and severe spasticity.

In this study, mood disorder was assessed using HADS, a measure which has been previously validated in MS and has high sensitivity and specificity for diagnosis of depression and anxiety (Honarmand & Feinstein, 2009). The study found that depression was significantly more common ($p<0.001$) in patients with moderate (30.4%) and severe spasticity (45.3%) compared to none (17.1%) or mild spasticity (14.5%). In contrast, no statistical significant difference was found in cases of anxiety across the groups, although there was a positive trend between anxiety and spasticity. The shortcomings of the HADS anxiety subscale might be responsible for failure to find a significant relationship between anxiety and spasticity. While the HADS-A has high specificity and sensitivity for generalised anxiety disorder, it is a poor measure for other anxiety disorders (Honarmand & Feinstein, 2009). In light of these limitations, it is premature to conclude that spasticity is not associated with anxiety since several qualitative studies repeatedly found that patients with spasticity often felt anxious (Bhimani et al., 2012; Morley et al., 2013; Nicolson & Anderson, 2001). Indeed, in a study on SCI patients (n=26) Fleuren et al. found that 25% of patients reported that mental stress worsened spasticity, suggesting that anxiety may also be a cause, rather than a result of spasticity.

Literature on the determinants of depression in MS is conflicting. Disability, disease duration, relapse rate and MS type have been linked to depression in MS in some, but not all studies (Chwastiak et al., 2002; Patten, Lavorato, & Metz, 2005; Zabad, Patten, & Metz, 2005). In this study, patients with depression were significantly more likely to have progressive disease (49.5% vs. 31.5%, $p=0.008$) and be

unemployed (42.5% vs. 42%, p=0.001). Patients with depression were more likely to have EDSS >6.5%, however this was not statistically significant (17.6% in depression groups vs. 12.1% in depression free, p=0.247). It is difficult to ascertain what role spasticity plays in depression in MS due to multiple confounders such as fatigue and pain, which may be related to both depression and spasticity. However, understanding the factors that drive depression in MS is of particular importance, since depression is one of the strongest predictors of poor QOL in MS (Amato, Ponziani, Rossi, et al., 2001; Janssens, van Doorn, de Boer, van der Meche, et al., 2003; Lobentanz et al., 2004). The findings of this study also support this. In all five regression models depression remained a significant predictor of QOL. Further study is required to determine the independent contribution of spasticity to depressive disorder in order to better understand its effects on QOL.

The findings also have some important clinical implications. Particular attention should be paid to depressive symptoms when treating MS patients with spasticity. In addition, it may be relevant to assess depressive symptoms in studies investigating antispasticity therapies in MS. Equally, assessment of spasticity during treatment of depression in MS may also be important. Stolp-Smith et al. reported a case of increased spasticity in a patient with SCI as a result of commencement of selective serotonin receptor inhibitor (fluoxetine) and suggested that increased motor neurone reflex activity and denervation supersenstivity could be responsible (Stolp-Smith & Wainberg, 1999). The effect of antidepressants on spasticity was not analysed in this study. Information obtained from interventional studies would give further insight into causal relationships between spasticity and depression.

5.5.2. Fatigue and sleep

Fatigue has been reported to affect more than 90% of patients with MS and is often rated as one of the most debilitating symptoms (Hemmett et al., 2004). Although a number of studies have examined the relationship between fatigue and disability, depression and sleep, none of the quantative studies specifically examined the relationship between spasticity and fatigue (Bakshi et al., 2000; Kroencke, Lynch, &

Denney, 2000; Mills & Young, 2011). The possibility of a significant relationship between fatigue and spasticity was reported in several qualitative studies in patients with MS and SCI (Fleuren et al., 2009; Nicolson & Anderson, 2001). Nicolson et al. in a qualitative study with 18 patients with MS-related spasticity reported that spasticity and spasms in particular contributed to tiredness and lack of energy (Nicolson & Anderson, 2001). Similarly, Fleuren et al. and Mahoney et al. found that a proportion of patients with SCI reported that fatigue worsened spasticity (Fleuren et al., 2009; Mahoney et al., 2007).

To determine the relationship between fatigue and spasticity, three subscales (physical, cognitive fatigue and abnormal nocturnal sleep) of the NFI-MS were employed. NFI-MS is a rigorously developed measure, which meets robust standards of measurement unlike other measures of fatigue such as the Fatigue Severity Scale and the MS Fatigue Impact Scale (Mills, Young, Nicholas, Pallant, & Tennant, 2009; Mills et al., 2010a; Mills, Young, Pallant, & Tennant, 2010b). Using NFI-MS as a measure of fatigue, this study found that spasticity was significantly associated with overall fatigue and abnormal nocturnal sleep. Physical fatigue correlated more closely with spasticity ($r = 0.52 - 0.61$) than cognitive fatigue ($r = 0.41 - 0.5$) or abnormal nocturnal sleep ($r=0.35 - 0.47$).

Again, no causal relationships can be drawn from these observations. In fact, the relationship between fatigue could also be bidirectional, i.e. higher levels of fatigue may cause more spasticity. Since the pathophysiology of fatigue is poorly understood, it is difficult to explain the association between spasticity and fatigue. A number of studies that used brain MRI to investigate central causes of fatigue found only weak or absent correlations between fatigue and structural changes of the brain, such as brain atrophy or lesion load (Bakshi et al., 1999; Codella et al., 2002; van der Werf et al., 1998). However, studies using functional MRI (magnetic or diffusion transfer MRI and PET-FDG) identified significant functional changes in the frontal cortex, thalamus and basal ganglia (Inglese et al., 2007; Mainero et al., 1999; Tellez et al., 2008). It could be

hypothesised that CNS changes seen in MS-related fatigue also affect the pathways responsible for the development of spasticity.

Significant positive correlation between spasticity and cognitive fatigue observed in this study supports the idea that spasticity is related to central causes of fatigue. Gandevia et al. investigated the origin of central fatigue by stimulating motor cortex and motor point in healthy subjects during voluntary isometric contractions (Gandevia, Allen, Butler, & Taylor, 1996). The authors demonstrated suboptimal cortical output during fatigue and suggested that the motor cortex is the most likely site for generation of central fatigue. However, not all of the studies support this. In a study of 14 patients with MS Morris et al. assessed walking and fatigue (measured by VAS) in the morning and afternoon on the same day (Morris, Cantwell, Vowels, & Dodd, 2002). While fatigue levels increased significantly, walking patterns remained constant. The authors suggested that mechanisms controlling locomotion may be different to the ones responsible for fatigue. However, as spasticity was not assessed, conclusions regarding the relationship between spasticity and fatigue cannot be drawn.

There is also some evidence to suggest that some interventions can simultaneously improve both spasticity and fatigue. Mori et al. in a pseudorandomised control trial investigated the effects of exercise training (ET) and intermittent transcranial magnetic theta burst stimulation (iTBS) on spasticity, fatigue and disability in 30 patients with MS (Mori et al., 2011). The rationale for using ET and iTBS is based on the idea that repetitive motor tasks cause plastic changes of intracortical neurones. The study found significant improvements in spasticity (measured by the Modified Ashworth Scale) and fatigue (measured by FSS), but not disability after combining ET and iTBS together. iTBS alone improved spasticity, but not fatigue. The study suggests that there may be common as well as distinct mechanisms underlying both spasticity and fatigue.

It is also possible that antispasticity medication, particularly baclofen, could have accounted for increased fatigue levels in patients with more severe levels of spasticity. Again, no data regarding spasticity medication was available for analysis.

Literature regarding fatigue and QOL in MS has consistently shown strong inverse correlation between the two constructs (Amato, Ponziani, Rossi, et al., 2001; Goksel Karatepe et al., 2011; Hemmett et al., 2004; Lobentanz et al., 2004). Similar findings were reproduced in this study. Fatigue was found to be a significant predictor in all multiple regression models, except for WHOQOL-BREF social relationships and environment domains. Lack of the effect of fatigue on these domains has also been reported in a study of 530 patients with MS in Poland (Wynia et al., 2008). Wynia et al. investigated effects of multiple disabilities (measured by MS Impact Scale) on QOL and found that fatigue was not a significant predictor for any of the four domains of WHOQOL-BREF, but significant for physical functioning domain of SF-36 (Wynia et al., 2008). The authors postulated that fatigue might have a more direct effect on physical aspects of QOL, while mental components of QOL might be mediated by fatigue through other factors such as disability or depression. Similar finding was reported in a study of 504 patients with MS by Lobentanz et al., in which fatigue was found to be predictive of physical subscales of Quality of Life Index, but not mental (Lobentanz et al., 2004).

In conclusion, the findings of this study provide the first insight into a positive relationship between spasticity and fatigue. Future studies investigating both therapies for fatigue and spasticity will provide a better understanding regarding the relationship between these two impairments in MS.

5.5.3. Pain

Mechanisms of pain in spasticity have been poorly researched and are not well understood (Ward & Kadies, 2002). Spasticity may cause pain in several ways. Biomechanical changes may occur in hypertonic muscles, which may lead to muscle shortening and contractures (Ward & Kadies, 2002). Reduced mobility and misalignment of the joints causes poor posture and musculoskeletal pain. Frozen

shoulder is a typical example of the consequences of spasticity. Spasms associated with spasticity may directly cause pain. Although the pathophysiology of spasticity-related pain is unknown, one hypothesis suggests that pain might be caused by muscle ischaemia (Mense, 1993; Travell & Rinzler, 1952). Prolonged muscle contraction or tonic activation causes compression of the muscle vasculature leading to reduced oxygen delivery. Ischaemic contractions cause release of nociceptive substance, such as prostaglandins (PGE2) and potassium ions, which trigger pain and further muscle contraction, initiating a vicious cycle.

Pain affects around 60% of patients with MS and may occur independently from spasticity (Osterberg, Boivie, & Thuomas, 2005). By definition, spasticity is a sensori-motor disorder, therefore any afferent input such as a nociceptive stimulus may have a role in driving spasticity. Unfortunately, evidence on the relationship between pain and spasticity in clinical studies is limited. A systematic review by Phadke et al. on physiological and psychological triggers of spasticity found no studies reporting pain as a cause of worsening spasticity (Phadke et al., 2013). The present study found a strong association between spasticity and pain. Patients with more severe spasticity experienced significantly more pain ($p<0.001$). Indeed, in a group of patients with no spasticity NPS total median score was 0 (IQR 20), which increased sharply as spasticity levels increased (NPS median score 47 in severe spasticity). Similar findings were reported in a pilot study of 19 patients with spinal cord injury by Voerman et al. (Voerman, Erren-Wolters, Fleuren, Hermens, & Geurts, 2010). The investigators found significant correlation ($r=0.43$) between pain and spasticity (both measured by NRS). In the present study, relationships between spasticity and specific types of pain were sought too. There was a trend for spasticity to correlate most strongly with deep somatic pain ($r=0.41$-0.62, $p<0.01$). This supports the theory that spasticity causes musculoskeletal type pain, possibly as a result of biomechanical changes in the muscles. Weaker, but statistically significant correlations were observed between spasticity and dysesthetic or allodynic type pain ($r=0.33$-0.45, $p<0.01$). These findings suggest that spasticity might also be influenced by afferent noxious stimuli. This is also supported by

studies that administered analgesic medications, such as morphine, to patients with severe spasticity and found improvement in muscle tone (Erickson, Blacklock, Michaelson, Sperling, & Lo, 1985; Sadiq & Poopatana, 2007). Cannabinoids have been used to treat both spasticity and pain in MS with some but not all studies reporting favourable results (Wade et al., 2010; Zajicek et al., 2003; Zajicek, Hobart, Slade, Barnes, & Mattison, 2012). Stimulation of CB1 receptors in the basal ganglia has been suggested to reduce painful muscle spasms (Hohmann & Herkenham, 1999). In addition, CB1 are largely populated in the pain pathway, which explains effects of cannabinoids on pain in MS, however whether it is implicated in reducing spasticity is unknown (Pertwee, 2001).

In conclusion, there is a complex interaction between pain and spasticity in MS. It is well established that spasticity produces pain, possibly through mechanical changes in muscles and joints as well as muscle ischaemia. Noxious stimulation, such as neuropathic pain in MS, is a likely source of aggravation of spasticity, however the pathophysiological mechanisms remain to be elucidated.

5.5.4. Bladder dysfunction

Bladder problems are present in 33%-90% of patients with MS (Giannantoni et al., 1998; Goldstein, Siroky, Sax, & Krane, 1982; Nortvedt et al., 2007). Neural pathways responsible for micturition descend from the cerebral cortex and pons to the sacral spinal cord and are particularly vulnerable to lesions affecting the spinal cord (Nicholas, Young, & Friede, 2010). As a result, concomitant occurrence of pyramidal dysfunction and bladder problems in MS may be expected. Several studies reported that EDSS pyramidal scale scores and extensor plantar reflexes significantly correlated with bladder dysfunction (Betts, D'Mellow, & Fowler, 1993; Giannantoni et al., 1999). In a study of 2029 patients with MS, urinary dysfunction was found in 70.4% of patients with spasticity compared to 29.2% without spasticity ($p<0.001$) (Oreja-Guevara, 2011). Patients with spasticity were also more likely to have disturbed sleep as a result of urinary urgency. The findings of the present study support these observations. There was a significant linear relationship between severity of spasticity and bladder

dysfunction ($p<0.001$). However only modest correlations were found between MSSS-88 subscales and SF-Qualiveen total and individual domain scores ($r=0.35$-0.45). One possible explanation is that SF-Qualiveen measures the impact of bladder problems to a patient's life, rather than individual symptoms of bladder dysfunction. According to Ferrans QOL model, a number of factors mediate the impact of biological symptoms on a patient's life, which might explain only modest correlations between spasticity and SF-Qualiveen (Ferrans et al., 2005).

Spasticity and bladder dysfunction most likely represent different manifestations of the same underlying pathology, i.e. damage to the descending tracts in the spinal cord. However, it would be of clinical importance to know whether one might aggravate another. It was postulated above that noxious stimuli from the periphery might increase spasticity. In the same vein, it could be hypothesised that sensory input originating in the bladder may affect spinal neural networks that control muscle tone. Several studies in spinal cord injury reported that bladder distension, infection and incomplete emptying caused an increase in spasticity (Fleuren et al., 2009; Meng et al., 2010; Ronco et al., 2011). A study by Laesoe et al. ($n=9$) found significant reductions ($p<0.01$) in spasms and the Modified Ashworth Scale score after penile vibratory stimulation suggesting that there might be a common pathway from bladder, bowels and organs of reproduction which connects to the neurones controlling muscle tone (Laessoe, Nielsen, Biering-Sorensen, & Sonksen, 2004). Future studies will confirm whether similar interactions exist between bladder dysfunction and spasticity in MS, as all of the previous studies were performed in the SCI population. Although this is likely, it should not be assumed due to the distinct nature of these conditions.

Two studies reported by Nortvedt et al. showed that bladder dysfunction was significantly associated with worse HRQOL (measured by SF-36 and MSQOL-54) (Nortvedt et al., 2007; Nortvedt et al., 2001). However, both studies did not control for confounding factors. In the present study, although bladder dysfunction was found to be a significant predictor of WHOQOL-BREF and LMSQOL in univariate analyses ($p<0.001$), it remained significant only in predicting the WHOQOL-BREF environment

domain after accounting for other factors ($p<0.01$). In addition, bladder dysfunction was also found to be a significant predictor of the WHOQOL-BREF psychological domain after accounting for associated conditions, but not disability ($p<0.05$). The study suggests that bladder problems are particularly important for psychological well-being of MS patients and adversely affects their interaction with the environment. It is unclear though how bladder dysfunction affects other domains of QOL.

5.6. Limitations of the study

There are a number of limitations in the present study. The most notable limitation is the cross-sectional design of the study. As a result, only associations, but not causations between spasticity and other variables could be made. Because self-reported measures for spasticity were used, it is possible that patients with lower QOL rate their spasticity worse. Although patient-reported measures are always at risk of such bias, it is possible to minimise this by applying Rasch measurement model. For this purpose, MSSS-88 was chosen to measure spasticity in the present study. Hobart et al. reported that MSSS-88 was free of differential item functioning (DIF) with reference to person's disability levels (Hobart et al., 2006). In other words, given the same level of spasticity, patients with different levels of disability rate the severity of spasticity the same. As a result, it is hoped that the present study addressed this issue by employing MSSS-88.

Secondly, the scales used in this study were ordinal, although the assumptions of interval-level scales were made when performing regression analyses. Although ordinal scales are widely used by researchers in the field of healthcare and psychology, differences between two scores may not be equal and technically do not meet requirements of interval scales (Knapp, 1990).

Multiple regression analysis is also not without limitations. While it allows examination of predictive values of multiple factors with regards to QOL, multiple regression does not take into account interaction between independent variables. This is particularly important in MS since many of the neurological impairments are related to each other and may mediate their effects on QOL indirectly. Hence, although some

factors may appear as non-significant predictors in the final models, it should not be inferred that they are not important in determining QOL.

It should be noted that multiple comparisons, especially multiple correlations, were performed, increasing the likelihood of committing type I error. While Benferroni adjustments were made for calculations of the Kruskal-Wallis statistic, these were not performed for bivariate correlations. The reason for is that Benferroni adjustments deflate α and increase the chance of type II error (Perneger, 1998). There is also a body of evidence to suggest that Benferroni adjustments should not be used at all (Gelman, Hill, & Yajima, 2009; Perneger, 1998).

Several issues regarding recruitment should be considered too. Firstly, patients were recruited from specialised neuroscience centres, which might not reflect standard care of the patients in the general population. It is possible that patients were receiving optimised care and felt confident about management of their MS. The alternative could also be true. Patients with more aggressive MS or difficult complications could have been referred to the tertiary centre for specialist input. However, demographics, EDSS and spasticity prevalence and severity was found to be similar to other population surveys (Arroyo et al., 2013; Flachenecker et al., 2014; Rizzo et al., 2004). There is also a risk of selection bias since a convenience sample was used. Patients that declined invitation to participate or were deemed unsuitable to be recruited often had emotional and social issues precluding their involvement in the study. Failure to include these patients in the study could have overestimated QOL of the sample. However, a previous study of 245 patients with MS by Wynia et al. found very similar WHOQOL-BREF scores (Wynia et al., 2012). Lastly, a proportion of patients were recruited over a year before completing questionnaires. This could have caused some discrepancy between clinical information (e.g. EDSS score) obtained from the case notes and questionnaire data.

Another possible limitation of the study is the lengthy format of the questionnaire. Several patients expressed difficulties completing the questionnaire due to its length. Although patients were instructed to aim to complete the questionnaire in

the shortest possible time, ideally during one day, in practice many took longer than one week to complete it. This could have affected correlation results, since spasticity can vary greatly over time (Skold, 2000). However, a 2 week time reference for spasticity was given on purpose to minimise these discrepancies.

The study acknowledges that QOL is a complex and multidimensional construct, which is under the influence of many factors. Although a number of factors were accounted for in the regression models, it is likely that many other variables (e.g. coping, hopelessness, personality traits, social support, self-efficacy etc.) could have important contributions. This is also reflected by a relatively small adjusted R^2 values for WHOQOL-BREF social relationships (0.35) and environment domains (0.49).

Finally, failure to establish an online questionnaire platform was an important setback for this pilot study. Having an online option would have increased the number of completed questionnaires as a proportion of patients were not able to complete the questionnaire because they expressed online preference. It would have also provided important information regarding feasibility and acceptability of an online version necessary for future progress of the study. In addition, study costs and work load of the research team could be reduced greatly once an online questionnaire becomes available.

5.7. Strengths of the study

Despite the limitations listed above, this study has several strengths. The sample included a broad range of severities of spasticity. In addition, all types of MS and disability levels (measured by EDSS) were included and were representative of the general MS population (Compston & Coles, 2008). Responder's bias was addressed in this study. Sociodemographic and clinical information of non-responders was similar to responders, except for age.

Spasticity assessment is complex and multidimensional. Previous similar studies investigating spasticity and QOL in neurological disorders used the Ashworth scale, which is considered a poor measure of spasticity, hence limiting the validity of their

results (Arroyo et al., 2013; Urban et al., 2010; Wissel et al., 2010). Other studies did not report any specific measure for spasticity and simply dichotomised patients into spasticity and no spasticity groups (Noonan et al., 2008; Post et al., 1998; Westgren & Levi, 1998). Dichotomisation of spasticity is also not appropriate, since there is a wide spectrum of severity of spasticity, which is also reflected in the findings of the present study. In addition to NRS, this study also employed three most clinically relevant subscales of MSSS-88. MSSS-88 has been derived from patients' experience of spasticity and has been shown to have robust psychometric properties (Hobart et al., 2006). Consequently, it is hoped that the present study achieved accurate and comprehensive assessment of spasticity. In addition, the relationships between different aspects of spasticity and QOL were examined.

Previous studies repeatedly failed to account for multiple factors that could confound the relationship between spasticity and QOL (Arroyo et al., 2013; Flachenecker et al., 2014; Rizzo et al., 2004; Wu et al., 2007). The present study for the first time controlled for these factors using the hierarchical multiple regression model. In addition, clear distinction was made between overall QOL and HRQOL. Unlike previous studies, the present study investigated the relationship between overall QOL and not HRQOL (Arroyo et al., 2013; Flachenecker et al., 2014; Rizzo et al., 2004; Wu et al., 2007). Administering both MS-specific and generic QOL measures enabled more comprehensive assessment of QOL and its relationship with spasticity.

Lastly, some important information regarding feasibility of the study was obtained. There were concerns about the lengthy format of the questionnaire, which might adversely affect response rate. However, 59.8% of patients returned completed questionnaires, which is not dissimilar from previous studies using shorter questionnaires in the MS population (Mills & Young, 2011; Mills et al., 2010b). Despite IT failures, data entry using Filemaker proved to be efficient and will be used before an online version becomes available.

5.8. Future research

The present study serves as a pilot study for future phases of TONiC. Data collected from other sites in the UK will provide additional sample of MS patients. Larger number of subjects will enable a more comprehensive assessment of both QOL and spasticity in MS. In order to address the current limitations, several improvements to the data analysis could be made.

Firstly, the scales should be transformed from ordinal to interval level using the Rasch method (Rasch, 1960). This will provide legitimate data for structural equation modelling (SEM). Using SEM the relationships between spasticity, QOL and other associated features could be interrogated in more detail. Ultimately, SEM would help to understand how spasticity influences QOL.

Secondly, larger sample size and validation of the new scales (coping, hopelessness, social withdrawal) will enable the addition of more factors to the QOL model. Relationships between spasticity and coping, hopelessness and social-withdrawal have not been explored to date in MS. A pilot study of 19 patients with spinal cord injury by Voerman et al. found that reassuring thoughts and low levels of hopelessness are associated with less severe spasticity (Voerman et al., 2010). Detailed investigation of the relationships between spasticity and the factors mentioned above using robust measures and advanced statistical techniques (e.g. SEM) would provide important information in understanding how spasticity mediates its effects on QOL in MS.

Data obtained from the longitudinal phase of this study will most certainly provide invaluable information regarding the relationship between spasticity and QOL. The present study found that spasticity is common even in patients with recent diagnosis of MS. It would be of clinical interest to know how spasticity evolves during the first 5 years of MS and how this relates to QOL trajectory.

Literature review in Chapter 2 indicated that there is paucity of research regarding spasticity and QOL in other chronic neurological conditions such as motor neurone disease and traumatic brain injury. It is hoped that data generated by TONiC

will fill this gap in literature. Qualitative interviews with MND patients on their experience of spasticity have already been completed and collection of quantative data is underway. Standardised measures for spasticity (NRS) and QOL (WHOQOL-BREF) used in the questionnaire packs will enable investigation of the relationship between spasticity and QOL, not only in one disease, but in a number of neurological conditions simultaneously.

5.9. Conclusions

Spasticity is a very common impairment in MS. Due to low efficacy of current antispastic therapies, spasticity is often severe and disabling. Previous research has shown that spasticity adversely affects physical functioning and health status, however its effects on QOL were largely unknown. The present study builds upon the findings of qualitative studies, which reported wide-ranging effects of spasticity on patients' lives. It was found that spasticity is associated with significantly worse overall QOL as measured by two robust QOL instruments. Due to the limitations of the study design and statistical methods, exact mechanisms explaining how spasticity affects QOL could not be determined.

In addition to determining the relationship between spasticity and QOL, significant associations between spasticity and fatigue, depression, pain and bladder dysfunction were found. Literature investigating these relationships is limited, hence the findings of the present study serve as a stepping stone for future studies. Although causal relationships were postulated, this needs further confirmation using experimental methods. Determining these relationships will help to understand how spasticity affects QOL and will ultimately inform clinicians about how to improve the lives of patients with MS.

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Appendix

Appendix 1 - Literature Search Strategy

1. MEDLINE; exp MUSCLE SPASTICITY/; 6697 results.

2. MEDLINE; spast*.ti,ab; 18778 results.

3. MEDLINE; 1 OR 2; 20675 results.

4. MEDLINE; exp QUALITY OF LIFE/; 120720 results.

5. MEDLINE; "quality of life".ti,ab; 153125 results.

6. MEDLINE; 4 OR 5; 197029 results.

7. MEDLINE; 3 AND 6; 565 results.

8. MEDLINE; 7 [Limit to: English Language and Humans and (Age Groups All Adult 19 plus years)]; 199 results.

9. EMBASE; spastcity.ti,ab; 1 results.

10. EMBASE; exp SPASTICITY/; 14152 results.

11. EMBASE; spast*.ti,ab; 22999 results.

12. EMBASE; 10 OR 11; 27164 results.

13. EMBASE; exp QUALITY OF LIFE/; 254068 results.

14. EMBASE; (""quality of life" AND ").ti,ab; 205382 results.

15. EMBASE; 13 OR 14; 297888 results.

16. EMBASE; 12 AND 15; 1078 results.

17. EMBASE; 16 [Limit to: Human and English Language and (Human Age Groups Adult 18 to 64 years)]; 257 results.

18. PsycINFO; exp MUSCLE SPASMS/; 233 results.

19. PsycINFO; spast*.ti,ab; 2609 results.

20. PsycINFO; 18 OR 19; 2743 results.

21. PsycINFO; exp QUALITY OF LIFE/ [Limit to: Human and English Language]; 23643 results.

22. PsycINFO; 20 AND 21 [Limit to: Human and English Language]; 35 results.

23. CINAHL; exp MUSCLE SPASTICITY/; 2270 results.

24. CINAHL; spast*.ti,ab; 3096 results.

25. CINAHL; 23 OR 24; 3837 results.
26. CINAHL; exp QUALITY OF LIFE/; 43493 results.
27. CINAHL; 25 OR 26; 47207 results.
28. CINAHL; 25 AND 26; 123 results.
29. CINAHL; 28 [Limit to: (Language English) and (Age Groups All Adult)]; 60 results.

Appendix 2 - Dealing with missing data

Measure	**Steps in dealing with missing data**
MSSS-88	Subscale score computed if <20% data missing. Mean of the subscale score is used to replace missing item
SF-Qualiveen	Subscale score computed if <20% data missing. Mean of the subscale score is used to replace missing item
NFI-MS	Subscale score computed if <20% data missing. Mean of the subscale score is used to replace missing item
HADS	Subscale score computed if <20% data missing. Mean of the subscale score is used to replace missing item
WHOQOL	Case should be discarded if >20% data missing Mean of the subscale score is used to replace missing item If >2 items missing from the domain, score should not be calculated, except for social relationships domain for which score should not be calculated if 1 item is missing
LMSQOL	Subscale score computed if <20% data missing. Mean of the subscale score is used to replace missing item
WHODAS	If <3 items missing from the domain, mean score is substituted

	for missing item. Working domain was not calculated since majority of patients were unemployed (65%)
NPS	Subscale score computed if <20% data missing. Mean of the subscale score is used to replace missing item

Appendix 3 - Results of univariate analyses

WHOQOL-BREF – Physical domain

Demographic and disease parameters	adjusted R2	B	SE B	Standardised β	p value
age	0.06	-0.07	0.02	-0.253	<0.0005
sex (female)	0.004	-0.05	0.43	-0.007	0.908
Married	0.002	0.32	0.45	0.04	0.482
Employment	0.213	3.08	0.37	0.47	<0.0005
Type (Relapsing)	0.129	2.41	0.39	0.36	<0.0005
Duration	0.03	-0.063	0.02	-0.19	0.002

Associated conditions	adjusted R2	B	SE B	Standardised β	p value
Fatigue	0.496	-0.328	0.02	-0.71	<0.0005
Depression	0.389	-0.54	0.04	-0.63	<0.0005
Anxiety	0.165	-0.32	0.05	-0.41	<0.0005
Pain	0.273	-0.07	0.01	-0.53	<0.0005
Bladder	0.261	-1.401	0.15	-0.51	<0.0005

	adjusted R2	B (CI)	SE B	Standardised β	p value
Spasticity	0.413	-0.195	0.01	-0.65	<0.0005

	adjusted R2	B (CI)	SE B	Standardised β	p value
Disability	0.611	-0.112	0.01	-0.78	<0.0005

WHOQOL- BREF Psychological domain

Demographic and disease	adjusted R2	B	SE B	Standardised β	p value

parameters					
age	0.001	-0.02	0.02	-0.07	0.252
sex (female)	0.003	-0.22	0.34	-0.04	0.545
Married	0.007	0.65	0.39	0.10	0.099
Employment	0.055	1.41	0.35	0.24	<0.001
Type (Relapsing)	0.042	1.24	0.36	0.21	0.001
Duration	0.002	-0.01	0.02	-0.043	0.489

Associated conditions	adjusted R2	B	SE B	Standardised β	p value
Fatigue	0.335	-0.24	0.02	-0.58	<0.001
Depression	0.535	-0.56	0.03	-0.73	<0.001
Anxiety	0.315	-0.39	0.04	-0.56	<0.001
Pain	0.120	-0.04	0.01	-0.35	<0.001
Bladder	0.233	-1.16	0.13	-0.49	<0.001

	adjusted R2	B	SE B	Standardised β	p value
Spasticity	0.225	-0.13	0.02	-0.49	<0.001

	adjusted R2	B	SE B	Standardised β	p value
Disability	0.456	-0.09	0.01	-0.68	<0.001

WHOQOL- BREF Social relationships

Demographic and disease parameters	adjusted R2	B	SE B	Standardised β	p value
age	0.011	-0.04	0.02	-0.12	0.049
sex (female)	0.022	1.17	0.45	0.16	0.01
Married	0.028	1.33	0.46	0.18	0.004
Employment	0.019	1.04	0.43	0.15	0.016
Type (Relapsing)	0.069	1.86	0.42	0.27	<0.001
Duration	0.002	-0.013	0.02	-0.04	0.541

Associated conditions	adjusted R2	B	SE B	Standardised β	p value
Fatigue	0.079	-0.14	0.03	-0.29	<0.001
Depression	0.242	-0.45	0.05	-0.50	<0.001
Anxiety	0.139	-0.31	0.05	-0.38	<0.001
Pain	0.063	-0.04	0.01	-0.26	<0.001
Bladder	0.102	-0.93	0.17	-0.33	<0.001

	adjusted R2	B	SE B	Standardised β	p value

Spasticity	0.105	-0.10	0.02	-0.33	<0.001

	adjusted R2	B	SE B	Standardised β	p value
Disability	0.177	-0.06	0.01	-0.42	<0.001

WHOQOL- BREF Environment

Demographic and disease parameters	adjusted R2	B	SE B	Standardised β	p value
age	0.003	0.01	0.01	0.03	0.68
sex (female)	0.003	0.43	0.34	0.08	0.20
Married	0.18	0.82	0.35	0.15	0.019
Employment	0.025	0.87	0.32	0.17	0.006
Type (Relapsing)	0.041	1.09	0.32	0.21	0.001
Duration	0.000	0.001	0.02	0.002	0.96

Associated conditions	adjusted R2	B	SE B	Standardised β	p value
Fatigue	0.212	-0.17	0.02	-0.46	<0.001
Depression	0.296	-0.37	0.04	-0.55	<0.001
Anxiety	0.179	-0.26	0.04	-0.43	<0.001
Pain	0.136	-0.04	0.01	-0.37	<0.001
Bladder	0.225	-1.03	0.12	-0.48	<0.001

	adjusted R2	B	SE B	Standardised β	p value
Spasticity	0.207	-0.10	0.01	-0.46	<0.001

	adjusted R2	B	SE B	Standardised β	p value
Disability	0.398	-0.70	0.01	-0.63	<0.001

LMSQOL

Demographic and disease parameters	adjusted R2	B	SE B	Standardised β	p value
age	0.004	-0.01	0.02	-0.01	0.835
sex (female)	0.004	0.03	0.63	0.003	0.966
Married	0.000	-0.65	0.66	-0.06	0.324

Employment	0.014	-1.37	0.60	-0.14	0.024
Type (Relapsing)	0.005	-0.90	0.60	-0.09	0.142
Duration	0.003	-0.02	0.03	-0.03	0.608

Associated conditions	adjusted R2	B	SE B	Standardised β	p value
Fatigue	0.284	0.36	0.04	0.54	<0.001
Depression	0.422	0.80	0.06	0.65	<0.001
Anxiety	0.326	0.64	0.06	0.56	<0.001
Pain	0.143	0.07	0.01	0.38	<0.001
Bladder	0.161	1.60	0.23	0.41	<0.001

	adjusted R2	B	SE B	Standardised β	p value
Spasticity	0.197	0.19	0.03	0.45	<0.001

	adjusted R2	B	SE B	Standardised β	p value
Disability	0.340	0.12	0.01	0.59	<0.001