PAIN IN MULTIPLE SCLEROSIS

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AUTHORS DECLARATION

I declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

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CONFERENCE PRESENTATIONS

The research within parts one and two of this thesis have been published at the national MS Society, UK conferences**:**

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ABSTRACT

Multiple Sclerosis (MS) is a chronic, progressive disease which presents as a variety of cognitive, motor and sensory deficits (Compston and Coles, 2008). Pain is one of the most common and often severe symptoms of the disease. It is associated with poorer general health, and its management is therefore an important therapeutic target. People with MS can suffer from neuropathic pain as a direct result of damage to the central nervous system, or nociceptive pain, as a result of changes to the musculoskeletal system, secondary to disease progression.

This was the first epidemiological study to measure the prevalence, characteristics, and impact of MS-related pain, using validated, IMMPACT-recommended measures. Neuropathic pain, common in MS, is a challenge to manage and is shown to impact on a person health-related quality of life (HR-QOL). Subsequently, the second part of this study explored the impact of Transcutaneous Electrical Nerve Stimulation (TENS) on neuropathic pain in MS, in a randomised controlled trial.

A postal survey design was used to target the MS population of the NHS Ayrshire and Arran health board area, who completed a questionnaire on their pain experience (n=302). Clinically significant pain, defined as ongoing bothersome pain, was experienced by over two-thirds (71.5%), whilst chronic pain, defined as pain present for at least six months, was experienced by over half (59.2%) of the MS population. Neuropathic pain, assessed using the PainDETECT screening tool, was experienced by almost one third (32.7%) of the sample, with a further 14.7% identified as potentially having neuropathic pain. Thus 47.4% of the sample could potentially have neuropathic pain, which is higher than previous estimates, and that experienced by the general population. Approximately half the population experienced painful tonic spasms (44.5%) and dysaesthetic pain (56.2%). Burning pain, unpleasant paraesthetic sensations (i.e. crawling, tingling), and sharp pain were commonly experienced in the population with neuropathic pain. Multiple logistic regression analysis revealed Type of MS ($p=0.001$) and disability level (Guys Neurological Disability Scale (GNDS) ($p<0.001$) as independent predictors of neuropathic pain, possibly related to the pathophysiology of the disease. Neuropathic pain was shown as statistically more severe (using the 11-point Numerical Rating Scale of pain intensity (NRS-11) ($p<0.001$), more emotionally unpleasant (using the SF-MPQ) ($p<0.001$), with greater sleep disturbance ($p<0.001$), than nociceptive

pain. Despite over two-thirds (68.5%) of those with neuropathic pain currently using prescribed, pain-relieving medication, over half (53.7%) still experienced severe (7-10 on NRS-11) pain. The presence of neuropathic also had a significantly negative impact on HR-QOL (EQ-5D) (*p<0.001*). The results of the epidemiological study increase understanding of the extent and demanding nature of pain in MS. Clinically, it will also facilitate timely screening for the neuropathic pain subtype, to minimise its impact on HR-QOL.

Following the epidemiological findings, a randomised, double-blind, placebo-controlled trial, explored the efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) in the treatment of chronic, neuropathic pain in MS (n=46). Participants were recruited from the MS Service, NHS Ayrshire and Arran, with a diagnosis of lower limb neuropathic pain (score of ≥19 on the PainDETECT Screening tool for neuropathic pain), experienced for a minimum of six months. For the active TENS group, standard 'Conventional' TENS settings were applied, whilst a low frequency, low intensity, long pulse duration electrical current was used for the placebo application, which has no known analgesic effect, but still provides a sensory stimulus. Both groups used the TENS machine for a minimum of four hours/day, for a two-week period. Two long self-adhesive, hypo-allergenic electrodes were placed paravertebrally over the lumbar spine to stimulate the spinal nerve roots. The primary outcome measure was the (NRS-11), whilst secondary outcome measures included the Neuropathic Pain Scale (NPS), and the Patients Global Impression of Change (PGIC). Level of pain related interference on function was measured using the *Brief Pain Inventory* (BPI).

Compared to the control group, the group receiving active TENS demonstrated a statistically *(p<0.001)* and clinically significant reduction in the intensity of neuropathic pain over the two-week intervention period. It was particularly effective for the *burning*, and *sharp* neuropathic pain qualities, that were commonly associated with neuropathic pain in the epidemiological study. TENS was also shown to reduce the emotional unpleasantness of pain (the affective component), which was high in those with neuropathic pain in the epidemiological study. This may have implications for the role of TENS in managing the psychological aspect of chronic neuropathic pain. TENS has no effect on pain–related interference on function, possibly due to the relatively short TENS intervention period. Future studies should explore longer intervention periods to explore the longer-term effects of TENS for pain in MS.

The pharmacological management of neuropathic pain is not without its challenges. TENS as an inexpensive, non-invasive modality, with no side-effects, could be considered for the management of neuropathic pain, a common phenomenon in the MS population.

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LIST OF ABBREVIATIONS

AFT	Alternating Frequency TENS
AL-TENS	Acupuncture-Like TENS
BPI	Brief Pain Inventory
CNS	Central Nervous System
DMT	Disease Modifying Therapy
EDSS	Expanded Disability Status Scale
EQ-5D	EuroQol-5 Dimension Quality of Life
GNDS	Guy's Neurological Disability Scale
HADS	Hospital Anxiety and Depression Scale
HIT	High Intensity TENS
HR-QOL	Health-Related Quality of Life
IASP	International Association of the Society of Pain
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ITT	Intention To Treat analysis
LIHF	Low Intensity, High Frequency
LILF	Low Intensity, Low Frequency
MS	Multiple Sclerosis
NeuPSIG	The Neuropathic Pain Specialist Interest Group
NPS	Neuropathic Pain Scale
NRS-11	11-point Numerical Rating Scale of Pain Intensity
PDN	Peripheral Diabetic Neuropathy
PD-Q	PainDETECT Questionnaire
PGIC	Patient Global Impression of change
PGT	Pain Gate Theory
PHN	Post Herpetic Neuralgia

PP	Per Protocol analysis
PPMS	Primary Progressive MS
PPRM	Prescribed Pain Relieving Medication
PRMS	Progressive Relapsing MS
PTS	Painful Tonic Spasms
QST	Quantitative Sensory Testing
RCT	Randomised Controlled Trial
RRMS	Relapsing Remitting MS
SBC	Strong, But Comfortable
SCI	Spinal Cord Injury
SF-MPQ	Short Form McGill Pain Questionnaire
SPMS	Secondary Progressive MS
TENS	Transcutaneous Electrical Nerve Stimulation
WDR	Wide Dynamic Range cell

Pain is one of the most challenging problems in medicine and biology. It is a challenge to the sufferer who must learn how to live with pain for which no therapy has been found. It is a challenge to the physician or other health professional who seeks every possible means to help the suffering patient. It is a challenge to the scientist who tries to understand the biological mechanisms that can cause such terrible suffering. It is also a challenge to society, which must find the medical, scientific and financial resources to relieve or prevent pain and suffering as much as possible.

(Melzack and Wall, 1988)

1 INTRODUCTION

Multiple Sclerosis (MS) is a chronic, progressive disease which presents as variety of cognitive, motor and sensory deficits (Compston and Coles, 2008). MS is the most common cause of neurological disability in young adults affecting at least 100,000 people in the United Kingdom (Multiple Sclerosis Society UK, 2013). Pain is one of the most severe symptoms of the disease, impacting negatively on all aspects of a person life (Kenner *et al*, 2007). This study focuses on pain in MS, measuring the prevalence, characteristics and impact of chronic and neuropathic pain. Neuropathic pain is a challenge to manage and is shown to impact on a person health-related quality of life (HR-QOL) (Doth *et al*, 2010). Subsequently, the potential management of neuropathic pain as a result of MS is explored using Transcutaneous Electrical Nerve Stimulation (TENS).

1.1 Multiple Sclerosis

MS is a demyelinating disease causing widespread degeneration of the Central Nervous system (CNS) which gradually results in a progressive development of neurological deficit (Compston and Coles, 2008). Destruction of the myelin sheath is caused by inflammatory and neurodegenerative processes that also involve the denuding of the axon itself (Carr and Shepard, 2010; Pittock and Lucchinetti, 2007). Perivascular inflammation, myelin depletion, oliogodentrocytes loss and astrologlial proliferation take place (Chari, 2007; Nakahara *et al*, 2012). Remyelination and repair may occur resulting in lesions (known as plaques), visible under magnetic resonance imaging, however repair may be incomplete, resulting in the clinical manifestations of MS (Smith *et al*, 2006). The most common sites of plaques are within the grey-white boundary in the cerebrum, the peri-ventricular regions, cerebellar white matter, optic nerves, brainstem and the cervical portion of the spinal cord (Carr and Shepard, 2010).

In the majority of cases clinical symptoms indicate the involvement of motor, sensory and autonomic systems which can be used for diagnosis. Empirical evidence of more widespread cerebral involvement can be found through MRI, where lesions indicate areas of damage; either T1 Gadolinium-enhanced brain lesions, showing currently active areas of MS, or T2 lesions which may, in addition, show older or inactive lesions (Van Waesberghe *et al*, 1998). Evidence of elevated immunoglobulin G in the cerebrospinal fluid is also a

notable indicator (Polman *et al*, 2011) of the disease. Diagnostic criteria are shown in Table 1-1.

Table 1-1: Diagnostic Criteria for MS

Clinical Presentation	Additional Data Needed for MS Diagnosis
Two or more attacks (relapses) Two or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
Two or more attacks One objective clinical lesion	Dissemination in space, demonstrated by: MRI or a positive CSF and two or more MRI lesions consistent with MS or further clinical attack involving different site 2010 Amendment**:** Dissemination in Space (DIS) can be demonstrated by the presence of 1 or more T2 lesions in at least 2 of 4 of the following areas of the CNS: Periventricular, Juxtacordial, Infratentorial, or Spinal Cord.
One attack Two or more objective clinical lesions	Dissemination in time, demonstrated by: MRI or second clinical attack 2010 Amendment: No longer a need to have separate MRIs run; Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack
One attack * One objective clinical lesion (clinically isolated syndrome)	2010 Amendment: For Dissemination in Space: 1 or more T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, Juxtacordial, Infratentorial, or spinal cord); or await a second clinical attack implicating a different CNS site; and Dissemination in Time: Simultaneous presence of asymptomatic gadolinium enhancing and non-enhancing lesions; or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or a second clinical attack.
Insidious neurological progression suggestive of MS (primary progressive MS)	One year of disease progression (retrospectively or prospectively determined) and two or three (2010 Amendment) of the following: Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP). Positive spinal cord MRI (two focal T2 lesions) or Positive CSF

Adapted from (McDonald *et al*, 2001)and (Polman *et al*, 2011)

MRI – Magnetic Resonance Imaging, CSF – Cerebrospinal Fluid, T2 – Lesion indicating evidence of MS, VEP - Visual Evoked Potentials (evidence on brain activity

Clinical manifestations of MS vary and may include; fatigue, mobility impairments, weakness, balance impairments, stiffness and spasms, memory and other cognitive problems, bladder and bowel problems, pain and unpleasant sensations, emotional problems, visual changes, and dizziness (McDonald and Compston, 2006). Symptoms can be heterogenic, for example mobility impairments may range from slight leg weakness to being fully wheelchair dependant, whilst some symptoms may never be experienced. This is depicted in Table1-2, providing information on the frequency of symptoms, as taken from a UK-based survey of MS patients (McDonald and Compston, 2006). This table highlights the most common symptoms (weakness, sensory symptoms, ataxia, bladder symptoms, and fatigue), as well as the fact that not all symptoms may present throughout the course of the disease.

Table 1-2: Prevalence of MS symptoms

Symptoms	Anytime Since Disease onset N (%)	At Present N (%)
Weakness	269 (89)	241 (80)
Sensory symptoms	263 (87)	219 (73)
Ataxia	248 (82)	218 (72)
Bladder symptoms	213 (71)	188 (62)
Fatigue	171 (57)	144 (48)
Cramps	156 (52)	133 (44)
Diploplia	155 (51)	77 (26)
Visual symptoms	148 (49)	98 (33)
Bowel symptoms	126 (44)	112 (37)
Dysarthria	110 (37)	74 (25)
Vertigo	107 (36)	57 (19)
Facial pain	106 (35)	42 (14)
Poor memory	96 (32)	81 (27)
Headache	90 (30)	51 (17)
Mental symptoms	68 (23)	49 (16)
Deafness	51 (17)	38 (13)
Facial weakness	48 (16)	15 (5)
Dysphagia	40 (13)	29 (10)

From (McDonald and Compston, 2006)

Disability as a result of these clinical manifestations is often measured using standardised scales, mainly the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) and Guys Neurological Disability Scale (GNDS) (Sharrack and Hughes, 1999). The (EDSS) describes both neurological and functional aspects of the disease. The scale quantifies neurological impairments, in each of eight neurological functional systems (FS); pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. These are combined with ambulation ability/mobility and give a measure of disability on a scale from 0 (normal) to 10 (death due to MS). The GNDS assesses function on a range of disabilities within the 12 domains of cognition, mood, vision, speech, swallowing, upper-limb function, mobility, bladder function, bowel function, fatigue, sexual function and other problems, such as spasms. Each of the 12 components are graded on a scale of 0 (normal level of function) to 5 (total loss of function) and combined to give a total disability score from 0 (no disability) to 60 (maximum level of disability).

The disease is characterised by episodes of relapse and subsequent remission. The relapse is conventionally an episode of neurological dysfunction attributed to a lesion of the CNS (Zajicek *et al*, 2007). Several subtypes, or patterns of disease progression, have been

described. Four clinical courses are proposed: relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), and progressive relapsing (PRMS) (Lublin and Reingold, 1996) (each depicted in Appendix 1, Section 1, Question 9). The relapsing-remitting subtype is characterized by unpredictable relapses followed by periods of remission with no new signs of disease activity (Lublin and Reingold, 1996). Deficits suffered during attacks may either resolve or leave sequelae, the latter being more common as a function of time. This describes the initial course of 80% of individuals with MS (Compston and Coles, 2008). Secondary progressive MS describes around 65% of those with an initial relapsing-remitting MS, who then begin to have progressive neurologic decline between acute attacks without any definite periods of remission (Rovaris *et al*, 2006). The primary progressive subtype describes the 10–15% of individuals who never have remission after their initial MS symptoms. It is characterized by progression of disability from onset, with no, or only occasional and minor, remissions and improvements (Miller and Leary, 2007). These are standard figures, used in several theoretical MS reference textbooks; however, it is unclear how authors have obtained the prevalence figures reported. Progressive relapsing MS (PRMS), the least common of all subtypes, describes those individuals who, from onset, have a steady neurologic decline but also suffer clear superimposed attacks (Lublin and Reingold, 1996).

The presence of pain has been associated with these factors of disease course and stage of disease as indicated by disability level (Solaro *et al*, 2004).

1.2 Pain in Multiple Sclerosis

There is potential to develop pain in MS, either as a result of damage to the CNS itself, or from the changes to the musculoskeletal system, such as contractures and postural dysfunction (Maloni *et al*, 2000). In addition, there are several MS-related pain syndromes, such as Lhermitte's phenomenon, and painful tonic spasm, outlined in Section 2.4.1.1. There is also the potential to develop persistent pain in MS, as a result of it being a degenerative, progressive disease.

However, the lack of epidemiological studies has meant that the true prevalence, nature and chronicity of pain in MS are unclear. Neuropathic pain, as a result of demyelination, is a common and disabling form of pain in MS (Svendsen and Bach, 2006), but again its prevalence, characteristics and impact are unknown. Neuropathic pain is shown as greatly impacting upon Health-Related Quality of Life (HR-QOL) in the general population (Doth

et al, 2010). However, the effect of neuropathic pain on HR-QOL has not previously been explored in the MS population. Therefore, the first part of this thesis is an epidemiological study measuring the prevalence and nature of pain in MS. In addition, neuropathic pain in MS is characterised, and its relationship with health-related quality of life (HR-QOL) explored. Cases of neuropathic pain are also compared with nociceptive pain to analyse key differences in the characterisation and impact of these two distinct pain types, which are managed differently in clinical practice. Validated pain measures are used in the study as advocated by the International Association for the Society of Pain (IASP). Furthermore, a multi-dimensional pain assessment is undertaken alongside the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin *et al*, 2005), and the Neuropathic Pain Specialist interest Group (NeuPSIG) recommendations (Haanpää *et al*, 2011).

1.3 Management of neuropathic pain in Multiple Sclerosis

The reduction of pain severity is related to improvements in HR-QOL (Jensen *et al*, 2007a), with reduced morbidity and health-care costs (Thomas *et al*, 1998). Recent NICE guidelines on the pharmacological treatment of neuropathic pain recommend pregabalin, or amitriptyline as first line treatment, or imipramine or nortriptyline if not tolerated, followed by opioids (National Institute for Clinical Excellence (NICE), 2010), and cannabinoids in MS, only if all other treatments fail (Attal *et al*, 2010). Due to side effects of pharmacological interventions and potential drug interactions in patients with pain and other co-morbidities there is an increased interest in non-pharmacological interventions such as TENS to manage pain (Dworkin *et al*, 2007).

Transcutaneous Electrical Nerve Stimulation (TENS) is a non-pharmacological, non-invasive electrical modality, used for the treatment of pain in a variety of disorders. It involves the application of low voltage electrical currents across the intact surface of the skin, using electrodes (Sluka and Walsh, 2003). The electrical output of a standard modern TENS unit can be altered to vary the duration, frequency, and amplitude of the electrical pulses. It is thought that by altering these electrical output characteristics; different physiological mechanisms can be activated, causing different hypoalgesic effects.

TENS has demonstrated efficacy over a control situation in chronic musculoskeletal pain disorders, such as chronic low back pain (Buchmuller *et al*, 2012; Moore and Shurman, 1997), and in the treatment of peripheral neuropathic pain, such as post herpetic neuralgia

(PHN) (Barbarisi *et al*, 2010) , and painful diabetic peripheral neuropathy (PDPN) (Kumar *et al*, 1998). A review by the European Federation of Neurological Societies (EFNS) Task force, recommended that TENS may be used as an additional therapy in the treatment of neuropathic pain (Cruccu *et al*, 2007). It has not, however, been adequately trialled in central neuropathic disorders, and has not been tested on the MS population with neuropathic pain. Part two of this thesis therefore explores whether TENS may reduce the severity of neuropathic pain in the MS patient. This involves a randomised, placebo-controlled trial, which adheres to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (Moher *et al*, 2012).

1.4 Thesis Layout

This thesis is divided into three sections: an introductory chapter for the entire thesis, followed by two main sections (part one and part two).

- **Chapter 2**: ***Theoretical Framework of Pain***

This chapter serves as a guide for pain theory and assessment for the entire thesis. The chapter begins with an overview of general pain, including pain terminology and neurophysiology. More specifically, this will be followed by MS-related pain, including its presentation and pathophysiology. The chapter finishes with a theoretical framework for the basis of pain assessment, which will act as a guide throughout this thesis.

- **Part one (Chapters 3-7): *The epidemiology of Pain in MS***

This section is based on an epidemiological study of the prevalence, characteristics, risk factors and impact of pain in MS. It begins with Chapter 3, the literature review, which focuses reasons for the variability in pain prevalence rates reported in previous studies. Chapter 4 then reviews the methodological rationale of an epidemiological study, as well as the optimum method of pain assessment in an epidemiological design. This is followed by the methodology (Chapter 5), results section (Chapter 6) and discussion (Chapter 7) of the epidemiology of pain in MS.

- **Part two (Chapter 8-12): *The Effect of TENS on Neuropathic Pain in MS***

This section is based on a randomised, controlled trial of the effect of TENS on neuropathic pain in MS. It begins with Chapter 8, which reviews the findings of previous studies of TENS in both experimental and chronic pain. Subsequently, Chapter 9 explores the optimum TENS parameters and application to elicit pain relief, as well as the most appropriate form of placebo-TENS situation. This is followed by the methodology (Chapter 10), results section (Chapter 11) and discussion (Chapter 12) of the effect of TENS on neuropathic pain in MS.

The final chapter of the thesis (Chapter 13) highlights the novel findings of the study overall, integrating the key findings of both sections and outlines the recommendations from the study findings.

2 THEORETICAL FRAMEWORK OF PAIN

This chapter will outline a theoretical framework of MS-related pain and its assessment. The chapter begins with an overview of pain in general, including pain terminology and neurophysiology. Subsequently, the chapter will outline MS-related pain, including its presentation and pathophysiology. The chapter finishes with a theoretical framework for the basis of pain assessment, which will act as a guide throughout this thesis. The prevalence of MS-related pain is detailed in Chapter 3.

2.1 What is pain?

The International Association for the Study of Pain (IASP) define pain as *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"*(Merskey and Bogduk, 1994). Thus while nociception is the process by which peripheral sensory nerve fibres are activated by noxious stimuli, pain perception involves the cognitive and emotional processing of an aversive stimulus, requiring the capability of abstraction and elaboration of sensory information (Julius and Basbaum, 2001). Thus whilst nociception may be the original problem, other factors including sensitisation, genetics, cognition and emotions including past experiences of pain also play their part (Tracey, 2010).

This model of pain highlights its multidimensional nature, of which three components interact and modulate each other to produce the overall experience of pain: *sensory-discriminative* dimension which involves the translation of nociceptive signals into information on the intensity, duration, location and quality of noxious stimuli; *emotional-affective* dimension influenced by environmental factors surrounding the nociceptive stimuli which activates the limbic system (e.g. nature of the disease causing the pain, uncertainty about outcome, social support), making pain unpleasant, burdensome or unbearable; and *cognitive-evaluative* component which encompasses all the processes that modulate pain processing including psychosocial factors such as culture, religion, mood (Geisser *et al*, 2003), attention (Legrain *et al*, 2002), expectation (Benedetti *et al*, 2003), anxiety and previous experience (Villemure and Bushnell, 2002).

2.2 Terminology of pain

Pain occurs in normal, sensitised or modulated states. In a normal state noxious stimuli will cause a painful sensation and innocuous stimuli will result in a non-painful sensation. In a sensitised state pain may be caused by stimuli which are normally innocuous (allodynia) and noxious stimuli will cause an amplified painful response (hyperalgesia) (Merskey and Bogduk, 1994). However a painful response is diminished in a modulated state (hypoalgesia). Dysasthesias and paraesthesias are also related to a disturbance of the sensory nervous system. The term dysasthesias refers to an abnormal sensation that is unpleasant, whereas paraesthesias refer to an abnormal, sensation that is not unpleasant, each of which may be spontaneous or evoked (Merskey and Bogduk, 1994) .

2.2.1 Time-bound definition of pain

Historically pain as a response to a noxious stimulus which abates following tissue repair is categorised as *acute pain*, but when pain is a response to a noxious stimulus which has healed and therefore has no straightforward symptom-pathology relationship it is categorised as *chronic pain*. The earliest time frame for this resolution is the three month period, but for research purposes, six months is the preferred definition of chronic pain (Merskey and Bogduk, 1994). The physiology behind the transference of acute into chronic pain is outlined in Section 2.3.

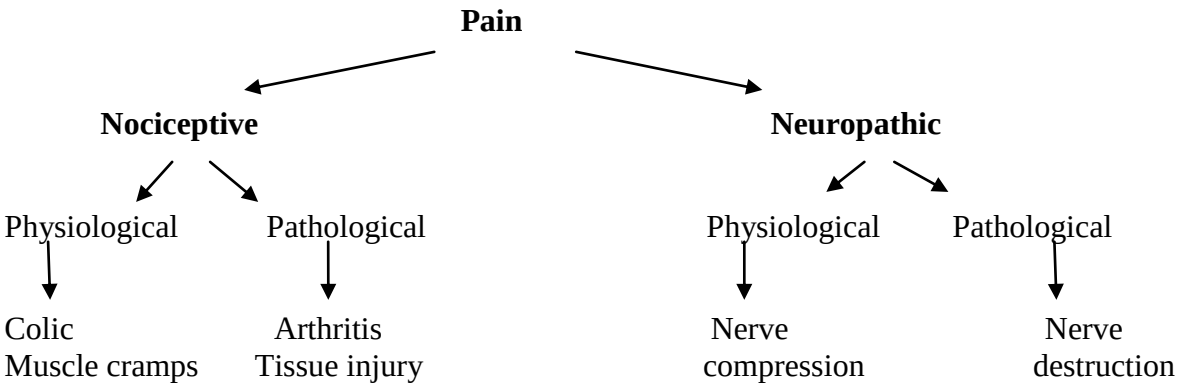
However, determining when tissue has healed can be difficult depending on the injury and the other variables associated with each patients healing process. Furthermore, some disorders such as MS have ongoing inflammation and incomplete healing of nerve tissue, where scarring may take place. Therefore mechanism-based definitions of pain are also often used, particularly in the clinical setting.

2.2.2 Mechanism-based definition of pain

Recently, a more fundamental, three-tiered mechanism-based classification broadly classifies pain by its underlying pathopysiological cause (Treede *et al*, 2008) (Figure 2-1), explained fully by (Bennett, 2010). Pain is either physiological (normal) or pathological (abnormal). Physiological pain results from activation of the nociceptive system (detailed in Section 2.3), and serves to warn of impending tissue injury. Here pain is a normal experience, essential for survival. Conversely, pathological pain is distinguished by a

change in the baseline sensitivity of the nervous system, and occurs after injury. This serves to protect the nervous system to any further injury while healing occurs, an adaptive response. Pathological pain is known as maladaptive when the sensitivity of the nervous system does not return to normal after tissue healing. Thus *nociceptive* pain is pain that occurs due to normal activation of the nociceptive system either by impending tissue injury or ongoing tissue destruction or inflammation. *Neuropathic* pain is defined as pain as a direct consequence of a lesion or disease affecting the somatosensory nervous system (Treede *et al*, 2008). Figure 2-1 shows that both nociceptive and neuropathic pain may be of physiological or pathological cause.

Figure 2-1: Three level classification of pain



From Bennett M. (2010). *Neuropathic Pain.* Oxford University Press. Oxford. 2nd Edition

2.2.3 Clinical definitions of pain

Clinically significant pain is a term often used in the clinical setting and in the pain literature, but with no consensus of an optimum definition. It is accepted that the term *clinically significant* equates a 'meaningful' phenomenon in the clinical setting. But, meaningful for whom? Meaningful pain can take several guises that may be of variable interest to the patient, clinician, health policy maker, or epidemiologist, and can vary depending upon the group being studied. For example, clinically significant pain has previously been defined by such factors as chronicity (Merskey and Bogduk, 1994), intensity (Grasso *et al*, 2008), level of pain-related disability (Webb *et al*, 2004), interference with every day activities (Smith *et al*, 2001a) and level of expressed need (use of analgesics and clinical contact) (Torrance *et al*, 2006), each of which may be of variable interest to a different audience.

There is much debate on what factors should determine whether pain is clinically significant (Von Korff, 2011). (Croft *et al*, 2011), for example, advocates for continuation of chronicity in definitions of clinically significant pain, alongside pain-related impact on daily life. However, regardless of specifics, the growing consensus is that the definition of pain must be fundamentally patient-orientated- the patient must decide whether their pain is in fact clinically significant. The many methods of ascertaining clinically significant pain, including validated tool such the Chronic Pain Grade (CPG) (Von Korff *et al*, 1992) and the Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994) as well as the word *bothersome* (highly correlated with pain intensity, pain-related disability, and activity limitation) (Webb *et al*, 2004) are discussed in detail in section 4.3.1.

2.3 The Physiology of Pain

Based on pathophysiology pain is classified into two distinct categories, **nociceptive pain** and **neuropathic pain** (Woolf and Decosterd, 1999).

2.3.1 Physiology of nociceptive pain

The nociceptive system

The role of the nociceptive system is to detect actual or potential tissue damage, and comprises of nociceptors, the transmission nerves and neurons in peripheral and central pathways, and the nerves and neurons for the nociceptive network processing in the brain. Various authors have provided comprehensive reviews of the central mechanisms of nociception (Almeida *et al*, 2004; Butler and Moseley, 2003; Loeser and Melzack, 1999; Markenson, 1996; Willis and Coggeshall, 2004; Wood, 2008). However for the purpose of this thesis an outline of the basic mechanisms is provided using these references.

Nociceptors

Noxious stimuli are detected by the peripheral terminals of the nociceptive afferent nerve fibres, called nociceptors, which consist of bare free endings embedded in the tissue. A nociceptor is defined as "a sensory receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged' (Merskey and Bogduk, 1994). The classification of the nociceptor is based on the nerve fibre, of which it is the terminal end. There are two types of nerve fibre in this situation: 1) small-diameter, unmyelinated nerves that conduct the nerve impulse slowly (2 m/sec), termed C fibres, and 2) larger diameter, lightly myelinated nerves that conduct nerve impulses faster (20m/sec), termed A-delta fibres (Butler and Moseley, 2003). The C-fibre nociceptors respond polymodally to thermal, mechanical and chemical stimuli, and the A-delta fibre respond to mechanical and mechanothermal stimuli. Stimulation of A-delta fibres results in sharp, fast pain, whilst stimulation of C fibres results in delayed, dull pain.

Peripheral and central transmission pathways

Primary afferent fibres terminate at the level of the spinal cord dorsal horn, where they synapse with interneurones or second order neurones. Two types of second order neurone receive noxious input from the periphery: nociceptive specific (NS) and wide dynamic range cells (WDR). NS cells are predominantly found in the lamina I (marginal layer) of the dorsal horn and respond only to noxious input. WDR cells are predominantly found in

the lamina V of the dorsal horn and receive mixed inputs from small nociceptive afferent fibres (A-delta and C) and also large afferent fibres (Aß), which under normal circumstances transmit information about non-noxious stimuli to produce touch sensations. The WDR cells are a key feature in the 'Pain Gate theory' (Melzack and Wall, 1967) (detailed in part two of thesis, Section 8.2.1.1). The dorsal horn also receives input from the supra-spinal structures (covered later in this section), which have an inhibitory effect on second order neurones. These pain modulation mechanisms are also considered again in relation to TENS in Section 8.2.1 (part two of the thesis). In the dorsal horn, the secondary order neuron projects the ascending fibre into the supra-spinal level via the anterlolateral pathways (Figure 2-2), to cortical structures for processing

The processing network in brain

The afferent fibres then primarily travel to the thalamus, where they communicate with the cortex and limbic systems, where the emotional, memory and learning responses to pain occur. The sensory cortex primarily serves the sensory dimension of pain to identify the extent, source, site and severity of the noxious stimulations. The co-operation between the hypothalamus and the limbic system is largely responsible for the autonomic reactions associated with pain experience, such as an increased breathing rate, and emotional reactions such as anger. The frontal lobe is activated for the cognitive assessment of pain related to one's past experience or personal characteristics (Butler and Moseley, 2003).

Physiology of chronic pain

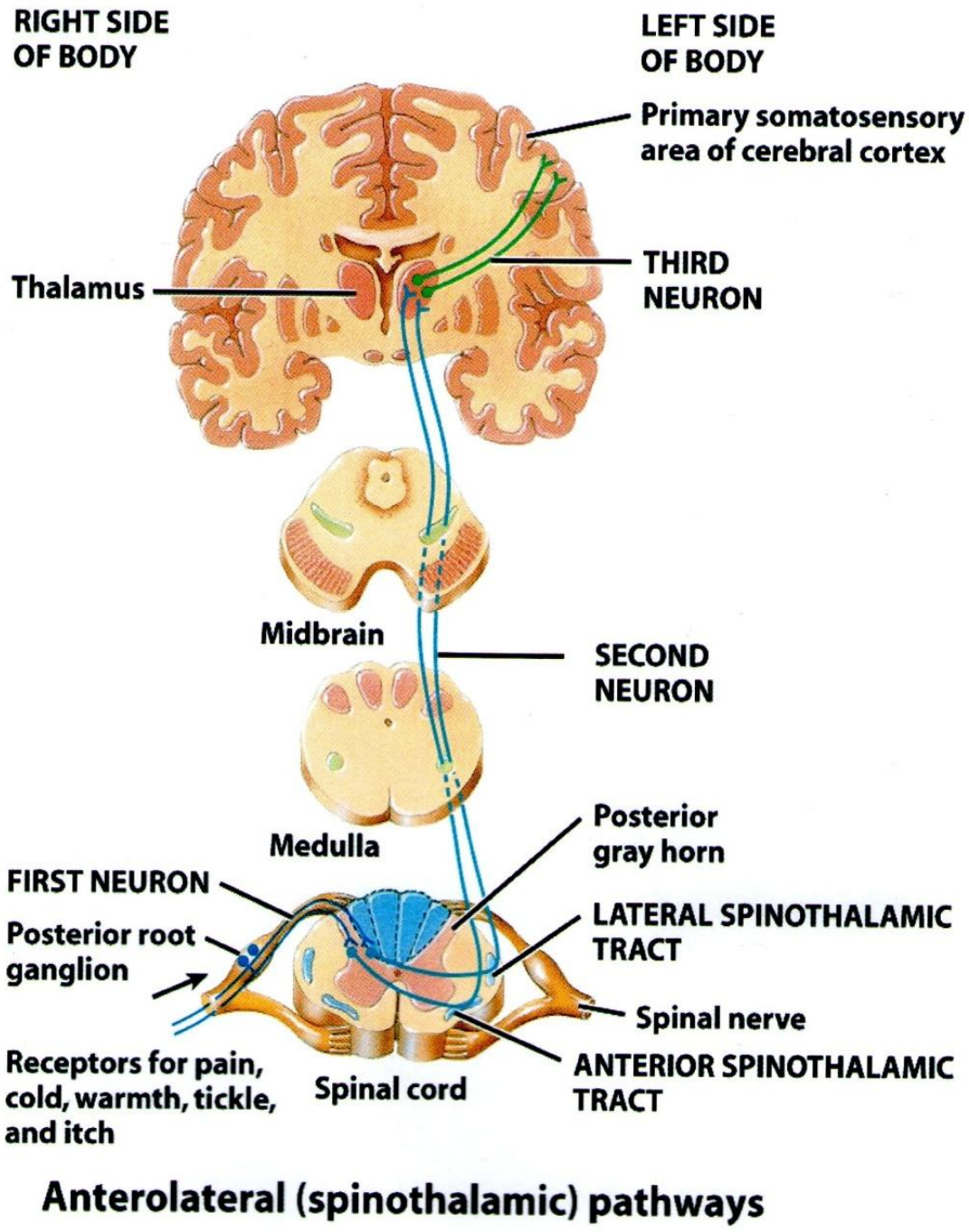
Both chronic pain and neuropathic pain have been described as maladaptive, in the sense that pain neither protects or nor supports healing and repair (Benett, 2010). Instead, these pain syndromes are caused by a malfunction of the somatosensory nervous system, which can be considered a disease in its own right.

Chronic pain is a result of a prolonged activation of the dorsal horn neurones caused by repeated or sustained noxious stimulation, which can trigger or maintain *central sensitisation* (increases responsiveness of nociceptors in the dorsal horn of the spinal cord) (Baranauskas, 1998). This is a complex process that is thought to involve a number of mechanisms: activation of the dorsal horn neurones leads to Nitric Oxide (NO) release, which has the capacity to diffuse in the spinal cord neurones, spreading sensitisation. Furthermore, NO may also enhance the release of substance P which can increase the

sensitivity of second-order neurones and facilitate the transmission of pain from the peripheral to the central nervous system (Luo and Cizkova, 2000). Consequently the characteristics of WDR neurones and NS neurones may be altered as they become increasingly sensitive and hyper-responsive causing exaggerated perception of painful stimuli (hyperalgesia). NS neurones may also start to function more like WDR neurones, therefore previous non-noxious afferent input (e.g. mechanical stimuli) may become noxious, leading to referred pain, hyperalgesia and allodynia across multiple segments (Markenson, 1996). Neuroanatomical reorganisation may also occur, for example following nerve injury myelinated axons can sprout and make synaptic connections with intrinsic neurones leading to normal afferent input being perceived as pain (allodynia) in the supraspinal structures (Woolf and Decosterd, 1999).

However, there is not always consistency between the degree of tissue injury and the level of pain experienced. Higher brain centres encompassing the limbic system, brain stem and periaqueductal grey region also play a pivotal role in facilitating and sustaining up-regulation of the nociceptive system in the absence of tissue damage or peripheral input (Chapman, 1996) (see descending pain inhibition/ facilitation systems in following sections).

Figure 2-2: Anterolateral pathways



From: Tortora and Derrickson (2007). Introduction to the human body: The essentials of Anatomy and Physiology.

Descending Pain Inhibition Systems

Substantia gelatinosa cells can also be influenced by higher descending inputs which can alter the excitability of second order neurons. This input mainly comes from the periaqueductal grey matter surrounding the cerebral aqueduct in the midbrain, and the raphe nucleus located in the medulla (Almeida et al, 2004) (Figure 2-3). Both these structures have excitatory effects on inhibitory interneurones and can reduce pain in the spinal cord by affecting transmission from C fibres (Wood, 2008). Within the periaqueductal grey there are two distinct regions that are able to elicit forms of analgesia, the ventrolateral column, which releases serotonin, and the lateral column, which releases noradrenalin (Fields and Basbaum, 1989). However, these two pathways are normally inactive due to other inhibitory interneurones in the brain. Nevertheless, the inhibition of periaqueductal grey matter and the raphe nucleus can be removed for example by the influence of the limbic system (e.g. amygdala, insula and anterior cingulate cortex). The limbic system is involved with a range of emotional behaviour (e.g. pleasure, stress, anxiety, fear), which can influence the pain experience by generating descending impulses to release opioids such as endorphins and enkephalins (Chapman, 1996). The release of opiates indirectly removes the inhibition from the peri-aqueductal grey matter and the raphe nucleus, thus, enabling modulation of pain by influencing substantia gelatinosa cells, which in turn inhibit second order neurons and prevents transmission of pain to the brain (Figure 2-3) (Wood, 2008). This process may be facilitated by the use of TENS detailed in part two of this thesis (Section 8.2.1.2).

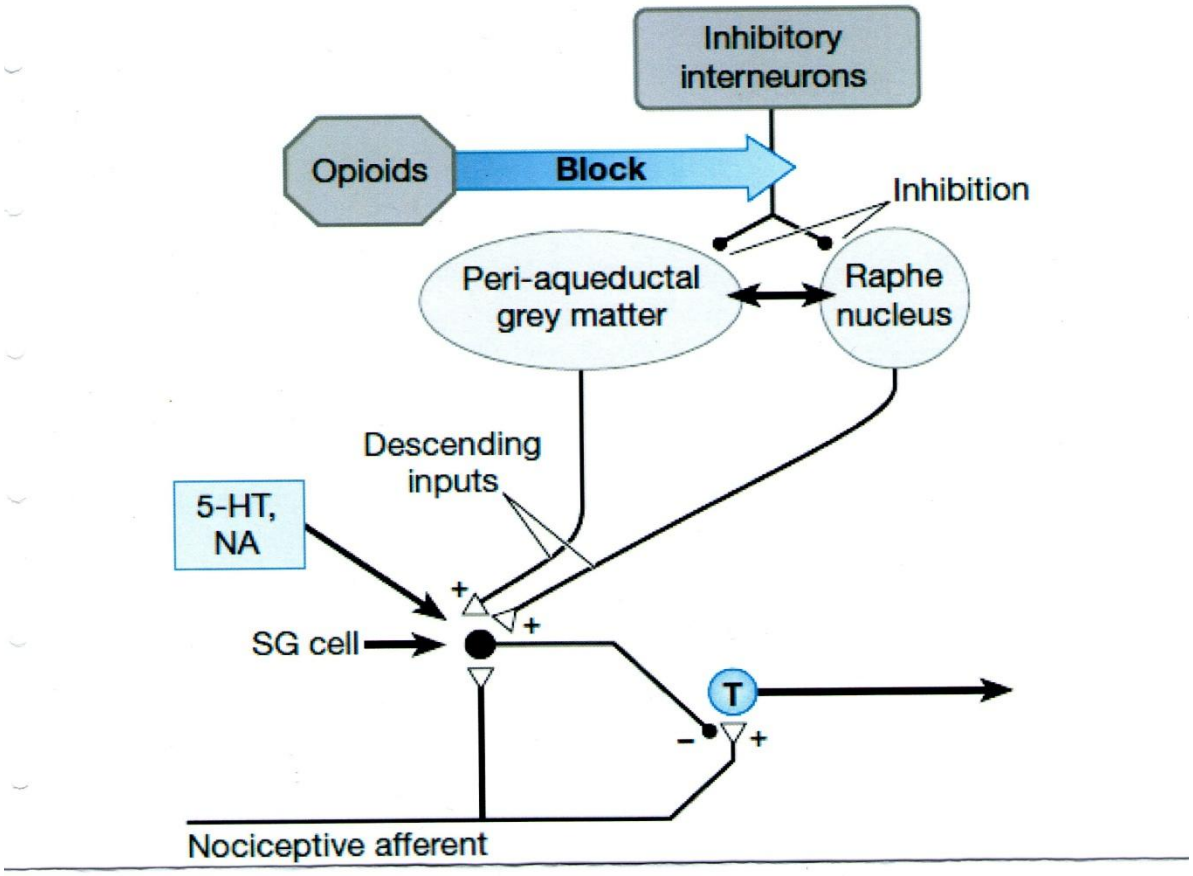
Descending pain facilitation systems

The higher centres of the brain which influence pain inhibition can also facilitate pain by up-regulation of the nociceptive system (Butler and Moseley, 2003). Research has demonstrated that forebrain regions, which produce emotion, attention and motivation, have the capability to control nociceptive impulses via descending bulbospinal pathways (Dubner and Ren, 1999). Therefore, the stronger the attention given to a stimulus, the more dominant the descending facilitation, which in turn leads to sensitisation of second order neurons. Due to the complex pain processes, the changes in the spinal cord triggered by the emotional experience of persistent pain (anxiety, avoidance, stress, anticipation, fear) can sensitise pain processing areas within the brain involved including the thalamus, anterior and posterior insula (Carlson *et al*, 2007) and although tissue damage may be absent, supraspinal structures maintain, amplify and develop the perception of pain (Butler and Moseley, 2003; Dubner and Ren, 1999). Functional brain imaging studies provide evidence

for the involvement of the rostral anterior cingulated cortex, insular cortex, amygdala and periaqueductal grey matter in pain perception (Casey, 1999) and the overlap between the areas modulating the nociceptive system, and the areas controlling autonomic and motor function, and emotional state (Apkarian *et al*, 2009).

Like chronic pain, neuropathic pain has also been described as maladaptive, in the sense that pain neither protects or nor supports healing and repair. The following section discuss neuropathic pain.

Figure 2-3: Descending pain inhibition



From: Wood L (2008). Physiology of pain. In Watson T: *Electrotherapy- Evidence-based Practice*. Churchill Livingstone Elsevier Lt

2.3.2 Physiology of neuropathic pain

As mentioned, neuropathic pain is due to a lesion or disease affecting the somatosensory nervous system (IASP, 2008). From Chapter 1 MS is understood as an inflammatory disease attacking the *central* nervous system (CNS). Returning to Figure 2-1, it is appropriate therefore to label MS as *pathological neuropathic pain*, as a result of ongoing nerve destruction. As MS affects the CNS, and has a distinct pathophysiology, the thesis will detail the pathophysiology of neuropathic pain, under the MS umbrella (Section 2.4.2.1). This is opposed to a general overview of the pathophysiology of neuropathic pain, which would not be relevant in the current topic.

This section has outlined the terminology and pathophysiology of pain in general. The thesis will now consider MS-related pain.

2.4 Pain in MS

Pain is a significant symptom in MS, causing disability in its own right (Kraft *et al*, 2008; O'Connor *et al*, 2008). Pain in MS may be acute or chronic, and based on pathophysiology is classified into nociceptive pain and neuropathic pain (O'Connor *et al*, 2008; Solaro *et al*, 2003). This section outlines the presentation and pathophysiology of these two distinct types of pain in MS.

2.4.1 MS-related nociceptive pain

Nociceptive pain arises as a result of abnormalities in the musculoskeletal system, secondary to the disease. An appropriate physiological response is experienced when nociceptor sensory units i.e. in bone, muscle, and ligament are activated to transmit afferent impulses at the conscious level. In this way pain has a protective role, warning of tissue damage and eliciting reflexes and behavioural changes. A common examples of nociceptive pain includes musculoskeletal pain, such as back pain from postural and gait-related abnormalities, which place stresses on muscles, bones and joints (Saffir and Rosenblum, 2002). Other examples of nociceptive pain in MS include visceral pain (i.e. pain from bladder or bowel spasm/infection), whilst immobility may lead to decubitus ulcers in people bed or wheel-chair bound.

Painful tonic spasms (PTS) are paroxysms of brief, (unilateral or bilateral) dystonic, repetitive posturing, often spreading to multiple joints, preceded and accompanied by radiating pain of the limbs, usually lasting less than two minutes, and often associated with other sensory symptoms such as dysasthesias (Spissu *et al*, 1999). In the upper limb, the seizures are characterised by tetany-like spasm of the hand, flexion of the elbow and adduction of the shoulder (Moulin *et al*, 1988). PTS can be triggered by non noxious stimuli (allodynia), such as tactile stimulation. PTS should not to be confused with spasticity related pain, which is pain during exaggerated flexor or extensor contracture–like spasms, or pain from the resulting stiffness or contractures of joints, a separate phenomenon from PTS (Svendsen and Bach, 2006).

Additionally, pain may be of iatrogenic origin due to the medical treatments in the management of the disease. For example, long-term steroid treatment may lead to osteoporosis, which may causes vertebral fractures. Disease modifying therapies (e.g. Interferon), commonly used in the treatment of MS, may also cause considerable pain such as headache, flu-like symptoms or localised cutaneous reactions (Rosenblum and Saffir, 1998).

2.4.2 MS-related neuropathic pain

It has been discussed that MS is a disorder of the central nervous system. The IASP defines central neuropathic pain as *"pain as a result as a lesion or dysfunction of the central nervous system*" (Merskey and Bogduk, 1994). The demyelinating lesion seen in MS is the second most common cause of central pain after stroke (Boivie and Osterberg, 1996). Central pain in MS is directly related to the demyelination process of the disease, and is associated with dysaesthetic pain, allodynia and hyperalgesia (Boivie, 2006; Solaro *et al*, 2003), as mentioned in the previous sections. The MS patient, displaying typical central pain has been described as: *".....tending to wear as little clothing as possible, will seek a zone of tolerant ambient temperature, and may suffer from the touch of the sheets at night....*" (McHenry, 2002). Common examples of dysaesthetic pain in MS include *burning, tingling and aching* of the extremities (Boivie, 2006). This type of pain is often chronic, presenting daily; with some 30% of patients reporting only short intervals of pain freedom, lasting minutes to hours, which can worsen during a period of relapse (Osterberg *et al*, 2005). Other pain syndromes related to central neuropathic pain in MS include**, *trigeminal neuralgia, Lhermitte's phenomenon, paroxysmal extremity pain, and migraine headache*** (Boivie, 2006). These conditions can often be paroxysmal in nature,

with sudden, severe, episodes of pain, lasting from seconds to minutes, which may occur multiple times a day during a relapse (Maloni *et al*, 2000). The relapsing-remitting nature of MS has implications for recurring episodes of these syndromes throughout the course of the disease. Chronic dysasthesias are typically less intense than paroxysmal episodes of pain, but their persistent nature can be challenging for the patient (Solaro *et al*, 2003). The aetiological classification of each of the syndromes is discussed further in Chapter 4, Section 4.4, but they are briefly outlined here, as follows:

Dysaesthetic pain

Dysaesthetic pain in MS has previously been introduced in this section.

Trigeminal Neuralgia

Trigeminal Neuralgia (TN) is characterised by bursts of brief, recurrent sharp pain of high intensity in the distribution of the branches of the fifth cranial nerve (Zakrzewska and Linskey, 2009). Touch, chewing or talking may evoke the pain. Focal demyelination leads to increased excitability in the trigeminal afferent neurones and altered threshold for repetitive firing causes spontaneous firing and paroxysm of pain (Devor *et al*, 2002). This presentation should be differentiated from atypical facial pain, in which pain is described as constant with periods of transient paroxysm, and a sensory deficit in the trigeminal nerve area is never reported. In this case the lesion is most likely along the leminiscus lateralis pathway (Hutchins *et al*, 1990). TN occurs more frequently in MS patients than in the general population with an estimated prevalence of 2–6.3% (Hooge and Redekop, 1995; Moulin *et al*, 1988; Vermote *et al*, 1986) versus 0.7 % in the general population (Putzki *et al*, 2009). Bilateral TN is more often seen in MS patients (Hooge and Redekop, 1995) and TN associated with MS begins at a lower age than other types of TN (De Simone *et al*, 2005).

Lhermitte's phenomenon

Lhermitte's phenomenon (LP) is a short-lasting paroxysmal (sudden) pain radiating down the spine to the lower extremities. Often this symptom can be transient and self-limiting, however increased frequency and intensity during a relapse are disabling (Solaro et al. 2003). A previous survey revealed that LP occurred as the first symptom of MS in 16% of patients and rarely occurred in conditions other than MS. Previous studies reported painful

LP in 2–25% of MS patients (Clifford and Trotter, 1984; Fryze *et al*, 2002; Indaco *et al*, 1994; Moulin *et al*, 1988; Stenager *et al*, 1991). Demyelinating lesions of sensory axons in the cervical posterior column may cause this phenomenon (Smith and McDonald, 1999). LP has been reported as lasting usually for 4-6 weeks during an MS relapse (Kanchandani and Howe, 1982).

Paroxysmal extremity pain

Paroxysmal extremity pain (not associated with PTS) has been described as pain lasting seconds to minutes located in the extremities (Maloni *et al*, 2000; Moulin *et al*, 1988; Nurmikko *et al*, 2010). Paroxysmal limb pain occurs in about 1–4% of MS patients (Moulin *et al*, 1988; Vermote *et al*, 1986). It has been suggested that paroxysmal extremity pain in MS is due to ectopic activity at sites of demyelination in the CNS (Smith and McDonald, 1999). It is experienced as sharp, lancating or electric-shock like pain.

Optic neuritis

Optic neuritis may be accompanied by subacute periorbital pain aggravated by eye movement (Svendsen and Bach, 2006). During the disease course, pain associated with optic neuritis may be seen in about 8% of the patients, and it is a common symptom at onset (Indaco *et al*, 1994). It is assumed that this pain occurs when the meninges surrounding the swollen optic nerve are stretched (Nurmikko *et al*, 2010) thus cannot be classified as central neuropathic pain, but is included here for completeness.

Migraine headache

MS lesions affecting the brainstem or C2 dorsal horn have been reported to cause migraine (Putzki *et al*, 2009). Migraine occurs in 22% of MS patients, and accounts for 41% of all headaches in MS (Rolak and Brown, 1990). Other possible sources of headache are cervicogenic headaches due to musculoskeletal changes, and headache as a side effect from DMTs (Smith and McDonald, 1999).

2.4.2.1 Pathophysiology of central neuropathic pain in MS

Central, neuropathic pain in MS is thought to be a consequence of demyelination, and plaque formation throughout the CNS (Boivie, 2006; Kenner *et al*, 2007). However, as with other central neuropathic pain disorders, the exact mechanisms are poorly understood. An MRI relating plaque location to pain complaints in MS found a preponderance of lesions in the periventricular grey matter, corpus callosum, pons, brachia pontis, cerebellum, medulla oblongata, and thalamus (Osterberg *et al*, 2005). Thalamic lesions were seen in one-third of these patients, with lesions affecting the fibres projecting to the ventroposterior thalamus, resulting in reduced inhibition and were considered most crucial in the development of pain. Spinal cord lesions were present in over half of the patients with pain, many of which had pain confined to both lower extremities.

It is thought that two key mechanisms are responsible for central pain in MS:

1) The generation of ectopic impulses at demyelinated lesions in response to neural damage (Boivie, 2006; Herman *et al*, 1992; Kenner *et al*, 2007; Moulin *et al*, 1988; Solaro *et al*, 2013).

2) The interruption of inhibitory impulses from the brain, which removes the modulation of afferent A-delta and C pain pathways (Vaney, 1996). The absence of the inhibitory impulses from the brain leads to central sensitisation. Dorsal horn cells develop reduced thresholds, which are prolonged after discharges and increased spontaneous activity with expansion of peripheral fields, causing allodynia and hyperalgesia (Aicher *et al*, 2004; Olechowski *et al*, 2009; Solaro *et al*, 2013)

The generation of ectopic impulses at demyelinated lesions in response to neural damage, may explain paroxysmal symptoms such as Lhermitte's phenomenon and Trigeminal neuralgia. These ectopic impulses can spread to surrounding unaffected neurons (O'Connor *et al.* 2008; Vaney 1996). Pain arising from damaged neurons in MS may also be due to an acquired channelopathy: abnormal sodium channel activity can contribute to hyperexcitability of injured neurones resulting in symptoms of paraesthesias and pain. In MS, dysregulated sodium channel gene expression may cause maladaptive healing during remyelination and continued abnormal action potential conduction, resulting in ongoing pain (Waxman *et al*, 1995; Waxman, 2001).

Dysaesthetic extremity pain is thought to be caused by MS lesions in the nociceptive spinothalamic tracts, affecting the inhibitory functions of gamma aminobutyric acid (GABA) interneurones (pain modulation at the spinal level is discussed in Section 8.2.1. Disinhibited nociceptor input leads to constant central pain sensation (central sensitisation) (Herman *et al*, 1992).

Glial cells (oligodendrocytes, astrocytes, and microglia) are now recognized as important modulators of pain. The oligodendroglia and astrocytes are most directly involved in the pathogenesis of MS plaques. Astrocytes and microglia act as immune cells in the CNS. They are most responsible for chronic pain and hyperalgesia. Some of the pain experienced by MS patients may stem from the association of microglial cells and astrocytes to other injured or reactive glial cells. Chemical substances released from activated microglia and astrocytes in response to nerve injury, infection, or pain states have been shown to amplify pain and mediate hyperalgesia (Watkins and Maier, 2000).

In summary, central pain disorders such as that found in MS, are thought to be a result of decreased inhibitory mechanisms and increased neuronal activity and reactivity along the somatosensory pathways.

2.4.1 MS-related pain of mixed origin

The term *mixed pain* is controversial in the pain literature (Baron and Binder, 2004; Ross, 2001), and is used less commonly in MS. It relates to the presence of pain of mixed aetiology. Examples of this include low back pain, in MS, which may be a result of two concomitant, but distinct aetiologies: 1) mechanical and postural related *(nociceptive*), as a result of the effect of MS on the musculoskeletal system, and 2) *neuropathic* due to the damage of the nervous system as a result of the demyelination of the CNS, or peripheral nerve damage (i.e. nerve root compression), due to mechanical changes of the spine. Due to its ambiguity it was deemed inappropriate to directly measure mixed pain in this thesis. This is particularly relevant when one considers the epidemiological basis of the study

2.5 Theoretical basis of pain assessment

The first part of this thesis, as a survey design study, attempted to assess the presence and experience of pain in the MS population. The second part of this thesis was a clinical trial of the efficacy of TENS on neuropathic pain in MS. Although two different types of study, a consistent self-report pain assessment approach was adopted throughout the thesis. This was guided by the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin *et al*, 2005), the Neuropathic Pain Specialist Interest Group (NeupSIG) guidelines on neuropathic pain assessment, (Haanpää *et al*, 2011) and current theoretical pain assessment frameworks (Jensen and Karoly, 2011). These were adopted in the context of epidemiological principles, including the IASP Epidemiology of Pain Professional Guidelines (Charlton, 2005a), and the Task Force on Epidemiology report (Von Korff, 1999), as well as the clinical context of the presentation of pain in MS.

IMMPACT develops consensus reviews and recommendations for improving the design, execution, and interpretation of clinical trials of treatments for pain. The NeuPSIG recommendations have been developed to standardise neuropathic pain assessment. Both recommendations highlight a multifaceted approach, using key outcome measures, including the sensory and affective aspects of pain itself, as well as physical and emotional functioning, and Health-Related Quality of Life (HR-QOL) (Dworkin *et al.* 2005) (detailed below). This thesis has adopted the recommended outcome measures to ensure a comprehensive pain assessment was undertaken. A literature review of appropriate measuring tools for each aspect of pain was conducted (Chapters 4 and 9). The most appropriate tool was selected, and used consistently in parts one and two of the thesis for continuity.

Both IMMPACT and the NeuPSIG guidelines recognise the importance of measuring both the sensory and affective components of pain (Dworkin *et al*. 2005; Haanpää *et al*. 2011). Whereas pain intensity reflects the overall magnitude of the pain, pain affect can be viewed as reflecting the distress caused by the pain (Jensen and Karoly, 2011). Both guidelines recommend measuring the fluctuation of pain over time by the use of pain "*at its worst*", "*average pain*", pain "*at its least*", and pain "*right now*". Both also advocate measurement of *location, quality* and the *temporal* aspects of pain. Pain location may be defined as the perceived location(s) of pain sensation, whilst quality refers to the specific physical descriptions of pain, such as "*hot*" or "*aching*" (Jensen and Karoly, 2011). The chronicity

and pattern of pain must also be recorded as part of a full pain assessment. The NeupSIG guidelines recommend recording the different components of neuropathic pain separately, for example ‘paroxysmal’ pain, which as detailed later, is a presentation of MS pain. The recording of analgesic use, and subsequent level of relief, as well as the use of other pain treatments is also recommended by both guidelines.

Both the IMMPACT recommendations on chronic pain and the NeuPSIG guidelines for neuropathic pain assessment highlight that a comprehensive pain assessment must also include level of sleep disturbance, psychological assessment (mood), assessment of the impact of pain on disability and HR-QOL, due to the inter-relationship of pain with these factors. Each of these factors is outlined in more detail in the appropriate sections of this thesis.

PART I: THE EPIDEMIOLOGY OF PAIN IN MULTIPLE SCLEROSIS

3 LITERATURE REVIEW: THE EPIDEMIOLOGY OF PAIN IN MS

3.1 Introduction to this chapter

This chapter will review literature on the prevalence, nature, an impact of pain in the MS population. It begins with the prevalence of pain in MS, including chronic pain, neuropathic pain, and MS-related pain syndromes (from Section 3.3). The second half of the chapter will review the nature of MS-related pain and its impact on Health-Related Quality of Life (HR-QOL) (Section 3.7). Lastly, potential predictors of developing pain for the MS patient will also be reviewed (Section 3.8). Methodological issues in relation to pain measurement will be more extensively discussed in Chapter 4.

3.2 Literature search method

This section reviews studies which have measured the prevalence of pain in the MS population. Electronic database searches identified 28 studies reporting the prevalence of pain in MS, covering the period 1980-2009 (summarised in Table 3-1). A systematic review was previously undertaken on the prevalence of pain in MS (O'Connor *et al*, 2008), identifying several of the key studies in the field, and is outlined in section 3.3.2.1. However, an independent literature search and review was also undertaken for the purpose of the current study. The O'Connor systematic review omitted two key studies (Ehde *et al*, 2003; Hadjimichael *et al*, 2007) which have greatly added to the evidence base of pain in MS. Methodological flaws were cited, which the current review disputed, (detailed further in Section 3.3.2.1). Furthermore, the O'Connor systematic review did not address the issue of study design in the literature, particularly the lack of epidemiological study design and how this may have influenced previous reports of pain prevalence. The validity of this systematic review was therefore questioned, prompting the additional literature review, carried out by the current study, instead of updating the existing work by O'Connor.

In addition, the current literature review identified several key studies, outwith the time frame of the previous literature review, which are outlined in this section, and added to Table 3-1. Databases searched included: the Cochrane Database of Systematic Reviews, Ovid-Medline, Ovid-Embase, and CINAHL. Search terms included: *Multiple Sclerosis, sensory symptoms, pain, chronic pain, neuropathic pain, central pain, paroxysms, Health-Related Quality of Life, systematic review, epidemiological/epidemiology, population-*

based study, prevalence, pain intensity, pain affect. The design and quality of individual studies are discussed throughout this section.

Table 3-1: Studies of the prevalence of pain in MS over the last 20 years							
Name, Date	**Location**	**Population and methodology**	**Sample size**	**Pain definition**	**Pain recall time frame**	**Exclusions**	**Prevalence of MS-related pain**
(Clifford and Trotter, 1984)	USA	Consecutive sample of patients currently attending MS OPC. Retrospective review of medical notes	317	Any MS-related pain, other than exclusions	NR	Headache, traumatic pain, minor pain relived by analgesics.	29%
(Vermote *et al*, 1986)	Belgium	Hospitalised patients. Questionnaire and examination.	83	Any MS-related pain, other than exclusions	Point prevalence only (no recall time period)	Headache, visceral pain	54%
(Kassirer and Osterberg, 1987)	USA	Long standing patients (mean duration of 29 years) attending MS OPC. War veterans. Pain Questionnaire	28	Any MS-related pain, other than exclusions	NR	Non-veterans	82%
(Moulin *et al*, 1988)	Canada	Consecutive sample of those currently attending OPC. Mixed methods, including pain questionnaire, retrospective medical notes review	159	Any paroxysmal stereotyped pain syndrome regarded as symptomatic of demyelinating disease, and any chronic pain present intermittently or continuously over a	Anytime during disease course	Minor pain relived by analgesics., HA	55%

		and interview		period of 1 year.			
Name, date	**Location**	**Population and methodology**	**Sample size**	**Pain definition**	**Pain recall time frame**	**Exclusions**	**Prevalence of MS-related pain**
(Warnell, 1991)	Canada	Patients currently attending MS OPC. Pain questionnaire	364	NR	NR	Those institutionalised	64%
(Stenager *et al*, 1991)	Denmark	Hospitalised patients, aged 25-45 years. Mixed methods: pain questionnaire, interview, neurological examination.	117	Chronic pain as consistent pain lasting more than one month, including dysasthesias, low back pain, spasms and extremity pain. Acute syndromes as transient symptoms of short duration, including Lhermitte's, optic neuritis and spasms.	Anytime during disease course	Minor pain relived by analgesics., HA	65%
(Stenager *et al*, 1995)	Denmark	5-year follow -up of above sample and methods.	49	As above	Pain in last 5 years	As above.	86%

Name, date	Location	Population and methodology	Sample size	Pain definition	Pain recall time frame	Exclusions	Prevalence of MS-related pain
(Archibald *et al*, 1994)	Canada	Consecutively, newly referred, outpatients at MS clinic. Pain questionnaire	85	NR	NR	None	53%
(Indaco *et al*, 1994)	Italy	Consecutive sample of those attending MS OPC. Pain questionnaire and interview.	122	Any paroxysmal stereotyped pain syndrome regarded as symptomatic of demyelinating disease, and any chronic pain present intermittently or continuously over a period of 1 year.	MS onset and during disease.	Minor pain relived by analgesics., HA	57%
(Goodin, 1999)	USA	Members of state MS society. Pain questionnaire.	168	NR	NR	None	62%
(Rae-Grant *et al*, 1999)	USA	Random sample of People with MS identified by local neurologists and 93 controls. Pain questionnaire	317	NR	NR	None	67%

Name, date	Location	Population and methodology	Sample size	Pain definition	Pain recall time frame	Exclusions	Prevalence of MS-related pain
(Howarth, 2000)	UK	Random sample of MS patients from database. No further details given of sample, database or methods.	436	NR	NR	NR	72%
(Heckman-Stone and Stone, 2001)	USA	Members of state MS society. Pain questionnaire	83	NR	NR	None	90%
(Buchanan *et al*, 2002)	USA	MS patients residing in a nursing home. Retrospective review of medical notes	14009	Any type of pain	Last week	None	51.2%
(Svendsen *et al*, 2003)	Denmark	Population based-study. MS population residing in a geographical area. Pain questionnaire	627	Any acute or chronic pain	Month	None	79%
(Ehde *et al*, 2003)	USA	Members of state MS society. Pain questionnaire	442	Persistent, bothersome pain as a result of MS	3 Months	None	44%
(Beiske *et al*, 2004)	Norway	All MS patients currently attending neurology hospital	142	Any chronic or episodic pain or sensory complaints	month	HA	66%

		departments. Pain interview					
Name, date	**Location**	**Population and methodology**	**Sample size**	**Pain definition**	**Pain recall time frame**	**Exclusions**	**Prevalence of MS-related pain**
(Solaro *et al*, 2004)	Italy	MS patients presenting across 26 MS outpatient centres. Pain questionnaire	1672	Any pain indicative of neuropathic pain (TN, LP, dysaesthetic pain) or somatic pain (back pain, PTS or visceral pain)	Now	HA, ON, Somatic pain other back pain	43%
(Kalia and OConnor, 2005)	Canada	Consecutive sample of community-based MS patients. Neurological exam and pain questionnaire	99	Chronic pain (constant or nearly constant pain in previous month)	Month and since MS onset	Chronic pain due to concomitant disease or trauma.	
(Osterberg *et al*, 2005)	Sweden	Patients attending hospital MS clinic. Pain questionnaire, interview and clinical assessment.	364	Central pain: based on detailed clinical history and neurological assessment, including QST	During MS	HA	32.4%
(Forbes *et al*, 2006)	UK	Patients of MS nurse specialists from multiple MS centres. Pain questionnaire	929	Any pain	Now	None	73%

Name, date	Location	Population and methodology	Sample size	Pain definition	Pain recall time frame	Exclusions	Prevalence of MS-related pain
(Hadjimichael *et al*, 2007)	USA	MS patients of the NARCOMS national MS patient registry. Pain questionnaire	15853	Any pain or uncomfortable sensations	Month	None	74%
(Piwko *et al*, 2007)	Canada	Sample attending MS OPC and members of the MS society. Patient and physician telephone interviews.	297	MS-related pain. No further details give.	Six months	None	71%
(Khan and Pallant, 2007)	Australia	Community-based sample of patients attending hospital clinic. Interview.	94	Any pain	Three months	Somatic pain, other than back pain	64%
(Grasso *et al*, 2008)	Italy	Consecutive series of MS outpatients attending neurology clinic. Pain questionnaire and interview.	274	Any pain of ≥3 on VAS	Month	Other known neurological diseases and disorders of the spine that could lead to pain.	47.7%
(Martinelli-Boneschi *et al*, 2008)	Italy	MS outpatients, already participating on a drug trial of DMT. Interview	428	Any chronic pain. Then classified into: Neuropathic pain (TN, LP, dysaesthetic pain) and somatic pain	Three month	Pain of less than 6 months duration	39.9%

				(LBP, PTS)			
Name, date	**Location**	**Population and methodology**	**Sample size**	**Pain definition**	**Pain recall time frame**	**Exclusions**	**Prevalence of MS-related pain**
(Douglas *et al*, 2008a)	Australia	MS society members. Pain questionnaire	219	Clinically significant pain, defined as not every-day type pain, as taken from the BPI.	Two weeks	None	67.1%
(Seixas *et al*, 2011)	Portugal	Consecutive patients attending an OPC. Retrospective medical note review	85	NR	NR	None	34%

NR=Not reported, HA= headache, ON= Optic neuritis, PTS=Painful tonic spasms, TN= Trigeminal neuralgia, LP=Lhermitte's phenomenon, LBP=Low back pain

Adapted from table of prevalence studies in systematic review from O'Connor *et al*, (2008). Studies added outwith this review are shaded.

(Nortvedt *et al*, 1999) is removed from the original table in systematic review as it does not actually state the prevalence of pain in MS.

3.3 The prevalence of pain in MS

The following section begins with an overview of the general body of literature on the prevalence of pain in MS. It focuses on the variance in pain definition and methodologies used in previous studies. This is followed by discussion of the findings of the recent systematic review and conclusions drawn from the more robust studies of recent years.

3.3.1 Overview of prevalence studies of MS-related pain in the last 20 years

The prevalence of pain in the MS population is unclear, as previous estimates over the last 20 years have varied from 29% (Clifford and Trotter, 1984) to as high as 90% (Heckman-Stone and Stone, 2001). The varied prevalence rates may reflect inconsistencies in the pain definition and methodologies adopted by different studies. Table 3-1 highlights this by presenting the key studies in this area over the last 20 years, listing the prevalence of pain reported, time frame measured, pain definition and sampling method used, as well as any exclusions of type of pain for each study. The following sections detail the variability in pain definitions and methodologies adopted by previous studies. Any pattern in methodology, pain definition and prevalence figures reported is briefly mentioned, although this is often obscured by the many inconsistencies between studies. A more detailed discussion of the impact of pain definition and methodology on previous estimates of the prevalence of pain is discussed later in section 3.3.1.2 and throughout Chapters 4 and 7.

3.3.1.1 Pain definition

Despite the many studies in this area, the prevalence of pain in MS remains unclear due to the many varied definitions of clinically significant pain used. Some studies defined pain as clinically significant by duration i.e. if it was "persistent" (Hadjimichael *et al*, 2007) or "ongoing, and bothersome" (Ehde *et al*, 2003); or of at least 2-weeks (Clifford and Trotter, 1984) one month (Beiske *et al*, 2004) three-months (Khan and Pallant, 2007) or six-months (Martinelli-Boneschi *et al*, 2008) duration. Several studies define pain solely in terms of severity, i.e. pain of at least three on a visual analogue scale of 0 to 10 for pain intensity (Grasso *et al*, 2008; Svendsen *et al*, 2005), or pain not relieved by analgesics (Clifford and Trotter, 1984; Indaco *et al*, 1994; Stenager *et al*, 1991).

Many studies defined clinically significant pain more broadly as any presentation of MS-related pain, often categorised into neuropathic or nociceptive subgroups (Beiske *et al*, 2004; Clifford and Trotter, 1984; Ehde *et al*, 2006; Grasso *et al*, 2008; Indaco *et al*, 1994; Khan and Pallant, 2007; Martinelli-Boneschi *et al*, 2008; Moulin *et al*, 1988; Piwko *et al*, 2007; Solaro *et al*, 2004; Stenager *et al*, 1991; Vermote *et al*, 1986). MS-related pain has also been ascertained by excluding non MS-specific pain types such as such as headache and musculoskeletal pain. However, exclusions were highly variable in the literature. Participants were excluded with headache (Beiske *et al*, 2004; Khan and Pallant, 2007; Moulin *et al*, 1988; Solaro *et al*, 2004; Stenager *et al*, 1991); 'somatic pain, other than back pain'(Khan and Pallant, 2007; Solaro *et al*, 2004), 'pain due to concomitant disease, other than MS' (Kalia and OConnor, 2005), 'pain relieved by analgesics' (Clifford and Trotter, 1984; Indaco *et al*, 1994; Stenager *et al*, 1991) pain from optic neuritis (Kalia and OConnor, 2005; Solaro *et al*, 2004), visceral pain (Vermote *et al*, 1986), pain in those not in the 25-45 age group (Stenager *et al*, 1991) pain from "occasional headaches or menstrual cramps" (Ehde *et al*, 2006) pain from "minor headaches, sprains and toothaches" (Douglas *et al*, 2008a), pain from other neurological disorders including herniated disc, diabetes mellitus, and other disorders of the spine, cancer, renal disease or diabetes (Grasso *et al*, 2008). Ehde *et al*, (2003) considered only "*pain related to your MS"* in their pain definition. In comparison, many studies failed to exclude any type of pain, either in their definition or in exclusion criteria, without explanation, which makes it difficult to establish if the authors were focusing specifically on MS-related pain or otherwise (Archibald *et al*, 1994; Goodin, 1999; Hadjimichael *et al*, 2007; Heckman-Stone and Stone, 2001; Seixas *et al*, 2011; Svendsen *et al*, 2003).

Studies which include all types of pain (MS-related or otherwise) report the higher prevalence figures reported to date, of 74.5% (Hadjimichael *et al*, 2007), 79% (Svendsen *et al*, 2003) and 90% (Heckman-Stone and Stone, 2001), which is what one would expect from less restrictive case ascertainment, reflecting possible non-MS specific cases of pain in the figures reported. The latter two studies do not provide any additional information used for pain definition, thus it is difficult to define how clinically meaningful pain is in these studies. The potential impact of excluding non-MS-specific pain is discussed in section 4.2.3.1. Unfortunately, many studies provide vague (Kassirer and Osterberg, 1987; Warnell, 1991) or no (Goodin, 1999; Heckman-Stone and Stone, 2001; Newland *et al*, 2005; Nortvedt *et al*, 1999; Rae-Grant *et al*, 1999; Seixas *et al*, 2011) definition of clinically significant pain, limiting comparison of findings between studies.

There is also great variability in the methodological design of studies, which may account for the broad spectrum of prevalence figures previously reported. This is discussed in the next section.

3.3.1.2 Methodological approaches

The variability in the methodologies of previous studies is illustrated in several key areas, including the time fame used to allow for recall of pain, the method of data collection, the study sample used and the study design. The high variability in each of these factors may account for the high inconsistencies in previous reports of pain prevalence.

In previous MS-related pain research the prevalence of pain was measured if present at the actual time of assessment (Solaro *et al,* 2004; Stenager *et al,* 1991; Vermote *et al,* 1986), within the last two weeks (Douglas *et al,* 2008b), within the last month (Archibald *et al,* 1994; Beiske *et al,* 2004; Grasso *et al,* 2008; Svendsen *et al,* 2003), within the last 3 months (Ehde *et al,* 2003; Ehde *et al,* 2006), within the last six months (Khan and Pallant, 2007; Piwko *et al,* 2007) and at any time since initial MS diagnosis (Indaco *et al,* 1994; Kalia and O'Connor, 2005; Moulin *et al,* 1988; Stenager *et al,* 1991). Similar high prevalence figures for clinically significant pain of between 70%-74.5% (Hadjimichael *et al,* 2007; Indaco *et al,* 1994; Piwko *et al,* 2007) were reported in studies using different recall periods, indicating no obvious pattern between duration of pain recall and prevalence of pain reported in previous MS literature. This is discussed further in section 4.2.1.

Variability also exists in relation to the instrumentation used for pain assessment in previous studies. Methods of data collection include survey methods (Douglas *et al,* 2008b; Ehde *et al,* 2003; Ehde *et al,* 2006; Goodin, 1999; Hadjimichael *et al,* 2007; Kalia and O'Connor, 2005; Rae-Grant *et al,* 1999; Solaro *et al,* 2004; Svendsen *et al,* 2003), structured interviews (Archibald *et al,* 1994; Beiske *et al,* 2004; Khan and Pallant, 2007; Stenager *et al,* 1991; Stenager *et al,* 1995), and retrospective chart reviews of medical notes (Buchanan *et al,* 2002; Clifford and Trotter, 1984; Moulin *et al,* 1988; Piwko *et al,* 2007), each of which can impact on outcome, explaining the high variability in prevalence figures reported. Furthermore, cohorts were widely dissimilar, and included MS patients in outpatient neurology clinics (Beiske *et al,* 2004; Osterberg *et al,* 2005; Pollmann *et al,* 2004; Seixas *et al,* 2011), nursing homes residents (Newland *et al,* 2005), hospitalised patients (Stenager *et al,* 1991; Vermote *et al,* 1986), and MS society membership (Douglas *et al,* 2008; Ehde *et al,* 2003; Hadjimichael *et al,* 2007; Heckman-Stone and Stone, 2001;

Khan and Pallant, 2007), whereby the demographics of participants were highly variable, (and not reflective of the wider MS community).

Other methodological issues in the MS pain research relate to a lack of epidemiological-based study. The majority of this research is not based on geographically-defined, population-based cohorts, reflective of the MS population, which may affect the reliability of the prevalence figures reported. They are instead subgroups of MS populations, i.e. all on MS disease modifying treatment (DMT) at research centres (Martinelli-Boneschi *et al*, 2008), currently residing in nursing homes (Buchanan *et al*, 2002; Newland *et al*, 2005), pre-existing samples of other clinical trials (Grasso *et al*, 2008; Khan and Pallant, 2007; Martinelli-Boneschi *et al*, 2008; Stenager *et al*, 1995) outpatients currently attending MS clinics, (Grasso *et al*, 2008; Martinelli-Boneschi *et al*, 2008; Osterberg *et al*, 2005; Rae-Grant *et al*, 1999), members of MS society membership databases (Beiske *et al*, 2004; Douglas *et al*, 2008a; Ehde *et al*, 2006; Hadjimichael *et al*, 2007; Khan and Pallant, 2007) or hospitalised patients (Stenager *et al*, 1991; Vermote *et al*, 1986). Samples were also sought from national, multi-centre, cross-sectional studies, which although have large sample sizes, actually cover widely dissimilar, geographical areas (with disparate cultural and environmental factors, a source of bias in an epidemiological study) (Goodin, 1999; Hadjimichael *et al*, 2007; Piwko *et al*, 2007; Solaro *et al*, 2004). Although large sample sizes have more statistical power, they must be based on representative samples of the target population. The study by Buchanan *et al.* (2002) for example, was a study of pain in 14009 MS patients, hospitalised in skilled nursing facilities in the US (as well as being a retrospective study design). Although this study is insightful for that particular population, wider inferences are limited.

The importance of an epidemiological study design to reliably measure pain in MS is discussed further in Chapter 4. One study to-date has undertaken a population-based survey of pain in MS, reporting a high prevalence of 79.4%, in a geographically-defined area of Denmark (Svendsen *et al*, 2003). Participants were asked to recall the presence of any pain, within the last month. No definition of pain was provided and no type of pain was excluded. The lack of a clear pain definition makes it difficult to establish the clinical significance of pain reported, and whether pain was MS-specific. Thus the prevalence of clinically significant pain in a population-based cohort of MS patients remains unclear.

This section has provided an overview of the MS-pain literature. It has highlighting the reasons for variability in previous reports of the prevalence of pain. The following section will now explore the recent key studies in this field in more detail.

3.3.2 Key studies of MS-related pain

This section considers the key studies of the prevalence of pain in MS in more detail. This firstly includes a systematic review and studies which have emerged outwith the review.

3.3.2.1 Systematic Review of MS-related pain

The inconsistency of previous findings prompted a systemic review of pain in the MS population. O'Connor et al (2008) included studies of the prevalence of pain in MS, based on the following criteria: 1) *definite MS diagnosis, 2) prospective study design, 3) clear description of how pain was defined,* specifically the time frame of which pain was to be recalled, and the exact criteria of how pain was defined. Nine studies were thus included: (Archibald *et al.* 1994; Beiske *et al.* 2004; Indaco *et al.* 1994; Kalia & OConnor 2005; Osterberg *et al.* 2005; Solaro *et al.* 2004; Stenager *et al.* 1991; Svendsen *et al.* 2003; Vermote *et al.* 1986). To avoid repetition, the methodology, pain definition and prevalence of pain in each of these nine studies are not discussed here individually but throughout this chapter (starting previously throughout section 3.3.1) and Chapter 4.

The systematic review was insightful in providing an evidence-based classification of the most common pain conditions associated with MS (discussed in Section 2.4.1.1), but failed to provide conclusions on the prevalence of pain, with prevalence rates ranging from 43% (Solaro *et al.* 2004) to 79% (Beiske *et al.* 2004). The authors highlighted that conclusions are hindered by the disparate pain definitions and methodologies adopted in previous studies. They elaborate that improved methods for assessing pain in MS are required in future research, using standardised definitions of pain based on the evidence-based classifications outlined in the review. The authors suggest that this will improve the reliability of future prevalence reports of pain and the ability of RCT's to determine efficacy of pain treatments for the MS population.

Two large scale UK-based studies were not considered in the systematic review, but do not add any further reliable estimates of the prevalence of pain. The first study, was a study of MS-related pain in 929 patients, using a postal survey (Forbes *et al*, 2006). With a

prevalence of pain of 55.9%, pain was not defined, nor was standard pain outcome measures used. Half the sample presented with primary progressive MS, which is very high (only 10-15 % of newly diagnosed patients typically present with primary progressive MS) (Miller and Leary, 2007), and reflective of the study population, which was a data set derived from the MS patients of clinical nurse specialists, as part of an evaluation of the efficacy of this role nationally. A second UK-based study reported the prevalence of pain as 72% from a postal questionnaire of a random sample of 300 MS patients from a database (Howarth, 2000). The database was not described, nor was the origin of the sample. The sample was not described in terms of disability level, or type of MS thus the generalisability of results is uncertain. Furthermore pain definition is given no description in this study of limited methodological quality.

Two important studies were however rejected by the systematic review, as a definite diagnosis of MS was not mentioned, (but neither was it refuted) (Ehde *et al.* 2003; Hadjimichael *et al.* 2007). However they provide useful information on MS-related pain. Both studies are included in the thesis as they have been cited in the majority of MS-related pain literature, were published in good quality journals, and have several merits: Hadjimichael *et al,* (2007), a large-scale postal survey of almost 16 thousand MS patients, recruited from the North American Research Committee on MS database (NARCOMS) reported a prevalence of pain of 74%. Although a definite MS diagnosis was not mentioned within the paper, NARCOMS is an MS patient registry, where all patients have a definite diagnosis of MS as per Poser criteria, (1992). The database is a project of the consortium of MS centres (CMSC), a longitudinal database initiated in 1996 to provide a resource for clinical trials and long term prospective studies. Patients are recruited through the national MS society, pertinent publications; support groups, the internet and neurologists offices. Furthermore, a clear definition of pain and a prospective study design was used, and the sample was representative of the target, North American MS population (Marrie *et al*, 2007): the sample had a typical 3:1 female male ratio, approximately 50% currently presenting with Relapsing Remitting MS, mean age approximately 52 years of age, and time since diagnosis of approximately 11 years, similar disability levels and similar socioeconomic factors, such as education level and marital status. These sample demographics are similar to the population based study of pain in MS (Svensden *et al*, 2003), as previously mentioned. Thus, although not a population-based study, it appears to be a representative sample.

Ehde, *et al*, (2003), conducted a postal survey of 442 members of a large American state MS society, reporting a prevalence of pain of 44%. A clear definition of pain was provided in this study, where only pain that was "*ongoing and bothersome*" within the last month was considered, unlike many of the studies previously mentioned, who provide no definition of pain. However, the membership was scattered over distant and disparate geographical areas, exposed to different geographical factors, and health care, which may have impacted on experience and/or reporting of pain. There are also associated biases when using a disease membership database as a sampling frame (Elwood, 2007c), as detailed in section 4.1.1. Furthermore, MS diagnosis was not based on any standardised tests or medical record review but solely from membership of the society. Thus, although this study clearly defines pain measured, its findings may be considered with caution.

However, although both studies have individual merits, they report disparately different pain prevalence figures, potentially due to the different methodological approaches.

3.3.2.2 Other recent key studies of MS-related pain

Since this review, further key studies have emerged which measured pain in the MS population. However, conclusions on the prevalence of pain are still limited due to flaws in pain definition and methodology as discussed:

Grasso et al. (2008)

Grasso *et al.* (2008) in interviews of 128 consecutive MS outpatients, attending an Italian MS clinic, measured pain over a period of 14 months, reporting a prevalence of pain of 47.6%. Measuring pain solely in a sample of outpatients currently attending an MS clinic may be not be a comprehensive assessment of the population in this geographical area. No details of the reason for the visits were given: were the outpatients attending a routine review, of which a broad range of patients would be captured over the 14 months? Or were they attending due to a change in condition or for treatment? Furthermore, almost half of the total sample (43%) was taking antiepileptic drugs (AEDs), for pain, at the point of assessment, as they were concurrently involved in a study of the efficacy of AEDs. The authors do not mention if this affected their sample recruitment for the pain prevalence study. The prevalence of those on AED's is much higher than other studies of pain in MS; where less than 10% of the total sample was currently on AEDs (Beiske *et al.* 2004; Douglas *et al.* 2008b; Hadjimichael *et al.* 2007; Svendsen *et al.* 2003). As AED's, such as

Gabapentin, have been shown as effective in decreasing pain intensity (Rice & Maton 2001), this may have affected the generalisability of results.

The sample had a high mean time since diagnosis of 17.6 years, which is higher than the majority of previous studies of MS-related pain, of between 9.0 and 12.8.years (Douglas *et al.* 2008b; Ehde *et al.* 2003; Hadjimichael *et al.* 2007; Kalia & OConnor 2005; Khan & Pallant 2007; Martinelli-Boneschi *et al.* 2008; Solaro *et al.* 2004; Svendsen *et al.* 2003). In this study a higher mean EDSS of 5.3 was also reported in relation to other studies of MS-related pain, reporting scores of between 2.0 (Martinelli-Boneschi *et al*, 2008) to 4.8 (Goodin, 1999). One may expect an association between EDSS and time since diagnosis. In two other studies of MS-related pain, a much lower mean time since diagnosis of 10.5 years, and EDSS score of 2.9 was reported in a multi-centre study of 1,672 MS patients (Solaro *et al.* 2004), whilst another lower mean time since diagnosis of 9.6 years and EDSS score of 2.0 was reported in an interview of 428 consecutive Italian MS outpatients (Martinelli-Boneschi *et al.* 2008). Grasso et al. (2008) provide no explanation of the higher mean disease duration and EDSS in this study; however it was a small sample, unlike the other two Italian studies of 1672 (Solaro *et al*, 2004) and 426 patients (Martinelli-Boneschi *et al*, 2008). The representativeness of this sample therefore is questionable, obscuring the true prevalence of clinically significant pain.

Martinelli-Boneschi et al. (2008)

Martinelli-Boneschi *et al,* (2008) in interviews of 428 consecutive MS outpatients in an Italian university MS centre, reported a low prevalence of pain of 39.8%. However, the sample was not a typical MS population for several reasons. Firstly, 98.3% of the sample was currently on Disease Modifying Therapy (DMT), and were participating in another clinical trial on the efficacy of DMT. The proportion on DMT is higher than that reported in previous studies of MS-related pain, of between 7.6%- 20.8% (Douglas *et al.* 2008a; Goodin 1999; Khan & Pallant 2007). The prevalence of DMT use will vary depending upon local healthcare practise, however, in a population based study of pain in the Danish population, only 15.3% were currently on DMT, whilst a recent UK economic survey of 1492 MS society members indicated that only 13% were currently on DMT (McCrone *et al*, 2008). DMT is used in MS to reduce relapse rate (Francis *et al*, 2005), and as such may modify pain symptoms, which can begin or worsen during a period of relapse. Not surprising, a high proportion (75%) of the Italian study presented with relapsing remitting MS (RRMS), this subtype being a clinical requisite to be eligible for DMT. The low mean

EDSS of 2.0 points reported in this study would also be expected in a sample attending for DMT. In a previous multi-centre, Italian study, by the same authors, a low prevalence rate of pain of 42.9% was similarly reported in a survey of 1672 patients, with the sample also having a low mean age of 40.0 years, and a total of 74% presenting with RRMS, and a high proportion (70%) currently using DMT. Thus the low prevalence figures reported may reflect the demographics and healthcare practices of this specific geographical area. Conversely, the majority of previous MS-related studies of pain reported approximately 50% with RRMS, and an older mean age from 48-52 years (Beiske *et al.* 2004; Goodin 1999; Hadjimichael *et al.* 2007; Piwko *et al.* 2007; Rae-Grant *et al.* 1999; Svendsen *et al.* 2003).

Piwko et al. (2007)

A survey of 297 MS patients throughout several Canadian health board providences (Piwko *et al,* 2007) was undertaken, reporting a prevalence of pain of 71%. In this study, designed to assess the economic burden of pain in Canada, patients were recruited through MS clinics and the MS Society. Pain was poorly defined as "MS-related", with no further information on pain definition used, or types of pain excluded, making it difficult to establish the true clinical significance of pain reported. Furthermore, the authors could not confirm if the sample was representative of the Canadian MS patient as the majority of the sample resided in the providence of Ontario, which differs to other geographical areas of Canada. A physician survey also accompanied the patient survey, where 12 neurologists intimated the number of their patients currently with pain. Interestingly, this was a much lower figure of 46%, of patients presenting with MS-related pain, which is far lower than the figure from the patient survey. This disparity between the two findings may highlight the unreliability of results. However, self-report is fundamental to pain assessment thus the higher figure must therefore be considered.

Douglas et al. (2008)

(Douglas *et al.* 2008b), reported the prevalence of pain as 67.1% using a survey method on 219 patients registered on the MS society of Queensland membership database, in Australia. Clinically significant pain was defined as any pain not due to recent injury or minor ailments, such as toothaches, which is insufficient to adequately capture clinically significant pain (outlined in Section 4.3). Cases of pain were included if present in the previous two weeks prior to assessment, where such a such a short recall period has been

criticised as invalid for the presentation of pain in the MS population, (outlined in Section 4.2.1). Furthermore, studies that rely on society membership databases are subject to higher selection bias, which may affect sample representativeness, (Section 4.2.3.1). Douglas *et al,* (2008) compares their prevalence rate of 67.1% to the findings of other previous studies of pain in the MS population, who reported figures of 50.7% (for pain of at least one month duration, in a survey of 142 patients of outpatient neurology departments, in several Danish hospitals) (Beiske *et al,* 2004) and 66%, (for pain defined as 'ongoing and bothersome', reported in a survey of 442 MS patients, registered on the MS Association of Washington, (USA) membership database) (Ehde *et al,* 2006). Douglas *et al,* (2008) postulates a pattern emerging from recent literature, where approximately two-thirds of the MS population report pain. However, such conclusions must be viewed with caution due to the variation in pain definition and methodological approaches used in these three studies, as well as the limited generalisability of the sample populations.

However, a similar prevalence of pain was again reported in another study: Khan and Pallant (2007) reported a prevalence of pain of 64% in a community based sample of 94 MS patients, who were on a hospital MS database for a large geographical Australian territory. However pain was measured differently again in this study, with no criteria reported to determine whether pain was clinically significant. The study was based on a small sample, curtailed by the large geographical areas covered in the study. Only those who lived within 60km were included, which could bias study findings. Furthermore, institutionalised patients were excluded from the study, as well as those who were more disabled (with an EDSS score of >8). Furthermore, only 20% of participants were eligible for the study as the majority did not have a definite MS diagnosis. Thus the generalisability of findings to the wider MS population is limited in this study.

3.3.3 Summary: the prevalence of pain in MS

Despite over 20 years of research, the prevalence of pain in MS remains unclear. The disparate methodologies and definitions of pain, as well as the use of non-representative samples in previous studies have contributed to this ambiguity.

The optimum methodological approaches of pain definition, timeframes for recall of symptoms and appropriate study samples are discussed further in Chapter 4.

The next section explores the prevalence of neuropathic pain in MS.

3.4 Prevalence of neuropathic pain in MS

This section will explore the prevalence of neuropathic pain in MS reported in previous literature. This will involve a comparison of previous methods of neuropathic pain diagnosis, which have impacted on the prevalence figures reported.

3.4.1 Prevalence of neuropathic pain in survey design studies

A prevalence of neuropathic pain of 17% was reported in a study of 85 hospitalised MS patients (Vermote *et al,* 1986). However, the sample was small, and at least moderately disabled (83% had an EDSS>6), and no description of the method of determining neuropathic pain was give. Two similar, Italian-based studies, reported inconsistent prevalence figures of neuropathic pain of 14% (Martinelli-Boneschi *et al.* 2008) and 40.4% (Solaro *et al,* 2004). Although both were larger, cross-sectional (questionnaire-based) studies of 1672 and 428 patients, both used non-validated measurements of neuropathic pain. Here neuropathic pain was indicated by the presence of: *trigeminal neuralgia*, *Lhermitte's phenomenon and dysaesthetic pain*, and non-neuropathic pain was indicated by *painful tonic spasms and back pain*.). Although this is useful from a treatment perspective, they do not provide a cumulative estimate of the total prevalence of neuropathic pain, required to gain the true impact of the problem, in comparison with other populations. Furthermore, all are recognised as clinical presentations of neuropathic pain in MS, but are not a validated method of screening for neuropathic pain. Methodological issues of measuring neuropathic pain are reviewed further in Chapter 4.

3.4.2 Prevalence of neuropathic pain in studies using clinical assessment

One study identified the overall prevalence of neuropathic pain in 364 MS patients as 27.5%, using the gold-standard in neuropathic pain assessment: the detailed clinical assessment (Osterberg *et al,* 2005). In this study non-trigeminal central pain was constant in nature in the large majority of patients; mainly affecting the lower extremities in 87% and the upper extremities in 31%. Its robust method of central pain diagnosis, using MRI and EMG studies must be commended; however, it was not a population-based cohort, reflective of the wider MS population, instead included MS outpatients attending neurology clinics throughout a large, disparate geographical area.

3.4.3 Summary: prevalence of neuropathic pain in MS

The prevalence of neuropathic pain in the MS population has yet to be established. A validated, general prevalence measure of neuropathic pain and its individual presentations are required.

3.5 Prevalence of MS-related pain syndromes

MS-related pain has been outlined in previous sections, focusing on the main categories of neuropathic and non-neuropathic pain. As mentioned, there are several key MS pain presentations related to these categories, including ***Lhermitte's phenomenon, trigeminal neuralgia, painful tonic spasms, paroxysmal limb pain, dysaesthetic pain, migraine headache, optic neuritis and visceral pain***. In keeping with the mechanism-based approach to pain assessment, as previously discussed, a study of MS-related pain must also measure the prevalence of these individual syndromes. It is beyond the scope of this thesis however, to review the different prevalence figures of each pain syndrome previously reported in the literature. However, prevalence figures of these syndromes are highly inconsistent. For example, when MS patients were asked to recall dysaesthetic symptoms within the last month, the prevalence was reported as 7.7% (Martinelli-Boneschi *et al*, 2008), 21% (Grasso *et al*, 2008), and 38.1 % (Svensden *et al*, 2003). This inconsistency is possibly due to several key flaws in methodology in these studies, which has been discussed in this chapter and continued in Chapter 4.

3.6 Prevalence of chronic pain in MS

The prevalence of chronic pain is MS in unclear due to inconsistencies in previous reports. The majority of previous studies have been based on non standardised definitions of chronic pain. Several studies defined chronic pain as pain, present for at least one month (Beiske *et al*, 2004; Indaco *et al*, 1994; Kalia and O'Connor, 2005; Moulin *et al*, 1988) reporting inconsistent prevalence figures of 50.7%, 70%, 58.7% and 48% respectively. Whilst another study defined chronic pain as "pain present for at least three months" and reported a prevalence figure of 64% (Khan and Pallant, 2007). Furthermore, two studies measured persistent pain, without any reference to a specific chronicity, i.e. pain that is "persistent" (Hadjimichael *et al*, 2007) or "ongoing and bothersome" (Ehde *et al*, 2003), reporting prevalence figures of 79% and 44% respectively. From these studies, the prevalence of chronic pain in MS is unclear and no pattern can be established between the definition of chronic pain adopted and its influence on the prevalence figure reported.

One previous study measured chronic pain in MS, defining it as pain "*of at least six months duration*" (Martinelli-Boneschi *et al,* 2008). The IASP guidelines on the definition of chronic pain recognise the three month period, but recommend for research purposes, pain of at least six months duration should be considered chronic (Merskey and Bogduk, 1994). In using this definition, the study reported a relatively low prevalence of chronic pain of 39.8%. As previously reported, the sample was an MS sub-group population, receiving disease-modifying therapy, which may account for the lower figure of chronic pain than previously reported.

Chronic pain therefore has yet to be suitably defined and measured in a population-based cohort of MS patients. The optimum definition of chronic pain for research purposes is discussed in more detail in Chapter 4.

3.7 Characteristics of MS-related pain

This section will outline the characterisation of MS-related pain in previous literature. It begins by considering studies which have reviewed the characteristics of pain in MS, and then studies which differentiate specifically between nociceptive and neuropathic pain. This will be set in the context of the IASP framework of a multidimensional pain assessment.

3.7.1 Characteristics of MS-related pain in previous literature

MS-related pain has been well characterised in the literature. The majority of previous literature has reviewed the overall nature of pain MS, without sub-analysis of neuropathic or somatic pain. In these studies, average pain intensity was reported as ranging from 4.6 to 5.8 using the numerical rating scale (NRS) of 0-10 for pain intensity, where '0' indicated *no pain* and '10' indicates *worst possible pain* (Archibald *et al,* 1994; Douglas *et al*, 2008; Ehde *et al*, 2006; Heckman-Stone and Stone, 2001; Howarth, 2000; Warnell, 1991).

There is a broad spectrum of pain qualities previously reported, which may reflect the different aetiologies of pain in MS, including *burning, aching, throbbing, shooting, sharp, cramping* (Beiske *et al,* 2004; Rae-Grant *et al,* 1999; Svendsen *et al,* 2003) as well as *tingling, itching and prickling* (Douglas *et al* 2008; Khan and Pallant, 2007). Each of these studies also show that pain can present anywhere on the body in MS, but most often the extremities and trunk.

One study particularly focused on neuropathic pain in a clinical study of 364 MS patients. Of the 100 patients with central neuropathic pain (27.5%), pain was most often found bilaterally, in the extremities. Using the Short-Form McGill Pain Questionnaire (SFMPQ) (Melzack, 1987), neuropathic pain was most commonly described as *burning*, followed by *aching* and *pricking* in quality. This type of pain was also severe in intensity, and constant in nature, and was described as being worse at night. In a recent clinical study of sensory abnormalities in 62 patients with central pain (by the same authors), once again *burning, aching and pricking* were the most common qualities reported, with 85% reporting lower limb, extremity pain (Osterberg and Boivie, 2010). Similarly, *burning* pain was the most common pain quality reported in those MS patients with dysaesthetic extremity pain, in three previous small-scale survey-design studies of pain (Clifford and Trotter, 1984; Moulin *et al*, 1988; Vermote *et al*, 1986). This was followed by a painful *tingling or throbbing "like toothache",* as well as *stabbing* and *dull* pain qualities.

One study undertook a direct comparison of neuropathic with somatic pain in MS patients, comparing the clinical characteristics of pain (Kalia and O'Connor, 2005). In a small clinical study of 68 MS patients, neuropathic pain was compared with nociceptive pain in relation to intensity. The mean pain intensity score of patients with nociceptive pain was significantly lower than that of MS patients with neuropathic pain, which is consistent with the wide view that neuropathic pain generally is greater in intensity (Haanpää *et al*, 2011). Furthermore, the study reported that almost three-quarters of patients with neuropathic pain experienced dysaesthetic pain, whereby *burning* extremity pain was most frequently reported. In a clinical study of 50 MS patients with sensory abnormalities, neuropathic pain was again revealed as being significantly more intense in nature (Svendsen *et al*, 2005). This concept therefore demands demanding further investigation in the current epidemiological study.

3.7.2 Pain measurement requirements

This section will explore whether MS-related pain has been explored fully in previous literature. The theoretical basis of pain measurement has been introduced in section 2.5. In their guidelines on pain measurement, the IASP states that:

"*.....pain is multidimensional. Appreciate that the pain experience may have sensory, emotional, and cognitive aspects. Also appreciate the potential impact of pain on function, affective status, and quality of life*." (Charlton, 2005b)

In meeting with the above IASP framework of pain assessment, the sensory components of MS-related pain including intensity, area and quality, have been reviewed in previous literature. The quality and area of MS-related pain is therefore clear, and this section has highlighted a need to explore the intensity of neuropathic pain further, in an epidemiological study. However, several aspects of the framework require further study: in particular, the affective component of pain, and the impact of pain on HR-QOL for the MS population.

3.7.2.1 The affective component of pain

The affective component of pain is conceptually and empirically distinct from pain intensity (Jensen *et al*, 1991b) and can be defined as, "*the emotional arousal and disruption engendered by the pain experience"* (Jensen and Karoly, 2011). Separate evaluations of the intensity and unpleasantness of pain are encouraged by the IASP, but are limited in the neuropathic pain literature (Haanpää *et al*, 2011). Furthermore, both the intensity and affective components of pain have been associated negatively with HR-QOL (De Andrade *et al*, 2010; Doth *et al*, 2010; Kalia and OConnor, 2005).

Both the McGill Pain Questionnaire (MPQ) (Melzack, 1983) and its shorter form version (SF-MPQ) (Melzack, 1987) have been used to explore the affective component of pain in MS. Both versions include two subscales of the affective and sensory components of pain, using verbal descriptors which can be used descriptively and combined to give a total score. The most common affective descriptors of pain in MS were *tiring-exhausting*, using the Short–Form McGill Pain Questionnaire (SFMPQ) (Seixas *et al*, 2011; Svendsen *et al*, 2003) *and tiring-exhausting*, *nagging* and *annoying*, using the MPQ(Douglas *et al*, 2008a). In one study, using the MPQ, the affective subscale total of pain was considerably lower than that of the intensity subscale total (Douglas *et al*, 2008), with the authors arguing that the affective pain scores are lower due to an acceptance of pain as less significant than other MS-related symptoms. Conversely, in another study using the SF-MPQ, the affective component of pain was higher than that of the intensity pain component(Seixas *et al*, 2011). Both studies are small-scale, and are not-population based cohorts, thus the affective and sensory components of MS-related pain should be evaluated in an epidemiological design. Unlike pain intensity, level of pain affect has not been compared between those with neuropathic and non-neuropathic pain presentations in MS, demanding investigation in the current study.

The use of prescribed, pain-relieving medication (PPRM) is often measured in epidemiological studies (Breivik *et al*, 2006) as it can impact on both the sensory and affective components of pain. The provision of adequate pain relief has also been shown to improve HR-QOL (OConnor, 2009). Although the use of prescribed, pain-relieving medication has been reported in the MS population, the amount of pain relief subsequently provided has not been studied, and is an area of study in the current study.

3.7.2.2 Impact of pain on HR-QOL in MS

Previous studies of pain and HR-QOL in MS

The presence of pain is associated with poorer HR-QOL in MS patients (Forbes *et al*, 2006; Kalia and O'Connor, 2005; Svendsen *et al*, 2005). In one study pain was shown to interfere on all components of the SF-36 measure of HR-QOL, including general health, physical function, emotional and physical role, mental health, social function and vitality (Svendsen *et al*, 2005). In two other studies of pain in MS, pain was shown to impact on the components of social functioning and mental health (Kalia and O'Connor, 2005; Khan and Pallant, 2007), as measured by the SF-36; and psychological well-being as measured by the Assessment of Quality of Life Scale (AQOL).

Pain in MS is associated with interference in the two major components of HR-QOL physical and emotional functioning (Jensen *et al*, 2007a). In one study, 30% of all MS patients reported at least moderate pain interference (Hadjimichael *et al*, 2007), whilst in another study pain interfered with daily function "all" or "most" of the time in 42% of MS patients, compared to 19% of age and sex-matched controls (Svendsen *et al*, 2003). In two other studies moderate to severe pain interference has been reported in almost 50% of those MS patients with pain (Beiske *et al*, 2004; Ehde *et al*, 2003). In a study of pain interference in MS, using the Brief Pain Inventory (BPI), pain was shown to interfere with all aspects of life, including relationships, normal daily activities and relationships (Ehde *et al*, 2006). Pain has also been found to significantly interfere with a person's overall enjoyment of life (Hadjimichael *et al*, 2007), employment (Archibald *et al*, 1994; Hadjimichael *et al*, 2007), sleep (Hadjimichael *et al*, 2007; Warnell, 1991) and relationships (Warnell, 1991).

Relationship between HR-QOL and neuropathic pain in MS

To-date the effect of neuropathic pain on HR-QOL has not been explored in the MS population. A systematic review of multiple neuropathic pain conditions has been undertaken on a variety of central and peripheral neuropathic pain conditions, i.e. peripheral diabetic neuropathy and post-stroke pain (Jensen *et al*, 2007). It was concluded that there is strong evidence that the presence of neuropathic pain is associated with impairments in HR-QOL, including physical and emotional role, social functioning, sleep and general health. There is therefore a need to confirm the relationship between neuropathic pain and HR-QOL for the MS population. As neuropathic pain has been shown to impact more on HR-QOL than nociceptive pain in the general population (Smith *et al*, 2007b)(Haanpää *et al*, 2011), it would be clinically meaningful to also compare scores between the two MS pain types.

3.7.3 Summary: characteristics of pain in MS

This section has highlighted the need to characterise neuropathic pain in MS, in terms of its level of emotional unpleasantness and intensity, relief from prescribed, pain-relieving medication, as well as its impact on HR-QOL. There is also a need to compare those with a neuropathic and non-neuropathic pain presentation for the following characteristics: pain intensity, pain affect, use and relief from PPRM, and impact of pain on HR-QOL score. Optimum measurement of these characteristics is discussed in Chapter 4.

3.8 Predictors of MS-related pain

Risk factors for the development of chronic pain have been categorised broadly as socio/economic, psychological and physical (Smith *et al*, 2007a). For example, age, sex, and educational attainment are examples of socioeconomic, risk factors, whilst emotional health, and pain coping behaviours are examples of psychological risk factors. In the Scottish general population chronic pain is associated with socioeconomic factors, such as living alone, being unemployed, lower socioeconomic group, and low educational attainment (Elliott *et al*, 1999; Smith *et al*, 2001a). Numerous neurological, immunological and genetic hypotheses have been put forward for the physical risk factors associated with the development of chronic pain, and are detailed extensively in a review paper (Smith *et al*, 2007a).

Risk factors for the development of pain in MS have been reviewed in previous studies, and include older age, longer disease duration, female gender, type of MS and greater disease severity, as measured by the Guys Neurological Disability Scale (GNDS) (Sharrack and Hughes, 1999) or the Expand Disability Scale (EDSS) (Kurtzke, 1983). Generally, previous studies assess risk factors at the bivariate level, not adjusting for confounding factors, and limiting conclusions about independent predictors of pain. Risk factors have not been considered for neuropathic pain specifically in the MS population.

3.8.1.1 Predictors of neuropathic pain

Ideally information on risk factors should come from prospective cohort studies. However there are few such studies available for review, thus most information on risk factors for neuropathic pain come from cross-sectional studies, from which it is impossible to determine causation. For the general population there are several socioeconomic risk factors associated with neuropathic pain, including age (>60), female gender, being unemployed and having low educational attainment (Bouhassira *et al*, 2008; Smith *et al*, 2007a; Torrance *et al*, 2006). Neuropathic pain was shown to be higher in those living in rural areas and in those living in council-rented accommodation (Torrance *et al*, 2006) indicating that relative deprivation may be a risk factor.

Although risk factors for neuropathic pain have not been studied in MS, a strong association between neuropathic pain and general health status has been explored for other neuropathic pain groups, such as those with peripheral diabetic neuropathy (PDN), post herpetic neuralgia (PHN) and post-surgical pain (Dieleman *et al*, 2008). For, example, in PDN, duration of diabetes and glucose tolerance have been established as risk factors, where hyperglycaemia–induced pathways result in nerve damage, leading to hyperexcitability of peripheral and central pain pathways (Jensen *et al*, 2006).

Hyperexcitability of the nervous system in response to damage is also seen in MS: as mentioned in Section 2.4.2.1. Deafferentation is caused by the occurrence of demyelinated lesions in the CNS, causing a state of hyperexcitability, leading to spontaneous and evoked increases in neurone activity, which is believed to cause pain (Kenner *et al*, 2007). Disability (as a marker of current disease state) is a result of the relationship between two related phenomenon in MS *relapse* and *progression* (discussed in Chapter 1). Current disease activity in MS is therefore associated with the variables :*current disability level*, *type of MS and time since diagnosis*, which is relevant as although relapses is the

presenting phenomenon in approximately 80% of those with MS, progression goes on to affect 80% of those with relapse-onset disease (Bennetto *et al*, 2011). As these factors have the potential to affect current disease activity they should be explored as potential disease-specific risk factors of neuropathic pain in MS.

Disease-specific risk factors should not be measured alone. As mentioned, pain is suggested to exist in MS because of the damage to the CNS. However, there have been inconsistent associations between the number of lesions and the amount of pain reported. There has also been inconsistency with respect to the relationship between the specific location of the lesion and the pain experienced (Maloni *et al*, 2000). Thus in addition to the potential disease-specific pain risk factors, as described above, analysis of the wider socioeconomic influences on pain, such as gender, and level of deprivation, should be considered.

4 LITERATURE PERTAINING TO METHODS: Pain Measurement in Epidemiological Studies

This chapter will outline the methodological issues of pain measurement in an epidemiological design. It will begin by exploring the advantages of a population–based study and outline the appropriate measurement of both general and MS-related pain. Lastly, the chapter will outline a comprehensive assessment of the sensory and affective components of pain.

4.1 Advantages of a population-based study

4.1.1 Epidemiology

Epidemiology is defined as a population-based science (Rothman, 2002b). Epidemiology measures the frequency with which disease occurs in a population, and the risk factors associated with the development of the disease. Such information can be used for planning of health care services. Epidemiology aggregates the health experiences of individuals, generalising findings to the population from which individuals have come (Bhopal, 2008b). Disease occurrence or *frequency* is measured in populations, in terms of *incidence* and *prevalence* rates. Incidence is the number of new cases to appear over a defined period of time, and relates to causality analysis, whilst prevalence studies measure the number of existing cases at a defined point in time, and is used to consider potential associations between variables and disease outcome (Webb and Bain, 2011a). This study measures pain at a defined point in time and is thus a study of prevalence.

Epidemiology considers the pattern of disease in populations in relation to the factors, of ***Person, Place and Time*** (Gerstman, 2003a). For the *person* component of this model, individual characteristics can be related to disease occurrence. For example, pain in the general population is associated with older age, female gender, and lower socioeconomic status. Whilst in MS-related literature, higher disability level, time since diagnosis and type of MS have all been associated with pain. The *time* of measurement can also affect disease occurrence, with seasonality known as a major factor in many diseases. Pain could be more prevalent at a specific period of time, as arthritic conditions are known to be more painful during winter months and MS symptoms, including pain, can intensify during heat (Multiple Sclerosis Society Australia, 2013)

The *place* of measurement can also affect disease occurrence, with ecological boundaries encompassing the common social and cultural groups of a naturally-occurring population (Gerstman, 2003a). Person's residing in a defined geographical area are privy to similar cultural, environmental and social factors, such as local disease screening, and healthcare policies and practices (Hennekens, 1987). Several large-scale epidemiological studies have measured MS-related pain over large and dissimilar geographical areas (Goodin, 1999; Hadjimichael *et al*, 2007; Piwko *et al*, 2007; Rae-Grant *et al*, 1999; Solaro *et al*, 2004). For example, a previous study measured MS-related pain in a national, multi-centre survey, conducted across Italy, using a random sample from many dissimilar geographical areas (Solaro *et al*, 2004). Although this was a large-scale study of almost 2000 patients, the geographical areas surveyed had social, environmental and cultural differences, which may have impacted on the overall prevalence figure reported. This would have been valid had all areas of the country been equally represented in the final sample, which is the challenge faced by ecological studies. However, this was not confirmed in the Italian study, unlike a national study of MS-related pain in Canada, where it was stated that some geographical areas were not represented and it could therefore not be guaranteed that the sample was representative of Canada as a whole. Furthermore, several of these large scale studies recruit from MS society membership databases (Goodin, 1999; Hadjimichael *et al*, 2007), which does not guarantee the naturally occurring range of socioeconomic and disease characteristics in the target population they represent. Younger and more recently diagnosed patients are underrepresented in MS society membership.

By standardising the aforementioned factors of *time* and *place* one can analyse the impact of individual characterises on the presence of a phenomenon, in this case pain. The current study of pain, within a small geographically-defined area, measured at a defined point in time will facilitate this analysis of pain and its risk factors in MS. The benefit of a population-based approach in this method is detailed over the next sections.

4.1.2 Validity of an epidemiological study

The validity of an epidemiological study is dependent upon whether inferences can be made about the target population from the actual sample (Kleinbaum *et al*, 2007; Webb and Bain, 2011b). Figure 4-1 illustrates the hierarchy of populations. (Kleinbaum *et al*, 2007). The collection of individuals from which data has been obtained is known as the sample, whilst the study population is the collection of individuals which the sample represents, and often is what is most practical to study. In the current study the sample was

those persons who completed the questionnaire, whilst the study population was the NHS Ayrshire and Arran MS population. Frequently a random sample from the study population is undertaken for practical reasons (Bhopal, 2008b), however the current study endeavoured to recruit from the entire population, (except for exclusions) using a disease register. The current study was fortunate to have access to a disease register of all patients diagnosed with MS, within the Ayrshire & Arran (A&A) health board area. Regional and national registries include nearly all patients with within the geographical area, as part of a population approach (Flachenecker, 2008). Scotland has one of the highest incidence rates of MS in the world, per population head (Koutsouraki *et al*, 2010), thus it is possible to access this large sample of MS patients within a small geographical area. The inconvenience of the scale of a population-based study would therefore be minimised in this situation. The target population is of course the MS population of the UK, whilst external populations could be comparable international MS populations, such as the European, Australian and American studies used in the MS-related pain literature. Providing the study population is representative of the target population, and the sample is representative of the study population, wider inferences can be made.

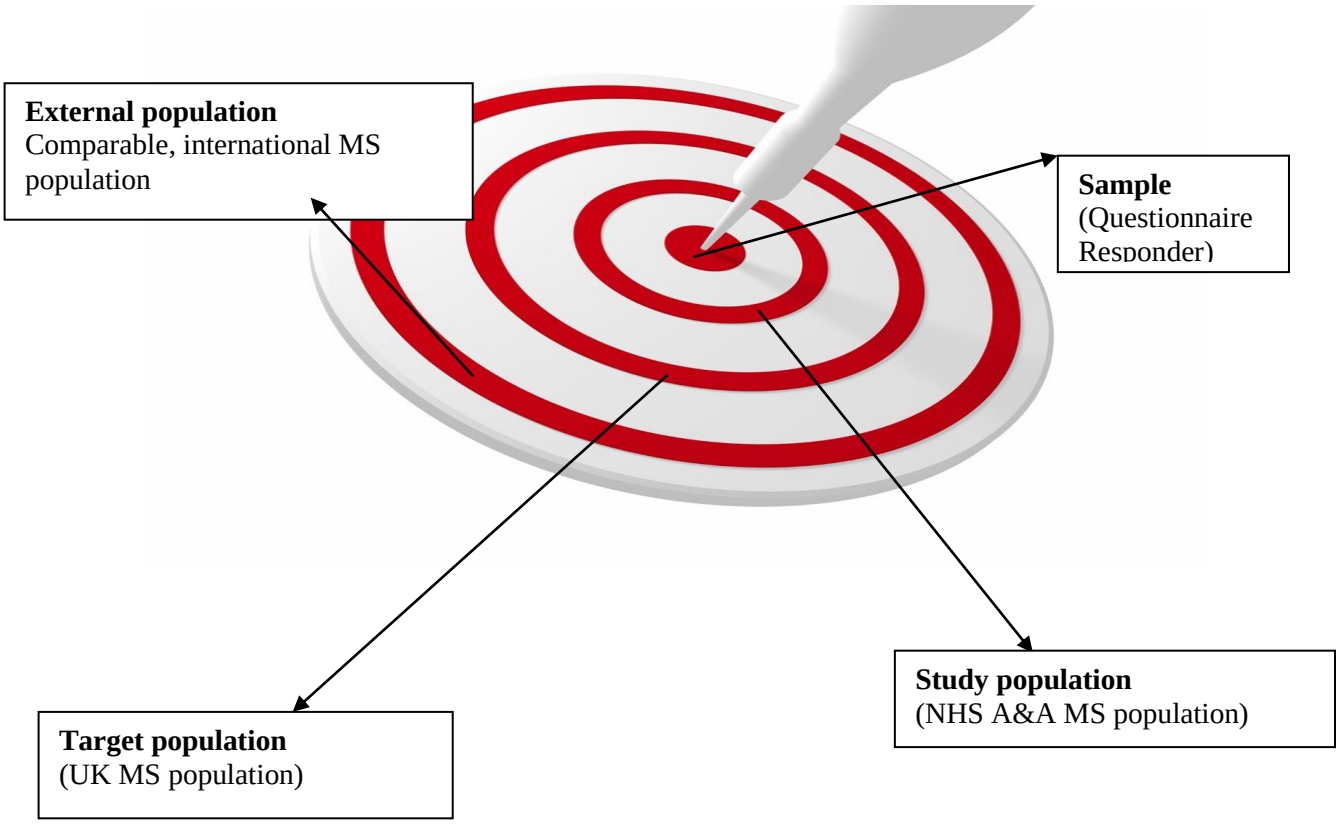


Figure 4-1: Hierarchy of populations **Adapted from : (Kleinbaum *et al*, 2007)**

4.1.3 International comparison of pain prevalence figures

Recent reviews of key MS disease registers have shown many similarities in demographic and disease characteristic throughout European and American MS populations, using registers such as the European MS Register (EUREMS) (Flachenecker *et al*, 2010) and the North American MS Register (NARCOMS) (Hurwitz, 2011a; Hurwitz, 2011b) . However as expected, there are slight variations in sample characteristics. It is beyond the scope of this thesis to compare disease characteristics and demographics of the world MS populations. Further reference can be made to the MS registries, as mentioned, or the largest population based longitudinal study of MS, the London, Ontario Cohort, based in US (Weinshenker *et al*, 1989; Weinshenker, 1995). From an epidemiological perspective, provided that studies display high internal validity (i.e. representative of their respective target populations) then international comparison of prevalence rates is acceptable (Bhopal, 2008a).

Several of the international studies of MS-related pain display comparable demographic and disease characteristics with the UK MS population (Beiske *et al*, 2004; Douglas *et al*, 2008a; Hadjimichael *et al*, 2007; Kalia and OConnor, 2005; Khan and Pallant, 2007; Piwko *et al*, 2007; Svendsen *et al*, 2003). These include: a female to male ratio of between 2.3-3:1, a mean age of between 48 years-52 years; and mean time since diagnosis of between 9.0-12.9 years. For type of MS, between 48%-58% present with RRMS, between 20-30% present with SPMS, PPMS and PRMS are more variable: between 9.6- 21% present with PPMS, and less than 10% present with PRMS (although many studies do not report this clinical course at all). The high variability in the presentation of type of MS is due to the variability in definition of each clinical course and methods of assessment. The majority of studies use EDSS as a measure of disability, with a broad range of EDSS scores (from 1-9), which one would expect in a 'typical' MS population, and a mean EDSS score of between: 3.8-4.8. A 'typical' UK MS population is an artificial construct, as population demographics show slight variations around the different geographical areas, also as a result of different database systems nationally. Despite this, the aforementioned sample demographics are comparable with the UK MS population, as shown from a number of UK-based epidemiological studies of MS (Ford *et al*, 1998; Ford *et al*, 2002; McCrone *et al*, 2008; McDonnell and Hawkins, 1998; McDonnell and Hawkins, 2001; Robertson *et al*, 1995; Robertson and Compston, 1995; Rothwell and Charlton, 1998), including the west coast of Scotland (Murray *et al*, 2004).

A population-based approach increases the likelihood of providing a sample representative of the target population (Elwood, 2007d; Somerville *et al*, 2012), and is discussed below.

4.1.4 Population-based approach

A population-based study endeavours to target all participants in a defined geographical area, and has several advantages. It allows exploration of an unbiased, naturally occurring sample; the gold-standard in epidemiology (Carr *et al*, 2007). This comprehensive approach has the potential to represent the broad spectrum of disease severity and other socio-economic and health variables in the population, avoiding the limitations of random sampling (Bailey *et al*, 2005; Bhopal, 2008b). As such, this method has greater potential to generate a sample, representative of the study population, target population and beyond (Elwood, 2007e). A population-based approach is likely to provide a sample with a broad clinical picture: some patients may be residing in the community, with low disability levels, whilst others may be living in long term care facilities with high levels of disability.

Conversely, studies of MS-related pain frequently recruit from patients currently attending outpatient MS clinics, as a convenient sample source (Grasso *et al*, 2008; Indaco *et al*, 1994; Warnell, 1991). This can often mean the inclusion of participants attending due to a relapse in condition, or those attending for routine review, as they present with RRMS and are currently on disease modifying therapy (DMT). This does not ensure the broad spectrum of patients within the geographical/health board area are represented. Patients with no/mild symptoms are unlikely to be routinely attending MS outpatient clinics. At the other end of the spectrum, those with advanced disease, requiring a high level of care, possibly residing in nursing facilities, would also not be attending MS outpatient facilities. There is no conclusive evidence to-date to suggest that patients from either end of the spectrum are more or less likely to experience pain. Using subgroups of the MS population for analysis, may distort the true picture of the prevalence of pain.

4.1.5 Cross-sectional versus longitudinal study design

A longitudinal study measures a phenomenon over a defined period of time. This is a more accurate form of measurement than measuring at a single point in time, as it accounts for seasonal trends in disease occurrence as well as the rate of disease frequency (Webb and Bain, 2011b). It therefore a more accurate method of determining disease occurrence and risk of developing a phenomenon than a cross-sectional study design.

By contrast a cross-sectional study design is a study which measures a phenomenon in a defined population, at a specific point in time (Gerstman, 2003). This should ideally be undertaken in the population-based context for the reasons outlined previously, although a random sample of the population is another accepted method, easier to undertake for practical reasons, and thus used more frequently (Bhopal, 2008b; Carr *et al*, 2007; Rothman, 2002a; Webb and Bain, 2011b). The cross-sectional study measures the burden of disease using prevalence rates, and potential associations between variables. Multivariate analysis, which is described further in Section 5.5.5.2 can also be performed within this type of study design, highlighting the person's *odds* of developing a phenomenon as opposed to their *risks (Bhopal, 2008c).* The benefit of this type of study over a *longitudinal* study (which provides a measure of incidence, as opposed to prevalence) is that of the reduced cost and resource implications of measuring at a single point in time, whilst still being able to accurately measure disease frequency and its determinants (Bailey *et al,* 2005).

4.2 Methodological issues in epidemiological studies of pain

This section explores several methodological challenges in conducting epidemiological studies of pain. It explores the optimum pain measurement period, the subjective nature of pain and issue of bias, such as recall and sampling bias.

4.2.1 Measurement period

Measures of pain prevalence quantify the proportion of the population with pain at a static point in time (*point prevalence*), during a defined period of time (*period prevalence*) and over the course of a lifetime (*lifetime prevalence*) (Crombie, 1999). As pain is a variable phenomenon over time, point prevalence measures have been criticised for potentially underestimating cases, wherein period prevalence measures are generally preferred. In epidemiological studies of pain, the retrospective report of pain status over a defined period of time, such as one, three or six months have been recommended for period prevalence measures (Von Korff, 2011). There are however, trade-offs for short versus long recall periods: assuming all else being equal, a short recall period should minimise recall bias, and is thus likely to maximise case ascertainment, but may not yield a reliable estimate of a subjects pain status because of the large within-subject variability in pain status overt time. There is therefore the potential for longer recall periods to result in higher prevalence figures. However, this pattern is not apparent in previous MS-related

pain studies. For example, similar high prevalence figures for clinically significant pain of 70% (Indaco *et al,* 1994), 71% (Piwko *et al,* 2007) and 74.5% (Hadjimichael *et al,* 2007) were reported in studies using different recall periods of: lifetime recall of pain; pain presence within the last six months and within the last month respectively. Study design and pain definition also varied amongst these studies, as previously discussed in Chapter 3, which may have counteracted the effect of recall period on results. Von Korff, (2011) states that "*given the favourable results of several validity studies, there appears to be sufficient empirical support for measuring pain in up to a 3-month recall period*". As MS is associated with cognitive deterioration (Krupp and Rizvi, 2002) it was felt that a one-month recall period would be the most suitable time period to reliably measure pain experience in the current study, minimising the level of recall bias.

Lifetime prevalence measures of pain, are more at risk of been affecting by recall bias (Von Korff, 2011), however they are useful in conditions whereby pain has an intermittent presentation, and is linked with chronic disease activity. In a previous, non-population based study, the *lifetime prevalence* of MS-related pain syndromes were reported in addition to point prevalence estimates, suitable when measuring pain in a chronic relapsing-remitting disease (Martinelli-Boneschi *et al,* 2008). Commonly MS-related pain can present intermittently, throughout the disease course. For example, trigeminal neuralgia and Lhermitte's phenomenon have been reported as causing severe, disabling episodes of pain, throughout a period of relapse, and may not be captured by either a point or period prevalence measure of pain. Thus in the current study both the *period* and *lifetime* prevalence of MS-related pain syndromes will be measured.

4.2.2 Subjective nature of pain

Pain is a subjective phenomenon. What one individual may perceive as 'painful' another person may not. However, it is generally recognised that the word 'pain' has negative connotations for the individual, whether this involve the physical, emotional or social facets of pain (Loeser and Melzack, 1999). In the IASP's recommendations for 'Pain Measurement in Humans', it is advised that measurement must reflect the difficulty patients have in differentiating between pain and unpleasant sensations (*dysasthesias, paraesthesias*) (Charlton, 2005b). As a result, the use of *unpleasant sensations* is often used when measuring central neuropathic pain disorders, as many patients would not view many of the associated sensory presentations as 'painful' in the traditional sense. For example, paraesthesia, burning sensations, or tonic spasms may or may not be categorised

as ‘pain’, by the individual although they may be highly unpleasant, and have a negative impact (Boivie and Osterberg, 1996). Several studies of pain in MS have adopted a version of *unpleasant sensations* in their pain definition (Beiske *et al*, 2004; Hadjimichael *et al*, 2007; Rae-Grant *et al*, 1999). Thus in the current study the following guidance was added before completing the questionnaire:

“*.....what some people might think of as ‘pain’, you may think of as ‘unusual’ or ‘unpleasant’. For example, a person may feel pins and needles on the skin as an uncomfortable sensation, which bothers them, but may not think of this as ‘pain’ in the traditional sense. If you experience these uncomfortable sensations please consider them as ‘pain’ for the purpose of this questionnaire*.” The definition of pain used in the current study is outlined in Chapter 5, Section 5.4.3.

4.2.3 Sources of bias in pain assessment:

This section will review potential sources of bias in undertaking pain assessment, and include sampling bias, measurement bias and response bias.

4.2.3.1 Sampling bias

Sampling bias occurs when the sampling process misses individuals whose characteristics are different to those included in the sample (e.g. more or less likely to present with pain (Elwood, 2007b). It was important therefore that the sample selection process be as inclusive as possible in the current study. Using the MS patient register, increased the chance of recruiting a sample with a broad range of sociodemographic and disease characteristics, which one would expect of a typical community MS population. As per the population-based approach, detailed previously, all patients on the MS register (who would have a confirmed MS diagnosis), and were over the age of 18 were included, except for those who did not meet the exclusion criteria.

As part of this inclusive approach, exclusion criteria were kept to a minimum. Patients were excluded with known cognitive impairment where they would be unable to complete (even with assistance) or consent to complete the questionnaire. Instead of a generic tool to assess cognitive impairment, as per previous literature (Douglas *et al*, 2008; Hadjimichael,

et al, 2007; Martinell-Boneschi *et al*, 2008; Solaro *et al*, 2004), clinicians were able to consider patients for inclusion, on an individual basis. A similar process was considered for those patients receiving end of life care. If required, participants were also able to complete the questionnaire by proxy (i.e. with the assistance of another), if required, i.e. if motor skills or vision was impaired. This ensured that patients with higher levels of physical or cognitive disability were not underrepresented in the sample. None of these factors were mentioned in previous studies of MS-related pain. For example, the previous Danish population-based study of MS-related pain included all patients with an MS diagnosis, of a particular geographical area, with no mention of any exclusion criteria. As the sample was also not described in terms of disability-level, it is not possible to establish the degree of sampling bias.

The many exclusions of non-MS related pain in previous studies were detailed in Section 3.1.1.1, which are mostly from interview-based studies. However, several previous survey-design studies are inclusive of all types of pain in the MS patient, regardless of their aetiology, which may account for their higher prevalence estimates of greater than 70% experiencing pain. Conversely, one of the lowest estimates for the prevalence of pain of 44% was that of Ehde *et al*, (2003), who in a survey design, solely measured pain "*related to your MS."* The exact aetiology of pain would be difficult for the patient to self-assess, as MS-related pain can mimic its counterpart, particularly confusing for a person with several pain complaints.

4.2.3.2 Measurement bias: Data collection

Measurement bias is a flaw in measuring exposure or outcome that results in different quality or accuracy or information (Kleinbaum *et al*, 2007). This is also true of pain assessment, as stated by the IASP, in their core curriculum for professional education in pain management chapter on pain measurement:

"*The goal of pain measurement is to capture true pain with as little measurement error as possible*" (Charlton, 2005b).

Each mode of data collection, whether an interview or postal survey method, has benefits and limitations to this effect. The IASP highlights the difficulty patients have with pain

measurement, and they therefore require assistance or careful instructions to overcome the following difficulties:

- Difficulties of separating pain from concomitant non painful sensations and anxiety.

- Recognising non-traditional sensations of discomfort (such as dysaesthetic symptoms) as pain

- Difficulty in assigning numbers to a dynamic, complex experience

- Difficulty in drawing upon memory of pain

(Charlton, 2005b)

Although interview methods allow more in-depth explanation of pain in the above terms, they are not feasible in large-scale epidemiological studies, whereby the postal questionnaire is the most frequently used mode of data collection. Clear patient instructions, accompanying survey methods of pain assessment, can also help with the difficulties as described above. Questionnaire methods allow the patient the time and convenience of completing self-report measures on pain experience in their own home, with no influence of an external investigator. Retrospective review of medical notes is also used as a method of data collection for pain measurement, but is a method highly affected by measurement bias (Farrar, 2006). The absence of a documented phenomenon does not confirm its non-existence for the patient, whilst the patient may have recorded their pain with their local general practitioner and not within specialist services.

The majority of previous MS-related pain research is based on survey design, postal questionnaires, with varying inclusion of standardised pain assessment tools (Douglas *et al,* 2008; Ehde *et al,* 2003; Goodin, 1999; Heckman-Stone and Stone, 2001; Kalia and O'Connor, 2005; Piwko *et al,* 2007; Rae-Grant *et al,* 1999; Seixas *et al,* 2011; Solaro *et al,* 2004; Svendsen *et al,* 2003). Several studies use a structured interview method of pain assessment (Beiske *et al,* 2004; Grasso *et al,* 2008; Indaco *et al,* 1994; Khan and Pallant 2007; Martinelli-Boneschi *et al,* 2008; Stenager *et al,* 1991; Stenager *et al,* 1995), whilst a few studies rely upon retrospective review of medical case notes (Clifford and Trotter 1984; Moulin *et al,* 1988).

No pattern exists in relation to data collection methods and pain prevalence reported in previous studies of pain in MS. Although interview methods have the potential for more detailed assessment of pain characteristics, several previous survey design studies apply a multifaceted approach for pain assessment in MS (Douglas *et al*, 2008; Ehde *et al*, 2003; Hadjimichael *et al*, 2007), as highlighted by the IMMPACT recommendations on pain assessment in clinical trials (Dworkin *et al*, 2005).

4.2.3.3 Response bias

Response bias is a systematic error due to differences in characteristics between those who participate in the study and those who do not (Elwood, 2007c). This is a serious concern for studies relying on data collected through mailed surveys.

Typically, non-responders have been characterised as being older, of lower SE status, smokers, and unmarried, less educated and unemployed. It has also been noted, that those not experiencing the phenomenon in question, i.e. those without pain are less likely to participate (Elliott *et al*, 1999). Thus, it was clearly stated in the present study that patients complete the questionnaire regardless if they had pain. To maximise response rate several strategies were undertaken in line with the findings of two systematic reviews (Edwards *et al*, 2002; Nakash *et al*, 2006). Although this review revealed that payment was an effective incentive for questionnaire completion, it was felt that this would be unethical. Members of the research community against the use of incentives believe that they are coercive and may influence a subjects' ability to give an informed consent (Muwonge, 2013).

- A covering letter was sent out initially from the lead clinician (Consultant in Rehabilitation Medicine) on behalf of the MS service of NHS Ayrshire and Arran, detailing the nature of the study.

- Questionnaires were addressed *personally* to participants.

- A stamp-addressed return envelope was provided.

- Clear instructions on questionnaire completion were given (Appendix 1, page1).

- Common problems in MS, which may hinder or compromise the reliability of pain assessment, such as problems with memory, vision, and motor skills were managed

by clearly highlighting that patients complete the questionnaire by proxy if required to do so.

- Furthermore a postal questionnaire method is more favourable over an electronic questionnaire method, so as not to alienate individuals less likely to use computer-based technology.

4.3 Pain Measurement

This section will consider methodological approaches to the measurement of *clinically significant pain*, *chronic pain,* and *neuropathic pain*. It will then more specifically consider the measurement of MS-related pain, including the MS-related pain syndromes.

4.3.1 Measuring clinically significant pain

This section begins with a review of the more traditional methods of measuring clinically significant pain, followed by the more patient focused approach used in recent studies. It then considers broader methods of defining clinically significant pain appropriate for the MS population and justifies the use of the method used in the current study.

4.3.1.1 Previous methods of defining clinically significant pain

A standardised definition of clinically significant pain is absent for MS, and indeed the wider pain literature, which is a challenge for epidemiological studies measuring the phenomenon. However, the term 'clinically significant' suggests that pain experienced has some meaning within the clinical setting. Meaningful pain can take several guises that may be of variable interest to the patient, clinician, health policy maker, or epidemiologist, and can vary depending upon the group being studied. For example, clinically significant pain has previously been defined by such factors as chronicity (Merskey and Bogduk, 1994), intensity (Grasso *et al*, 2008), level of pain-related disability (Webb *et al*, 2004), interference with every day activities (Smith *et al*, 2001a) and level of expressed need (use

of analgesics and clinical contact) (Torrance *et al*, 2006), each of which may be of variable interest to a different audience.

Traditionally, clinically significant pain has been defined by pain duration (chronicity). In fact, confusingly, studies often use the term clinically significant pain and chronic pain interchangeably (Asmundson *et al*, 2011; Von Korff and Miglioretti, 2005; Webb *et al*, 2004). However, (Von Korff and Dunn, 2008) states: "*...defining chronic pain by pain duration alone is less that optimum.*" The authors continue: "*Defining pain solely by duration does not indicate whether long lasting pain is clinically significan*t". This is true as many patients with persistent back pain are unaffected in their day to day life (Von Korff and Miglioretti, 2005). Pain intensity is also used to ascertain cases of clinically significant pain and has been used in the MS population (Clifford and Trotter, 1984; Grasso *et al*, 2008; Indaco *et al*, 1994; Stenager *et al*, 1991). However, some patients with fairly mild pain may still find symptoms difficult to cope with, impacting on their social and psychological well being (Von Korff, 2011). Help-seeking behaviours, such as use of analgesia or clinical consultations, are also used as a measure of identifying clinically significant pain (Smith *et al*, 2001a) and have been used in the MS population (Clifford and Trotter 1984; Indaco *et al*, 1994; Stenager *et al*, 1991). The Level of Expressed Need questionnaire (LEN) (Smith *et al*, 2001b) for example was developed to identify help-seeking behaviour for chronic pain in epidemiological studies in the general population. However, help-seeking behaviour is subject to other confounding factors: for example, age, gender, and socioeconomic status all may contribute over and above the severity of pain itself (Smith *et al*, 2001b). Each of these measures has limitations; the current study aimed therefore to consider more patient-focused measures of clinically significant pain.

There is a cultural shift towards patient involvement in individual health status and management. Furthermore, addressing the patient's report of their symptoms results in higher compliance with treatment programmes and a greater satisfaction with care (Brook *et al*, 2011). Since pain is a completely subjective experience, the 'gold standard' in defining pain is therefore the patient self-report (Turk and Melzack, 2011). There is a wealth of research to support that biological, behavioural, psychological and cultural factors all act as modulators of the individual pain experience (Farrar, 2006). Furthermore, the meaning attributed to pain will vary across populations, and among cultures, further demonstrating the individual nature of pain report (Niv and Kreitler, 2001).

The patient-focused approach introduced the concept of multifaceted assessment of clinically significant pain. As such, many studies identify clinically significant pain with the Chronic Pain Grade Questionnaire (CPG) (Von Korff *et al*, 1992) which measures pain in three dimensions: pain *persistence, intensity* and pain-related *disability*. This allows stratification of chronic pain into five categories of severity from 0 (indicating pain free) to 4 (indicating high disability, severely limiting), with categories 2-4 indicating the presence of clinically significant pain, which is of great use to both clinicians and health service and planners.

The WHO's International Classification of Functioning, Disability and Health (ICF) provides a standard framework for the assessment of health. For any health condition, such as pain, the ICF identifies three key factors of interest, impairment, activity limitation, and participation restrictions. The CPG has recently been praised for its ability to measure these aspects of functioning and disability as highlighted in the ICF (Dixon *et al*, 2007). Although the CPG has been validated in the community setting of the general population (Elliott *et al*, 1999) it was felt that it would be inappropriate for use in the MS population: the first question of the CPG ascertains chronicity of pain in terms of number of pain days within the last six months, resulting in the categories of: *non-persistent pain* (1-89 days) or *persistent pain* (90- 180). It has been suggested that to fully measure the burden of recurrent pain, number of pain days is the most suitable method; however number of days of pain is more accurately measured over long periods from six-month to a year (Von Korff, 2011). For example the IASP definition of persistent back pain has been defined as *"back pain present on at least half the days of a six-month period"*. The six-month recall period used to measure *days with pain* of the GCPG was concerning, as memory bias increases after a three-month recall period (Von Korff, 2011), which is particularly true for recall of pain intensity and pain-related disability. This would be even more of a concern in the MS population, with possible cognitive impairment. Furthermore, a main component of the CPG relates to the level of pain-related disability. This would be more complex to ascertain in the MS population who have previously been unable to differentiate between musculoskeletal, and pain-related disability (Douglas *et al*, 2008b), i.e. is disability due to musculoskeletal changes such as spasticity, or as a result of pain, or indeed, a mixture of the two? Thus, level of pain-related disability would not be suitable as a measure of clinically significant pain in the current study.

The determinants of clinically significant pain have not been established in the general population or specifically the MS population. Furthermore, the CPG has not been validated in a chronic neurological disease population; pain perception varies across populations, with different pain behaviours and coping strategies adopted in both individuals and in different clinical groups (Farrar, 2006). The current study therefore acknowledged the benefits of the CPG, in being more patient focused, but aimed to find a broader definition of clinically significant pain, as determined by the patient, which is detailed in the next section.

4.3.1.2 Broader methods of case definition

Multifaceted methods of assessment, such as the CPG, are complex, and more time consuming for the patient (Dunn and Croft, 2005) all of which may affect response rate (Edwards *et al*, 2002). By contrast, the term 'bothersome' in relation to pain has been put forward as a more simple, brief, and patient-focused measure of clinically significant pain (Dunn and Croft, 2005). The authors validated levels of 'bothersome' pain against the CPG in low back pain (LBP) patients, where more 'bothersome' pain was highly correlated with pain intensity, pain-related disability and activity limitations, and is therefore advocated as a reliable means of identifying clinically significant pain. 'Bothersome' describes the negative impact of a phenomenon, but is broad enough to allow this to be patient specific, whether it be in relation to intensity, duration, or impact on a number of possible facets. Although originally validated for use in a clinical setting of LBP patients (Dunn and Croft, 2005), it has since been used extensively to ascertain cases of clinically significant pain in migraine (Cramer *et al*, 2001); Parkinson's disease (Beiske *et al*, 2009), spinal cord injury (Turner *et al*, 2001) and sciatica (Patrick *et al*, 1995).

The use of the term 'bothersome' pain has been adopted successfully in a previous study of clinically significant, MS-related pain, for the patient–focused perspective as described above (Ehde *et al*, 2003). However, other methods have also been used to define clinically significant pain in MS. Douglas *et al,* (2008) uses the following extract from the Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994): *"Throughout our lives, most of us have pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday types of pain in the last two weeks?"* This eliminates non-meaningful pain, such as pain from minor ailments, and was thus used in the current study. However, pain persistence, severity and impact are given no mention by Douglas *et al*, (2008), which, as previously discussed, are viewed as factors of clinically significant pain.

4.3.1.3 Definition of clinically significant pain in the current study

The term 'bothersome' pain was used to define clinically significant pain in the current study, and was not limited by a fixed chronicity, severity or impact, as a more patient-focused measure. The determinants of clinically significant pain are likely to vary amongst different clinical populations (Croft *et al*, 2011) and have not as yet been explored specifically in the MS population. Therefore a more broad definition was preferred. However, the prevalence of severe pain in the MS sample was also of interest and so further stratification of chronic pain by intensity was undertaken outwith the initial screening question, at a later stage.

Croft *et al*, (2011) propose that future definitions continue to incorporate 'persistent' pain, alongside pain-related impact on daily life. It was felt that *ongoing* bothersome pain, was more patient-friendly and was used similarly in studies of pain in various patient groups, including those with neuropathic pain and the elderly (Engel *et al*, 2006; Mobily *et al*, 1994; Tremont-Lukats *et al*, 2006), as well as the MS population (Ehde *et al*, 2003). This is more amenable to intermittent, recurring presentations of pain, which are common in MS, as a relapsing-remitting disease. Alternatively, a medically-orientated, temporal-bound definition of pain was also adopted in the study and is discussed in the next section. The question used to ascertain cases of clinically significant is presented in section 4.3.2.2 of this chapter.

4.3.2 Measuring chronic pain

4.3.2.1 Temporal–based definition

The meaning of the word 'chronic' encompasses notions of time, especially of long duration. Thus, epidemiological studies add a measure of duration to standardise self-report questions about pain. The IASP defines chronic pain as: *"....pain which persists past the normal time of healing*" (Merskey and Bogduk, 1994). In the absence of further criteria, the normal healing time is open to interpretation. However, most studies tend to define pain as chronic if present for at least a three or a six-month period:

" *With non-malignant pain, three months is the most convenient point of division between acute and chronic pain, but for research purpose six months is the most preferred method*" (Merskey and Bogduk, 1994).

Unfortunately, the majority of previous studies of chronic pain in the MS population adopt the less reliable definition of chronic pain of pain of at least one month duration (Beiske *et al*, 2004; Kalia and O'Connor, 2005; Moulin *et al*, 1988; Svendsen *et al*, 2005), which does not surpass the normal healing time, and is thus not recognised as chronic by the IASP. Previous studies of chronic pain adopt the more reliable three-month duration period both in the MS literature (Khan and Pallant, 2007) and in the general population (Elliott *et al*, 1999; Smith *et al*, 2001a). However this has been criticised in favour of the longer period of six months, where (Verhaak *et al*, 1998) argue that the latter is a more reliable method in order to establish the true burden of chronic pain on well-being and disability. Furthermore, in a longitudinal study of low back pain, only when pain passed the six month duration threshold, did patients report increased pain intensity, and interference with daily life and emotional health (Dunn and Croft, 2005). Many studies of chronic pain in the general population therefore use the six-month period (Andersson *et al*, 1993; Birse and Lander, 1998; Brochet *et al*, 1998; Gureje *et al*, 1998). Furthermore, a six-month duration period has been adopted in the largest study of chronic pain for the general population, a multicentre study in over 15 European countries (Breivik *et al*, 2006).

Similarly, the current study will adopt this measure of chronic pain (pain of at least six months duration), so as results are comparable with wider chronic pain literature, but will also measure the prevalence of acute or episodic pain, in MS, which can also impact greatly on a person daily living and quality of life.

4.3.2.2 Patient-focused definition of chronic pain

As mentioned, duration–based approaches in chronic pain definition have been criticised in their limited capacity to represent the impact of pain for the patient (Von Korff and Dunn, 2008). The difference between acute and chronic pain is more than a semantic or arbitrary transition point at a particular time period. Expansions of the traditional definition which also consider the clinical significance and impact of pain, as discussed in the previous section get closer to the extended concept of chronic pain as a syndrome (Dionne *et al*, 2011). A common approach combines both chronicity and impact. For example, Dionne et al, (2011) defines chronic pain as *'pain that has persisted for 3 months or more and which interferes with activities of daily life'*. Other variations of this include: *current, continuous or intermittent pain or discomfort which has persisted for more than 3 months, with recent or frequent seeking of treatment or use of analgesic medicatio*n (Purves *et al*, 1998) and

"persistent pain that is bad enough to limit your usual activities or change your usual routine for more than one day" (Dionne et al. 2008).

However, these methods have been criticised as arbitrary and possibly omitting meaningful cases of pain. Thus a comprehensive measure of chronic pain was sought for the current study, incorporating the traditional time-bound (IASP) definition of pain, with a broad measure of pain impact.

In keeping with the patient-focused perspective, as discussed in the previous section, 'bothersome' pain is a validated, practical alternative, allowing the patient to give meaning to their pain. Cases of chronic pain were therefore ascertained using a two-tiered question, a method useful for categorising pain in prevalence estimates and used in previous epidemiological studies (Elliott *et al*, 1999; Smith *et al*, 2001a; Smith *et al*, 2007b; Torrance *et al*, 2006): The first established the presence of clinically significant pain, from the patient's perspective:

"*Throughout our lives, most of us experience everyday types of pain (such as minor headaches, sprains and toothaches). Other than these types of pain, at present or within the last month, have you experienced ongoing, bothersome pain? This pain may be constant or 'off and on'.*

Affirmative answers led to completion of the second question which ascertained cases of pain of at least 6 months duration. Cases of clinically significant pain of at least 6 months duration were deemed 'chronic'.

4.4 Measurement of pain in MS

This section outlines two methods which have previously been used to classify MS-related pain and include a temporal based definition of pain, and a mechanism-based definition of pain, as supported by the IASP.

4.4.1 Temporal classification of MS-related pain

Many studies of pain in MS classify pain in relation to temporal criteria, whereby pain presentations are classified as *acute, subacute or chronic*, regardless of their aetiology

(Beiske *et al*, 2004; Indaco *et al*, 1994; Moulin *et al*, 1988; Stenager *et al*, 1991; Svendsen *et al*, 2003). Table 3-1 categorises the pain syndromes in MS, based on temporal criteria

Table 4-1: Painful conditions of MS

Temporal classification	Pain syndromes
Acute	Trigeminal Neuralgia
	Episodic facial pain
	Lhermitte's phenomenon
	Painful Tonic Seizures
	Paroxysmal extremity pain
	Headaches
Subacute	Optic neuritis
	Decubitus ulcers
	Urinary Tract Infection (UTI)
	Vertebral compression fractures
Chronic	Dysaesthetic extremity pain
	Chronic back pain
	Painful spasms
	Musculoskeletal pain
	Visceral pain

From: (Maloni *et al*, 2000; Moulin *et al*, 1988; Perkins *et al*, 1999)

4.4.2 Mechanism-based classification of MS-related pain

The temporal–based definition has been criticised as somewhat confusing. Solaro et al. (2004) criticises studies such as (Moulin *et al*, 1988), for measuring the prevalence of both acute and chronic pain syndromes, combining chronic dysaesthetic pain, and back pain together, despite both having different pathogenesis and treatment approaches. Solaro *et al*, (2004) advocate the use of a mechanism-based definition of pain, whereby pain in MS is either neuropathic or non-neuropathic (nociceptive), as outlined in Section 2.2.2. This is also seen in general pain literature, which supports a move towards more mechanism-specific definitions to support, the pharmacological management to pain (Woolf and Max, 2001). O'Connor *et al*, (2008) supports this new classification for MS pain whereby pain would be deemed either neuropathic or non-neuropathic, and each of the individual MS pain syndromes are presented as distinct subcategories, fundamental to appropriate treatment (Table 3-3). This method also sub-classifies types of pain as either continuous or intermittent. The author highlights the importance of differentiating between pain caused by damage to the somatosensory pathways and damage to the upper motor neurone tracts. Some pain conditions in MS have sensory features, whilst others are marked by motor symptoms, such as spasticity. Pain should only be considered neuropathic when it is directly caused by lesions of the somatosensory nervous system.

Table 4-2 Proposed classification of pain conditions associated with Multiple Sclerosis

Pain condition	Example
Continuous central neuropathic pain	Dysaesthetic extremity pain
Intermittent central neuropathic pain	Lhermitte's phenomenon, Trigeminal neuralgia
Musculoskeletal pain	Painful tonic spasms, low back pain, muscle spasms
Mixed neuropathic and non-neuropathic pain	Headache

from O'Connor *et al,* (2008)

Using the preferred, mechanism-based definition of neuropathic pain means that neuropathic conditions would include: ***dysaesthetic pain***, ***trigeminal neuralgia, Lhermitte's phenomenon, paroxysmal extremity pain, and migraine headache***. The aetiology and presentation of each of these is covered previously in section 2.4.1.1. Noteworthy is the inclusion of migraine, which in some cases may be a result of damage to the somatosensory pathways (Putzki *et al*, 2009) however, as several other possible nociceptive mechanisms exist (D'Amico *et al*, 2004) it could also be considered of mixed aetiology. Also noteworthy is the absence of painful tonic spasms (PTS), and optic neuritis, which have previously been included as examples of neuropathic pain in MS literature (Maloni *et al*, 2000; Nurmikko *et al*, 2010; Pollmann and Feneberg, 2008; Spissu *et al*, 1999). PTS are likely due to lesions of the motor pathways (O'Connor *et al*, 2008), and not the somatosensory pathways, thus are not to be considered as categories of neuropathic pain. Similarly, optic neuritis, a common symptom at disease onset (Indaco *et al*, 1994), is believed to result when the meninges surrounding the swollen optic nerve are stretched (Nurmikko *et al*, 2010), thus not directly from an injury to the somatosensory nervous system, and cannot therefore be classified as neuropathic pain.

This thesis therefore adopts the mechanism based-classification of pain in MS, i.e. pain is either neuropathic or non-neuropathic. The measurement of neuropathic pain is specifically reviewed in the next section. The thesis also measures the presence of the specific pain syndromes in MS, i.e. dysaesthetic pain, Lhermitte's phenomenon, regardless of their aetiology. It is recognised that pain in MS may be of mixed quality; however mixed pain is not measured in this thesis.

4.4.3 Measuring neuropathic pain

In the absence of the definitive clinical assessment, screening tools for neuropathic are an acceptable way of highlighting the possibility of the presence of neuropathic pain. This is particularly useful in epidemiological studies. This section briefly introduces the role of clinical assessment in neuropathic pain and subsequently outlines the most appropriate neuropathic pain screening tools for use in the current study.

4.4.3.1 Neuropathic pain clinical assessment and diagnostic work-up

The degree of certainty regarding the presence of neuropathic pain requires evidence from a detailed clinical history, detailed bedside examination (testing for the presence of positive and negative signs) and laboratory tests, such as conventional electrophysiology and quantitative sensory testing (QST). This "diagnostic work-up" allows the performance of all relevant somatosensory sub-modalities to be tested (Bennett, 2010). The outcome of this process then determines whether the presence of neuropathic pain is '*definite', 'probable'* or '*possible'*, as per the neuropathic pain assessment grading system (Treede *et al*, 2008) This is in contrast to previous approaches, which historically viewed neuropathic pain as a binary phenomenon (Bennett *et al*, 2006). This oversimplifies the process: i.e. a standardised protocol for QST includes 13 parameters of sensory testing procedures to define the exact origin of neuropathic pain (Freeman *et al*, 2003). However, definitive diagnosis of neuropathic pain using clinical assessment is beyond the scope of this thesis.

By contrast, the NeuPSIG recommendations (Haanpää *et al*, 2011) and the EFNS guidelines on neuropathic pain assessment (Cruccu *et al*, 2010), accept several key pain questionnaires as reliably screening for the presence of neuropathic pain. These screening tools have the benefit of reliably assisting the non-specialist in the identification of the possibility of neuropathic pain. They do not replace a thorough clinical assessment (May and Serpell, 2009), but fit with an epidemiological design and are useful in highlighting the potential burden of neuropathic pain in populations. As per the diagnostic work-up criteria of neuropathic pain being '*definite', 'probable' or 'possible',* (Treede *et al*, 2008) screening tools only allow a maximum of a *possible* diagnosis as they do not involve any confirmatory clinical tests, such as positive/negative sensory signs or neuroimaging (Haanpa and Treede, 2010) .

4.4.3.2 Neuropathic pain screening tools

All of the screening tools use verbal descriptors characteristic of neuropathic pain. One of the first studies to evaluate sensory-pain description terms was that of (Boureau *et al*, 1990). Using the MPQ, the six sensory descriptors most commonly used by patients with neuropathic pain were: *electric-shock, burning, cold, prickling, tingling and itching*, which has been used in a number of neuropathic pain screening tools.

There are currently five key screening tools used to identify potential cases of neuropathic pain: the 'Leeds Assessment of Neuropathic Pain Symptoms and Signs' (LANSS) (Bennett, 2001); the 'Douleur Neuropathique en 4' (DN4) (Bouhassira *et al*, 2005); the 'Neuropathic Pain Questionnaire (NPQ)' (Krause and Backonja, 2003); the 'ID-Pain' (Portenoy, 2006) and the 'PainDETECT Questionnaire (PD-Q)' (Freynhagen *et al*, 2006). There is considerable overlap in all of these tools, and all depend on the pathogonomic value of verbal descriptors. The LANSS, and DN4 require clinical assessment and thus are not suitable for epidemiological studies. However, the S-LANSS (Bennett *et al*, 2005a) has been extended from the original LANSS to include patient self-assessment, suitable for epidemiological use.

4.4.3.3 Suitable screening tool for neuropathic pain in MS population

There is no MS-specific screening tool for the assessment of neuropathic pain and no screening tool has been validated in the MS population. Each of the five screening tools were therefore considered for use in the current study, and compared for their construct and face validity.

Construct validity is the extent to which what was intended to be measured was actually measured. Sensitivity is the probability that a test will be positive when the test is administered to people who actually have the condition in question. Specificity is the probability that a test will be negative when administered to people free of the condition in question. The Positive Predictive Value (PPV) is calculated using the sensitivity, specificity and prevalence of the condition; and is a useful figure of overall construct validity. Each of these concepts is outlined in (Gerstman, 2003b). Table 4-3 illustrates the sensitivity, specificity and PPV of each of the screening tools in question. The DN4, PD-Q, and LANSS show the highest PPV scores. The S-LANSS, (with the introduction of patient

self assessment of brush allodynia and light touch) has a PPV of 76%, which is reduced from the figure of 82% of the original LANSS, which involved assessment by a clinician.

Table 4-3: Validity of neuropathic pain screening tools (highest-lowest for PPV)

	Sensitivity (%)	**Specificity (%)**	**Positive Predictive Value (%)**
DN4	61	92	88
P-DQ	85	80	83
LANSS	85	80	82
S-LANSS	74	74	76
ID-PAIN	58	78	72
NPQ	65	79	71

Face validity assesses whether a test looks valid, using intuitive judgment. This would involve consideration of whether each of the included characteristics is valid in the MS population. However, this must be undertaken by a professional with appropriate experience in the field. The research team (detailed in Chapter 4), met this criteria and judged the appropriateness of each of the screening tools for use in the MS population, using the following process, which considered the characteristics of each of the screening tools (summarised in Table 4-4)

- Both the DN4 and LANSS could be removed due to their unsuitability for epidemiological research, due to the need for clinical assessment by a trained professional. This left the S-LANSS (using patient sensory assessment), PD-Q, NPQ and ID-Pain.

- All four included paraesthetic sensations, electric-shock/ shooting pain, and burning, pain, which are key features of neuropathic pain in MS.

- The S-LANSS was deemed unsuitable for a number of reasons. The patient self assessment section of the S-LANSS was a concern, as previously mentioned, the reduction in PPV by 11% was obvious when clinical assessment was added. Furthermore, there was a concern that those with mobility issues may have difficulty performing the self assessment in the extremities, which is a common area of neuropathic pain in the MS population. Also *'autonomic changes'* are included in the S-LANSS, and are given a high point value of a possible 5 points, which was of concern. Autonomic changes are not synonymous with a presentation

of neuropathic pain, and until recently pain associated with autonomic dysfunction was considered separately from neuropathic pain (Bennett, 2010). Although it is accepted that autonomic changes are more common in MS than in the general population (Haensch and Jörg, 2006), the prevalence of *sudomotor* (oedema, sweating change, or asymmetry) and *vasomotor* (temperature asymmetry, skin colour change or asymmetry) dysfunction is not known for the MS population. By contrast, common descriptors of central pain in MS such as burning pain and sharp pain, which are known to be prevalent (Osterberg *et al*, 2005) were given maximal possible scores of 1 and 2 points respectively. Furthermore, the S-LANSS did not include numbness, which the MS patient may perceive as a decrease in sensation, or as an unpleasant, confusing dull, numbness,(sometimes associated with cold) , known as '*alien perception'* (Rog *et al*, 2007a).

- Only the NPQ, ID Pain and PD-Q were then considered further:

  The MS patient with central pain has been shown to have either increased or decreased sensation to light touch, pressure, pinprick or temperature (Boivie 1999). The PD-Q, NPQ and ID-Pain all included evoked pain to light touch. However, only the PD-Q included evoked pain by heat, cold or mild pressure. For this reason the P-DQ was deemed the most appropriate tool to screen for neuropathic pain.

PainDETECT (PDQ)

The Pain DETECT (PD-Q) (Appendix 1, Section12) was validated in a multi-centre study of 1700 low back pain patients with either neuropathic or nociceptive pain, demonstrating a high PPV of 83%, with a sensitivity of 85%, and specificity of 80% (Freynhagen *et al*, 2006). It is an easy to use, self-report questionnaire that does not require clinical examination. There are seven weighted sensory descriptor items (never to very strongly) and two items relating to the spatial (radiating) and temporal characteristics of the individual pain pattern. Results are scored from –1 to 38; where –1 to12 represents non-neuropathic pain; 13 to18 possible neuropathic pain and 19 to 38 indicates definite cases of neuropathic pain. Although the original validation study of the PD-Q was for peripheral neuropathic pain, it has recently been validated for use in Fibromyalgia, which has similar features to central neuropathic pain (Amris *et al*, 2010).

Table 4-4: Characteristics of neuropathic pain screening tools

Sensory descriptors	**[a]LANSS***	**[a]DN4**	**NPQ**	**PainDETECT**	**ID Pain**
Pricking, tingling, pins and needles	•	•	•	•	•
Electric shocks, shooting pain	•	•	•	•	•
Hot or burning	•	•	•	•	•
Numbness		•	•	•	•
Evoked pain by light touch	•		•	•	•
Cold or freezing pain		•	•		
Evoked pain by mild pressure				•	
Evoked pain by hot or cold				•	
Pain limited to joints					•
Itching		•			
Temporal patters				•	
Radiation				•	
Autonomic changes	•				
Clinical examination:					
Brush allodynia	•	•			
Raised soft touch threshold		•			
Raised pinprick threshold	•	•			

[a] tools that involve clinical examination

*S-LANSS is similar to the LANSS, but for examination section, which is adapted in order to be carried out by patient.

4.4.3.4 Validation of the Neuropathic Pain Scale in MS

The Neuropathic Pain Scale (NPS) (Galer and Jensen, 1997) also measures neuropathic pain, and has been validated for use, in the MS population (Rog *et al*, 2007a). It includes the pain sensations: *burning, sharp, dull, cold, and itchy* as well as *sensitivity* to touch or clothing, however, it does not include paraesthesias, which have previously been reported in those with central pain in MS (Osterberg *et al,* 2005; Svendsen *et al,* 2005; Vermote *et al,* 1986). The NPS has not been designed, or validated as a diagnostic for neuropathic pain, but is a measure of the different characteristics of neuropathic pain, and is thus often used as an efficacy measure in drug trials. Although not included within the epidemiological study, the NPS was a secondary efficacy measure, used in part 2 of this thesis, detailed in Chapter 9.

4.4.4 Measurement of MS Pain syndromes

The key MS pain syndromes ***Lhermitte's phenomenon, trigeminal neuralgia, painful tonic spasms, paroxysmal limb pain, dysaesthetic pain, migraine headache, optic neuritis and visceral pain***, have been insufficiently measured in previous literature. Several key methodological flaws have been found, which shape previous prevalence figures and the development of the current study methodology.

4.4.4.1 Problems with point prevalence measurement of MS pain syndromes

The majority of previous studies measure the prevalence of pain syndromes, such as painful tonic spasms, at the point of assessment (*point prevalence*) (Solaro *et al,* 2004) or within a short period of time prior to assessment (period prevalence), such as one month (Grasso *et al,* 2008; Hadjimichael *et al,* 2007), or three months (Khan and Pallant, 2007), but as MS is a relapsing–remitting disease, findings from point or period prevalence methodologies are limited. Only one study has focused on MS-related pain syndromes at any point since MS diagnosis (*lifetime prevalence)* (Martinelli-Boneschi *et al,* 2008). Others studies provide no indication of the time frame used for measurement, which also affects the reliability of findings reported (Clifford and Trotter, 1984).

The current study endeavoured to measure both the point and lifetime prevalence of the MS-related pain syndromes.

4.4.4.2 Lack of a clear definition of MS-related pain syndromes

The lack of definition is discussed firstly in relation to the pain syndromes in general, followed by specifically in relation to dysaesthetic pain.

There is a general lack of definition of the pain syndromes measured in previous studies, with authors assuming they are standardised terms. For example, several authors measure '*painful tonic spasms'* in MS but provide no definition (Grasso *et al,* 2008; Martinelli-Boneschi *et al,* 2008; Moulin *et al,* 1988; Rae-Grant *et al,* 1999; Solaro *et al,* 2004), reporting inconsistent prevalence figures of between 4.5% (Grasso *et al,* 2008) and 13% (Moulin *et al,* 1988). The lack of description is concerning as several of the syndromes, although distinct in aetiology and presentation, share characteristics which may lead to overlap, and confusion by participants, particularly in a questionnaire design. For example, painful tonic spasms (PTS) are paroxysms of brief, (unilateral or bilateral) dystonic posturing, often spreading to multiple joints, preceded and accompanied by severe radiating pain of the limbs, usually lasting less than two minutes, and often associated with other sensory symptoms such as dysasthesias and numbness (Spissu *et al,* 1999). In the upper limb, the spasms are characterised by tetany-like spasm of the hand, flexion of the elbow and adduction of the shoulder. PTS differs from spasticity-related pain, which is generally pain during involuntary muscle spasm, and thus should be categorised as a separate phenomenon from PTS (Svendsen and Bach, 2006). Furthermore, as paroxysmal spasms are not always painful, a broad range of terms have been used interchangeably with painful spasms, including paroxysmal spasms, paroxysmal dystonia, tonic spasms, tonic seizures and muscle spasms.

A further example of similar pain presentations with different aetiologies is that of TN and atypical facial pain. Atypical facial pain in the trigeminal area has also been described as affecting the MS population and is distinguished from TN as constant burning, aching, dull or nagging pain, without the paroxysms seen in TN (Pollmann and Feneberg, 2008). A clear description of TN is provided in Chapter 1 and was used in the current study to discriminate between that of atypical facial pain.

The lack of definition is particularly evident in relation to previous approaches in the measurement of dysaesthetic pain. In many previous survey-design studies, dysaesthetic

pain appears as a vague term, rarely underpinned with actual descriptors of the phenomenon, which is concerning as central pain is not pathogonomic, as previously discussed in Chapter1 (Grasso *et al*, 2008; Martinelli-Boneschi *et al*, 2008; Rae-Grant *et al*, 1999; Solaro *et al*, 2004). Two previous studies provided definitions of dysaesthetic pain: One study limited descriptors to that of *burning, numbness, itching, and prickling* (Khan and Pallant, 2007), reporting a prevalence of 60.7%, whilst another study defined dysaesthetic pain as "*unpleasant sensation evoked by touch"* (inaccurately, as dysasthesias may be evoked or spontaneous), reporting a much lower figure of 38.1% (Svendsen *et al*, 2003). Two such different descriptions may have lead to the inconsistent figures reported. Furthermore, in the former study those specific pain qualities are only a few of the verbal descriptors of dysaesthetic pain previously reported in MS. *Burning* pain is the most often cited examples of dysaesthetic pain in MS, but *aching, pricking, stabbing, and squeezing* are also common examples (Boivie, 2006; Osterberg *et al*, 2005; Svendsen and Bach, 2006). Several other presentations of dysasthesias exist in MS. For example, when validating the use of the 'Neuropathic Pain Scale' for description of neuropathic pain in the MS population, it was reported that *burning (like being on fire), sharpness (like jolts, stabbing), cold (like frost- bite), itchiness (like stinging nettles), and dull, aching pain* (like a bruise, or toothache) were all very common in those with central neuropathic pain (Rog *et al*, 2007a). The authors also highlights the phenomenon of "*alien perception*", in MS, where patients have a difficulty in characterising a sensation in which dull, aching pain (absurdly) combines with numbness (and sometimes the sensation of cold).

Thus there is a broad spectrum of presentations of dysaesthetic pain, which is a challenge for survey design studies. For case definition, the current study used the definition of dysaesthetic pain as outlined by the IASP: *"an unpleasant, abnormal sensation, whether spontaneous or evoked*" (Merskey and Bogduk, 1994). This highlights the feature of a disturbing, unfamiliar sensation, common to all the aforementioned descriptors of dysaesthetic pain. A broad spectrum of examples of dysaesthetic pain would be a helpful descriptive addition to this approach (Appendix 1, Section 8, Question 4).

In summary, the absence or poor definitions of MS-related pain syndromes has limited interpretation of previous inconsistent prevalence figures. Definitions in the current study were clearly provided to avoid confusion for the patient (Section 5.4.3.2, and Appendix 1, Section 8).

4.5 Measurement of pain characteristics

This section will review optimum measurement of pain characteristics, including: pain intensity and affect; use and relief from PPRM, and sleep disturbance.

4.5.1 Pain intensity

Pain intensity is a quantitative estimate of the magnitude of perceived pain (Jensen and Karoly, 2011). There are several methods for measuring the intensity of pain including a visual analogue scale (VAS), verbal rating scale (VRS), and numerical rating scale (NRS). Although all are applicable in the clinical setting, the most appropriate method must be considered for use in an epidemiological study. The VRS usually consist of four descriptors: *no pain*, *mild pain*, *moderate pain*, and *severe pain*. The NRS-11, is based on an 11-point numerical rating scale (NRS) where 0= no pain, and 10 = worst pain. The VAS consists of a line, usually 10cm long, whose ends are labelled with the extremes of pain intensity, with patients indicating the point on the line that best indicates their pain. The NRS is preferred over the VRS, which is criticised for having relatively few response categories in comparison (Jensen and Karoly, 2011). Furthermore, the NRS has been shown as easier to use and understand than the VRS in cancer patients (Brunelli *et al*, 2010). The NRS is often preferred over the VAS, as it is not affected by visual acuity and motor skills, required to draw on the line accurately. Furthermore, the IMMPACT guidelines recommend the use of the NRS-11 for chronic pain in clinical trials (Dworkin *et al*, 2005).

The Chronic Pain Grade (CPG) (Von Korff *et al*, 1992) has previously been used to measure the severity of pain, by scoring pain intensity and interference with activities (Section 4.3.1.1). Although this is a useful tool in measuring a more multifaceted picture of pain severity, it was deemed not suitable for inclusion in the current study due to the needs of the sample population, as outlined in Section 4.3.1.1.

4.5.2 Pain affect: Short-Form McGill Pain Questionnaire

The Short-Form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987) (Appendix 1, Section 10) is derived from the original McGill Pain Questionnaire (MPQ) (Melzack 1975), known as the 'gold-standard' against which to validate pain measures. It has been recommended by IMMPACT for chronic pain measurement in clinical trials (Dworkin *et*

al, 2005) as it provides multidimensional assessment of the sensory and affective components of pain. The SF-MPQ is a commonly used pain measure, and has previously been used in the MS population (Seixas *et al*, 2011). It consists of 15 words from the sensory (n=11) and affective (n=4) categories of the standard MPQ. Pain intensity is classified for each word, using a four-point scale (0=no pain, 1=mild pain, 2=moderate, 3=severe). Two scores are obtained from the sum of the sensory (known as the Pain Rating Index-Affective (PRI-A) and affective scores (known as the Pain Rating Index-Sensory (PRI-S). Both the PRI-S, and the PRI-A correlate very highly with their equivalent in the original MPQ (Dudgeon *et al*, 1993). Factor-analytic studies of the SF-MPQ support the two factors: sensory and affective in varied populations, including chronic pain (Beattie *et al*, 2004) and fibromyalgia (Burckhardt *et al*, 1992).

The original MPQ includes a greater variety of verbal descriptors of both sensory and affective pain. However, the main purpose of the SF-MPQ in the current study was measurement of the affective component of pain; which it does adequately with use of the most common affective verbal descriptors of the original. Furthermore, the SF-MPQ is preferred in epidemiological studies to the original MPQ for its brevity and user friendliness (Dworkin *et al,* 2005).

4.5.3 Use of Prescribed Pain-Relieving Medication and subsequent relief

The use of prescribed, pain-relieving medication (PPRM) is often measured in epidemiological studies of pain (Breivik *et al,* 2006), as it can impact on both the sensory and affective components of pain. Although, PPRM, as an umbrella term, has not been used in MS pain literature, the use of individual pain medications has been charted, including NSAIDs, antiepileptics (used for pain), antidepressants (used for pain), spasmolytics, and analgesics: opioid and non-opioid. Not surprisingly, the frequency of use is variable, depending on the demographics and disease characteristic of each sample. Adequate pain relief has been associated with improved HR-QOL scores (Bennett *et al*, 2005b; Eriksen *et al*, 2006). Pain relief from medication has not been considered in the MS pain literature and will be measured in the current study using the percentage pain relief scale from the Brief Pain Inventory (BPI) (Chapter 5).

4.5.4 Pain–related sleep disturbance

Sleep disturbance has been associated with interference in aspects of emotional and physical health and is often included in pain interference measures such as the BPI, which was not used in its entirety in the current study. Sleep disturbance is also a key feature of clinical pain assessment (Dworkin *et al*, 2005), but has not been considered in the MS population. The current study therefore included a question on sleep disturbance, to be compared between those presenting with neuropathic and non-neuropathic pain.

4.5.5 Other pain-related outcome measures

HR-QOL, disability, and emotional health have previously been associated with pain, and are therefore measured in the current study. The most appropriate measurement tool for each is outlined later in Chapter 5.

The literature review (Chapter 3) and literature pertaining to methods (present chapter) chapters have now been undertaken for the epidemiological study. The findings of these two chapters will now be used to shape the aims and objectives of the epidemiological study.

4.6 Study aims and objectives for epidemiological study

AIM 1: To estimate the prevalence of pain in the MS population

1. To estimate the prevalence of persistent, clinically significant pain
2. To estimate the prevalence of chronic pain (at least 6 months duration):
3. To estimate the prevalence of neuropathic pain
4. To estimate the prevalence of key MS-related pain syndromes

AIM 2: To compare those with neuropathic and non neuropathic pain for the following:

1. Pain intensity
2. Pain affect
3. Use and level of pain relief from prescribed, pain-relieving medication (PPRM).
4. Health-Related Quality of Life (HR-QOL)
5. Sleep disturbance

AIM 3: To identify potential predictors of neuropathic pain

AIM4: To explore any potential association between neuropathic pain and HR-QOL.

The next section will detail the **methodology** of the epidemiological study.

5 METHODOLOGY: EPIDEMIOLOGICAL STUDY

This chapter presents the methodology used to meet the objectives of the epidemiological study (Section 4.6). The research design, sampling method, and study procedure will be detailed, as well as outcome measures and statistical methods used for data analysis.

5.1 Research design and sampling frame

An epidemiological study design was used, using a postal questionnaire method. A population sampling approach was used, which aimed to target the entire (diagnosed) MS population of the NHS Ayrshire and Arran (A&A) health board area, who met the inclusion criteria. Participants were recruited from the clinical register of the NHS A&A Multiple Sclerosis service, where all patients within the health board area are referred upon MS diagnosis.

5.2 Participants

5.2.1 Inclusion criteria

Inclusion criteria were: i) confirmed diagnosis of MS by a neurologist, according to the 2005 revised McDonald Criteria (Polman *et al*, 2005) ii) patient on the clinical register of the A&A MS Service; iii) being over the age of 18, so as to ensure participants could give consent on their own behalf; iv) being fluent in English language in order to complete the questionnaire.

5.2.2 Exclusion criteria

Exclusion criteria were: i) persons incapacitated to the extent that they lacked the level of comprehension to complete the questionnaire. Where necessary completion by proxy was permitted, i.e. participants with physical or visual impairments, which would make questionnaire completion difficult were assisted ii) patients at end of life, where it would be unethical to recruit, or patients who lacked the level of comprehension required to provide informed consent;

iii) Persons with any medical condition, which could lead to neuropathic pain other than MS (this included central and peripheral nerve damage), examples include spinal cord

injury and peripheral diabetic neuropathy. Medical conditions which could mimic the presentation of MS-specific neuropathic pain were also excluded. Examples of this include lupus and fibromyalgia.

The Lead Clinician (Consultant in Neurological Rehabilitation) and Consultant physiotherapist in MS were involved directly with exclusions i) and ii), whereby clinical knowledge of each individual was used in decision-making. Such patients were routinely reviewed by the team as part of usual care. Exclusions i) and ii) were undertaken prior to questionnaire mailing, using the on-site MS clinical register. Exclusion iii) was undertaken upon questionnaire return. The researcher identified medical conditions that may mimic or cause neuropathic pain (other than MS) from completed questionnaires (Appendix 1). The ID number from such questionnaires were given to clinicians of the MS service, who considered the participants full clinical presentation to determine whether the presence of neuropathic pain was the result of a condition other than MS. As patient contact is high in the A&A MS service, potential exclusion was considered on an individual basis and not with the use of arbitrary exclusion criteria.

5.3 Procedure

5.3.1 Ethics and Research & Development approval

In May 2009, the study gained favourable ethical opinion from the NHS Research Ethics Committee and Research and Development management approval from NHS Ayrshire and Arran (A&A) (Appendix 2). The ethics committee stipulated that participants initially be sent a letter seeking permission for the research team to post the questionnaire on pain experience (Appendix 2). It was stipulated that participants must return a consent slip to this effect, prior to the questionnaire being posted. Once consent was obtained the questionnaire, and an accompanying patient information sheet (Appendix 3) were mailed to participants. Participants were instructed to read the information sheet and discuss it with anyone they wish. The option to contact the researcher or an independent contact about the study was provided, so that informed consent was obtained before completing the questionnaire. A pre-paid return envelope was included with the initial letter seeking permission and with the questionnaire. The participant information sheet made clear to participants that consent was implied by the return of the initial consent slip and by completing and returning the questionnaire.

5.3.2 Sample

At the time of recruitment, there were 712 patients on the MS clinical register of the A&A MS Service. 37 patients were excluded for lacking the level of comprehension required to complete (or consent to complete) the questionnaire. In May 2009, 675 patients were mailed the initial letter, asking permission to mail the pain questionnaire. In June 2009, reminder letters were sent out to those who had not yet replied to the initial permission letter. Subsequently, in July 2009, 388 patients consented, and were mailed the pain questionnaire. In August 2008, reminder letters were sent out to those who had not yet returned the questionnaire.

5.3.3 Questionnaire monitoring

Questionnaires were numbered with a unique identification number, so that returned questionnaires could be monitored. The questionnaire contained no identifiable details. Pseudo-identifiers were held on a separate database, of which only the manager of the MS service had password-protected access. A study database was set up using Microsoft Excel, held in a secure location at the Douglas Grant Rehabilitation Centre. The database was updated as questionnaires were returned. The presence of conditions that could cause neuropathic pain, other than MS, were established when questionnaires were returned and participants were subsequently excluded at this point.

5.3.4 Instrumentation

Data was obtained using a questionnaire on the pain experience, which took approximately one hour to complete. The questionnaire included four sections demographics, MS disease characteristics, disability and health related quality of life (HR-QOL) and a pain section (including identification and description of pain), each of which used standardised assessment tools. Each instrument has been discussed in relation to issues of reliability, validity and clinical applicability in Chapter 4.

5.3.5 Instrument selection process

The choice of pain instrumentation used in the questionnaire, was based on the literature review, which revealed the complexity of pain assessment. Pain, as a multidimensional phenomenon, is discussed in detail in the previous chapters, therefore no one tool was sufficient to evaluate the total pain experience. For each dimension of pain, a plethora of pain assessment tools were considered for reliability, validity and clinical applicability as highlighted in pain assessment recommendations (IMMPACT recommendations, 2005) (Dworkin *et al*, 2005). With this in mind, expert advice was sought from anaesthetic colleagues from the chronic pain service, department of anaesthesia, at Gartnavel General Hospital, in Glasgow, as well as leading pain assessment academics from the IASP. The study aimed for a comprehensive understanding of the pain experience but was also designed with patient burden in mind. Consultation with the MS Society (Scotland) Patient Advisory Group was undertaken to determine both the clinical applicability and patient-friendliness of assessment tools. Generic, versus disease-specific tools in both disability and HR-QOL assessment were considered. It was felt that in the case of HR-QOL, an instrument which allowed comparison with other populations would be more useful. A description of each instrument used is provided as follows.

5.4 Measurement tools included in questionnaire

The following section lists the assessment tools included in the questionnaire. Cases of pain were considered if present at the point of assessment, or within the previous month prior to assessment. For continuity, all other outcome measures were adapted to this specific timeframe. This ensured that potential associations between pain and variables, such as level of disability were anchored in the same time period, to ensure validity. The importance of this standardisation, when dealing with disease occurrence rate (whether prevalence or incidence), is detailed in epidemiological literature (Bhopal, 2008a; Elwood, 2007d; Webb and Bain, 2011a).

5.4.1 Demographics

Age, gender, employment, educational and marital status were recorded using categorical variables consistent with those used in other chronic pain literature (Appendix 1, page 2).

Socio-economic status was established using the Scottish Index of Multiple Deprivation (SIMD) (Scottish Government National Statistics, 2009), where postcode is indexed to a deprivation decile level from 1-10 (where10 = least deprived, and 1=most deprived).

5.4.2 Disease characteristics

5.4.2.1 Type of MS

Type of MS (Relapsing Remitting (RR), Secondary Progressive (SP), Primary Progressive (PP) and Progressive Relapsing (PR) was ascertained by asking participants to select one of four diagrams that most closely corresponded to their disease course over time, since diagnosis (Lublin and Reingold, 1996) (Appendix 1, Section 1, Question 9). This method has demonstrated strong agreement, between clinicians and patients when comparing the relapsing remitting subtype with other subtypes of MS (k=0.62) (Bamer *et al*, 2007). Participants were also asked to record the time (in years) since MS diagnosis.

5.4.2.2 Anxiety and Depression

Level of anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) (Appendix 1, Section 4), where each scale for anxiety and depression range from 0-21, with high scores reflecting more symptoms of anxiety or depression (Zigmond and Snaith, 1983). Scores between 8 and 10 and considered clinically borderline and 11 or greater is considered clinically definite cases of anxiety or depression (Bjelland *et al*, 2002) et al, 2002). The HADS was validated in the MS population, with a sensitivity of 90% and specificity of 87.3% (Honarmand and Feinstein, 2009).

5.4.2.3 Disability

The standard, self-report, Guys Neurological Disability Scale (GNDS) (Appendix 1, Section 2) was included to determine level of neurological disability, similarly to other studies of pain in MS (Douglas *et al*, 2008a; McCrone *et al*, 2008). It assesses function on a range of disabilities within the 12 domains of cognition, mood, vision, speech, swallowing, upper-limb function, mobility, bladder function, bowel function, fatigue, sexual function and other problems, such as spasms. Each of the 12 components are graded on a scale of 0 (normal level of function) to 5 (total loss of function) and combined to give

a total disability score from 0 (no disability) to 60 (maximum level of disability). The self-report scores of the GNDS have previously been proven to correlate with scores of another traditional measure of neurological disability- the Expanded Disability Status Scale (EDSS), when completed by means of a clinical neurological assessment (Hoogervorst *et al*, 2001). The GNDS was chosen over the EDSS, for its brevity and user-friendliness. Furthermore, the EDSS has been criticised for being based on a medical model of disability, limited to aspects of physical functioning (Nortvedt *et al*, 1999), unlike the GNDS, which considers the wider aspects of disability.

5.4.2.4 Health Related Quality of Life (HR-QOL)

HR-QOL was measured using the EuroQol-5 Dimension Quality of Life questionnaire (EQ-5D) (EuroQol Group, 1990). (Appendix1, Section 3). It consists of 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is rated as 1 (no problems), 2 (some problems), or 3 (major problems). This results in a five-figure score, which is converted to a utility value from 0 (death) to 1 (full health). The IASP, in their guidelines for neuropathic pain assessment have recently recommended the use of either the SF-36 or EQ-5D (Haanpää *et al,* 2011). The EQ-5D has previously been validated in populations which display cognitive deficit (Wolfs *et al*, 2007), disorders of the CNS (Schrag *et al*, 2000), and is used frequently in populations with neuropathic pain (Taylor, 2006; Toth *et al*, 2009), including MS (Kappos *et al*, 2007). It also has the advantage of being brief, and user-friendly, over the SF-36 HR-QOL assessment tool.

5.4.3 Pain: case definition

Cases of chronic pain, neuropathic pain and MS-related pain syndromes were identified using validated measures as follows:

5.4.3.1 Clinically Significant Pain and Chronic Pain

Cases of pain were identified as pain experienced within the month prior to assessment, and was established using a two-tiered screening method. The first question was adapted from previous studies of MS-related pain (Ehde *et al,* 2003; Hadjimichael *et al,* 2007), and the Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994), and identified cases of clinically significant, persistent pain:

"*Throughout our lives, most of us experience everyday types of pain (such as minor headaches, sprains and toothaches). We also may experience pain as a result of a recent injury. Other than these types of pain, at present or within the last month, have you experienced ongoing, bothersome pain? This pain may be constant or 'off and on'.*

Patients with an affirmative answer to the first question progressed to a second question on the duration of this pain. This ascertained cases of chronic pain of at least a six-month duration, in accordance with the recommendations of the IASP (Merskey and Bogduk, 1994). The two-tiered screening method thus ascertained the period prevalence of persistent, clinically significant pain, and chronic pain. Alternatively, persons identified without clinically significant pain at this point, were subsequently asked whether they had *ever* experienced such pain, since being diagnosed with MS. This provided an additional measure of the *lifetime prevalence* of clinically significant pain, which was pain experienced, at any time, since MS diagnosis. Persons never having experienced such pain were asked to terminate questionnaire completion at this point, returning it as instructed.

Patients with clinically significant pain were asked if the source of their pain was related to the musculoskeletal complications of MS, such as stiffness, gait problems and altered sitting or standing postures. This was used for descriptive purposes only; cases of non-neuropathic pain were identified using the PainDETECT Questionnaire (PD-Q), detailed in section 5.4.3.3.

5.4.3.2 MS–related pain syndromes

The key MS-related pain syndromes were identified if experienced within the month prior to assessment (period prevalence) and at any time since MS diagnosis (lifetime prevalence) and were: Lhermitte's phenomenon, optic neuritis, trigeminal neuralgia, dysaesthetic pain, migraine headache, painful tonic spasms, and visceral pain, paroxysmal extremity pain. The pain syndromes were identified using patient-friendly definitions, previously outlined in MS literature (Svendsen and Bach, 2006) and were pre-tested for acceptability by lay members of the MS patient population, as well as the MS Society's research patient advisory group. Descriptions of each pain syndrome can be found in Appendix 1, Section 8).

5.4.3.3 Neuropathic pain

To measure the prevalence of neuropathic pain, participants completed the PainDETECT questionnaire (PD-Q) (Appendix1, Section 12), which has previously shown a high sensitivity and specificity of 85% and 80% respectively, in the screening of neuropathic pain (Freynhagen et al, 2006). The questionnaire includes nine items: which are scored from –1 to 38; where –1 to12 represents non-neuropathic pain; 13 to18 possible neuropathic pain and 19 to 38 definite cases of neuropathic pain. Cases of neuropathic pain were identified by the PD-Q if present at the point of assessment (point prevalence), and were not limited by chronicity. However, only those with chronic pain (at least six-month duration) were included in the section comparing neuropathic and non-neuropathic pain, to standardise the two groups for comparison.

5.4.4 Pain characteristics

5.4.4.1 Pain intensity

Average intensity of pain (within the last month) was measured using an 11-point numerical rating scale (NRS), where 0= no pain, and 10=worst pain, as recommended by the IMMPACT guidelines on pain assessment (Dworkin *et al,* 2005). Average pain intensity was the primary outcome measure, however *present* pain intensity and *strongest* pain intensity, within the previous month, were also recorded in line with pain assessment guidelines (Dworkin *et al,* 2005). The three measures of pain intensity were included

within the PainDETECT questionnaire (PD-Q). Pain intensity was also measured using the Short-Form McGill Pain Questionnaire (SF-MPQ), detailed in the next section.

5.4.4.2 Pain affect

The Short-Form McGill Pain Questionnaire (SF-MPQ) evaluates both the sensory and affective components of pain, both qualitatively and quantitatively (Melzack, 1987), and was included in the questionnaire. It includes 15 verbal descriptors of pain, 11 representing the sensory category of pain and 4 representing the affective elements of pain, taken from the long version of the MPQ. It also rates each particular description of pain on a scale of 0-3 of pain intensity, (where: 0= no pain, 1= mild pain, 2= moderate pain and 3= severe pain). Two separate scores are obtained from the sum of the sensory and affective scores; known as the affective pain rating index (affective PPI) and the sensory pain rating index (sensory PPI), a total score is also obtained by adding the sensory and affective scores. Each of the three scores was recorded in the current study.

5.4.4.3 Use and relief from Prescribed, Pain–Relieving Medication (PPRM)

Current use of PPRM was also recorded, similarly to other epidemiological studies of pain (Breivik *et al*, 2006), and included analgesics (opioid and non-opioid), NSAIDs, spasmolytics, antidepressants, used for pain, and antiepileptics, used for pain. Percentage relief from PPRM was also recorded, (from the Brief Pain Inventory (BPI) using the NRS of pain relief in 10% increments from 0-100%.

5.4.4.4 Pain-related sleep disturbance

Level of sleep disturbance was ascertained by asking participants if their sleep was disturbed by pain: *never, occasionally, frequently, or every night*, similarly to other epidemiological studies of pain.

5.4.4.5 Other pain characteristics

The purpose of this study was to measure the characteristics of pain in MS poorly identified by previous literature. However, in accordance with the IMMPACT recommendations for pain assessment (Dworkin *et al.* 2005), area of pain, and use of non

pharmacological pain-relieving treatments, such as TENS and Reflexology were also measured. Pattern of pain was also included in the PainDETECT (PD-Q) questionnaire.

5.5 Data analysis

Quantitative data analysis was undertaken using the Minitab statistical package (Version 16). This involved four key steps: firstly, the data was coded and input in to the database, then it was checked and 'cleaned' for any errors, then descriptive statistics were undertaken, followed by substantive analysis for each research question.

5.5.1 Data input

Data from the questionnaire was appropriately coded and input into Minitab. There were instances when a section was not applicable: for example, individuals who had answered that they currently did not have clinically significant pain would have been instructed not to answer questions on current pain location, intensity etc. In this case a (–999) value was given to highlight a not applicable input in the dataset. For the neuropathic pain section (as measured by PDQ), participants could score a possible *–1 to 35*. A 'not applicable' value was also possible, (for participants whom did not have clinically significant pain) and was re-coded as a '0', indicating no neuropathic pain. In Minitab, any cell non-entry in the data automatically converts to a missing value, indicated by a * in the data set. It was decided that for the GNDS and HADS questionnaires, more than two individual missing sections would render the overall score invalid, and hence a missing value. Less than (or equal to) two missing sections were given the mean value (subsequent to all other scores being input).

5.5.2 Raw data preparation

Verification of data was undertaken by re-entry of a random sample of 10 questionnaires. No errors were encountered using this approach. A tally of each individual variable, using frequency distribution tables was undertaken to screen for errors or duplicates. A small number of errors were identified (invalid codes) and corrected by verifying again with questionnaires. The data set was also screened for inconsistencies, i.e. patients who answered initially that they did not currently have clinically significant pain, should not have completed the rest of the questionnaire, which screened for neuropathic pain, and considered the presentation of pain, such as intensity, quality etc. After consultation with

the research team it was decided that as pain is a subjective phenomenon information given by the patient should be entered exactly as such and not changed, regardless of whether it highlighted inconsistencies. It is acknowledged that this may affect the validity of results but was only in a small number of participants (<1%) and has been supported in other comparable literature (Douglas *et al*, 2008b). The data set was also checked for missing values: Generally there was minimal missing data across the entire data set (<5%). For each of the individual questionnaire sections, the PD-Q (on the last page of the questionnaire) had the most missing values. A total score was unable to be obtained for <10% of the eligible sample (Section 6.3.3).

5.5.3 Data analysis approach

As studies of pain in MS have given conflicting findings, and the study of neuropathic pain in MS is a new area of research, no specific hypotheses were set in the study. Exploratory analysis was undertaken to measure the prevalence, characteristics, predictors and impact of pain on HR-QOL in MS. When relationships were considered between pain and variables, such as QOL, it was their existence, nature and magnitude, rather than a directional hypothesis that was considered.

5.5.4 Planned analysis

5.5.4.1 Aggregation of variables: Socio-economic

At the point of pain-predictor analysis, two key sociodemographic variables were aggregated in order to both simplify results and assess the effect of the key factor that have been shown to be associated with pain in previous literature: For employment status, the key risk factor is currently being in any form of employment versus not and for marital status the key factor is living alone or with another person. Therefore, for 'employment', the original 5 categories in the questionnaire were collapsed down to two categories: currently employed/currently unemployed. 'Student' was added to the employed category, along with those in part-time or full-time employment, whilst those retired, or unable to work, due to MS, were included in the 'unemployed' category. For marital status, the five original categories in the questionnaire were aggregated into two categories: married or co-habiting/other. Married and living with partner were combined into the former, and single, widowed, divorced were combined to form the latter category.

The disease course questionnaire (Appendix 1, Section 1, and Question 9) originally has five pictures representing MS disease course. The authors state that for analysis purposes, it is perfectly acceptable to aggregate these down into the four separate disease courses that are associated with MS: Relapsing Remitting (RRMS), Primary Progressive (PPMS), Secondary Progressive (SPMS), and Progressive Relapsing (PRMS), by combining sections a and b (both of which represent a relapsing remitting disease course). This was therefore undertaken in the data set.

5.5.4.2 Aggregation of variables: neuropathic pain

For neuropathic pain, the PDQ provides a continuous variable score from -1 to 35, and was designed to be categorised into cases of neuropathic pain (score 19-38), cases of non-neuropathic pain (-1 to 12), and possible cases of neuropathic pain (13-18). For clinical interpretation, the PDQ is most useful when applied diagnostically, i.e. identifying cases of neuropathic pain, over that of its statistical use as a continuous variable. It is for this reason that, at the level of multivariable analysis, logistic regression was used over linear regression in determining predictors of pain as discussed previously (Section 4.1.5). In this way a dichotomous outcome was required, identifying cases or non-cases of neuropathic pain. Following sensitivity analysis (Appendix 4), it was deemed appropriate for participants with PDQ scores of 13-18, (indicating 'possible' cases of neuropathic pain) to be coded as actual cases of neuropathic pain. However, when the prevalence of neuropathic pain was considered, the separation of definite cases, non-cases and possible cases of neuropathic pain are still maintained.

5.5.4.3 Exclusion of cases from neuropathic pain analysis

Section 5.2.2 of this chapter describes the exclusion of any medical condition, other than MS, that could lead to (or mimic) neuropathic pain. Such participants were not completely removed from the dataset. Participants were only excluded from the neuropathic pain column of the dataset and NOT from the 'clinically significant pain' or 'chronic pain' columns of the dataset.

5.5.4.4 Determining potential predictors of neuropathic pain

Factors associated with pain were drawn upon from both the MS literature and general chronic pain literature, and included age, gender, SE status, employment status, marital

status, level of education, deprivation level (as measured using the SIMD), course of MS disease activity, time since diagnosis, disability level (GNDS) and level of anxiety and depression. Factors associated with pain were considered both at the bivariate and multivariable level of analysis.

5.5.5 Statistical analysis

5.5.5.1 Bivariate analysis

The following method was used to evaluate the prevalence of pain, pain characteristics, predictors of neuropathic pain and the impact of neuropathic pain on HR-QOL. Firstly, continuous variables were assessed for normality through visual inspection of histograms, and calculation of skewness and kurtosis coefficients. Basic descriptive statistics were used to explore the prevalence, characteristics and impact of pain on HR-QOL. At the bivariate level, chi-square tests were used to test for associations between categorical variables; t tests were used to assess the mean difference in normally distributed variables, whilst the Mann-Whitney test was used for variables not normally distributed. P values were from 2-sided tests, and statistical significance was determined by a p value of <. 05.

5.5.5.2 Multivariable Analysis

Multivariable level analysis was used to determine factors independently associated with the presence of neuropathic pain. The identification of confounding factors in an epidemiological study is an important procedure. Confounding is the process by which the estimated effect of an exposure of interest is distorted by the effects of an extraneous factor (Elwood, 2007a). As MS pain literature has shown conflicting findings in the study of predictors of pain, it was felt that all variables should be considered for the potential effect of confounding, thus all variables were considered for multivariable analysis, which identifies independent predictors of pain.

Logistic regression analysis was used to test for independent associations with a dichotomous dependent variable and is an effective way of screening the large number of potential predictors of pain included in the study (a list of all variables considered in this study are detailed in section 5.5.4.4 of this chapter). There are many different types of logistic regression analysis (Hosmer, 1989). In this research, backward, stepwise logistic regression was used to obtain a parsimonious model that included the variables

independently associated with pain. All variables shown to have a p value of 0.2 or less from bivariate analysis were entered into the model. In the backward elimination procedure, regression is first carried out on all appropriate variables. The least significant variable was then eliminated and regression carried out until the retained regression coefficients were significant, and the model showed goodness of fit (using the Hosmer-Lemeshow Goodness of Fit Test). As with bivariate analysis, p values were from 2-sided tests, and statistical significance was determined by a p value of <.05

6 RESULTS OF EPIDEMIOLOGICAL STUDY

This section will present the results of the study and relates to the aims and objectives detailed in Section 4.6. The chapter begins with a description of the sample, including response rate, demographics, and disease characteristics. The chapter then focuses on the prevalence of pain, including clinically significant pain, chronic pain, neuropathic pain and the prevalence of the key MS-related pain syndromes. Following this, neuropathic and non-neuropathic pain are compared for factors such as level of pain intensity, and the affective component of pain. Lastly, the chapter considers the potential predictors of neuropathic pain, and explores any potential association between its presence and HR-QOL.

6.1 Response rate

The original MS clinical database contained 712 patients. Initially, 37 patients were excluded for ethical reasons, i.e. patients who were currently receiving end of life care or had severe cognitive impairment to the extent that consent could not be obtained. There were no patients excluded at this stage on the basis of being under the age of 18 or not using English as a first language. Following this, 675 patients were sent a letter detailing the study, which also contained a consent slip to gain permission to send out the pain questionnaire. This consent slip was returned by 391 patients- 388 of which consented to being sent the questionnaire. Of the 388 postal questionnaires sent out, 302 were completed and returned, giving a response rate of 77.8 %. Information on non-respondents was not available due to the requirements stipulated by the ethics committee. Upon questionnaire return, 10 participants were excluded specifically from neuropathic pain analysis for conditions other than MS that could lead to (or mimic) neuropathic pain. This process is summarised in Figure 6-1.

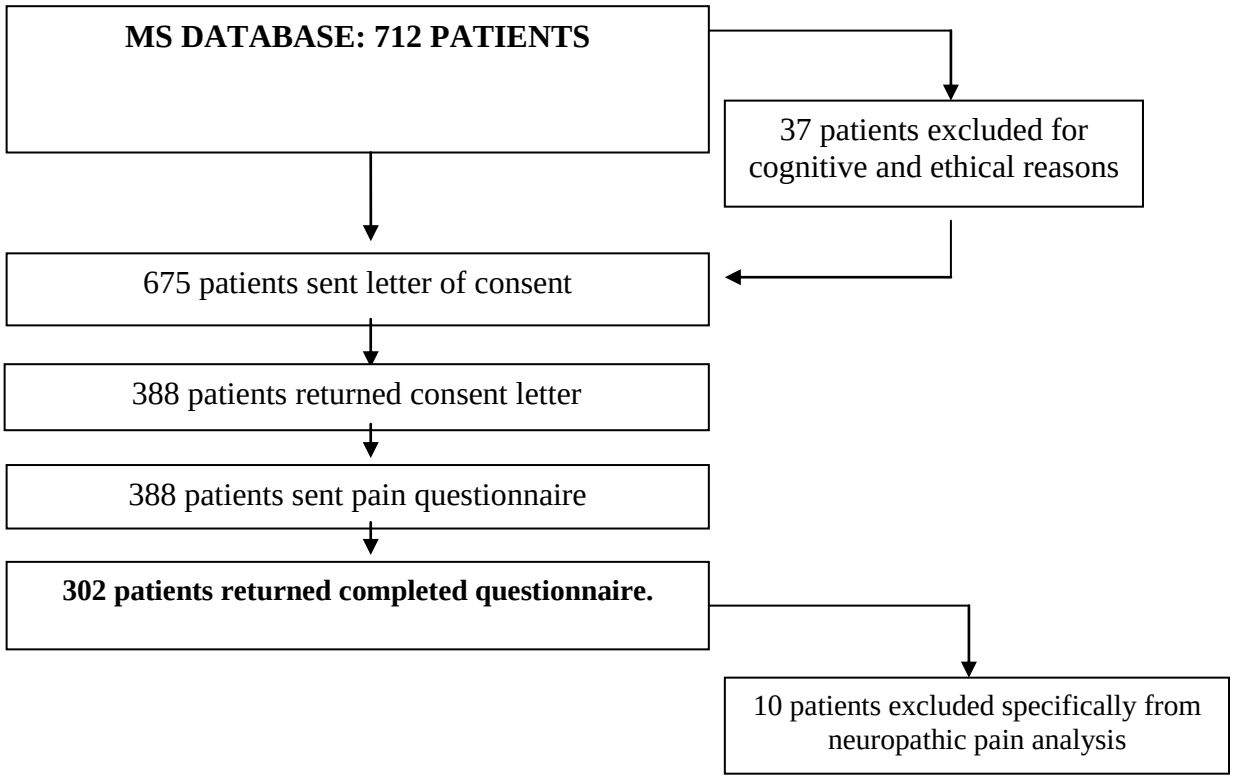


Figure 6-1: flowchart of questionnaire process

6.2 Sample characteristics

This section presents the sample characteristics (n=302), including the demographic (Section 6.2.1) and disease characteristics (Section 6.2.2) of participants.

6.2.1 Demographics

The sociodemographic characteristics of the sample are summarised in Table 6-1. Almost three-quarters of the sample were female (74.1%), with a mean age of 51.5 years (SD 10.2, range 25-81yrs). The sample was predominately married (66%), white, Scottish women. The majority of the sample had attained a minimum of secondary-school level qualifications (83.4%), were living in less deprived postcode areas and were currently either retired (25%) or unable to work due to MS (39.7%)

Table 6-1: Sociodemographic characteristics

Characteristics	n= 302	
	n	%
Gender:		
Female	223	74.1
Male	78	25.9
Marital Status:		
Married	198	66.0
Divorced	37	12.3
Single	31	10.3
Living with partner	24	8.0
Widowed	10	3.3
Employment:		
Unable to work	119	39.7
Retired	75	25.0
Employed full time	48	16.0
Employed part time	40	13.3
Unemployed	16	5.3
Student	2	0.7
Education:		
Higher education	143	47.7
Secondary education	107	35.7
No qualifications	50	16.7
Ethnicity:		
White: Scottish	272	90.3
English	25	8.3
Irish	3	1.0
Welsh	1	0.33
Deprivation Category [a]:		
1-3	48	16.1
4-7	117	39
8-10	132	44.4

Where n< 302 for above variables = missing values

[a] Using the Scottish Index of Multiple Deprivation (SIMD), (Scottish Government National Statistics, 2009), where postcode is indexed to a deprivation decile level from 1-10 (10 = least deprived).

6.2.2 Disease characteristics

For disease course, 53.7% (n=158) of the sample presented with RRMS, 19.4% (n=57) with PPMS, 14.9% (n=44) with SPMS and 11.9% (n=35) with PRMS. The median time since diagnosis was 11.0 years (IQR: 6.0-18.0). Median HADS anxiety score was 7.0 (IQR: 4.0-10.0) and median depression score was 6.0 (IQR: 4.0-9.0), out of a possible score of 21, where cases of anxiety or depression are indicated by a score of at least 11. Thus the sample displayed low mean levels of mood disorder.

As measured by the GNDS, the median disability score was 17.0 (IQR: 11-24.4), out of a possible score of 60. Table 6-2 illustrates the distribution of GNDS scores amongst the sample. The scores of over half of the population fell within the first two categories (58%) of lowest levels of disability. Only 14% of the sample fell within the last two categories of greater levels of disability. Thus although the sample showed a wide range of disability levels, on average the cohort displays a mild level of disability. The demographic and disease characteristics of the sample reported here are typical of a UK MS population (McCrone *et al.* 2008; Murray *et al.* 2004).

Table 6-2: Distribution of disability score

GNDS score range	N (%)
0-9	57 (19.1)
10-19	118 (39.6)
20-29	80 (26.9)
30-39	36 (12.1)
≥40	7 (2.4)

0= least disabled, 60= most disabled,
N= 298, four people did not complete this section.

The section has explored the characteristics of the sample. It will now present the findings on the prevalence of different types of pain in the MS sample

6.3 Pain

This section presents the prevalence of clinically significant pain (Section 6.3.1), chronic pain (Section 6.3.2), neuropathic pain (Section 6.3.3), and the prevalence of MS-related pain syndromes (Section 6.3.4).

6.3.1 Clinically significant pain

The prevalence of clinically significant pain was 71.7% (n=213/297, with 5 missing values) (95% CI= 62.4%-82.0%), showing that almost three quarters of the sample currently suffered "ongoing bothersome pain". The mean chronicity of this pain was 4 years (±SD of 5.9), ranging from one month to 30 years.

The lifetime prevalence of clinically significant pain was 84.9% (n=252/297, with 5 missing values) (95% CI= 75.8%-92.0%), showing that the vast majority of the sample have suffered "ongoing bothersome pain" at some point since diagnosis.

The percentage of people who felt that this was related to the secondary musculoskeletal changes of MS was 67.8% (n=139/205).

The location of clinically significant pain is shown in Table 6-3. The most common area of pain was that of bilateral lower limb pain (including feet and legs), experienced by over three-quarters of the sample, followed by back/ trunk pain and bilateral upper limb pain (including arms and hands) at 49.3% and 42.4% respectively. Over two-thirds (66.7%, n= 137/203, with 10 missing values) experienced pain in at least 2 separate body areas. Over half of the sample (33.9%, n=69/203, with 10 missing values) experienced pain in at least 3 body areas, whilst over a quarter (26.1%, n= 53/203) experienced pain in at least 4 body areas. Widespread pain was therefore common in the sample.

Table 6-3: Body areas of pain

Body area	Prevalence n (%) n=203*
Neck	38 (18.7)
Head	43 (21.2)
Face	26 (12.8)
Back/trunk	100 (49.3)
Abdomen/pelvis	39 (19.2)
Limb upper (arm/hand) unilateral	36 (17.7)
Limbs upper bilateral	86 (42.4)
Limb lower (leg/foot) unilateral	42 (20.7)
Limb lower bilateral	167 (82.2)

*10 missing values

6.3.2 Chronic pain

The prevalence of chronic pain (≥ 6 months) was 59.2% (n=174/294*) (95% CI: 53.3%-64.9%), with a median duration of 5.0 years (IQR: 2.0-10.0) (*includes 8 missing values).

6.3.3 Prevalence of neuropathic pain

Following the exclusion of 10 people with non-MS related neuropathic pain, the prevalence of neuropathic pain as identified by the pain DETECT (P-DQ), was 32.7% (n=87/266) (95% CI: 27.1%-38.7%), with a further 14.7 % (n=39/266) scoring as having 'possible' neuropathic pain, indicating the figure could be as high as 47.4% (95% CI: 41.2%-53.6%). Also, there were 26 missing values, as these people did not complete the PD-Q when it was indicated for them to do so.

6.3.4 Prevalence of MS-related pain syndromes

The point and lifetime prevalence of the key MS-related pain syndromes are shown in Table 6-4. The most common pain syndromes reported were that of dysaesthetic pain (74.1%), and painful tonic spasms (62.2%). Lhermitte's phenomenon was experienced by 36.4% of the sample, and over a fifth (23.8%), of people had experienced paroxysmal extremity pain, trigeminal neuralgia (21.4%), and migraine headache (24.8%) since their diagnosis. The most common syndromes currently experienced were that of dysaesthetic pain and painful tonic spasms. The most common types of dysaesthetic pain currently reported include burning pain, unpleasant paraesthesias, sharp pain and aching (Table 6-5).

Table 6-4: Prevalence of key MS pain syndromes

MS Pain syndrome	**Prevalence (n=294)** N (%)	
	Period Prevalence	**Lifetime prevalence**
Dysaesthetic pain	163 (56.2)	218 (74.1)
Painful tonic spasm	129 (44.5)	183 (62.2)
Visceral pain	53 (18.5)	69 (23.5)
Lhermitte's phenomenon	52 (17.7)	107 (36.4)
Optic neuritis	36 (12.4)	129 (43.9)
Migraine headache	34 (11.7)	73 (24.8)
Paroxysmal extremity pain	30 (10.2)	94 (32.0)
Trigeminal neuralgia	21 (7.2)	63(21.4)

Table 6-5: Prevalence of individual type dysasthesias

Type of dysaesthesia	Prevalence (n=163) N (%)
Burning, stinging, nipping	95 (58.2)
Unpleasant paraesthesia: i.e. pins and needles, tingling, crawling	89 (54.6)
Sharp, stabbing, shooting, electric-shock-like	57 (34.9)
Aching	51 (32.0)
Tightness: tight band like, squeezing, cramping, vice-like	34 (21.0)
Cold, freezing	26 (15.9)
Dull, numbness (alien perception)	24(14.8)
Itching	23 (13.5)
Wetness, liquid on skin	16 (9.8)

6.3.5 Comparison of those with neuropathic and non-neuropathic pain

This section focuses on those with chronic pain, and compares those with neuropathic and non-neuropathic pain presentations (Table 6-6).

For the total sample with chronic pain, almost two-thirds (59.5%) were using PPRM, and almost half (43.6%) were currently suffering severe pain, (as identified by the NRS of pain intensity). Those with a neuropathic pain presentation had significantly lower HR-QOL scores, than those with a non-neuropathic pain presentation (*P=0.007*) (Table 6-6). Those with neuropathic pain described a significantly more intense pain experience overall, which included a higher total SF-MPQ score (*p<0.001*), consisting of higher sensory (*p<0.001*) and affective (*p<0.001*) component scores as well as a higher intensity score on the NRS (*p<0.001*). Those with neuropathic pain were more likely to be currently using PPRMs than the non-neuropathic pain group (*p=0.01*), but with less subsequent pain relief (*p=0.20*) (although not statistically significant). Furthermore, despite over two thirds (68.5%) currently using PPRM, over half (53.7%) of those with neuropathic pain were still experiencing pain of severe intensity.

Those with neuropathic pain also showed greater pain-related sleep disturbance than those with non-neuropathic pain ($p<0.001$), with almost two-thirds having frequent disturbed sleep as a result of pain.

Table 6-6: Chronic pain subgroup: comparison of those with neuropathic and non-neuropathic pain for key pain characteristics

Pain component	Total sample with chronic pain [a] (n= 164) [b]	Neuropathic pain (NeuP) (n=96)[c]	Non-Neuropathic pain (non-NeuP) (n=54)[c]	Comparison between NeuP+ non-NeuP (p value)
HR-QOL score Median Utility value (IQR)	0.52(0.09-0.62)	0.52 (0.03-0.62)	0.59 (0.31-0.69)	0.007[d]
SF-MPQ Total Score Median score (IQR)	12.0 (6.0-19.0)	15.0 (9.0-23.0)	6.0 (3.0-12.3)	<0.001[d]
SF-MPQ: Affective PRI Median score (IQR)	2.0 (0.0-5.0)	3.0 (0.0-6.0)	1.0 (0.0-3.0)	<0.001 [d]
SF-MPQ: Sensory PRI Median score (IQR)	10.0 (5.0-33.0)	12.0 (8.0-33.0)	6.0 (3.0-23.0)	<0.001[d]
Intensity Mean NRS score (SD)	5.5 (2.2)	6.4 (1.9)	4.7 (2.3)	<0.001[e]
Intensity [f]				
Mild (NRS: 1-4)	39 (26.2)	14 (14.7)	25 (46.3)	
Moderate (NRS:5-6)	45 (30.2)	30 (31.6)	15 (27.8)	
Severe (NRS: 7-10)	65 (43.6)	51 (53.7)	14 (25.9)	<0.001[g]
Current use of PPRM:	n (%)	n (%)	n (%)	
Use of PPRM	88 (59.5)	63(68.5)	25 (46.3)	
Non-use PPRM	60 (40.5)	29 (31.5)	29 (53.7)	0.01[g]
% Relief from PPRM mean NRS score (SD)	5.5(2.5)	5.7 (2.4)	6.3(2.3)	0.20[e]
Sleep affected:				
Never n (%)	18 (11.9)	4 (4.3)	14 (25.9)	
Occasionally	58 (38.6)	33 (34.4)	25 (46.3)	
Frequently	41 (27.3)	31 (33.0)	9 (16.7)	
Every Night	33 (22.0)	26 (27.7)	6 (11.1)	<0. 001[g]

[a] sample with pain ≥6 months duration

[b] 10 people excluded from chronic pain sample for neuropathic pain of origin other than MS. Where n <164 =missing values. [c]14 missing values- people who did not complete the P-DQ (96+54+14=164).

[d] Mann-Whitney test; [e]2-Sample t.test. [f] using categories, as outlined by (Serlin *et al*, 1995), for mild (NRS of 1-4), moderate (NRS of 5-6), and severe (NRS of 7-10) pain. [g]Chi-squared test.

6.3.6 Impact of neuropathic pain on HR-QOL

For the total sample (n=302), there was a statistically significant relationship between the presence of neuropathic pain and HR-QOL (as measured with the EQ-5D), with the presence of neuropathic pain being associated with lower HR-QOL scores (Table 6-7).

Table 6-7: Impact of neuropathic pain on HR-QOL

	Neuropathic pain present (n=126)*	**Neuropathic pain absent[a] (n=150)***	**p. value[b]**
HR-QOL score Mean (SD)	0.37 (0.35)	0.56 (0.33)	<0.001

*10 people excluded with non-MS related neuropathic pain, 16 missing values
[a] includes people with no pain and people with non-neuropathic pain.
[b] using 2-sample t- test, t=4.75

6.3.7 Predictors of neuropathic pain

The section presents the findings on the predictors of neuropathic pain, using a bivariate and Multivariable level of analysis.

6.3.7.1 Bivariate analysis

The relationship between neuropathic pain and key variables are presented in Table 6-8. At the bivariate level, statistically significant associations were shown between neuropathic pain and secondary progressive MS (SPMS), female gender, greater disability level and higher levels of anxiety and depression. No statistically significant associations were shown for the variables: marital status, employment status, educational attainment, age, SE status, and time since diagnosis.

6.3.7.2 Multivariable level analysis

The final model, from multiple logistic regression, showed acceptable fit (Hosmer-Lemeshow goodness of fit test, p=0.55) and showed disability level and type of MS as independent predictors of neuropathic pain (Table 6-9). For type of MS, the odds of having neuropathic pain were greatest for SPMS, and least for PPMS. For people with SPMS the odds of having neuropathic pain were over five times greater than in those with PPMS. For disability as a predictor, each unit increase on the GNDS scale increased the odds of having neuropathic pain by 7%.

Table 6-8: Factors associated with neuropathic pain [a]

Variable	Neuropathic pain n=126 n (%)	Non-neuropathic Pain [b] n= 140 n (%)	p. value
Gender: Male Female	 46 (33.1) 93 (66.9)	 23 (18.3) 103 (81.8)	 0.006
Marital status: Married/Co-habit Other	 99 (71.7) 39 (28.3)	 95 (75.4) 31 (24.6	 0.50
Employment: Employed Unemployed	 42 (30.2) 97 (69.8)	 37 (29.4) 89 (70.6)	 0.88
Education [c] NO QF SS QF HE QF	 25 (18.0) 47 (33.8) 67 (48.2)	 20 (15.9) 47 (37.3) 59 (46.8)	 0.80
Type of MS Relapsing Remitting Secondary Progressive Primary Progressive Progressive Relapsing	 68 (54.9) 26 (21.0) 14 (11.3) 16 (12.9)	 76 (54.7) 11 (7.9) 37 (26.6) 15 (10.8)	 0.001
Age (yrs), mean (SD)	50.1 (9.2)	51.5 (10.8)	0.37[d]
SE. Status[e]**,** median (IQR) [f]	5.0 (2.0-7.0)	4.0 (2.0-6.0)	0.24
Time since diagnosis (yrs)	12.0 (6.0-18.0)	11.0 (6.1-18.0)	0.92
Disability (GNDS)	21.0 (14.0-29.0)	15.0 (9.0-21.8)	<0.001
Anxiety	9.0 (5.0-11.0)	6.0 (3.0-9.0)	<0.001
Depression	6.0 (4.0-10.0)	6.0 (3.0-8.0)	0.03

[a] PDQ score ≥13 (10 people excluded for neuropathic pain of origin other than MS)
[b] Includes all other respondents, i.e. those with no pain and those with non-neuropathic pain
[c] Max level of qualification obtained: NO QF= no qualifications, SSQF=Secondary school qualifications, HEQF=Higher education qualifications.
[d] p value calculated with 2-Sample t.test. All further p values below calculated using Mann–Whitney test; all other p values above by X^2 test.
[e]SE= Socio-economic, measured using SIMD (score of 1-10, where 10=least deprived).
[f] All other variables below includes median score (IQR)

Table 6-9: Logistic regression model of predictors of neuropathic pain (n=263)

PREDICTOR	P value	Odds Ratio	95% CI
TYPE OF MS[a]			
Relapsing Remitting	0.005	2.87	1.37-6.00
Secondary Progressive	0.001	5.52	2.07-14.7
Progressive Relapsing	0.075	2.45	0.91-6.57
DISABILITY (GNDS)	<0.001	1.07	1.04-1.10

[a] primary progressive as reference category.

7 DISCUSSION: THE EPIDEMIOLOGY OF PAIN IN MS

This chapter will discuss the key findings of the study in relation to its aims (Section 4.6) and discuss them in context with previous findings. The implications for the MS population, clinical services and future research in this field will be considered, throughout the chapter. The final section will consider the benefits of the study, including its original contribution to the literature and potential study limitations. Future recommendations will be outlined at the end of the chapter.

7.1 The prevalence of clinically significant pain in MS

This section will compare the prevalence of clinically significant pain with previous reports. It will consider the impact of different study designs, study samples and case definitions used in studies of MS-related pain, and how this affects the prevalence figures reported.

7.1.1 Impact of study design on the prevalence of clinically significant pain

In this, the first UK-based epidemiological study of pain in MS, the prevalence of clinically significant pain was higher than previously estimated. Almost three-quarters of the sample (71.7%) currently experienced clinically significant pain, which is greater than reported by the majority of previous non-population-based studies, reporting prevalence figures from 29%-67% (Archibald *et al*, 1994; Beiske *et al*, 2004; Clifford and Trotter 1984; Douglas *et al*, 2008b; Ehde *et al*, 2003; Goodin 1999; Grasso *et al*, 2008; Hadjimichael *et al*, 2007; Indaco *et al*, 1994; Kalia and O'Connor 2005; Khan and Pallant 2007; Martinelli-Boneschi *et al*, 2008; Moulin *et al*, 1988; Solaro *et al*, 2004; Stenager *et al*, 1991; Svendsen *et al*, 2005; Vermote *et al*, 1986). A similarly high figure was reported in the only other population-based study of pain in MS, which reported a prevalence of pain of 79%, in a geographically defined, Danish cohort, with similar demographic and disease specific characteristics to the current sample (Svendsen *et al*, 2003), which is representative of a typical UK MS population (McCrone *et al*, 2008; Murray *et al*, 2004). In a recent systematic review it was stated that epidemiological studies are required to provide accurate estimates of the prevalence of pain in MS (O'Connor *et al*, 2008). The epidemiological approach of these two studies in including geographically-defined, population-based samples, representative of the wider MS population, have provided a more reliable estimate of the high prevalence of clinically significant pain in this

population. The current study was an improvement upon the Danish epidemiological study, in clearly defining significant pain, with more restrictive case definition, and as such provides a slightly lower prevalence than the Danish study.

The prevalence of pain of 71% in the current study is also similar to two large non-population based studies of MS-related pain, recruited from MS Society membership databases: A figure of 71% was reported in a study of 297 Canadian MS patients (Piwko *et al,* 2007), and a figure of 74% reported in a study of 9115 North American MS patients. Although not a comprehensive population-based cohort, both studies displayed similar demographics to both the current and Danish population-based studies, which may explain the similarity of prevalence figures. Prevalence figures and sample demographics have been outlined previously in chapters 3 and 4.

On further investigation, it appears that studies reporting higher prevalence figures for MS-related pain of over 60% generally originate from more representative samples (Beiske *et al,* 2004; Douglas *et al,* 2008b; Kalia and O'Connor 2005; Khan and Pallant 2007), unlike those who report lower pain prevalence figures of under 60% (Archibal et al, 1994; Clifford and Trotter, 1984; Ehde *et al,* 2003; Martinelli-Boneschi *et al,* 2008; Moulin *et al,* 1988; Seixas, 2011; Solaro *et al,* 2004; Vermote *et al.* 1986). For example, a figure of 39.8% was reported by a subgroup of patients all on disease modifying therapy, (Martinelli-Boneschi *et al,* 2008) with low disability levels and the majority presenting with RRMS.

Other possible explanations for the lower prevalence rates of previous studies are discussed in the next section.

7.1.2 Impact of case definition on prevalence of clinically significant pain

This section considers how case definition has impacted on estimates of clinically significant pain in MS. It then considers future methods of pain case-definition in MS.

The lower prevalence of clinically significant pain reported in previous studies may be a result of more restrictive case definition. The current study, using a broad patient-focused perspective of clinically significant pain, identified cases of "*ongoing bothersome pain"*, within the last month, using a section of the BPI, modified to meet the needs of the current study population (Ehde *et al,* 2003). Conversely, previous studies have defined clinically

significant pain in MS as pain of a specific intensity (Grasso *et al,* 2008), or pain that is unresponsive to analgesia (Clifford and Trotter 1984; Indaco *et al,* 1994; Moulin *et al,* 1988). These methods have been discussed in the literature review (Chapter 4) as unreliable and may have contributed to the underestimation of the prevalence of clinically significant pain in previous research. Also, several studies defined clinically significant pain as any acute or chronic pain presentation, associated with MS-related pain, reporting prevalence figures from 54-67.1% (Beiske *et al,* 2004; Clifford and Trotter 1984; Douglas *et al,* 2008b; Grasso *et al,* 2008; Indaco *et al,* 1994; Khan and Pallant 2007; Martinelli-Boneschi *et al,* 2008; Moulin *et al,* 1988; Solaro *et al,* 2004; Stenager *et al,* 1991; Vermote *et al,* 1986). To ensure pain was MS-related, exclusions in these studies included minor ailments and injuries, headache, visceral pain, and somatic pain, other than back pain. With the exception of the former, each of these presentations could be attributed to MS, and thus were not excluded in the current study. For example, without a detailed history and clinical assessment one cannot confirm the true aetiology of headache, which could be disease-related, i.e. from demyelination, or as a side-effect of DMT, or even cervicogenic in nature, and thus not related to the disease. The arbitrary exclusion of conditions which may lead to substantial pain in the MS population may have contributed to the lower figures reported for clinically significant pain in these studies.

By contrast, the definition of clinically significant pain used in the current study was broad allowing the patient to interpret whether they experienced '*ongoing bothersome pain'*. This was important as the determinants of clinically significant pain have not been standardised in the MS population or the wider general population. In the general population, the CPG questionnaire has been frequently used to determine the presence of clinically significant pain, which measures pain in three dimensions to determine clinical significance: pain *persistence*, *intensity* and pain-related *disability*. The CPG has not been validated for use in MS, nor in a chronic neurological condition, and would not have been a suitable tool to define clinically significant pain in this population (Section 4.3.1.1). However, categorising pain by levels of severity, and disability is important from a clinical perspective (the current study further categorised pain by severity, after the case ascertainment stage, the results of which are discussed later in Section 7.2.2). Future studies should explore this topic in MS: popular generic measures of clinically significant pain, used frequently in epidemiological studies, such as the CPG or Level of Expressed Need (LEN) questionnaires (Section 4.3.1.1) could be validated in MS, and compared with more subjective definitions, such as that used in the current study of '*ongoing bothersome*

*pain', w*hich is also used frequently in the clinical setting. This would also allow comparison of the severity of pain in the MS population with other patient groups. Qualitative research on the determinants of clinically significant pain from the MS patient's perspective as a starting point would shape this process.

7.1.3 Clinically significant pain in MS and its implications

The high prevalence of clinically significant pain reported in the present study is not surprising. As mentioned in Chapter 1, there are many sources of nociceptive pain for the MS patient; visceral pain, postural-related back pain, pain from chronic spasticity and joint contractures, painful tonic spasms and pain from MS treatments, such as Interferon therapy. It was not possible to measure all potential nociceptive sources of clinically significant pain for the MS patient, but each of the aforementioned may have contributed to the high prevalence of pain reported. Painful tonic spasms and visceral pain affected a high proportion of the sample at almost a half (44.5%) and a fifth (18.5%) respectively. Other common somatic pain syndromes in MS include postural related back pain and spasticity, which have been reported in previous studies as affecting 38% (Martinelli-Boneschi *et al,* 2008) and 40-60% (Beard et al, 2003) of the MS population respectively. The high prevalence of neuropathic pain reported in the present sample of approximately one third (32.8%), and high prevalence of neuropathic pain presentations such as dysaesthetic pain (56.2%) may also correlate with the high figure of clinically significant pain reported in the current study. The results of neuropathic pain are discussed further in Section 7.3 of this chapter.

The possibility of concomitant episodes of these pain conditions is also a possibility in MS (Maloni *et al,* 2000). The current study showed that over half of the present MS sample experienced pain in at least 3 separate body areas, whilst over a quarter of the sample experienced pain in at least 4 separate body areas, which is similar to a previous study of pain in MS (Douglas *et al,* 2008a). Multiple pain sites have a greater impact on the individual than a single pain site and are associated with reduced physical functioning, feelings of anxiety and depression, and sleeping problems (Kamaleri *et al*, 2008; van der Windt *et al*, 2008). Conversely, experiencing pain in a single site had little impact on physical fitness, emotions, or daily and social activities; functional consequences largely depended on how wide-spread the pain was. Although the relationship between the number of pain sites and impact of pain was not the focus of this study, the high frequency of

widespread pain in the current MS sample has the potential to have a notable impact on the individual with MS.

The study also explored the patient's view of the source of their pain. Although not a validated method for determining the aetiology of pain, results were interesting: over two-thirds (67.8%) of the sample felt that their pain was, in some way, related to the secondary changes of MS, such as spasticity, joint deformities, gait-related and postural disturbances. As many of these musculoskeletal changes can be avoided or minimised with appropriate intervention, the need for timely screening and management of musculoskeletal pain is highlighted by the findings of the study.

7.1.4 Conclusion

The current study confirms the high prevalence of clinically significant pain in MS, experienced by almost three quarters of the sample, which has implications for the individual and MS services. Clinically significant pain was defined using a broad, patient-focused definition. By contrast the next section considers the prevalence of chronic pain, as defined by the IASP.

7.2 The prevalence of chronic pain in MS

This section discusses the prevalence of chronic pain in MS, comparing it to previous studies in both the MS and wider chronic pain literature. The section then interprets the impact of chronic pain, and service implications, as well as its natural history in MS. The last part of this section discusses the impact of severe chronic pain in MS.

7.2.1 Prevalence of chronic pain

This is the first population-based study to measure the prevalence of chronic pain in MS, in accordance with the IASP recommendation for the definition of chronic pain of at least six-month duration (Merskey and Bogduk, 1994). The prevalence of chronic pain was 59.2%, which is much higher than the figure of 39.9% reported by the only other study of chronic pain, of at least six-month duration, in MS (Martinelli-Boneschi *et al*, 2008). The latter

study was, however, as mentioned, an unrepresentative sample of patients on disease-modifying therapy, (Section 3.1.2.2), explaining the lower prevalence figure reported.

Adopting a time bound definition of pain, as outlined by the IASP, means that findings are comparable with the wider literature, as discussed in the next section.

7.2.1.1 Prevalence of chronic pain in the wider population

Previous estimates of chronic pain in the general population vary from 7% (Bowsher *et al*, 1991) to 46.5% (Smith *et al*, 2001a), as a result of different pain definitions and methodologies, with disparate sample populations. The latter figure was based on a study of chronic pain (>3 months duration) in the general population of the Grampian region of Scotland (n=4611), and is the highest figure by far-to date. Whether Scotland has a particularly high prevalence of chronic pain, is outwith the scope of this thesis. By contrast, in the largest study of chronic pain undertaken to-date in the general population, involving 15 European countries, 19% of 46,394 respondents had suffered pain for ⩾6 months (Breivik *et al.* 2006), which is much less than the figure of 59.2% experiencing chronic pain in the current MS sample. The extent of the burden faced by the MS population and service providers can be appreciated.

However, although chronic pain was defined similarly between this European epidemiological study (Breivik *et al*, 2006) and the current study, the comparison of prevalence rates amongst different studies will always be limited by the differences in methodological design. To combat this, one study of pain in MS has used a reference group of age and sex-matched controls, which was from the general Danish population. This study reported no difference in the prevalence of pain between those with MS and those without (Svendsen *et al,* 2003). However, as previously mentioned, pain was not defined in this study, thus the susceptibility of the MS population to chronic pain over that of the general population remains unclear.

The current prevalence figure for chronic pain of 59% falls towards the centre of a spectrum of prevalence figures for other disorders of the central nervous system: The prevalence of chronic pain in MS is greater than that of stroke, with a prevalence of between 32% (Jönsson *et al*, 2006) and 42% (Kong *et al*, 2004) previously reported. The prevalence of chronic pain in MS is a similar level to traumatic brain injury, with a prevalence of 57.8% (Nampiaparampil, 2008), and is less than the prevalence reported in

both spinal cord injury and Parkinson disease, with figures of 63% (Dijkers *et al*, 2009) and 83% (Beiske *et al*, 2009) respectively. This spectrum of prevalence figures may reflect methodological differences between studies, but may also be related to the aetiology, and clinical presentation of each condition. In the investigation of why some disorders of the CNS lead to a higher prevalence of chronic pain than others, future studies should also explore other factors such as the psychological, and disability status of the sample, which can also impact on the reporting of chronic pain. It would also be interesting to compare pain management in these groups, to see if this impacts upon the burden of pain in these populations.

7.2.1.2 Future definitions of chronic pain in MS

It is interesting that the prevalence of chronic pain (*pain of at least six months duration*) in the study was 59.2%, in contrast to the other study finding for the prevalence of clinically significant pain, of 71.7%, (where cases were defined only as *ongoing, bothersome).* Thus, in the present study, when cases of ongoing bothersome pain were further categorised into those of at least 6 months duration, 12.5% of the sample were lost from this figure. One could therefore argue that the measure of clinically significant pain was more sensitive to MS-related pain than the IASP, time-bound definition. The relapsing-remitting nature of MS means that clinically meaningful episodes of pain may not be captured by the traditional time–bound definition of pain (Section 4.3.1.3). The debate on whether generic or disease-specific pain definitions are more appropriate is ongoing: the benefits of the former are that of comparable results with the wider population, as per the previous section (Croft *et al*, 2011). However, a broader measure may be more sensitive in capturing the true burden of pain in specific populations. The inclusion of both methods, as with the current study is undoubtedly informative, and should be encouraged in future studies of pain in specific populations.

7.2.1.3 Impact of chronic pain and service implications

In the general population, chronic pain has been associated with adverse physical, psychological, social and economic well-being, and those with chronic pain use health care services up to five-times more frequently than the rest of the population, and have higher absence from employment (Elliott *et al*, 1999). Piwko *et al*, (2007) estimated that the six-month burden of pain cost Canadian MS services almost $80 million. Furthermore, 85% of participants with pain had consulted a health care provider in the last month. For the six-

month study period, participants reported an average of 2.3 visits for pain. The individual, societal, and resource implications of chronic pain therefore make it a public health problem (Croft *et al*, 2011), where early screening and primary care based intervention has been recommended to prevent its impact on HR-QOL (Smith *et al*, 2001a). Considering the high prevalence of pain reported in the current study, this would be advisable for the MS population.

7.2.1.4 Natural history of chronic pain in MS

In the current sample, the median duration of chronic pain was 5 years, with an IQR of 2-10 years, indicating that ongoing pain throughout the disease course is common. This is of similar duration to chronic pain in other studies of MS-related pain, reporting mean pain duration of between 6-9 years (Douglas *et al*, 2008a; Ehde *et al*, 2003; Khan and Pallant, 2007). However, the natural history of chronic pain in MS cannot be adequately explored retrospectively by a prevalence study design. One small-scale longitudinal study of MS-related pain has been undertaken to-date in a sample of 49 MS patients (Stenager *et al*, 1995). In this study the prevalence of chronic pain syndromes increased by 41% over a period of 5 years, with no actual recovery rate, which has implications for long term management by health services. However, in this study chronic pain was not defined using a standardised measure but as, "*constant or intermittent pain lasting more than one month",* and was limited to several pain presentations, including "*dysaesthesia, low back pain, spasms, tension and pain in the extremities"*, which does not cover all possible presentations of chronic pain in MS. The study was also a small unrepresentative sample of 49 hospitalised patients, which may give a biased view of the outcome of chronic pain in MS. However the pattern of chronic pain in the general population is persistent for the majority of people. In a 4-year longitudinal study of 3605 responders from the Scottish general population, the annual incidence of new-onset chronic pain was at a rate of 8.3%, with an annual recovery rate of 5.4%. This means that chronic pain persisted in most people, with 78.5% of individuals at baseline still reporting chronic pain after 4 years (Elliott *et al*, 2002).

Of course, MS-related pain has a neurological aetiology, a chronic, degenerative condition, generally characterised by increasing levels of disability. The ongoing effect on the musculoskeletal system, such as spasticity, changes in posture, and gait disturbances, are therefore a potential source of prolonged or repetitive noxious stimulation that could lead to chronic pain (Elliot and Smith, 2009). Furthermore, ongoing disease activity in the CNS,

in relation to demyelination also has implications for the development of neuropathic pain, throughout the disease course. Larger scale longitudinal studies are required in the MS population to confirm the natural history of chronic pain.

7.2.2 Prevalence and impact of severe chronic pain

This section discusses the prevalence and impact of severe pain in MS, comparing it with other clinical populations.

7.2.2.1 Comparison of results with previous studies of pain in MS

It is concerning that almost half (43.6%) of those with chronic pain in the current sample describe it as of severe intensity (≥7NRS), which is similar to the figure of 49% reported in another epidemiological study of pain in MS in over ten thousand participants (Hadjimichael *et al,* 2007). Severe pain has been less commonly reported in smaller, unrepresentative samples with approximately only 25% of the sample reporting severe chronic pain (Douglas *et al,* 2008a; Ehde *et al,* 2003; Ehde *et al,* 2006). Previous risk factors for severe MS-related pain, include female gender and higher levels of disability (Douglas *et al,* 2008a; Hadjimichael *et al,* 2007), whereas being married (or in de facto relationship) and having a longer time since diagnosis were associated with lower pain intensity scores (Douglas *et al,* 2008a). Differences in sample characteristics and demographics may therefore have lead to previous underestimates of the prevalence of severe pain in MS.

Higher levels of anxiety and depression have also been associated with increased severity of pain in MS (Hadjimichael *et al,* 2007; Kalia and O'Connor, 2005), but do not explain the current findings as the current sample reported low mean levels of anxiety and depression, as measured by the HADS. Pain beliefs, coping and catastrophizing have also been shown to impact on report of pain intensity in MS (Osborne *et al,* 2007). These factors were not measured in this study but may also have contributed to the high severity of pain reported in the current sample.

7.2.2.2 Impact of severe chronic pain in MS

More severe MS-related pain has been related to higher levels of pain-related interference in daily life, independent of disability (Hadjimichael *et al,* 2007). In this study severe pain

affected daily activities, recreational activities, work, mood, sleep and overall enjoyment of life as measured by the Pain Effects Scale. Furthermore, a previous study found that more severe chronic pain in MS had a greater impact on all dimensions of HR-QOL, as measured by the SF-36 (Kalia and O'Connor, 2005). Higher levels of help-seeking behaviour for pain (i.e. the seeking of pain relieving-treatments and use of analgesia) have also been associated with more severe chronic pain, leading to high utilisation of health services in this group, which has resource implications (Smith *et al*, 2001b). Of greater concern is the recent report that severe chronic pain is associated with increased mortality (Torrance *et al*, 2010). Thus severe pain is common in the MS population and has implications for health services, the individual and their work, social and family life. A recent study has indicated that a reduction in pain severity is associated with improvements in pain related interference on sleep, daily functional activities and mood (i.e. anxiety and depression) (van Seventer *et al*, 2011). Thus there is a need to reduce the severity of pain for the MS patient if these negative impacts on functional life are to be avoided.

7.2.3 Conclusion

The high prevalence of clinically significant and chronic pain in MS has been confirmed in this study. Both figures are higher than the majority of previous estimates. As the first UK-based epidemiological study of pain in MS, results are similar to that of the other (Danish) population-based study, and to several other international studies of pain in MS. The study also confirmed the high proportion of the sample with severe chronic pain in this group.

The prevalence of neuropathic pain, specifically, will be discussed in the next section.

7.3 The prevalence of neuropathic pain in MS

This section discusses the prevalence of neuropathic pain, as measured by the PD-Q and its implications.

7.3.1 The prevalence of neuropathic pain

As the first epidemiological study to use a validated assessment tool to measure the prevalence of neuropathic pain in MS using the PainDETECT questionnaire (PD-Q), results demonstrated that 32.7% of the sample currently experienced central neuropathic pain. This is over four times greater than the 8.2% reported for the general population, in a similar geographical area (Torrance *et al,* 2006). The current figure is similar to that of 32.6%, previously reported in a Swedish study of neuropathic pain in MS (including TN) (Osterberg *et al*, 2005). Here, back pain, optic neuritis and migraine were excluded, but not in the present study, as these conditions may be (at least partly) associated with damage to the central nervous system. However only 0.8% of the sample (n=3) were thus excluded, which may not have had a significant impact on study findings. Osterberg *et al*, (2005) diagnosed neuropathic pain using the gold-standard somatosensory assessment, as previously discussed in Chapter 3, and was not a population-based study, but a convenience sample of MS patients, attending routine outpatient appointments. Despite the trade-off between the use of the gold-standard clinical diagnosis of neuropathic pain and a non-epidemiological study design, the two estimates of neuropathic pain discussed here are highly consistent, which confirms the high prevalence of neuropathic pain in MS.

In the present study, a further 14.7% of participants were classified as having 'possible' neuropathic pain, as scored by the PD-Q, indicating an even greater potential prevalence of up to 47.7%. This idea of neuropathic pain being on a spectrum, rather than a binary phenomenon is a relatively new ideology and is currently accepted clinically and in epidemiological studies (Torrance *et al,* 2006), where it is useful in highlighting the high potential burden of neuropathic pain for clinical services. The IASP has proposed a new grading system for neuropathic pain allowing 'Possible', 'Probable', and 'Definite' cases, where the latter two require clinical assessment and the former may be based on symptoms alone (Treede *et al,* 2008). This system is more relevant clinically as it allows treatment to proceed pragmatically on the basis of probability. This is useful in the non-specialist clinical care setting; the possibility of neuropathic pain can be highlighted, and subsequently confirmed by more specialist assessment. It is also helpful in epidemiological

research supporting a case definition which is not reliant on intensive clinical assessment. However, these categories are empirical and the suggested criteria for each have yet to be validated. The dichotomous clinical diagnosis of neuropathic pain in the other previous study of central pain in MS (Osterberg *et al*, 2005) would not have the advantage of highlighting a group *potentially* suffering from neuropathic pain.

Lately, literature has highlighted the burden that is "refractory neuropathic pain", significant, long-term neuropathic pain, which does not respond to treatment (Torrance *et al*, 2013). It has been described by the Scottish Medicines Consortium as patients who "have not achieved adequate pain relief from or have not tolerated conventional first and second line treatment for neuropathic pain" (Scottish Medicines Consortium, 2009). The importance of detecting these cases is important as they are the most difficult to treat, use health services more frequently and require informed direct treatment for neuropathic pain (Smith *et al*, 2012). In the current study, for those with chronic neuropathic pain, over half (53.7%) presented with pain that was severe in intensity (NRS of 7-10). Although one cannot define these cases as 'refractory' as their pharmacoresistance was not ascertained, this is a significant problem for the MS population. This is of particular significance when one considers the higher prevalence of neuropathic pain in MS in comparison to that of the general population (as discussed in Section 7.3.1). Future studies could confirm the prevalence of the MS population with refractory neuropathic pain, useful for service providers.

7.3.2 Methodological issues in the screening of neuropathic pain

The use of a validated tool to measure neuropathic pain in MS had not previously been undertaken and was critical in the current study to meet with the recommendations of the IASP on the use of an appropriate screening tool for neuropathic pain (Haanpää *et al*, 2011). The use of a standardised neuropathic pain screening tool would also have the advantage of allowing results to be comparable with the wider literature. At the time of screening tool selection, the PD-Q had not been used, or validated in central neuropathic pain disorders; however more recently it has been validated and used extensively in fibromyalgia (Amris *et al*, 2010; Aparicio *et al*, 2011) which has been compared to a central neuropathic pain disorder, with features such as loss of descending analgesic activity and central sensitization (Lee *et al*, 2011). It has also been used recently in Parkinson's disease (Gierthmühlen *et al*, 2010) and validated for use in spinal cord injury (SCI) (Hallströâm and Norrbrink, 2011). As with MS, pain in SCI has been classified as

either nociceptive or neuropathic and has similarities with central pain in MS, with shared feature, such as dysaesthetic pain (Cruz-Almeida *et al*, 2009). Hallströam and Norrbrink, (2011) determined the usefulness of the four key screening tools for neuropathic pain in SCI, comparing the, DN4, PD-Q, LANSS and NPQ (reviewed in Chapter 4). The study concluded that diagnostic accuracy (overall proportion of correct classification of pain) was highest overall for the DN4, followed by the PD-Q, NPQ and LANSS, with figures of 88%, 78%, 65% and 55% respectively. For the present study, use of the DN4 was ruled out due to the inclusion of a sensory exam, by a trained clinician, which would not have be suitable in the current epidemiological study. The high diagnostic accuracy of the PD-Q of 78% in a central neuropathic pain presentation (SCI) over other screening tools is good, whilst it could be postulated that the inclusion of expert clinical assessment in the DN4 may have increased diagnostic accuracy over the PD-Q.

The present study revealed that dysaesthetic pain was currently the most common central neuropathic pain presentation in the sample (Table 6-4). The most common descriptors of dysaesthetic pain reported were that of *burning pain* and *paraesthesias*, (each reported by over 50% of those with dysaesthetic pain (Table 6-5) which were also the most common descriptors reported in the another key study of neuropathic pain in MS (Osterberg *et al*, 2005). The presence of both burning pain and paraesthesias are assessed in the PD-Q, and would have therefore captured these common qualities in the MS sample, highlighting its validity in measuring central neuropathic pain in MS.

However, several verbal descriptors are not included in the PD-Q and have been commonly associated with central pain in MS. *Aching* pain has been commonly associated with central pain in MS in several studies, (Boivie, 2006; Clifford and Trotter, 1984; Moulin *et al*, 1988; Vermote *et al*, 1986) including a clinical study of central pain in MS (Osterberg *et al*, 2005). However, the verbal descriptor '*aching*' is not strictly a neuropathic pain quality, and is generally associated with nociceptive pain in the wider literature (Jensen, 2006). In fact, in one study of pain in MS it was used (with the presence of other verbal descriptors) as a diagnostic of nociceptive pain (Khan and Pallant, 2007). Furthermore, the dysaesthetic sensation of '*tightness*', i.e. a tight-band like sensation, squeezing or cramping sensations (without actual muscle spasm), also does not feature in the PD-Q, but has been associated with central pain in MS in reference literature (Boivie, 2006; Canavero and Bonicalzi, 2011; Maloni *et al*, 2000) albeit the frequency has been reported less commonly in another key study of central pain in MS (Osterberg *et al*, 2005).

The implication of the absence of these central pain qualities from the P-DQ is unclear and deserves further exploration in future research, where the PD-Q could be validated in MS against the gold-standard clinical assessment.

7.3.3 Conclusions

Using the PD-Q screening tool, neuropathic pain appears to affect approximately one-third of the MS population, confirming the findings of a previous non-epidemiological study (Osterberg *et al*, 2005). A group who scored as 'possibly' having neuropathic pain may increase this figure to a potential 47.4% (section 6.3.3). The high prevalence and severity of neuropathic pain presents a challenge for MS services.

The recent diagnostic accuracy of the PD-Q of 78% in a central neuropathic pain disorder (SCI), without the use of clinical assessment, is high and consolidates the findings of our study, however future research should validate the PD-Q for use specifically in the MS population. Diagnostic accuracy is important because the treatment of nociceptive and neuropathic treatment differs. The PD-Q can therefore facilitate pain classification in the MS population, which would be valuable clinically, particularly in non-specialist pain services, in health service planning and in research. Whilst the PD-Q is useful in highlighting the potential presence of neuropathic pain, it should NOT replace the gold-standard clinical assessment, using bedside assessment of the somatosensory system and clinical judgement (Haanpää *et al*, 2011).

7.4 Comparison of neuropathic and non-neuropathic pain

This section will focus on chronic pain, and compares characteristics in those with non-neuropathic and neuropathic pain presentations in this group. It will discuss the differences between neuropathic pain and non-neuropathic pain for pain severity, which includes both the sensory and affective components of pain, subsequent use and relief from prescribed pain-relieving medication (PPRM) and effect, as well as the impact of pain on sleep disturbance. It will then interpret differences in HR-QOL scores between the two groups and consider the implications of this.

7.4.1 Summary of key differences between neuropathic and non-neuropathic pain

Those with neuropathic pain showed significantly lower HR-QOL scores than those in the non-neuropathic pain group *(p=0.007)* (Table 6-6). Those with neuropathic pain described a significantly more severe pain experience overall, with higher affective *(<0.001*) and sensory (*p<0.001*) mean scores on the SF-MPQ. The total mean SF-MPQ score for those with neuropathic pain was almost three times that of those with non-neuropathic pain (*p<0.001*). This highlights the individual behaviour and impact of the two pain types, as discussed previously in the literature review. As mentioned by O'Connor et al, (2008), in a proposed classification of pain in MS, there is therefore a need to assess and manage the two pain types individually, rather than characterising 'MS-related' pain as undertaken by the majority of previous literature of pain in MS. As such, this is the first epidemiological study to compare neuropathic and non-neuropathic pain in MS, allowing a better understanding of each of these conditions separately. Each of the differences will be discussed in the following sections.

7.4.2 Severity of pain

This section compares the intensity and affective component of neuropathic and non-neuropathic pain in MS, and also discusses the use and relief from prescribed, pain-relieving medication (PPRM).

7.4.2.1 Pain intensity

Significantly higher pain intensity was found in those with neuropathic pain, with a mean difference of 1.7 points on the NRS-11 of pain intensity (of 0-10, with 10 being the most intense pain imaginable) (Table 6-7). This is consolidated by the sensory component scores of the SF-MPQ which show a difference of 6.0 points between those with neuropathic and non-neuropathic pain, with neuropathic pain being significantly more intense. This is similar to two previous studies of pain in MS, which also noted that neuropathic pain was of greater intensity, in small non-population based studies. In these studies a difference of 11.9 mm (Kalia and O'Connor, 2005) and 15 mm (Svendsen *et al*, 2005) were noted between those with neuropathic and non-neuropathic pain, using a visual analogue scale (VAS) of pain intensity of 0-100. Although different measurement tools, the VAS and NRS-11 of pain intensity have been shown as highly correlated in the measurement of pain intensity (Farrar, 2006), thus comparisons can be made with these preliminary studies.

Previous findings that neuropathic pain is more severe in MS, is thus confirmed by the current study with an epidemiological study design. It is also similar to two further studies of chronic pain in the general population who demonstrated that chronic pain with neuropathic characteristics is more severe than chronic pain with non-neuropathic characteristics, using the NRS-11 scale of pain intensity (Bouhassira *et al*, 2008; Torrance *et al*, 2006). These results fit with the wider view that neuropathic pain is of greater intensity than non-neuropathic pain (Grond *et al*, 1999) which had not been confirmed specifically in MS.

The level of pain relief in the present study may also explain the higher intensity of neuropathic pain. Over half of those with neuropathic pain in the current study described it as severe (≤7NRS), despite almost three-quarters of this group currently using prescribed, pain-relieving medication (PPRM) (Table 6-6). By contrast, only a quarter of those with non-neuropathic pain in the sample described it as severe. Those with neuropathic pain experienced less pain relief from PPRM than those with non-neuropathic pain, which has been found previously in the general population (Torrance *et al*, 2006). It is accepted that neuropathic pain is a challenge to manage. Previous research has found that a diagnosis of neuropathic pain was significantly associated with a judgment by clinicians of poor pain outcome (Mercadante *et al*, 2000).

The use of PPRM and subsequent relief in those with neuropathic compared to non-neuropathic pain has not previously been measured in MS. However, 59.6% of the total sample with chronic pain were using PPRM, which is similar to the other Danish population-based study of MS-related pain, who reported that 60.9% of participants were currently using PPRM. This finding is also similar to several other large-scale studies, reporting between 54-62% of MS patients were currently using PPRM (Goodin 1999; Hadjimichael *et al*, 2007; Piwko *et al*, 2007). One could therefore hypothesise similar findings for relief from PPRM in these studies.

Sleep disturbance in the present study may provide a further explanation for the higher intensity of neuropathic pain reported. It has been shown that duration of sleep contributes to next-day pain reporting of pain frequency and intensity in the general population (Edwards *et al*, 2008). In the current study those with neuropathic pain showed significantly more disturbed sleep than those with non-neuropathic pain ($p<0.001$) (Table 6-6). Almost 60% of those with neuropathic pain were disturbed at least *frequently* during the night, in contrast to those with non-neuropathic pain, where only 27.8% were disturbed

frequently during the night with pain. It could be postulated that sleep disturbance may have therefore contributed to the higher intensity of neuropathic versus non-neuropathic pain.

7.4.2.2 Affective component of pain

As the first study to consider the affective component of pain in MS, the study revealed that those with neuropathic pain were significantly more emotionally affected by their pain; with a mean affective SF-MPQ score three times higher than that of non-neuropathic pain. Comparison with previous MS pain literature is limited in this respect: a previous study has compared the two pain types in MS for pain severity, but used total scores only, from the McGill Pain Questionnaire (MPQ) (combining the sensory and affective components) (Svendsen *et al,* 2005), whilst other MS studies have also measured overall pain severity for the total sample, using the SF-MPQ (Seixas *et al,* 2011) and MPQ (Douglas *et al,* 2008a) respectively. Data, specifically on the affective score of the SF-MPQ, from population-based studies of other neuropathic pain conditions could not be found. However, several studies of other neuropathic pain conditions document total severity scores on the SF-MPQ, as discussed in the next section.

Explanations for the greater affective burden of neuropathic pain than nociceptive pain can only be postulated at this stage. One study revealed that those with a neuropathic pain condition were more likely to refer to their pain as a result of "damage" than those with non-neuropathic pain (Daniel *et al,* 2008), which may contribute to the psychological impact of pain. Furthermore, those with neuropathic pain were more likely to cite touch, air movement and stress as pain aggravators than those with non neuropathic pain (Torrance *et al,* 2013). The authors describe that the paroxysmal nature of neuropathic pain is a challenge. Pain grasps the attention and takes over cognitive processes. Is it therefore, the unpredictability that gives neuropathic pain more emotional unpleasantness? (Attal *et al,* 2011) postulates that it is the peculiar symptoms of neuropathic pain that can be distressing. For example in SCI, the sensations *burning, aching* and *sharp* were the most distressing verbal descriptors of neuropathic pain experienced (Felix *et al,* 2007). Similarly, the present study has shown that sensations such as *burning*, unpleasant paraesthesias (i.e. *crawling, tingling*) and *sharp* pain were highly common in the current sample (Table 6-5). There are many potential explanations for the greater affective component of neuropathic pain, which could be quantified in future studies.

7.4.2.3 Overall pain severity: total SF-MPQ score

The total SF-MPQ score (of 15.0) for the neuropathic pain group in the present sample is comparable with that of other central chronic neuropathic pain conditions, including post-stroke pain (Kim *et al*, 2011; Klit *et al*, 2009) and SCI (Capel *et al*, 2003; Siddall *et al*, 2006) with SF-MPQ scores of 13-17 points. Interestingly, peripheral neuropathic pain conditions including post herpetic neuralgia (Kochar *et al*, 2005), peripheral diabetic neuropathy (Backonja *et al*, 1998; Rosenstock *et al*, 2004), low back pain with nerve root compression (Dashfield *et al*, 2005; Schiff and Eisenberg, 2003), and complex regional pain syndrome (Bruehl *et al*, 2003) appear to display higher overall pain intensities than the current MS sample, with SF-MPQ scores of ≤20. Future research could explore potential mechanisms behind the higher severity of peripheral neuropathic pain conditions.

Interestingly, in the current study, the total SF-MPQ score of the non-neuropathic group (of 6.0) is less than many other non-neuropathic chronic pain conditions, including osteoarthritis (Stelian *et al*, 1992), rheumatoid arthritis (Burckhardt *et al*, 1992), musculoskeletal pain (Crofford *et al*, 2005; Harris *et al*, 2006), and low back pain (Beattie *et al*, 2004), with SF-MPQ scores from 10-20 points. A previous study has demonstrated high acceptance of pain as a permanent consequence of disability in MS patients, one that becomes an enduring part of life (Douglas *et al*, 2008b). Attitudes to pain were not measured in the current study but may offer one possible explanation for this pattern as well as adequate pain relief in this group, which has already been mentioned as another possibility.

7.4.2.4 Conclusion: severity of neuropathic versus non-neuropathic pain

Those with neuropathic pain had more intense and emotionally unpleasant pain than those with non-neuropathic pain in the MS sample, with use of PPRM being less effective for pain relief in this group. As higher levels of affective pain have previously been associated with poorer emotional health (Lerman *et al*, 2011) and more intense pain is associated with poorer HR-QOL, the need for effective pain management is highlighted for this group.

The next section discusses the specific relationship between neuropathic pain and HR-QOL.

7.4.3 Health-Related Quality of Life

For the total sample, there was a statistically significant relationship between the presence of neuropathic pain and lower HR-QOL scores ($p<0.001$) (Table 6-7). This is a significant finding considering the high prevalence of neuropathic pain reported in the sample. This highlights the need for timely screening and management of neuropathic pain in MS in the primary care setting to minimise its impact on the patient. Furthermore, in the chronic pain group, those with a neuropathic pain presentation also had significantly lower HR-QOL scores than those with non-neuropathic pain (Table 6-7). Although the current study did not specifically explore a relationship between severity of pain and HR-QOL, a relationship between pain characteristics and HR-QOL has been previously reported, with more intense (Doth *et al*, 2010; Kalia and OConnor, 2005), and emotionally draining pain (De Andrade *et al*, 2010) being associated with lower HR-QOL scores. In other neurological disorders, including painful diabetic neuropathy (PDN) (Gore *et al*, 2005) postherpetic neuralgia (PHN) (van Seventer *et al*, 2006) and non-MS related Trigeminal neuralgia (TN) (Tölle *et al*, 2006) higher severity of pain had an inverse effect on HR-QOL score. However, it has been argued that the lower levels of HR-QOL seen in patients with neuropathic pain may not be explained by the actual characteristics of neuropathic pain itself, but are instead a reflection of other co-morbidities that exist alongside neuropathic pain (Doth *et al*, 2010). Emotional health is one possibility; with Lerman *et al*, (2011) reporting that pain perception is crucial in determining the emotional impact on the individual, with patients with more severe affective pain levels, having poorer emotional health. Conversely, poor existing emotional health can impact on the overall perception of pain, and interestingly in the present study anxiety level was significantly higher in those with neuropathic pain, as opposed to non-neuropathic pain (*$P<0.001$)* (Table 6-8). (Motl *et al*, 2009) further confirm the complexity of the relationship by suggesting pain, fatigue and depression as a symptom cluster that correlates with reduced QOL in persons with MS. Fatigue was not measured in the present study but may have the potential to confound the relationship between neuropathic pain and HR-QOL reported in the current study.

The clinical presentation of neuropathic pain in MS may also explain its high impact on HR-QOL: The EQ-5D converts scores into a utility value, where 0 indicates death and 1 indicates 'perfect health'. In the current sample, those with **chronic** neuropathic pain showed a mean HR-QOL score of 0.52 (Table 6-6), whilst in those with combined **acute and chronic** presentations of neuropathic pain, the HR-QOL score is a much lower 0.37

(Table 6-8). Thus, it could be postulated that it is the presence of the **acute** neuropathic pain presentations, including severe paroxysmal pain syndromes, such as trigeminal neuralgia, optic neuritis, paroxysmal extremity pain, and Lhermitte's phenomenon, which have the greater impact on HR-QOL, as opposed to the chronic dysaesthetic pain seen in MS. This would have to be further explored in future research with direct comparison of those with acute versus chronic neuropathic pain.

The utility value of the EQ-5D also allows comparison of health states across different medical conditions. The mean HR-QOL utility value of 0.52 for those with chronic neuropathic pain in the sample is lower than in peripheral neuropathic pain conditions, including PDN (Gore *et al*, 2005), PHN (van Seventer *et al*, 2006), and non-MS related TN (Tolle *et al*, 2006), with average utility values of between 0.60 to 0.75, as measured using the EQ-5D. HR-QOL scores in the current group with neuropathic pain are, however, higher than that reported in other central neuropathic pain disorders, including stroke (Pickard *et al*, 2004) and SCI (Vranken *et al*, 2011) with low average EQ-5D utility values of 0.25 and 0.35 respectively. It is beyond the scope of this thesis to reason these differences in HR-QOL scores between other neuropathic pain conditions. There are many factors, which may impact on HR-QOL, and could be explored further in future research.

When exploring a potential relationship between neuropathic pain and HR-QOL, the current study utilised global HR-QOL scores, without factor analysis of the individual components of the HR-QOL measure (the EQ-5D), which would be useful in highlighting key areas of intervention. Conversely, other studies have found that pain in MS is specifically associated with two main aspects of HR-QOL: physical and emotional functioning (Kalia & OConnor 2005; Khan & Pallant 2007; Svendsen *et al.* 2005). Although not specific to neuropathic pain alone, each of these factors may have contributed to the relationship between neuropathic pain and HR-QOL reported in the present study. The relationship between pain, emotional health and HR-QOL has previously been discussed, but disability may also have been a confounding factor. Level of disability (as measured by the GNDS) was higher in those with neuropathic pain (Table 6-8) in the current study and provides a possible explanation for the relationship between neuropathic pain and HR-QOL reported. As the relationship between neuropathic pain and HR-QOL was explored at the bivariate level in the present study, the effect of potential confounders, such as disability and emotional health cannot be determined. One therefore cannot infer whether neuropathic pain directly impacts upon HR-QOL, or whether this is a

multi-factorial relationship. Future studies are thus indicated to explore the relationship between neuropathic pain and HR-QOL at the multivariate level in the MS population.

7.4.3.1 Methodological issues in the measurement of HR-QOL

The EQ-5D, which includes the domains of *mobility, self-care, usual activities and anxiety and depression,* was deemed the most appropriate for use in the current study. Due to the many other factors measured in the questionnaire, a succinct measure of HR-QOL, incorporating the key areas of pain-related impact in MS was required. From the literature review, pain in MS is strongly associated with two main aspects of HR-QOL: physical and emotional functioning (Jensen *et al*, 2007b), both of which are included in the EQ-5D, which also benefits from being the most user-friendly and succinct, generic measure of HR-QOL (McDowell, 2006). However, as a consequence, there are several other facets of HR-QOL not measured by the EQ5D, which may have biased the relationship found between HR-QOL and neuropathic pain in the present study. For example, pain has also been correlated with the HR-QOL components: general health, physical role, social functioning and vitality in the MS population, using the broader SF-36 measure (Svendsen *et al.* 2005). However, completion of the EQ-5D was a high 99% in the current study, which is likely due to its brevity and user-friendliness, unlike broader measures of HR-QOL, which can suffer from higher missing values rates (McDowell, 2006). The balance between increased participation and comprehensive assessment was a challenge in the present study, particularly in relation to the many aspects of health measured in the questionnaire, whereby HR-QOL was only one of a suite of measures.

7.4.3.2 Conclusion: the impact of neuropathic pain on HR-QOL

HR-QOL was measured using the EQ-5D a validated tool, advocated for use in neuropathic pain conditions. In the present study, those with neuropathic pain had significantly poorer HR-QOL scores than those without neuropathic pain, which was true for those who were pain-free and those who presented with non-neuropathic pain.

The study did not aim to identify the interplay of factors in this relationship, such as emotional health and disability level, as well as sensory and affective aspects of pain; and did not use multivariate analysis in this respect. Future research may consider the complexity of the relationship between neuropathic pain and HR-QOL in MS.

7.4.4 Conclusion: the burden of neuropathic pain

Those with neuropathic pain described a significantly more severe pain experience overall, with higher pain intensity and emotional impact than those with non-neuropathic pain. Those with neuropathic pain achieved less pain relief from PPRM, and showed greater sleep disturbance. Finally, the presence of neuropathic pain had a negative impact on HR-QOL.

It has been said that epidemiology shapes health care practice (Croft *et al*, 2011): the high prevalence of neuropathic pain (of a possible 47.7%) in the current MS population should therefore highlight the need for appropriate management of this condition. Health care providers should be alerted by the high prevalence and demanding nature of neuropathic pain in MS, particularly relevant in populations like Scotland, where the incidence of MS is high.

The management of neuropathic pain is a challenge: Further research is required to identify effective methods of neuropathic pain relief in the MS population, one of which (TENS) is considered in part two of this thesis

7.5 Predictors of neuropathic pain in MS

Both *type of MS* and *disability* level were illustrated as independent predictors of pain (Table 6-19). This section explores the rationale for this:

Neuropathic pain was found to be associated with higher disability level illustrating that the more advanced the disease, the greater odds of having neuropathic pain, with each unit increase on the GNDS scale increasing odds of having neuropathic pain by 7%. Similarly, Solaro *et al,* (2004) hypothesised that the relationship between neuropathic pain and disability level (when measured with the EDSS) could be associated with disease activity in the CNS. In the current study, type of MS was also confirmed as an independent predictor of neuropathic pain (*p=0.001*), which is again similar to Solaro *et al,* (2004) who found that dysaesthetic pain, Lhermitte's phenomenon, and trigeminal neuralgia (used as a measure of neuropathic pain) were less likely to be associated with a primary progressive disease course. In the current study, people with Secondary Progressive MS (SPMS) had five times the odds of experiencing neuropathic pain than those with Primary Progressive MS (PPMS). With disability level also established as an independent predictor of neuropathic pain, the other obvious difference between the two MS subtypes is the *pattern of disease course*:

A dual pathogenic model of MS has been proposed (Smith *et al*, 2006). This model proposes an early phase dominated by multifocal inflammation and relapses (Relapsing-Remitting MS (RRMS), and a later phase dominated by progressive neuroaxonal loss and degeneration with increasing disability (Progressive MS). Remissions occur because of the healing of damaged nerve tissue, which includes the remyelination of demyelinated lesions. However this process is often incomplete. When demyelinated axons successfully regain the ability to conduct, they contribute to the restoration of function, but conduction in such axons is unstable, sometimes resulting in a range of peculiar sensory symptoms. In some axons the alterations lead to hyperexcitability with these axons becoming spontaneously active, which is thought to explain the variety of positive symptoms, such as paroxysmal pain, paraesthesias and dysasthesias. Albeit, evidence for this does come from experimental pain studies.

The current study has highlighted those with Secondary Progressive MS (SPMS) as most likely to currently experience neuropathic pain, and those with primary progressive MS (PPMS) as least likely to experience neuropathic pain. Thus perhaps it is the dual

pathogenic model of MS which explains the presentation of neuropathic pain in this disease. The dual model may explain why neuropathic pain symptoms may appear/flare up during a relapse and continue throughout disease course, even when the initial inflammatory phase of the disease has settled down. However, as the study measured this phenomenon at a single point in time, the natural history of neuropathic pain with disease course (and disability) cannot be followed. Future longitudinal studies are indicated to follow the relationship between these factors over time to elucidate the mechanism involved.

Early detection and management of neuropathic pain is important if the patient is to avoid the consequences described in the previous sections, such as deterioration in HR-QOL. Clinicians could screen efficiently for neuropathic pain if they are aware of these potential risk factors, including increasing disability, and the Secondary Progressive subtype of MS.

7.6 Conclusion

This section concludes part one of this thesis. It begins with a review of the original contribution the research has made, and outlines potential methodological limitations. It then summarises the key study findings, outlining recommendations for clinical practice and future research.

7.6.1 Original Contribution of study

This was the first epidemiological study of pain in MS, using validated measures of pain. Both the IASP definition of chronic pain and a broader definition of clinically significant pain were used to capture the true burden of pain in MS. Unlike previous studies, neuropathic pain was measured using a validated screening tool. Although generic pain measures were used, disease-specific measures were also adopted, i.e. in capturing the MS-related pain syndromes. The study adhered to the IMMPACT recommendations when exploring the characteristics of pain to ensure a multi-dimensional assessment was undertaken. It was also the first epidemiological study of the prevalence, risk factors and presentation of neuropathic pain in MS. As such, this study has confirmed the high prevalence of both chronic and neuropathic pain in MS, highlighting the severity and impact, particularly of the latter. To standardise comparison, the study only compared

cases of *chronic* neuropathic and non-neuropathic pain, unlike previous research in this field. This was also the first study to identify neuropathic pain as a predictor of lower HR-QOL in MS, highlighting its burden in this population.

7.6.2 Study Limitations

A population-based study was attempted, using a comprehensive disease register, as opposed to a random sample of the population, which would ensure the broad range of patients in a health board area would be captured. In order to ensure sample representativeness, exclusions were kept to a minimum and participation by all groups was encouraged i.e. completion of the questionnaire by proxy, if required. However, due to the ethical requirements one cannot confirm if the sample was representative of the study population (Ayrshire MS population), as the researcher was not allowed to ascertain the demographics of non-responders. Fortunately, the sample demographics are representative of the UK MS population (as outlined in Section 4.1.3), and therefore comparable with other MS pain studies with high internal validity as mentioned in this section). One would therefore assume that the sample was representative of the study population.

The two-tiered system of receiving the questionnaire (participants initially returned a consent slip, allowing the questionnaire to be sent) meant two stages of participant response, affecting overall response rate, which was 59%. However response rate was a higher, 77.8% by the point of questionnaire return. Theoretically, response bias (i.e. only those with pain would be more likely to complete the questionnaire) could therefore be doubled in this process. Future studies should reinforce the point laboured by the research team to the ethics committee, that questionnaire completion is itself 'consent'. This would avoid the need for a two-tiered response process, which provides unnecessary administration, and is time consuming in an epidemiological study.

With less time constraints, it would have been useful to validate the PD-Q in the MS population, as this previously had not been done. However, at the time, the research team saw it as a valid and reliable tool to capture neuropathic pain in MS. Since then, it has been validated in other central neuropathic pain disorders, such as spinal cord injury, and Parkinson's disease.

7.6.3 Key messages from epidemiological study of pain in MS

- Pain is a common problem in MS: The prevalence of clinically significant pain, chronic pain (pain of at least six months duration), and neuropathic pain is higher than previously estimated in non-population based studies with unrepresentative samples. The prevalence of pain is higher than that experienced by the general population, which has implications for the MS population and service providers. The most common presentations of neuropathic pain in MS are dysaesthetic pain, followed by painful tonic spasms. The most common description of dysaesthesia was that of burning-type pain, and unpleasant paraesthesia-type pain (i.e. tingling crawling), and sharp pain.

- Severe and widespread pain is common in those with chronic pain, with a high use of prescribed, pain-relieving medication (PPRM) in this group. Pain experienced for many years, throughout disease course is common.

- Neuropathic pain is more intense and emotionally demanding than non-neuropathic pain, with a higher use of PPRM, but with less subsequent relief reported. Those with neuropathic pain also have more disturbed sleep and lower HR-QOL scores than those with non-neuropathic pain. Neuropathic pain was shown to significantly impact on HR-QOL.

- Predictors of neuropathic pain were type of MS and level of disability.

The study highlights the high burden of pain experienced by the MS population, which is useful for service providers, planning the provision of pain services in health boards. This is particularly relevant in populations like Scotland, where the incidence of MS is high.

These findings will also help clinicians better understand the prevalence, severity, nature and chronicity of pain experienced in MS. It highlights the severity of neuropathic pain and its impact on sleep and HR-QOL. Neuropathic pain is a challenge to treat, with the study demonstrating the need for management to prevent the deterioration in HR-QOL. The first stage of this process lies within the screening for neuropathic pain, which will now be facilitated by the risk factors identified in the study. Secondly future studies must continue

to trial methods of neuropathic pain management. Part two of this thesis, explores whether Transcutaneous Electrical Nerve Stimulation (TENS) could be used in the management of neuropathic pain.

7.6.4 Future Studies

Future studies are indicated to explore the following themes:

- The use of other, validated, generic measures of clinically significant pain in MS. The CPG or Level of Expressed Need (LEN) questionnaires (Section 4.3.1.1), used in epidemiological studies of pain in the general population could be validated in MS, and compared with more subjective definitions, such as that used in the current study of '*ongoing bothersome pain'*. This would also allow comparison of the severity of pain in the MS population with other patient groups

- Why do some disorders of the CNS lead to a higher prevalence of chronic pain than others? Future studies should also explore other factors such as the psychological, and disability status of the sample, which can also impact on the reporting of chronic pain. It would also be interesting to compare pain management and effect in these groups, to see if this impacts upon the burden of pain in these populations. It would also be useful to explore the prevalence of chronic pain in disorders where the neurological insult is static (unlike MS), such as adult cerebral palsy.

- What are the potential mechanisms behind the higher severity (SF-MPQ scores) of peripheral neuropathic pain conditions, such as peripheral diabetic neuropathy and complex regional pain syndrome when compared to CNS disorders, such as stroke and MS.

- What is the prevalence of 'refractory' neuropathic pain in MS?

- Explore the relationship between neuropathic pain and high affective component in the MS population. Test previous theories in relation to pain beliefs (i.e. neuropathic pain is a result of 'damage'), pattern and quality of neuropathic pain over nociceptive pain.

- To better compare pain in MS with the general population: Comparison of pain experience (i.e. intensity, affect, sleep, HR-QOL, use of /relief from PPRM), in a sample of MS patients, with age and sex-matched controls.

- Validation of the PD-Q in MS

- The relationship between neuropathic pain and HR-QOL at a multivariate level of analysis, including factors, such as anxiety and depression, functional status etc.

- Why acute neuropathic pain presentations impact more on HR-QOL than chronic neuropathic pain presentations in MS. The relationship between the *acute* (Lhermitte's, proximal extremity pain, trigeminal neuralgia, optic neuritis) and *chronic* presentations of neuropathic pain (dysaesthetic pain) in MS and HR-QOL should be compared.

- Longitudinal studies are required to explore the relationship between disease course, disability and neuropathic pain, as well as the natural history of pain in MS.

- Interventions to manage neuropathic pain in MS.

Part one of this thesis has shown that neuropathic pain is common in MS; it is severe, emotionally unpleasant and has a negative effect on sleep and HR-QOL. It is also a challenge to mange pharmacologically. Due to the many side-effects from pharmacological therapies, there is a move to alternative therapies in the treatment of neuropathic pain. Part two of this thesis (from Chapter 8) considers the effect of TENS on neuropathic pain in MS.

PART II: THE EFFECT OF TENS ON NEUROPATHIC PAIN IN MS

8 LITERATURE REVIEW: THE EFFICACY OF TENS ON CHRONIC NEUROPATHIC PAIN

This chapter begins by introducing the electrical characteristics and clinical application of TENS, followed by its theoretical role in pain modulation. Literature on the efficacy of TENS is briefly considered for experimental pain, followed by chronic and neuropathic pain, with emphasis on central neuropathic pain disorders. The next chapter (Chapter 9) will specifically review the optimum TENS parameters and application to elicit a hypoalgesic effect.

8.1 Introduction to TENS

This section introduces the electrical characteristics and clinical applications of TENS.

8.1.1 Electrical characteristics of TENS

Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological treatment for pain relief used commonly by health professionals. It involves the application of low voltage electrical currents across the intact surface of the skin, using electrodes (Sluka and Walsh, 2003). The electrical characteristics of TENS can be altered to influence pain relief using the components of frequency (Hz), intensity (mA), pulse duration (μs), and pattern of stimulation (burst, frequency modulated, random) (Chesterton *et al*, 2002). The common features of a TENS machine are summarised in Table 8-1.

Table 8-1: Characteristics of TENS

TENS characteristics	Description
Pulse waveform (fixed) *Symmetrical biphasic* *Asymmetrical biphasic*	Monophasic
Pulse Frequency (adjustable)	1-250 Hz
Intensity (adjustable)	0-50 mA
Pulse width (duration) (often fixed)	10-1000 ms
Pulse pattern	Continuous, burst (random frequency, modulated amplitude, modulated frequency, modulated pulse duration)
Channels	1 or 2

Adapted from (Johnson, 2001))

8.1.2 Clinical application of TENS

TENS intensity can be applied so that it is "*just perceptible,"* "*strong but comfortable*," (low intensity TENS (LI) or "*strong and uncomfortable but not painful"* (high intensity TENS (HI) (Bennett *et al*, 2011). Intensity is applied at sensory level, giving rise to a tingling sensation (stimulating A-beta nerve fibres) or a more intensely, pricking sensation (stimulating A-delta nerve fibres) and at motor level, inducing muscle contractions (Walsh, 1997). Frequency is categorised clinically as low (<10Hz) or high (>10Hz)], (Johnson, 2001). The stimulation site may be *local* (over painful area/segmental), *remote* (over the corresponding peripheral nerve, nerve trunk or nerve root/extrasegmental), or both local and remote (concurrent) to the pain site (Walsh, 1997).

Several authors have documented standards for appropriate TENS application: TENS must be delivered at an intensity, so that the patient reports a "strong" sensation (with or without a tetanic and visible muscle contraction), pulse duration 50ms to 200ms, in the frequency range 1 to 250Hz, using a continuous or modulated pattern, applied over the pain site, nerve bundles of the pain site, or within the same neuroanatomical area as the pain site (Bennett *et al*, 2011; Claydon *et al*, 2011; Johnson and Walsh, 2010). Studies of experimental pain show that strong non-painful TENS is superior to just perceptible TENS (Aarskog *et al*, 2007; Lazarou *et al*, 2009; Moran *et al*, 2011b), implying that clinically patients must learn to titrate current to achieve a *strong but comfortable* (SBC) sensation (Johnson and Bjordal, 2011). This application of active TENS is used in the current study and will be justified in Chapter 9. Conversely, suboptimal TENS is used in this thesis as a placebo, and will also be discussed in Chapter 9.

Traditional applications of TENS include *AL-TENS* and *Conventional* TENS, which use different parameters to induce different physiological effects. Current IASP guidelines state that *Conventional TENS* is the application of high frequency (50-100hz), low intensity (painless paraesthesia), short pulse duration (50-200 μs) TENS. Whilst AL-TENS is the application of low frequency (2-4hz), higher intensity (to tolerance level), longer pulse duration (100-400 μs) TENS (Charlton, 2005c).

Less frequently used clinically, is *Intense* TENS, which uses high frequency (10-200 hz), high intensity application. Although literature points to the efficacy of high intensity TENS in experimental pain (Aarskog *et al*, 2007; Chesterton *et al*, 2002; Chesterton *et al*, 2003;

Claydon *et al*, 2008; Claydon *et al*, 2011; Lazarou *et al*, 2009; Moran *et al*, 2011a), its efficacy in clinical populations does not necessarily translate (Claydon *et al*, 2008). Higher TENS intensities are less easily tolerated by patients (Searle *et al*, 2008) and may therefore be less appropriate for the MS patient with chronic pain. It will therefore not be reviewed in detail in this thesis, unlike conventional and AL-TENS.

A further mode of TENS, Alternating-Frequency TENS, also has limited evidence of efficacy in clinical populations. Several clinical studies investigating the morphine-sparing effects of electrostimulation found that alternating-frequency (2/100 Hz), high-intensity (9 to 12mA) stimulation of acupoints had greater than 50% morphine-sparing effect in patients after gynaecological surgery (Chen *et al*, 1998; Hamza *et al*, 1999; Wang *et al*, 1997). However, a study of the effects of alternating-frequency TENS for pain in those with OA of the knee, found no differences in efficacy between alternating-frequency, low-frequency, and high-frequency TENS (Law and Cheing, 2004). Furthermore, recently (Claydon *et al*, 2013) showed no effect of alternating frequency TENS over placebo in experimental pain. Thus Alternating-Frequency TENS will not be considered further in this thesis.

8.2 Pain modulation and TENS

The physiology of pain was detailed previously in section 2.3 (Chapter 2). This section will focus on pain modulation and the use of TENS in this process.

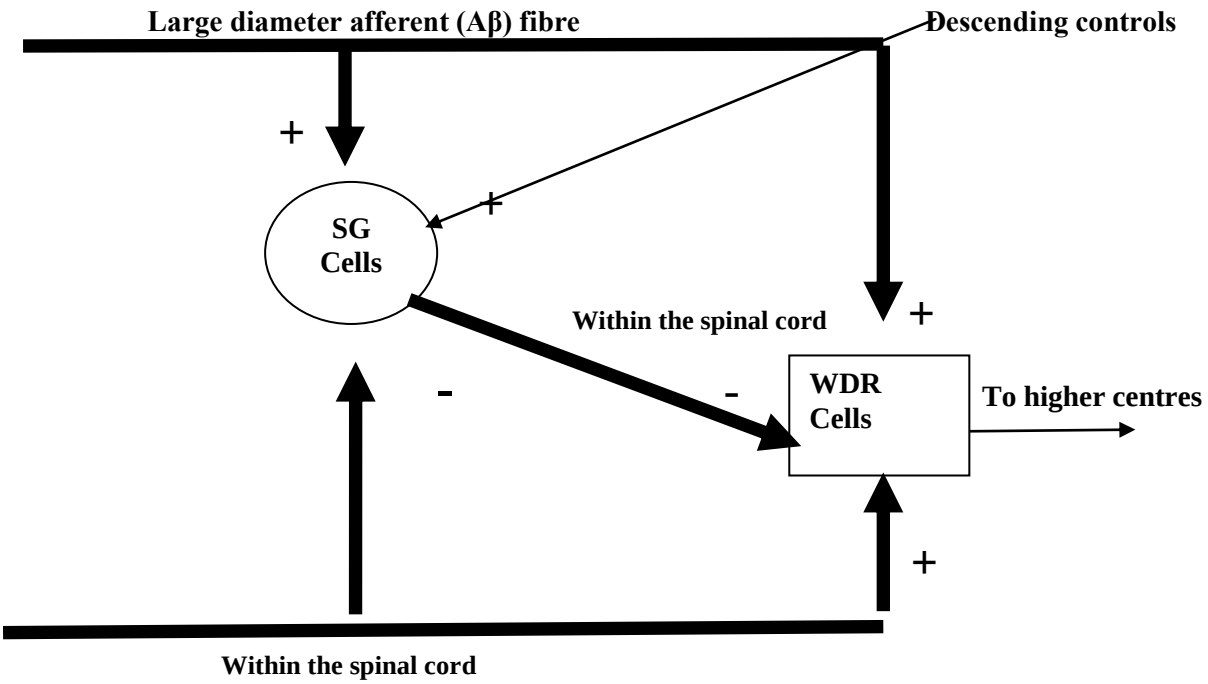
8.2.1 Pain modulation and the role of TENS

Mechanisms have been proposed for pain modulation using TENS and include *segmental inhibition* (at a spinal level) and *descending inhibition* from supraspinal structures. Neurophysiological studies have demonstrated the effect of TENS on these mechanisms, inhibiting transmission of nociceptive information in the CNS. These mechanisms are less clear for clinical pain, but are briefly outlined to provide a plausible theoretical rationale for the use of TENS in the clinical population. The theoretical rationale for the use of TENS in pain modulation is outlined in this section, a more detailed review of optimum TENS parameters to elicit a hypoalgesic effect are outlined in Chapter 9.

8.2.1.1 The role of TENS in segmental inhibition

The 'Pain-Gate' theory (PGT) (Melzack and Wall, 1967) proposes that the transmission of noxious information to higher centres can be blocked at the level of the spinal cord (segmental inhibition). The wide dynamic range (WDR) cells, which have a key role in the PGT, were introduced previously, in Chapter 2, Section 2.3.1. The WDR cells are responsible for relaying peripheral information regarding pain to the higher centres. As well as receiving excitatory input from primary afferent nociceptor fibres (A-delta and C fibres), the WDR cells are also subject to inhibitory input from the substantia gelitanosa (SG) interneurones in the spinal cord. These SG cells are excited by large-diameter, low threshold mechanosensetive afferents (A-beta fibres). The WDR cells therefore receive excitatory inputs from nociceptor afferents, and inhibitory inputs from mechansosensetive afferents via SG cells. TENS-induced activity in the A-beta fibres in the periphery is thought to lead to the inhibition of SG cells (via the release of gamma amino butyric acid (GABA) (Johnson, 2001; Ma and Sluka, 2001; Maeda *et al*, 2007; Sluka and Walsh, 2003; Wood, 2008). Although a certain level of excitatory input to the WDR cells is present via the nociceptive afferents, this is effectively abolished by the higher level of inhibition from SG cells (which also receive descending excitatory inputs from the brainstem and higher centres) (Figure 8-1), closing the gate to pain transmission at the level of the spinal cord.

Figure 8-1: Pain Gate Theory



Adapted from (Patel, 2010)

The pain-gate theory (PGT) is believed to be the key mechanism of conventional TENS (Low intensity, High Frequency (LIHF) stimulation) in pain relief. The physiological intention of conventional TENS is to selectively activate the large-diameter A-beta (touch-related) fibres, without concurrently activating small-diameter A-delta and c fibres (pain-related) or muscle efferents (Jones and Johnson, 2009). Theoretically high frequency (low intensity) currents would be the most effective in selectively activating A-beta fibres. As large diameter fibres have short refractory periods, and are thus more able to generate nerve impulses at higher frequencies. This means that they are more able to generate high-frequency volleys of nerve impulses when high-frequency currents are delivered, resulting in a greater afferent barrage into the CNS (Watson, 2011). Animal studies have demonstrated that TENS-induced activity in A-beta fibres inhibits the ongoing transmission of nociceptive information in the spinal cord, thought to be a result of the PGT (Garrison and Foreman, 1997; Ma and Sluka, 2001; Sandkühler, 2000). Conventional TENS has shown hypoalgesic effects over placebo in both experimental pain settings (Chesterton *et al*, 2002; Johnson and Tabasam, 2003; Walsh *et al*, 1995b) and clinical pain settings (Cheing *et al*, 2003; Hsueh *et al*, 1997; Law and Cheing, 2004; Moore and Shurman, 1997), although the quality of these studies will be reviewed, later in Section 8.4.4.1.

The WDR cells, key in segmental inhibition, are also influenced by descending inputs from higher centres, which is covered in the next section.

8.2.1.2 Role of TENS in extrasegmental inhibition

Detailed description of descending inhibition has previously been covered, in Section 2.3.1., of Chapter 2. Key areas of the brain, proposed in this system include the Periaqueductal Grey (PAG), the Rostral Ventral Medulla (RvM), and the Nucleus Raphemagnus (NRM). Stimulation of A-delta fibres using TENS may lead to activation of these brain areas (activating descending pain inhibitory pathways) and inhibition of descending pain facilitatory pathways, by the release of serotonin, opioids and noradrenalin (Jones and Johnson, 2009). The physiological intention of AL-TENS (Low Frequency, High Intensity (LFHI) stimulation) is to activate the A-delta fibres, causing phasic muscle contractions implicated in the recruitment of descending pain pathways (Jones and Johnson, 2009). AL-TENS has also been shown as effective in reducing pain in both experimental (Chesterton *et al*, 2002; Tong *et al*, 2007; Walsh *et al*, 1995b) and clinical pain conditions (Ng *et al*, 2003; Topuz *et al*, 2004).

Recently it has been postulated that the release of opioid peptides is highly dependent on the frequency of stimulation parameters. Animal studies have indicated that LF and HF stimulation both activate supraspinal structures, producing different opioid receptors equally important in analgesia (Han, 2003; Kalra *et al*, 2001; Sluka *et al*, 1999). Furthermore, the aforementioned studies by Sluka *et al*, (1999) and Kalra *et al*, (2001) delivered TENS at sensory level, whilst the remaining studies delivered TENS at motor level. Many studies actually report AL-TENS as a LFHI application, with no reference to muscle contraction, which will have distinct physiological effects (Warke *et al*, 2006). Intensity is therefore a further parameter which may affect optimum hypoalgesic effects, and will be reviewed further in Chapter 9.

From neurophysiological studies then, it would appear that individual TENS parameters determine physiological effect, which may be frequency, and/or intensity dependent.

8.2.2 Neuropathic Pain modulation by TENS

TENS has proven effective for neuropathic pain in several clinical conditions (described in more detail in Section 8.4.4.2). However, the mechanisms for this are unclear, particularly in central neuropathic pain disorders. From section 2.4.2.1 we saw that the key components of neuropathic pain in MS relate to the generation of ectopic impulses at demyelinated lesions, the interruption of inhibitory impulses from the brain, leading to central sensitisation, and increased amplification of normal sensory input, causing allodynia and hyperalgesia. This study aims to explore the efficacy of TENS on clinical neuropathic pain and not to investigate the physiological mechanisms of TENS in this process; however a brief theoretical rationale is outlined from Johnson (2011) as follows. The mechanisms of TENS and pain modulation detailed in the previous section are based on nociceptive models of pain, but this may provide a rationale for the use of TENS in the neuropathic pain model.

TENS has the potential to influence each of the aforementioned features of neuropathic pain as it can affect all levels of the neuraxis (as outlined in the previous section) (Johnson, 2011). TENS has been shown to inhibit ectopic activity in the WDR and nociceptive-specific cells, firing spontaneously or when evoked by noxious stimuli. In animal studies high frequency TENS was shown to decrease central sensitisation. Johnson (2011) does however, highlight that these findings are not based on studies with actual nerve injury, but

by other models of pain. Thus, despite the lack of evidence, TENS-related hypoalgesia in neuropathic pain disorders is conceivable.

There is also therefore, little guidance from neurophysiological studies on optimum TENS parameters specifically for use in neuropathic pain disorders. Parameters used in clinical studies are detailed later, in section 8.4.4.

8.3 Summary

TENS can be used to modulate pain throughout the neuraxis, where careful selection of sensory stimulation parameters may target specific anti-nociceptive mechanisms. Both conventional TENS and AL-TENS have previously been successful in modulating pain in neurophysiological and clinical studies; however it is unclear which specific parameters would be most appropriate for neuropathic pain. Optimum clinical parameters for eliciting a hypoalgesic effect in the current study population are reviewed in more detail in Chapter 9. The following sections consider the efficacy of TENS in both experimental and clinical pain populations.

8.4 Efficacy of TENS in hypoalgesia

This section reviews literature on the efficacy of TENS in hypoalgesia. Literature was sought from electronic database, including: the Cochrane Database of Systematic Reviews, Ovid-Medline, Ovid-Embase, and CINAHL, covering the period 1970-2011. Search terms included: *Transcutaneous Electrical Nerve Stimulation, TENS, pain, sensory symptoms, chronic pain, neuropathic pain, central pain, Multiple Sclerosis, systematic review, randomised controlled trial.*

As this is a clinical study, the majority of literature focuses on clinical studies of TENS and chronic pain (from section 8.4.4). However evidence of the effect of TENS on experimental pain was also sought from high quality studies, and is reviewed from section 8.4.2. The systematic review is the gold-standard in evidence based medicine (Chalmers *et al*, 2002). Recent systematic reviews have been undertaken in relation to the efficacy of TENS in both experimental and clinical pain conditions and are the basis of this section. Individual studies of high methodological quality are considered in more detail for the

section on clinical pain and in relation to optimum TENS parameters for use in the current study (Chapter 9).

Prior to exploring the efficacy of TENS on hypoalgesia, the following section introduces TENS control applications used in efficacy based studies.

8.4.1 TENS control applications used in efficacy-based studies

In studies of TENS and pain relief, TENS is either compared to either a control situation (no active treatment) or more commonly a placebo (*sham, dummy*) situation. Sham devices have been used which mimic an active TENS device in appearance, but are completely inactive. However, sham TENS units have recently been criticised for inadequate blinding as TENS units are easily accessible to the general public, who have a high awareness of the sensory sensation of TENS, (even in those who are TENS-naive). The lack of sensation could indicate to participants that they are in the placebo group, thus unsuccessful blinding. Alternatively suboptimal applications of TENS have been more recently advocated as a more suitable form of placebo, allowing adequate blinding (Rakel *et al*, 2010). This was initially suggested by Chakour and colleagues (Chakour, 1998; Chakour *et al*, 2000) based on the lack of physiological rational for the combination of a low frequency, with a low intensity application. Furthermore, a recent systematic review highlighted the lack of efficacy of low intensity, low frequency, long pulse duration, TENS (LILF), based on the findings of seven high quality RCTs (Chesterton *et al*, 2003; Cramp *et al*, 2000; Foster *et al*, 1996; Lazarou *et al*, 2009; Walsh *et al*, 2000; Walsh *et al*, 1995a; Walsh *et al*, 1998). The majority of the studies used settings of 4Hz and 200ms, using intensity of a "*strong, but comfortable* (SBC)" level. This has the benefit of eliciting a sensory sensation (blinding the patient), but with no physiological effect.

8.4.2 Efficacy of TENS in experimental pain

This section considers the efficacy of TENS using experimental models of pain. Although this thesis is focused on *clinical* pain, many robust randomised controlled trials of the effect of TENS are based on the experimental pain model in humans.

Experimental pain is the application of a standardised stimulus employed to activate nociceptors and evoke pain from a specified tissue where a quantitative measure of psychophysical, behavioural or neurophysiological response can then be made (Graven-

Nielson *et al*, 2001). Albeit with limitations, conclusions from experimental pain studies can be applied to the clinical situation and as a result, experimental pain models are used extensively to determine the analgesic efficacy of pharmaceutical agents and physical modalities, determining mechanisms by which analgesics may modulate pain (Staahl and Drewes, 2004). There are three main types of experimental pain (Walsh, 1997): 1) Cutaneous: noxious stimulation to the skin; 2) deep somatic: noxious stimulation to muscle, bone or periosteum and 3) Visceral: noxious stimulation to the viscera and organs. The first two are have been used to determine the efficacy of TENS in pain reduction, using ischaemic, thermal, cold, pressure and delayed onset muscle pain as models (Reddy *et al*, 2012).

Electrophysiological experimental pain model studies have been crucial in understanding the mechanisms of TENS on hyperalgesia.

8.4.2.1 Efficacy of TENS in experimental pain: systematic review

Claydon *et al*, (2011) undertook a recent systematic review to determine hypoalgesic efficacy of different TENS parameters on experimental pain models in healthy humans using robust RCTs (Claydon *et al*, 2011). Active TENS was compared with inactive control groups (regardless of specific TENS parameters used). Subgroup analysis then investigated the effects of different TENS parameter combinations compared with inactive control groups. Parameter combinations included: conventional TENS, AL-TENS, intense TENS and suboptimal TENS (low frequency, low intensity TENS). The review categorised the methodological quality of studies, using the standardised 'Jadad' scale (Jadad *et al*, 1996), as well as level of statistical power, which allows the quality of evidence behind recommendations to be assessed. The Jadad scale evaluates potential sources of bias, such as lack of /inappropriate randomisation and blinding, as well as small sample size and concealment of participant withdrawals and drop-outs. A study is deemed of being high quality if it scores three or more points on this scale (Moher *et al*, 1999). Furthermore, only studies with the standard TENS applications as recently highlighted by expert opinion (Section 8.1.2) were included. A meta-analysis was deemed inappropriate as there were many differences in relation to type of experimental pain used (i.e. ischemic, pressure, thermal) as well as the different outcome measures and study methodologies used.

Overall, there was conflicting evidence of TENS efficacy (regardless of parameters used) compared with inactive controls. Subgroup analysis of specific TENS parameter

combinations was also inconclusive from this systematic review (Claydon *et al*, 2011): It was concluded that both AL-TENS (LFHI) and Conventional TENS (HFLI) had conflicting evidence of efficacy, with the majority of trials being inadequately powered and of low methodological quality. For conventional TENS, similar proportions of positive and negative trials were classified as being of high quality, although noteworthy is that the three adequately powered studies did report positive outcomes (Chen and Johnson, 2009; Chesterton *et al*, 2002; Simmonds *et al*, 1992). For AL-TENS only two high quality studies were found in the review, displaying conflicting results for efficacy in experimental pain (Lazerou *et al*, 2009; Chesterton *et al*, 2002).

Despite the positive outcomes reported for the three adequately powered studies of conventional TENS in this systematic review, one must remember that the relevance of experimental pain to the clinical situation has been challenged (Curatolo *et al*, 2000). There are obvious differences between laboratory-induced pain and clinical pain: Shortcomings in the psychophysical methods used to quantify pain threshold or intensity to an experimental pain stimulus may affect study outcome. Despite this, experimental studies are useful in solving methodological differences encountered in clinical studies. Furthermore, analgesic drugs reduce clinical pain and experimental pain to similar levels, supporting experimental studies as a precursor to clinical trials of therapeutic interventions for pain. The next section considers the efficacy of TENS in clinical pain.

8.4.3 Summary

Both conventional TENS and AL-TENS show conflicting evidence of efficacy in experimental pain, although the quality of research is relatively poor. However there does appear to be more adequately-powered, quality evidence for the use of conventional TENS at this time.

8.4.4 Efficacy of TENS in clinical studies

This section considers the efficacy of TENS in patients with chronic pain (of any origin), followed specifically by neuropathic pain. This is relevant to the current clinical population, with chronic neuropathic pain related to MS. Firstly, for chronic pain, the findings of six key systematic reviews are discussed. This is followed by the findings of high quality studies of chronic pain in more detail. No systematic reviews specifically for neuropathic pain have been published (although one such review is pending). Evidence on the efficacy of TENS for any other neuropathic pain conditions (peripheral and central), are consulted.

8.4.4.1 Efficacy of TENS in chronic pain

Summary of findings from systematic reviews of TENS and chronic pain

There is conflicting evidence on the efficacy of TENS in the treatment of chronic pain. Six reviews have been undertaken on the use of TENS in chronic pain with conflicting results. Positive outcomes in pain reduction for active TENS over placebo were reported in three of the reviews (Bjordal *et al*, 2007; Johnson and Martinson, 2007; Osiri *et al*, 2009), whilst insufficient evidence to make conclusions was reported in the remaining three (Brosseau *et al*, 2003; Khadilkar *et al*, 2008; Nnoaham and Kumbang, 2008). For specific chronic pain conditions, four reviews have been undertaken: chronic low back pain (CLBP) (Khadilkar *et al*, 2005), osteo-arthritis of the knee (OA) (Bjordal *et al*, 2003; Osiri *et al*, 2000), and rheumatoid arthritis of the hand (Brosseau *et al*, 2003). The number of trials and participants in these reviews were small and should not be used to make clinical recommendations (Johnson and Walsh, 2010). For example, in the review of TENS and chronic LBP (Khladikar *et al*, 2008) only four studies were highlighted as being of high quality (Cheing and Hui-Chan, 1999; Deyo *et al*, 1990; Jarzem *et al*, 2005; Topuz *et al*, 2004). However one study (Cheing and Hui-Chan, 1999) applied a single dose of TENS only and its methodological quality is contested by another author (Claydon and Chesterton, 2008). Another study provided no details of TENS application, including settings or electrode placement (Jarzem *et al*, 2005), proven as influential factors in TENS outcome.

Conversely, two larger reviews have been undertaken for more general chronic pain, including chronic pain of any origin (Nnoaham and Kumbang, 2008), and chronic

musculoskeletal pain (Johnson and Martinson, 2007), giving conflicting findings. The meta-analysis used in the latter was criticised for the heterogeneity of their clinical sample, which included 21 RCTs and 1227 participants, with a wide variety of MSK conditions, including myofascial pain, LBP, OA, RA, and ankylosing spondylitis, highlighting the overall efficacy of TENS in chronic pain (Novak and Nemeth, 2007). The subsequent rebuttal from the authors was of the "*trade-off between increased heterogeneity and increased clinical and statistical validity"* (Johnson and Martinson, 2007). This review has limitations however, as it includes any form of electrical stimulation, such as interferential therapy and percutaneous electrical nerve stimulation (PENS), which are different to TENS. Furthermore, results from this review are based on those purely with nociceptive pain, which may not be comparable with the current study population who may have both nociceptive and neuropathic pain. Conversely, Nnoaham and Kumbang (2008), in the largest systematic review of TENS and chronic pain to-date (25 trials, 1281 participants), did not conduct a meta-analysis due to heterogeneity of clinical populations, and concluded that there is conflicting evidence of the efficacy of TENS over placebo in chronic pain.

A summary of these six systematic reviews highlighted the overall inconclusive evidence on the efficacy of TENS in chronic pain (Claydon and Chesterton, 2008). The authors felt this was a result of a lack of high quality trials, which adopt IMMPACT recommended outcome measures. As previously mentioned in Chapter 2, the Initiative on Methods, Measurement and Pain Assessment in clinical trials (IMMPACT) has published recommendations on specific outcomes for use in clinical trials, and highlights the need for robust methodologies (Dworkin *et al*, 2005). Each of the aforementioned six systematic reviews on TENS and chronic pain graded the methodological quality of studies, using the five-point Jadad scale (Jadad, 1996). Claydon and Chesterton, (2008) state that only 24 (out of 85) trials contained within the six reviews (comparing active TENS to placebo) used validated measures as recommend by IMMPACT, which is the use of either the NRS or VAS of pain intensity, and only 12 of these were high quality (3/5 on Jadad scale), randomised controlled trials. Of these, only seven used a multiple dose of TENS, which is more clinically relevant. For high quality trials, the effect of multiple doses of TENS is inconclusive, as five trials were positive (Fargas-Babjak *et al*, 1989; Fargas-Babjak *et al*, 1992; Law and Cheing, 2004; Moore and Shurman, 1997; Topuz *et al*, 2004), and four trials were negative (Cheing *et al*, 2002; Deyo *et al*, 1990; Lewis *et al*, 1994; Moore and Shurman, 1997). Of the five of these studies which used *conventional* TENS, three showed efficacy over placebo (Law and Cheing, 2004; Topuz *et al*, 2004; Moore and

Shurman, 1997), and only one used AL-TENS, which also showed efficacy over placebo (Topuz *et al*, 2004). The authors also highlighted the high quality study by Deyo *et al*, (1990) of TENS on chronic LBP, giving it 5 points on the Jadad scale. This study showed no difference between TENS and sham TENS in a sample of 125 participants with chronic LBP, when TENS was applied to the lumbar spine. However, this study allowed patients to choose between conventional and acupuncture TENS half way through the intervention, which does not allow the true efficacy of either mode to be evaluated without bias.

From six systematic reviews, there is therefore a lack of high quality evidence of the effect of TENS on chronic pain, with the need for adequately powered future studies of strong methodological quality, using IMMPACT recommended outcome measures (Claydon and Chesterton, 2008). There does appear to be more high quality evidence available for the use of conventional TENS over AL-TENS in this respect, although this is only based on a small number of studies. The findings of high quality studies (≥3/5 on the Jadad scale) are discussed in more detail in the next section. Direct comparison between AL-TENS and conventional TENS are discussed in Section 9.1.4, in relation to optimum parameters to elicit a hypoalgesic effect.

High quality studies from recent systematic reviews of TENS and chronic pain

Three high quality studies, included in the Claydon and Chesterton, (2008) review, showed positive results for conventional TENS over placebo (Moore and Shurman, 1997; Topuz *et al*, 2004 and Law and Cheing, 2004) and two showed no statistically significant difference when compared with placebo TENS (Cheing *et al*, 2002; Lewis, *et al* 1994). These studies will now be reviewed in more detail:

The three positive studies applied an optimal dose of TENS, as outlined by Bennett *et al*, (2011), where TENS must be delivered so that the patient reports a "*strong, but comfortable*" (SBC) sensation, applied over the pain site, or proximal to the pain site within the same neuro-anatomical area. TENS must be applied "regularly throughout the day, whenever they are in pain and for at least 30 minutes at a time" (Bennett, 2011). Conventional TENS was applied over the area of pain in chronic LBP patients (Moore and Shurman, 1997; Topuz *et al*, 2004) and acupuncture points around the knee in patients with knee OA (Law and Cheing, 2004). Frequency was 100Hz, with a pulse width of 200 ms. Intensity was titrated to a "SBC" level and participants were instructed to maintain this throughout the trial intervention period. Participants applied TENS on several occasions

thought the day for between three (Law and Cheing, 2004) to five (Moore and Shurman, 1997) hours/day. Interestingly, in studies by both Topuz *et al*, (2004) and Law and Cheing, (2004), LF TENS was also shown as having analgesic effects over placebo, in addition to conventional TENS, although only Topuz *et al*, (2004) could be described as using AL-TENS, for combining low frequency with a high intensity. There were no differences between the HF and LF TENS groups in this respect.

A significant effect of conventional TENS over placebo TENS was also shown in other trial of high methodological quality, which also met with the "SBC" application of TENS intensity: (Oosterhof *et al*, 2007), a randomised, controlled, double-blind study of 163 participants with chronic pain of benign origin, was allocated 2/5 by both Nnoaham and Kumbang, (2008) and Claydon and Chesterton, (2008), for a lack of description of randomisation and blinding procedures. However, it has been republished more recently, providing more adequate description of both randomisation and blinding procedures (Oosterhof *et al*, 2007). Conventional TENS was applied to the skin over the superficial cutaneous nerves in the painful segment daily for an average of 9.8-11.6 hours/day for 7 days, also meeting recent criteria for an optimal dose of TENS for a therapeutic effect (Bennett, 2011). This is a large RCT, which applied TENS optimally to elicit a hypoalgesic effect, suggesting the benefit of conventional TENS in chronic pain. However, one must also consider its use of a non-IMMPACT primary outcome measure- willingness to continue with TENS treatment- which is to be viewed with caution.

Conversely, no significant differences between active TENS and placebo TENS were shown in two high quality studies by Cheing *et al*, (2002) and Lewis *et al*, (1994), which may be explained by TENS application and study design: Lewis *et al*, (1994) in a cross-over study of 36 patients with knee OA, randomly allocated participants to either sham or conventional TENS groups. "Conventional TENS" was applied for a minimum of 90 minutes/day. A frequency of 70 Hz was used and intensity was titrated to "*supra sensory*" threshold, which is not a standardised method, and does not guarantee a strong enough current was applied to elicit physiological effects. It is also unclear whether participants were instructed to maintain this throughout treatment time, vital to ensure optimal TENS application. Sham TENS was an identical machine, set to the same parameters, but with no current supplied to the electrodes. The efficacy of blinding by a sham TENS machine has been criticised in Section 8.4.1. Inadequate blinding has even greater potential in a cross-over design, which may have impacted on the lack of statistical significance of TENS over,

sham TENS in this study. The addition of a concurrent pharmacological intervention and placebo situation may also have played a part in the lack of a statistically significant treatment effect between groups: participants were randomly allocated to one of three groups: 1) *Conventional TENS + oral placebo, 2) sham TENS + oral placebo,* and 3) *Naproxen + sham TENS*, with no statistically significant difference between groups. Unfortunately as two interventions were simultaneously studied in each group, the effect of conventional TENS alone was not actually investigated in this study, which limits conclusions about the efficacy of TENS.

Cheing *et al,* (2002), in a parallel-design study of 62 patients with knee OA, randomly allocated participants to either conventional TENS or sham TENS groups. Conventional TENS was applied to acupuncture points around the knee. A frequency of 70Hz was selected, and intensity was applied to "*3-4 times the sensory threshold"*, which again is not a standardised method, and does not ensure intensity is strong enough to elicit physiological effects. Although TENS was worn for 60 minutes continually in one session (optimal dose is at least 30 minutes/application), this was the maximum daily dose, unlike the four previous studies which showed positive effects of conventional TENS over placebo, and used much higher daily doses of TENS, of ≥3 hours/day (Moore and Shurman, 1997; Topuz *et al*, 2004; Law and Cheing, 2004; Oosterhof *et al*, 2007).

Both Lewis *et al,* (1994) and Cheing *et al,* (2002) were deemed as being of strong methodological quality, in the systematic reviews by both Nnoaham and Kumbang, (2008) and Claydon and Chesterton, (2008). However, despite this, TENS application showed less fidelity (suboptimal application) than the three studies which showed positive results over placebo for conventional TENS (Moore and Shurman, 1997; Topuz *et al*, 2004; Law and Cheing, 2004, Oosterhof *et al,* 2007). Inadequate TENS application may therefore explain the lack of effect of conventional TENS over placebo in these studies.

(Koke *et al,* 2004) also failed to show the efficacy of TENS in a randomised, cross-over, controlled study of 180 patients with chronic pain, of any origin. This study was not considered by Claydon and Chesterton, (2008) in their review but was considered by Nnoaham and Kumbang, (2008), as a large study of high methodological quality. Participants were randomly allocated to one of 3 groups: 1) conventional TENS (80Hz, pulse width of 80ms, intensity at "*sensory threshold"* for one hour, 4-6 times/day, for a 2-week, 2) high frequency, high intensity TENS (HIT) (80 Hz frequency, pulse width 250ms, at maximum tolerated intensity, for 30 minutes/day, for a 2-week period), and 3) control

(participants choose stimulus intensity and frequency they preferred). All groups displayed analgesic effects over the 2-week period (as measured by a VAS of pain intensity), but there were no statistically significant differences between groups. This could be explained by the application of TENS, whereby conventional TENS was not titrated to an standardised intensity to ensure a physiological effect as with the "SBC" level, and participants were allowed to place the electrodes wherever they felt it was most needed, which is not a standard application of TENS (Bennett, 2011). The lack of statistical significance may also be explained by the choice of control, which may have elicited treatment effects.

Although only based on a few robust studies, conventional TENS, titrated to a "SBC" level, for a minimum duration of 3 hours/day appears to elicit hypoalgesic effects in chronic pain. The optimum parameters and dose of TENS to elicit a hypoalgesic response is explored further in Chapter 9.

The next section now considers the efficacy of TENS specifically in neuropathic pain conditions.

8.4.4.2 Efficacy of TENS in neuropathic pain

This section will review existing literature on the effect of TENS on neuropathic pain for both the peripheral and central neuropathic pain subtypes.

Overview of TENS in neuropathic pain

The European Federation of Neurological Societies (EFNS) Task Force report on neurostimulation therapy found that TENS showed efficacy over placebo in nine clinical studies (Cruccu *et al*, 2007). Hypoalgesic effects were reported for diabetic neuropathy, traumatic peripheral mononeuropathies, cervical radiculopathy and chronic pains with a neuropathic component. However, studies were not adequately powered and were of low methodological quality. Therefore the EFNS recommended TENS as an additional treatment only, as it is a safe and non-invasive modality.

Peripheral neuropathic pain conditions

Evidence of the efficacy of TENS in peripheral neuropathic pain is limited. Three inadequately powered studies of peripheral diabetic neuropathy did not use standard TENS devices, but alternatively used 'H-Wave therapy', which differs from the waveforms used by TENS (Forst *et al*, 2004; Kumar *et al*, 1998; Kumar and Marshall, 1997).

One study of 30 patients with postherpetic neuralgia (PHN) reported the combination of TENS and pregabalin was more effective for pain relief than pregabalin and sham TENS (Barbarisi *et al*, 2010). Conventional TENS was applied to the painful area, using a *SBC* intensity, as recommended in recent work (Bennett *et al*, 2011). Conventional TENS was also used in a small placebo-controlled-trial on 19 patients with allodynia of the hand, as a result of peripheral nerve injuries, reducing pain significantly over placebo over a two-week treatment period (Cheing and Luk, 2005).

The effects of TENS on radicular pain were explored in a randomised, controlled trial of 64 patients with sciatica due to lumbar disc herniation (Ghoname *et al*, 1999). Participants were randomised to one of three groups: 1) AL-TENS, 2) Percutaneous Electrical Nerve Stimulation (PENS) and sham PENS. Both AL-TENS and PENS showed statistically significant effects over sham PENS. However as no sham TENS group was included; one cannot make conclusions about the efficacy of TENS in radicular pain from this study. Two studies of low back pain (with or without radicular pain) have also been conducted (Deyo *et al*, 1990; Jarzem *et al*, 2005). However, information on the outcome specifically for those with radicular pain is not provided.

There is therefore very limited evidence of the efficacy of TENS in peripheral neuropathic pain conditions. The next section considers the effect of TENS on *central* neuropathic pain conditions.

Central neuropathic pain conditions

There are very few clinical trials on the use of TENS for central neuropathic pain. Studies of TENS have been undertaken on Spinal Cord Injury (SCI) (Norrbrink, 2009) and MS (Chitsaz *et al*, 2009; Warke *et al*, 2006) with limited conclusions. Their methodologies are considered in more detail in the next chapter in relation to optimum parameter selection to elicit a hypoalgesic effect.

Of these three studies of central neuropathic pain, only Warke *et al*, (2006) compared TENS with a placebo condition. Here TENS was applied to MS patients with chronic LBP, with no statistically significant reduction in pain intensity shown between groups. LBP was not further categorised i.e. of a neuropathic or non-neuropathic aetiology. As discussed in part I of this thesis, this is a challenge, as many pain presentations in MS may be of mixed origin. Although this study may be useful in exploring the efficacy of TENS in patients with LBP, it has limited value in determining the effect of TENS specifically on MS-related neuropathic pain, which is the goal of the present study.

Although studies of central neuropathic pain conditions, studies by Norrbrink, (2009) and Chitsaz *et al*, (2009) do not assess the efficacy of TENS over a placebo condition. Norrbrink (2009), conducted a small study of low methodological quality, comparing two different TENS applications (HF versus LF) in SCI patients, reporting no difference between groups. Chitsaz *et al*, (2009) compared conventional TENS and the drug nortriptyline, reporting no statistically significant difference between groups, despite a clinically significant reduction of pain in both groups. This was a study of 59 MS patients with pain or sensory problems of the upper extremities. In this study, TENS was deemed to be *as effective* as nortriptyline, which is clinically useful, but does not confirm the efficacy of TENS in this situation. Furthermore, as patients were not actually diagnosed with neuropathic pain, but with "pain or sensory complaints" of the upper limb, which may include a variety of different pain aetiologies, the effectiveness of TENS specifically for neuropathic pain in MS cannot be concluded.

There is a lack of evidence in relation to the effect of TENS on both peripheral and neuropathic pain conditions.

8.5 Chapter summary

The effect of TENS, in experimental and chronic pain is inconclusive, due to a lack of methodologically robust, adequately powered studies. Several robust studies show tentative evidence for the efficacy of conventional TENS, titrated to SBC intensity in chronic pain, with less available evidence for AL-TENS in this respect. The next chapter will revisit several of the studies mentioned in this section in more detail and will consider optimum TENS application to elicit a hypoalgesic effect.

Further randomised controlled trials are required to explore the efficacy of TENS in neuropathic pain, particularly in central neuropathic pain conditions, where evidence for the efficacy of TENS is scarce. No studies have investigated the efficacy of TENS for the treatment of central neuropathic pain in MS. As part one of the thesis has highlighted the burden of neuropathic pain in the MS population, there is much need for the current study.

The findings from this chapter have formed the aim of the TENS study, outlined in the following section:

8.6 Aim and objectives of TENS study

Study Aim

The aim of the study was to investigate if TENS was effective in reducing neuropathic pain in people with MS.

Study objective:

To explore if conventional TENS is more effective at reducing neuropathic pain than placebo TENS in the MS patient.

9 LITERATURE PERTAINING TO METHODS: TENS STUDY

This chapter firstly explores optimum TENS application (including electrical parameters) for eliciting hypoalgesic effects, and uses the recent recommended guidelines for TENS methodologies in research. The second part of this chapter looks at optimum measurement of neuropathic pain.

9.1 Optimum TENS application for pain reduction

The previous chapter confirmed that TENS may be effective over placebo in both clinical and experimental pain studies. Furthermore, both AL-TENS and Conventional TENS may individually have hypoalgesic effects in this respect. This section considers the optimum TENS parameters and application to elicit a hypoalgesic effect, which will be used in the current study, and includes a direct comparison of parameters, such as HF and LF TENS applications.

Reference is made to the '*guidelines of a RCT of TENS for pain relief*', as set by Bennett *et al,* (2011), in accordance with the IASP, IMMPACT and CONSORT recommendations. The recommendations are found in Table 9-1 at the end of the chapter.

9.1.1 Frequency

Electrophysiological studies suggest that the frequency of stimulation is a major determinant of effect (DeSantana *et al*, 2008; Han, 2003). However, often studies do not standardise other TENS parameters, such as intensity, to isolate frequency as an independent variable. This is particularly true of clinical studies, where often intensity is not standardised, i.e. a comparison between LIHF TENS and LFHI TENS (Graff-Radford *et al*, 1989; Hamza *et al*, 1999; Hansson and Ekblom, 1983; Law and Cheing, 2004; Mõystad *et al*, 1990). A direct comparison of HF (80Hz) and LF (3hz) TENS, using an optimal intensity of *'strong, but comfortable intensity'* (with all others parameters set as constant), showed superiority of HF TENS in both pressure pain (Chen and Johnson, 2010) and ischaemic pain models (Chen and Johnson, 2011). Both studies were adequately powered, and double-blind. Standardised TENS applications were adopted in both studies (Table 9-1) and outcome measures were as recommended in the IMMPACT guidelines (Dworkin *et al*, 2005). However, the former study was a cross-over design, of the two groups, HF and LF TENS, with only 30 minutes wash-out between the different TENS

applications, which may not be sufficient to reduce carry-over effects. The latter study was a parallel design, and compared three groups: HF TENS, LF TENS and an additional placebo TENS group. This had the additional benefit of confirming the efficacy of TENS (against placebo) in this situation, as well as the superiority of a HF TENS application.

Clinical studies comparing HF with LF TENS, have found no statistically significant differences between groups (Jensen *et al*, 1991a; Law and Cheing, 2004; Nash *et al*, 1990; Topuz *et al*, 2004; Warke *et al*, 2006), although a clinically significant pain reduction was greater for HF TENS in the majority of these studies. Warke *et al*, (2006) as previously mentioned in Chapter 8, was a methodologically robust, double-blind, parallel-design study of low back pain in 90 MS patients, comparing HF (110Hz) with LF (4Hz) TENS and placebo. Although neither of the active TENS groups showed a statistically significant improvement over placebo, (all showed pain reduction over the six weeks intervention period), the reduction was most marked and considered clinically significant for the HF TENS application and least for the LF application (Warke *et al*, 2006). The percentage of patients showing a greater than 20 mm reduction in VAS of pain intensity at week 6 was 63% for HF TENS, 57% for placebo, and 42% for LF TENS, with the authors stating that the placebo group were taking additional analgesics, which could have masked the true effect of HF TENS over placebo.

Although research is limited, it would appear that HF TENS appears to be more beneficial over LF TENS in experimental studies, although this is only based on two robust studies from the same research group. There is limited evidence on the choice of frequency in clinical studies.

9.1.2 Duration

Section 8.4.4.1 highlighted that a shorter duration of TENS may lead to ineffective pain reduction. A lack of statistical significance for active TENS over placebo has been noted by clinical studies of chronic pain conditions who applied (multiple dose) TENS for 20 minutes (Ng *et al*, 2003) 30 minutes (Jensen *et al*, 1991a; Koke *et al*, 2004; Nash *et al*, 1990); 45 minutes (Al-Smadi *et al*, 2003; Deyo *et al*, 1990); 60 minutes (Cheing *et al*, 2002) and 90 minutes (Lewis *et al*, 1984; Norrbrink, 2009; Warke *et al*, 2006), whilst efficacy over placebo was shown in studies who used higher daily doses of TENS of a minimum of 2 hours to a maximum of 11.5 hours, for a minimum of 60 minutes/session (Law and Cheing, 2004; Moore and Shurman, 1997; Oosterhof *et al*, 2007; Topuz *et al*,

2004). However, despite this trend, all other methodological factors were not standardised in these studies, thus one cannot confirm duration as a definite factor in TENS success in this situation.

There is a paucity of literature directly comparing TENS duration on outcome in clinical studies. (Cheing *et al*, 2003), in a randomised, placebo-controlled (inactive unit) trial examined the comparative analgesic effects of 20,40 and 60 minutes of TENS delivered five days a week for two weeks on 30 patients with OA of the knee. Pain was assessed using a VAS ("no pain" to "pain as bad as it could be") before, immediately (20 minute intervals over one hour in clinic) and over a prolonged monitoring period after each individual TENS session (2 hour intervals for up to 10 hours at home using patient diaries), and at a 2-week follow up session after completion of the full 10 day treatment programme. The authors reported that TENS delivered for both 40 and 60 minutes produced significantly greater overall analgesic effects than TENS administered for 20 minutes/day and placebo TENS over the two-week treatment period. This was maintained at the two week follow-up session.

In a cross-over randomised trial, (Miller *et al*, 2007) applied TENS primarily to treat spasticity in 32 patients with MS, who had increased tone in their lower limbs. The authors compared TENS delivered for 60 minutes or 8 hours (accumulated total treatment time or continuous application) per day, for two-weeks (14 treatment days). The authors reported a statistically significant reduction in both pain and spasm when applied for 8 hours compared to 60 minutes per day. Although this is only one study, there may be a trend towards longer applications of TENS being more effective in achieving pain relief for the MS patient. However, further evidence is required to explore the minimum therapeutic duration required for pain relief.

Bennett *et al*, (2011) states that a minimum of 30 minutes/ application is required in clinical studies, however no further guidelines are provided on how many times/day this should be applied, affecting the overall daily/weekly dose of TENS, which is relevant for those with chronic pain conditions where pain can be experienced throughout the day. The use of TENS throughout the day for chronic pain conditions has been previously advocated (Walsh, 1997), as long as the patient regularly monitors the skin for irritation. Johnson, (2012), reports that maximal benefit may occur during TENS stimulation, with successful long-term users administering TENS for *many hours/day* (Johnson, 1991).

In summary, a total daily duration of TENS application of at least 2 hours, with at least 40 minutes/individual session may have beneficial results. A daily TENS dose of 8 hours was also effective in an MS sample, although this may be perceived as a burden for participants in a clinical trial. As there is insufficient evidence to be any more prescriptive at the current point in time, a mid-point dose of 4 hours/day would be sensible for the current study.

9.1.3 Intensity

According to the principles of axonal activation, pulse intensity also has a key role in excitation alongside frequency (Howson, 1978). Recent studies have concluded that higher TENS intensities have the greatest hypoalgesic effects in experimental pain studies (Aarskog *et al*, 2007; Claydon *et al*, 2011; Lazarou *et al*, 2009; Moran *et al*, 2011a), although this is not necessarily applicable to the clinical setting. Köke (2004) compared conventional TENS (HFLI) with intense TENS (HFHI), showing no significant difference between groups in 180 chronic pain patients. Furthermore, low intensity TENS (when combined with a HF, long pulse duration, segmental application (Conventional TENS) is also effective, as shown from both experimental (Chen and Johnson, 2009; Chesterton *et al*, 2002; Cowan *et al*, 2009; McDowell *et al*, 1999; Simmonds *et al*, 1992; Walsh *et al*, 1995a; Webster *et al*, 1992) and chronic pain conditions (Bennett *et al*, 2008; Cheing *et al*, 2003; Hsueh *et al*, 1997; Law and Cheing, 2004; Moore and Shurman, 1997; Oosterhof *et al*, 2007; Topuz *et al*, 2004) and specifically in neuropathic pain conditions (Barbarisi *et al*, 2010; Cheing and Luk, 2005; Chitsaz *et al*, 2009).

Although higher intensities are the optimum selection for hypoalgesia in the experimental setting this may not translate into the clinical population. Studies of long-term TENS users demonstrate preferences for TENS frequencies based on the comfort of TENS sensation, with high intensities reported as less comfortable for the patient (Johnson *et al*, 1991; Walsh, 1997). However, TENS must not be delivered at a suboptimum level. Experimental pain studies have shown that strong, non-painful TENS is superior to barely perceptible TENS, implying that patient must learn to titrate current to a "SBC" level (Johnson, 2011). Patient comfort is important, particularly where TENS is being tested in a population with chronic pain, where sustained use would be expected. TENS frequency and intensity may have a symbiotic relationship- one study demonstrated that higher TENS frequencies require lower peak-current intensities to activate sensory motor and pain nerves (Palmer *et*

al, 1999). Thus there is rationale for the use of LI TENS, when combined with HF settings (conventional TENS), as long as the patient maintains the strong, but comfortable ("SBC") level recommended.

9.1.4 Conventional TENS versus AL-TENS

The previous sections have already pointed to the use of HF LI (Conventional) TENS, as an effective combination to elicit hypoalgesia. A further reason to use conventional TENS in the current study relates to the effect of TENS on spasticity: Spasticity (defined in section 2.4.1) is a painful and common feature of MS. In a survey of people with MS, 74% reported symptoms of spasticity and 78% of these people felt their quality of life was moderately to severely affected as a direct result of this symptom (The MS Society UK, 1998). The majority of studies have shown that high frequency TENS reduces spasticity. This has been proven in CVA (Potisk *et al*, 1995), spinal injury (Bajd *et al*, 1985; Goulet *et al*, 1996; Gregoric, 1998; Levin and Hui-Chan, 1992) and in MS (Armutlu *et al*, 2003). Conversely, low frequencies were found to be ineffective, or increase spasticity (Han *et al*, 1994; Sonde *et al*, 1998). For intensity, most authors have used stimulation intensities above sensory threshold, but below motor threshold, avoiding muscle contraction with positive results (Bajd *et al*, 1985; Dewald *et al*, 1996; Hale and Chan, 1986; Wang *et al*, 2000). Conversely, some authors have suggested that stimulation above motor threshold with higher intensities, exacerbate spasticity (Daly *et al*, 1996; Dewald *et al*, 1993; Hardy *et al*, 2002). Thus, it would appear that low intensity, high frequency (conventional) TENS settings would not exacerbate spasticity in the current sample. Although the main aim of the study is to reduce pain and not spasticity, any exacerbation of the latter may have an effect on pain level reported. There is therefore further reason to adopt conventional TENS over AL-TENS to avoid any exacerbation in spasticity in the current study.

Further research also supports the use of Conventional TENS over AL-TENS: (Léonard *et al*, 2011) reported that the analgesic effect of AL-TENS is reduced in patients taking opioids on a regular basis, whilst the analgesic effect of conventional TENS was not affected. Although this was a small preliminary study (n=23), it is of high methodological quality and provides an additional reason for the use of conventional TENS in the current study, as MS patients may be taking opioids.

9.1.5 Electrode placement:

The previous chapter outlined a series of studies on experimental pain by Chesterton and colleagues (Chesterton *et al*, 2002; Chesterton *et al*, 2003; Claydon *et al*, 2008; Claydon *et al*, 2011). They concluded that TENS efficacy is based on a combination of intensity and frequency, as well as *site*, with both extrasegmental and segmental applications generating hypoalgesia. Specifically for conventional TENS, they conclude that the optimum application for hypoalgesia is a segmental application. This may not always be applicable to the clinical setting. There is no research on optimum application site on clinical populations. Clinically, electrodes are often positioned so that the sensation of paraesthesia covers the painful area. However, this may not be appropriate for the MS patient. Allodynia is a common in MS, particularly in the limbs of those with central neuropathic pain (Osterberg and Boivie, 2010). The paraesthetic sensation could therefore be interpreted as painful, which may elicit muscle spasm, in a person with MS. An extrasegmental application would be more appropriate in this population.

An extrasegmental application includes either the peripheral nerve or the spinal nerve roots that innervate the painful area (Walsh, 1997; Johnson, 2012; Watson, 2011). However, there is no available evidence of the superiority of either application in the clinical setting. The precise area of pain and area affected by allodynia in MS is highly variable. It would therefore be difficult to standardise application by using an application over a peripheral nerve. For the current MS population, it would instead be more practical to apply electrodes over the spinal nerve roots. The nerve roots which innervate the lower limbs can be covered with the use of longer electrodes which would standardise the application, ensuring coverage for a variety of dermatomal areas of pain in the population (Walsh, 1995). Walsh (1995) also advocates the use of placing the electrodes parallel to the spinal column, and not in a transverse direction to ensure maximum stimulation of a maximum number of nerve roots. It has also been shown that large electrodes are better than small, for deeper nerve reception (nerves at depths of 11mm), which would be true of the spinal nerve roots (Kuhn *et al*, 2010).

9.1.6 Suitable placebo

As mentioned in Section 8.4.1, a recent systematic review highlighted the lack of efficacy of low intensity, low frequency, long pulse duration, TENS (LILF), based on the findings of six high quality RCTs The majority of the studies used settings of 4Hz and 200ms, using

intensity of a "SBC" level. This has the benefit of eliciting a sensory sensation (blinding the patient), but with no physiological affect, and thus may be an appropriate placebo for future TENS studies. This mode of placebo will thus be adopted in the current study.

This chapter has reviewed the most appropriate methods of TENS application for the current study. As the study aims to assess the impact of TENS on neuropathic pain, the next half of this chapter will review the optimum assessment of neuropathic pain, including efficacy measures. It will then review research design considerations for confirmatory chronic pain clinical trials as outlined by the IMMPACT recommendations.

9.2 Neuropathic Pain Assessment

The Neuropathic Pain Specialist Interest Group (NeuPSIG) have produced guidelines for neuropathic pain screening/diagnosis and a comprehensive neuropathic pain assessment in clinical trials (Haanpää *et al*, 2011). From Chapter 4, the PainDETECT Questionnaire (PD-Q) is recognised as a valid and reliable screening tool for neuropathic pain as a result of MS, whilst, Chapter 2 highlighted the NRS-11, as the most appropriate tool to measure pain intensity. This section will review the most appropriate tools to assess the quality of neuropathic pain and the impact of neuropathic pain on functional life.

The NeuPSIG guidelines (Haanpää *et al*, 2011) also recommend the assessment of the quality of neuropathic pain, using generic tools, such as the Short-Form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987) (outlined in Section 4.5.2), or neuropathic pain-specific tools, including the Neuropathic Pain Scale (NPS) (Galer and Jensen, 1997) (outlined in Section 4.4.3.3), and the Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira *et al*, 2004), a self-complete questionnaire, containing 10 verbal descriptors grouped into 5 distinct dimensions(burning, paroxysmal, deep, evoked, paraesthesia) and 2 temporal items which assess pain duration and the number of paroxysms). The SF-MPQ was designed as a generic pain questionnaire, thus was used in Part 1 of the thesis to describe the qualities of chronic pain, but has not been specifically validated for neuropathic pain assessment. The NPSI was also considered for use in the current study. However, a qualitative study of neuropathic pain sensations identified several pain descriptors commonly used by patients with neuropathic pain that are not included on the NPSI (Crawford *et al*, 2008), including: *numb, itchy and sharp/shooting* pain. As each of

these descriptors commonly feature in those with neuropathic pain in MS (Part 1 of thesis, Chapter 6, Table 6-5), the NPSI may not be a valid tool to assess neuropathic pain for the current population. By contrast the NPS has been successfully validated for use in MS (Rog *et al*, 2007a), and is thus the most appropriate choice to measure the quality of neuropathic pain in the present study. It is used commonly in drug trials of neuropathic pain disorders, including MS (Breuer *et al*, 2007; Langford *et al*, 2013).

The NeuPSIG (Haanpää *et al*, 2011) guidelines also recommend measuring the impact of pain on function. Neuropathic pain is shown to have a negative effect on both physical and psychological functioning, leading to disability (Gore *et al*, 2006; McDermott *et al*, 2006; Meyer-Rosberg *et al*, 2001). The International Classification of Functioning, Disability and Health (ICF) describe functioning as the interplay of functions, body structures, activities and participation, environmental and personal factors and provides a theoretical framework for evaluating function and disability. Disability is defined as a physical or mental condition that limits a person's movements, senses or activities (The World Health Organisation (WHO), 2002).

The NeuPSIG guidelines recommend either the Pain Disability Index (PDI) (Tait *et al*, 1990) or the Brief Pain Inventory (BPI) (Cleeland and Ryan, 1994) (Appendix 5) as tools to measure the impact of pain on function. The PDI has been used in drug trials of central neuropathic pain disorders, such as spinal cord injury and stroke (Vranken *et al*, 2011), as has the BPI, which has been used in drug trials for those with neuropathic pain as a results of MS (Breuer *et al*, 2007; Langford *et al*, 2013). However, only the BPI has actually been validated for use in central neuropathic pain disorders, including SCI (Raichle *et al*, 2006) and MS (Osborne *et al*, 2006). Furthermore, changes in pain severity have been correlated with changes in pain interference, using the BPI in patients with neuropathic pain (Hoffman *et al*, 2010). This information will be useful for comparison with the results of the current study, and is discussed in Section 12.1.3. The BPI is therefore the most suitable choice to measure neuropathic pain in the current study.

The NeuPSIG guidelines recommend the assessment of the impact of neuropathic pain on HR-QOL. This was undertaken in part one of the thesis, but was deemed inappropriate in the current study due to the short nature (2 weeks) of the intervention period. It was felt that any reduction in neuropathic pain severity in the 2 week intervention period would be unlikely to impact on HR-QOL at this time. Literature could not be found to support the

minimum duration of analgesia required to impact on HR-QOL; this decision was made for practical reasons. It would be important to include a measure of HR-QOL in longer studies of the effect of TENS on neuropathic pain in MS.

9.3 Measures designed to assess treatment efficacy

Both The NeuPSIG guidelines (Haanpää *et al*, 2011) and the IMMPACT recommendations (Dworkin *et al*, 2005) advocate the use of the NRS/VAS pain intensity scales to assess the effect of treatment on neuropathic pain. Endpoint change from baseline (compared with placebo) is used as the primary outcome measure in the majority of the TENS/chronic pain literature.

In addition to absolute changes in pain intensity, the *proportion of responders* is a reliable measure of treatment efficacy (Haanpää *et al*, 2011). A 'responder' is generally defined as achieving the gold-standard reduction in pain intensity (NRS/VAS) of 50%. However, a 30% reduction is also clinically important (Farrar, 2000). A 30% reduction has been used as the co-primary or secondary outcome measure in several drug trials for neuropathic pain (Baron *et al*, 2009; Nurmikko *et al*, 2007; Siddall *et al*, 2006; Van Seventer *et al*, 2010), including MS (Langford *et al*, 2013). In the TENS literature, number of responders is only used by three studies: (Al-Smadi *et al*, 2003; Buchmuller *et al*, 2012; Norrbrink, 2009; Warke *et al*, 2006). Bunchmuller *et al* (2012) used a 50% reduction to denote a responder, whilst the others use the proportion of participants to achieve a reduction of 2 points on the NRS of pain intensity. A clinically significant reduction in pain has also been defined as a reduction of at least 2 points in the raw data of the NRS-11 scale (Farrar *et al*, 2001; Salaffi *et al*, 2004; Todd *et al*, 1996), which correlates with a 30% reduction from baseline (Dworkin *et al*, 2008).

The 30% and 50% reduction in pain relief methods have been compared with scores from a measure of overall treatment efficacy, as rated by the patient: the Patient's Global Impression of Change (PGIC) (Appendix 6). The PGIC is a 7-point categorical scale, where the participant assesses their overall change since the beginning treatment, ranging from "*very much improved*" to "*very much worse*"). The PGIC is now used extensively in drug trials of chronic pain, and is recommend by the IMMPACT recommendations (Dworkin *et al*, 2005). Patient reported outcomes are recognized as providing valuable information associated with disease improvement, patient satisfaction, and health resources

utilization (Fischer *et al*, 1999). Farrar *et al*, (2001) examined data from 10 clinical trials of 2,724 patients with painful diabetic neuropathy, postherpetic neuralgia, low back pain, fibromyalgia, and osteoarthritis. Participants completed a 0 to 10 pain intensity NRS, and the PGIC, before and after treatment. Pre- to post-treatment decreases in pain intensity of 2 points or 30% were associated with patient ratings of "*much improved."* These thresholds did not differ as a function of diagnostic group, trial duration, treatment condition (placebo versus Pregabalin), or demographic characteristics. Decreases of 4 points or 50% were associated with patient ratings of "*very much improved*." In receiver operating curve (ROC) analyses, a decrease of 1.7 points or 28% best distinguished patients who rated their improvement in pain as "much improved". Thus, the 30% reduction in pain intensity method (reduction of 2 points on the NRS) relates to achieving a "much improved" rating on the PGIC, which has been benchmarked as at least *of moderate importance* to the patient.

The current study will consider the primary outcome measure as the mean endpoint change in pain intensity score (NRS-11) from baseline. In addition, the proportion of responders to achieve a reduction in pain intensity (NRS-11) of 30% from baseline will be presented. As this correlates with the other efficacy measure of a 2-point reduction on the NRS-11 of pain intensity, used in the TENS literature, this will also be presented to facilitate comparison with other studies. The PGIC will be used alongside the NPS and BPI as secondary outcome measures.

Table 9-1: Proposed requirements of a clinical trial of TENS for pain:

From Bennett *et al*, (2011)

Table 2
Proposed requirements for a clinical trial of TENS for pain.

Domain	Criterion	Operational explanation
Allocation	Randomised by adequate method	Using computer generated codes
	Adequate sample size per treatment arm	This will need to be interpreted alongside the power calculation for the size of benefit expected within the context of the study. Most reliable trials will include >200 patients per arm, but in practice between 50 and 199 patients per arm may be suf cient depending on the clinical context
	Allocation independent and blind to investigator	Treatment allocation concealed from investigative team (though therapist may be un-blinded)
	At least double blind	Treatment allocation concealed from patient and outcome assessor (though therapist may be un-blinded). It is not possible to blind the patient to the sensory experience generated by different types of TENS and placebo (no current) TENS. However, the characteristics of the TENS intervention can be concealed (see below)
	Calibration of patient expectations regarding sensations	In placebo (no current) TENS trials, patients could be told that: (i) some types of TENS do not produce sensations during stimulation (i.e. microcurrent therapy) (ii) they may or may not experience sensations from the TENS device
	Maintenance of blinding monitored and described	Blinding should be monitored and instances of leakage documented. Measures should be taken to reduce chance of un-blinding eg patients instructed not to reveal what sensations they have experienced
Application	Intervention TENS over pain or segmental area	Electrodes applied over the painful area or proximal to the painful area along neuro-anatomical distribution
	Intervention TENS titrated to strong but comfortable	For active TENS interventions subjective intensity should be within therapeutic window; this means well above the sensory detection threshold but below the pain threshold
	Authentic placebo control devices used	If a placebo (no current) device is used, this should look and behave similarly to the intervention device. This includes appearance of the device, flashing lights and functioning display panel
	Placebo control TENS over same site as intervention TENS	Electrodes applied over the painful area or proximal to the painful area along neuro-anatomical distribution
	Placebo control TENS titrated to specified setting	Patients instructed that if they do not feel a sensation to set the device at a fixed setting on the display, for example just over half way on the intensity setting
	Intervention self administered and compliance monitored	Patients shown how to apply, titrate and remove device. A record of use or assessment of compliance made
	Duration of TENS applications >30 minutes	Optimal therapeutic effect can be expected after 30 minutes. In home trials, patients should use TENS regularly throughout the day whenever they are in pain and for at least 30 minutes at a time
	Duration of study >6 weeks in chronic pain trials	Acute pain trials should extend to cover the expected duration of pain in that context eg post-operative pain, procedural pain. In chronic pain trials, barriers to effective longer term TENS use need to be assessed and resolved before the start of the trial using a run-in period
	Concurrent analgesia standardised and monitored	For example, maintaining consistent doses of regular analgesic medication as far as possible, and recording use of as needed analgesia
Assessment	Primary outcome is pain intensity	Using pain measures recommend by IMMPACT
	Outcomes measured during TENS application	While TENS is still applied and switched on
	Responders de ned as >50% intensity reduction from baseline	Clinically meaningful improvement may also be reported as numbers of patients experiencing >30% reduction in pain intensity, or whose final intensity score is <30 mm
	Proportion of responders reported	Absolute numbers and percent of patients in each trial arm achieving response
	Adverse effects described	Including local reactions, increase in pain, and other adverse events

10 TENS STUDY METHODOLOGY

10.1 Introduction

This chapter presents the methodology used to meet the study objective:
To explore if conventional TENS more effective at reducing neuropathic pain than placebo TENS in the MS patient? The research design, sample and study procedure will be discussed, as well as outcome measures and statistical methods used for data analysis.

The recent IMMPACT recommendations: *Research design considerations for confirmatory chronic pain clinical trials* (Dworkin *et al*, 2010) have been produced to ensure trials are of a high methodological standard. Although many of the criteria are catered towards drug trials, the current study has adopted as many principles in the current study as appropriate. The recommendations are broken down into two phases: *study subjects* and *phases of clinical trials.* The recommendations will be briefly cited throughout this chapter.

The Consolidated Standards of Reporting Trials (CONSORT) statement comprises a checklist of essential items that should be included in reports of RCTs, such as a diagram for documenting the flow of participants through a trial (Schulz *et al*, 2010). It is aimed at primary reports of RCTs with two groups, parallel designs. The objective of CONSORT is to provide guidance to authors about how to improve the reporting of their trials (Moher *et al*, 2012), and is used as a guide for the reporting of the information in this chapter.

10.2 Ethical approval

Ethical approval was sought from the West of Scotland Research Ethics Committee (WOSRES), and granted in May, 2011 (Appendix7). Permission was also granted for the study from NHS Ayrshire and Arran Research and Development department (Appendix 7).

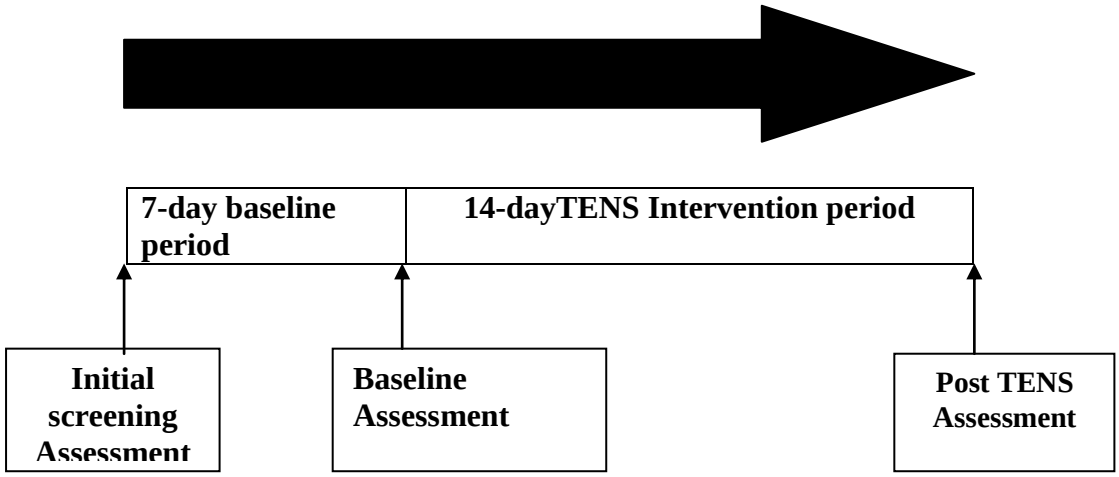
10.3 Study design

The study was a randomised, placebo-controlled, double-blind study. In a parallel-group design, one group were randomly allocated to receive active TENS and the other group randomly allocated to receive placebo TENS.

A detailed description of the study protocol is found in Section 10.7, but a brief outline is provided here to introduce the study terminology:

A seven-day baseline period allowed all participants to record their pain intensity on a daily basis, prior to the use of TENS. A14-day TENS intervention period followed, where participants again recorded their pain daily, whist either using active or placebo TENS. Participants were initially screened, completed the seven-day baseline period (*baseline period),* and returned at the end of the seven-day period for a further *baseline assessment.* Participants were then randomised, completed the 14-day *intervention period* and finally returned for *post TENS assessment* (Figure10-1).

Figure 10-1: TENS Study Process



10.4 Recruitment

This section details the recruitment procedure, inclusion and exclusion criteria.

10.4.1 Recruitment Procedure

Participants were recruited at the Douglas Grant Rehab Centre (DGRC), Irvine, from June-October 2011. The DGRC is an NHS secondary care rehabilitation centre, where patients of the NHS Ayrshire & Arran, MS Service are regularly reviewed. MS clinics are held on a daily basis by several health professionals, including MS consultant review clinic, MS clinical nurse specialist clinic, physiotherapy, occupational therapy and psychology clinics. All clinicians were asked to inform appropriate patients about the study, and distribute the letter of invitation and participant information sheets accordingly. The letter of invitation

(Appendix 8) asked participants to contact the researcher if they were interested in participating in the study (contact details were provided). The information sheet (Appendix 9) detailed the study and participants were encouraged to read it thoroughly and discuss it with others if they wished, before contacting the researcher. Upon first contact with the researcher by telephone, participants were asked if they had read the information sheet and had any questions. In the situation where clinicians were in contact with appropriate patients via telephone consultation, permission was asked for both the letter of invitation and patient information sheet to be mailed to the patient.

10.4.2 Inclusion criteria

Inclusion criteria included: i) definite diagnosis of MS, as per the revised McDonald Criteria, 2005 (Polman *et al*, 2005); ii) the presence of neuropathic pain, as confirmed by the PainDETECT questionnaire (PDQ) (score of ≥19); iii) the presence of lower limb pain (or abnormal unpleasant sensations)- bilateral or unilateral, with or without foot/feet pain; iv) no previous TENS use for lower limb neuropathic pain symptoms and v) the presence of pain of at least 4 on a numerical rating scale (0-10) of pain intensity (NRS-11) (Dworkin *et al*, 2010).

10.4.3 Exclusion criteria

Exclusion criteria were the presence of neuropathic pain, as a DIRECT result of conditions other than MS, which includes: central neuropathic pain (i.e. stroke, spinal cord injury); any form of peripheral neuropathy (i.e. peripheral diabetic neuropathy, spinal nerve root compression); and other conditions that could cause (or mimic) neuropathic pain (i.e. Lupus (SLE), Fibromyalgia, Rheumatoid Arthritis, Cancer). For participants with neuropathic pain of uncertain origin, the full clinical presentation of pain was considered, and discussed with the relevant clinicians of the MS service, where a collective decision on potential exclusion was made.

Further exclusions were i) acute MS relapse one month preceding study commencement or during trial period; ii) poor cognitive function as assessed by a score of less than 24 on the 'Mini Mental State Examination' (Folstein *et al*, 1975); iii) major change in analgesic consumption/prescription within the two weeks prior to commencing study or during study; iv) major co-existing illness (e.g. unstable cardiac conditions, active malignancy); v) individuals who would require translation of outcome measures into a language other than English; vi) individuals currently participating in another research study; vii) gross

decreased sensation (i.e. the whole of the trunk area); viii) contraindications to the use of TENS, as outlined by the Chartered Society of Physiotherapy (CSP) (Chartered Society of Physiotherapy, 2006) (pregnancy, epilepsy, pacemaker, percutaneous central venous catheter (PCVP), allergic reaction to electrodes, dermatological lesions over electrode site area) and viiii) previous TENS use.

10.5 Sample size

No suitable intervention studies could be found which utilised a parallel-group design method (appropriate for TENS study where blinding is an issue), and appropriate statistical analysis using the NRS-11 as the primary outcome measure of neuropathic pain in an MS population. The sample size calculation was therefore based on the use of the NRS-11 as the primary outcome measure in a population with neuropathic pain as a result of spinal cord injury, in a placebo-controlled trial (Siddall *et al*, 2006). As SCI is also a disorder of the CNS, it was felt appropriate to use this study for the power calculation. This study showed a standard deviation (SD) of 2.1 for mean NRS-11 score, which was used as the basis of the sample size calculation. Analysing the data using a two-sample t test with a two-sided 5% significance level, and with a power of 80% to detect a mean difference of 2 on the NRS, 19 participants would be required per group. Assuming a 10% dropout rate, 22 patients were required in the placebo group and 22 in the TENS group, giving a total required sample of 44 participants.

10.6 Pain outcome measures

This section describes the primary and secondary pain outcome measures used in the study. The validity, reliability and components of each of the outcome measures have been discussed in the literature review. Figure 10-2 shows at what point each outcome measure was used. Data was anonymised with an ID number only, and did not have any identifiable details included.

10.6.1 Primary outcome measure

The primary outcome measure of the study was the 11-point numerical rating scale of pain intensity (NRS-11), a generic scale of pain intensity from 0-10, where ‘0’ indicates no pain and ‘10’ indicates the worst pain imaginable. Participants were asked to record their average leg pain within the last 24 hours on the NRS-11, on a daily basis, with assessments

at the same time each daily. Scores were recorded on a daily basis for the 7-day baseline period and for the 14 day TENS intervention period (discussed further in protocol Section10.7). The NRS-11 was used in part I of the study, and is detailed in Section 4.5.

10.6.2 Secondary outcome measures

This section describes the secondary pain outcome measures used in the study and includes: *The Neuropathic Pain Scale (NPS*), the *Brief Pain Inventory (BPI)* and the *Patient's Global Impression of Change (PGIC*).

i) The Neuropathic Pain Scale

The Neuropathic Pain Scale (NPS) questionnaire (Galer and Jensen, 1997) (Appendix 10) was used as a specific measure of the severity of neuropathic pain. The scale rates the intensity of ten individual components of neuropathic pain, including: *pain intensity, sharpness, heat, dullness, cold, sensitivity, itchiness, level of unpleasantness, intensity of deep pain and intensity of superficial pain.* Each individual section is rated on a scale of 0-10, where, '0' indicates *no burning pain*, and '10' indicates *the most intense burning pain imaginable.* Participants could score a potential total score of 0- 100, with higher scores indicating more intense neuropathic pain. Participants completed the NPS questionnaire on three consecutive days, at the end of the seven-day baseline period, and on three consecutive days, at the end of the intervention period.

ii) *The Brief Pain Inventory*

The Brief Pain Inventory questionnaire (BPI) (Cleeland and Ryan, 1994) (Appendix 5) was completed once, at baseline, and again, at the post-TENS assessment, at the end of the intervention period. Scores related to the interference of pain, within the previous week. The BPI has two distinct components: the **Pain Severity** and **Pain Interference** sections, both of which were completed by participants.

For the **Pain Severity** section, participants completed four individual numerical rating subscales of pain intensity on a scale of 0-10, where '0' indicates *no pain* and '10' indicates *worst pain imaginable.* The four subscales included: *worst pain, least pain, average pain and pain right now*. Participants could score a potential *total pain severity score* of 40, with higher scores indicating more intense pain overall.

For the **Pain Interference** section, participants completed seven individual numerical ratings subscales of pain interference *(general activity, mood, walking ability, normal work, relationships, sleep and enjoyment of life*), on a scale of 0-10, where '0' indicates *no interference* and '10' indicates *maximum interference due to pain*. Participants could score a potential *total pain interference score* of 70, with higher scores indicating higher levels of pain interference.

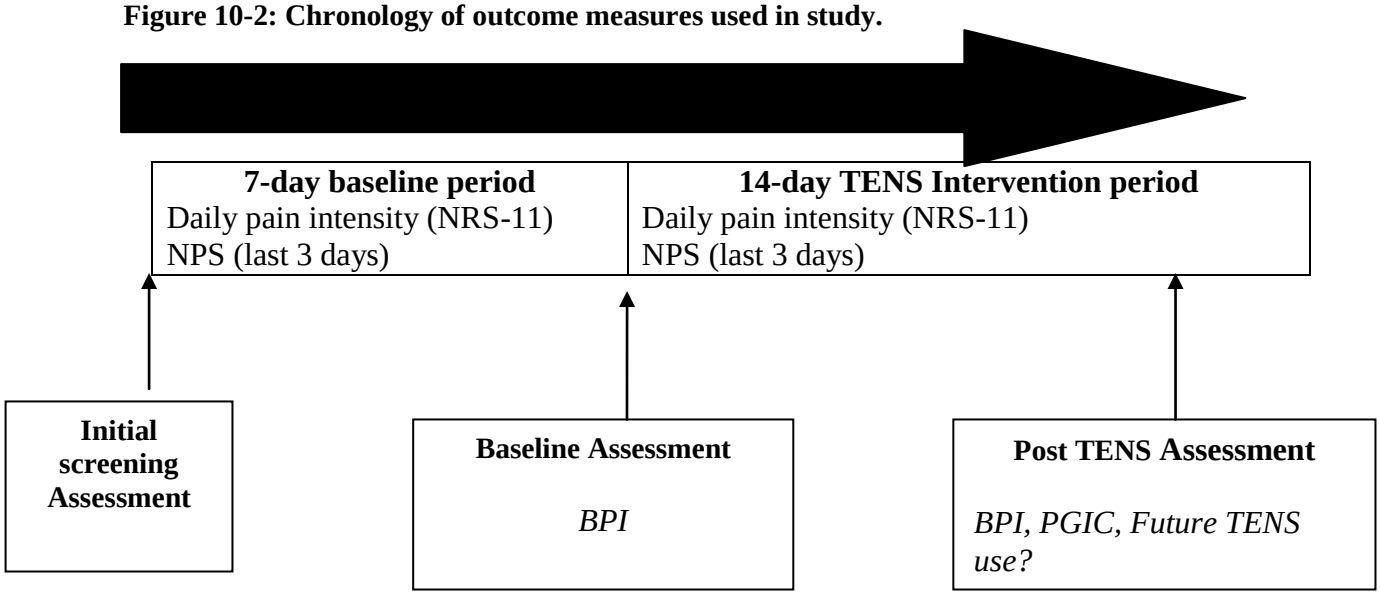
iii) *Patient's Global Impression of Change*

Patients Global Impression of Change (PGIC) (Appendix 6) was used as a measure of overall effectiveness from the patient's perspective, in relation to the broad themes of **change** in *activity limitations, symptoms, emotions and overall quality of life.* Participants could score a possible score of 1-7, the lower scores indicating greatest change in the aforementioned factors. A score of '1' indicates: *very much improved* whilst a score of '7' indicates *very much worse*. The PGIC was completed at the post TENS assessment.

iv) Likelihood of future TENS use

At the post TENS assessment, each participant was also asked whether they would use TENS again for pain relief, for this specific type of leg pain, with a binary Yes/No answer given.

Figure 10-2: Chronology of outcome measures used in study.



10.7 Study protocol

This section details the overall study procedure including the research team, initial screening assessment, baseline pain recording, randomisation and TENS application.

10.7.1 Research team

The chief investigator obtained informed consent and performed the initial screening assessment and gave instructions on pain recording for the baseline period. At the baseline assessment, the chief investigator was responsible for randomisation, applied the TENS unit, provided demonstration and instructions for the intervention period, and advised on pain recording during the intervention period. The chief investigator was responsible for telephoning the patient after 24 hours of the intervention period to check for any potential problems, and was contactable throughout the intervention period. An independent, assessor supervised pain outcome measures at the post-TENS assessment only. The chief investigator was a chartered physiotherapist, currently practising within NHS Ayrshire and Arran, familiar with the application of TENS. The assessor was a senior physiotherapy assistant at the Douglas Grant Rehabilitation Centre in Irvine, and was blind to the group allocation of participants.

10.7.2 First visit: Initial Screening

At the first visit to the DGRC, consent was obtained and demographic details were ascertained, as well as time since MS diagnosis and disease course, including last relapse in their condition. Participants were screened by the chief investigator for eligibility to participate in the study in relation to inclusion/exclusion criteria (Section10.4.2/3) using the initial study *screening questionnaire* (Appendix 11). Using this questionnaire, participants were also asked about previous TENS use and effect. Participants were screened for specific medical conditions in which the use of TENS is contraindicated (as outlined by guidelines from the Chartered Society of Physiotherapy(Chartered Society of Physiotherapy, 2006), or medical conditions which would indicate the presence of neuropathic pain, not related to MS. Patients were asked about the area, pattern, quality and intensity of their pain (or abnormal sensations), as well as any analgesic use and amount currently taken/prescribed, including any recent changes. Participants were asked about all current medication use, MS-related or otherwise. At this initial visit, screening for the presence of neuropathic pain of the lower limbs was undertaken using the self-report

'PainDETECT' Questionnaire (PD-Q) (detailed in Section 4.4.3.1) Only participants who had definite neuropathic pain, as determined by a score of at least 19 points on the PD-Q were eligible for the trial (where the PD-Q has a score of -1 to 38). Participants were then asked to complete the Mini Mental-State Exam (MMSE) to screen for cognitive problems (Folstein *et al*, 1975). During the screening process, assessment of the skin on the lower lumbar/sacral area was carried out to ensure adequate skin condition for electrode placement. A sensation test was performed over the area of electrode placement to check for any decreased skin sensation using the sharp/blunt clinical instrument for gross sensation.

10.7.3 Baseline period

Following screening visit, eligible participants were asked to report on the intensity of their pain for a period of seven days. No TENS was applied during this time. Self- report of mean daily pain intensity was done using the '*Numerical Rating Scale'* (NRS-11) and completed once per day for a seven day period. Participants also completed the '*Neuropathic Pain Scale'* (NPS) questionnaire once per day on the 3 consecutive days at the end of the baseline period. Participants were asked to complete both scales at the same time each day. Participants recorded the above in a daily pain journal, which also asked them to record any changes in general health condition, medication or other pain-relieving modalities used.

10.7.4 Second visit: Randomisation, baseline assessment and TENS issue

After the seven-day baseline period participants returned to the DGRC for their second visit. At the start of this visit participants were randomised into group one (active TENS) and group two (placebo TENS). Baseline data was then collected, TENS was demonstrated and issued to participants for the 2-week intervention period.

Randomisation and concealment

Randomisation was performed using a computer-generated random numbers table. Randomisation occurred in the order in which patients were enrolled in the study according to the randomisation schedule prepared. A blocking randomisation procedure was performed, with a 1:1 ratio, to generate a sequence of allocation to ensure that there was a close balance of numbers in each group.

The chief investigator (who was not involved with the outcome assessment) carried out the randomisation process. The separate assessor (physiotherapy assistant) was blind to group allocation, and was permitted from communicating with participants during the intervention period. Participants were also advised not to communicate any information about their TENS experience to the blinded assessor at the next visit for outcome assessment (after the 2-week intervention period) and were asked to leave their TENS machine at reception at this next visit. This ensured that both participants and the assessor were blinded to treatment allocation. This was justified on the basis that inadequate blinding can overestimate treatment effects by up to 17%, whilst non-randomisation has been shown to exaggerate results by up to 40% (Schulz *et al*, 1995).

Baseline data collection

Then the participant's seven-day baseline pain journal was collected and the '*Brief Pain Inventory* (BPI) was completed: Prior to completion, the chief investigator provided a thorough explanation of the BPI, allowing time for any questions. The chief investigator then left the room and allowed completion of the BPI in private. The chief investigator did not look at individual responses but placed them immediately in a sealed box, along with the 7-day baseline data.

Application of TENS

Following the collection of baseline data, TENS (active or placebo) was applied for a period of 30 minutes for all participants. This allowed any potential problems with the use of the TENS unit to be identified Participants were instructed in the use of TENS which was to be applied daily for a two week period. The application of TENS is detailed in Section 10.8.

10.7.5 Intervention period

Participants were asked to use the TENS unit daily for a 14-day period. Similar to the baseline period participants were asked to complete a daily pain journal, recording their mean daily pain intensity (in the last 24 hours) on the '*Numerical Rating Scale (NRS-11)',* once per day for the two-week TENS treatment period. They also complete the '*Neuropathic Pain Scale*' (NPS) questionnaire, on 3 consecutive days at the end of TENS treatment. Participants were asked to complete both scales at the same time each day. Participants were also asked to detail the pattern, quality, area and duration of pain. They

were also asked to record the duration of TENS application each day, as well as any changes in general health or medication prescription (or consumption) in the pain diary given. Any other pain-relieving treatments, such as massage were also recorded in the diary.

10.7.6 Third visit: Post-TENS Assessment

At the end of the intervention period, all participants, returned for a final assessment. At this third visit, all participants returned the TENS unit and the 14-day pain journal. They then completed the BPI, as outlined previously, as well as the self-report *Patients Global Impression of Change (PGIC) questionnaire* and answered whether they would continue to use a TENS unit for pain relief, for this particular type of pain. Outcome measures were undertaken as outlined in section 10.7.4, however, they were supervised by an independent blinded assessor, (as opposed to the chief investigator), who had no role in the follow-up assessment. Outcome measure data was stored as before in the sealed box.

10.8 TENS intervention protocol

Group one received active TENS, whilst group 2 received placebo TENS. The following description is for both the active and control TENS applications, unless stated otherwise.

10.8.1 TENS calibration

The TENS units were calibrated by the Medical Physics Department at Crosshouse Hospital, Kilmarnock, who confirmed that, for the specific model of TENS used in the study, the delivery of frequencies were as indicated on the dial. 44 TENS units were purchased for the study and a random sample of ten was selected for this calibration process.

10.8.2 TENS unit and settings

For both active and placebo TENS, the same TENS devices were used (‘*TPN 200 Plus TENS unit’*, from ‘Physio MED’) where pulses were delivered with an asymmetrical biphasic waveform in a continuous pattern. For the active TENS group ‘Conventional’

TENS settings were based on the findings of the literature review: A high frequency, low intensity electrical current was selected. A stimulation pulse frequency of 120 Hz and pulse width of 200 microseconds was pre-set by the chief investigator. A low intensity was created by slowly turning up the intensity dial until the point where the patient reported a *strong, but comfortable sensation* ('SBC').

The placebo TENS application was based on the initial theory of Chakour and colleagues (Chakour, 1998; Chakour *et al*, 2000), as well as settings identified from a recent systematic review as having no analgesic effect, but still providing a sensory stimulus (Claydon *et al*, 2011) (Section 8.4.1). A low frequency, low intensity, electrical current was used for this purpose: a pulse frequency of 4Hz and pulse width of 200 microseconds was pre-set by the chief investigator. As with active TENS, the intensity dial was turned up until the point where the patient reported a *strong, but comfortable sensation*. In this way, both placebo and active TENS settings were standardised, so that only the frequency differed between the two applications. The compartment which contained the output dials was taped up to ensure blinding was not compromised and that participants could not change settings, accidentally or otherwise. As placebo TENS still provides a sensory stimulus, all participants were adequately blinded to treatment group allocation. Treatment compliance was monitored in both the placebo and TENS groups as a means of evaluating successful group blinding (Koke *et al*, 2004; Oosterhof *et al*, 2007). Participants were thus asked to record their daily TENS application time in the participant pain diary (section 10.7.5).

In both the active and placebo TENS groups, to avoid tolerance to TENS, patients were advised to maintain the "*strong, but comfortable"* level of sensation by turning up the intensity dial if necessary. Patients were shown how to do this and were advised to do this as required during their TENS treatment.

10.8.3 Electrode Application

The skin was cleaned with a soap and water solution and checked again for any dermatological lesions. Any body hair was removed using a disposable razor and shaving foam. Two (13x 5cm) self-adhesive, hypo-allergenic electrodes were placed paravertebrally over the lumbar and sacral spinal area. Electrodes were placed 3cm lateral to the spinous process (SP). The top of each electrode was placed adjacent to the third lumbar vertebral spinous process. This was done using the bony landmark identification of

the spinous process of L4, which was identified using the intercrestal line joining the superior aspect of the iliac crests posteriorly (Kim *et al*, 2003; Render, 2008). This placement ensured that the length of the electrodes covered the spinal nerve roots L2 to S2. Electrodes were connected to a single TENS channel. The exact site of electrode placement was marked out on the skin, using indelible ink. Participants were carefully instructed on electrode placement, using the ink outline as mentioned, a mirror, and the use of bony landmarks. If a carer was going to apply the electrodes, they were also instructed in this process. The exact position of electrodes was illustrated in a diagram on the TENS information sheet. Participants were shown how to connect the lead to the unit and a spare battery was issued with instructions to replace after 28 hours of TENS use, or earlier if there were signs of low battery (i.e. diminished TENS sensation or light flickering or going out). Participants were instructed on safety, electrode and skin care and to contact the researcher immediately if any reaction occurred. In this case, extra-sensitive electrodes would be used if appropriate. Each participant was telephoned 24 hours after initial TENS application to check if there had been any problems in relation to TENS application.

10.8.4 Duration of TENS

Instructions were given to wear the TENS unit every day for a two–week period. Participants were advised to apply the TENS unit when they experienced pain. To standardise TENS use, participants were asked to wear it for a minimum of four hours per day (for at least one hour at a time). For example, participants could wear the unit for 4x 1 hour blocks throughout the day or continuously for four hours in one block. For ease of use, the electrodes could be left on for extended periods throughout the day, with the TENS lead disconnected from the machine, with instructions to check the skin regularly on a daily basis for any skin irritation. If the electrodes became in any way uncomfortable they were to be removed immediately and the researcher contacted.

10.9 Statistical Methods

Statistical methods used in the study are outlined as follows:

10.9.1 Sample size calculation

This was performed as outlined in Section 10.5

10.9.2 Primary outcome measure data

As the primary outcome measure, participants completed the 11-point numerical rating scale (NRS-11) of pain intensity once daily for the seven-day baseline and 14-day intervention periods. For statistical analysis, the mean score of the seven-days of baseline was used as the mean baseline score, whilst the mean endpoint score was the mean of the last seven scores recorded during the intervention period.

10.9.3 Secondary outcome measure data

The NPS was completed for 3 consecutive days at the end of the seven-day baseline period and 3 consecutive days at the end of the intervention period. For statistical analysis, the mean score of the 3 consecutive days of baseline was used as the mean baseline score, whilst the last 3 day scores recorded during the intervention period were used as the mean endpoint score. This was undertaken for the total mean NPS score (NPS-10), which is the sum of the ten subscales: *intensity, sharp, heat, dull, cold, sensitive, itchy, unpleasant, deep and superficial*, and for each of the ten individual components, as mentioned.

The BPI was completed once at baseline to give a baseline score and once post-intervention to give an endpoint score; both of which were used in statistical analysis. Mean baseline and endpoint scores were used in statistical analysis. This was done for the **total pain severity score** of the BPI (sum of the four subscales of: *worst pain, least pain, average pain and pain right now*), as well the four individual severity components.

This was also done for the **total Pain Interference score** of the BPI (sum of the seven subscales of: *general activity, mood, walking ability, normal work, relationships, sleep and enjoyment of life*) as well as changes in the seven individual interference components.

A single score was used from the PGIC, for statistical analysis; post TENS, based on completion of the 1-7 categories of the questionnaire. Binary data (*yes=1, no=0*) was entered for the measure '*would you use TENS again for this type of pain*?'

10.9.4 Data entry of the above variables

Raw data from outcome measures were entered into the Minitab statistical package (version 12). It was deemed that for all outcome measures used in the TENS study any missing values would render the total score invalid, and would be entered into Minitab as a missing value. Unlike the GNDS and the HADS used in the epidemiological study, there were not any sensitive questions within the TENS study questionnaires that potentially participants may to choose to omit. Missing values were not foreseen as a potential issue in the TENS study.

10.9.5 Data analysis

Continuous variables were assessed for normality through visual inspection of histograms, and calculation of skewness and kurtosis coefficients. Descriptive statistics were used to compare baseline data between the placebo and TENS groups for demographics and relevant pain variables, including: mean baseline duration and intensity of pain, NPS score, PDQ score and concomitant medication. This is supported by the IMMPACT recommendations for appropriate design of pain trials (Dworkin *et al*, 2010). Any differences between groups were further analysed: Chi-square analysis was used for categorical variables, and a 2-sample t.test used for normally distributed variables, whilst the Mann-Whitney test was used for variables not normally distributed. P values were from 2 sided tests, and statistical significance was determined by a p value of $<.05$.

The intention to treat population (ITT) was used for all efficacy analyses, as it is widely accepted as the most preferred analysis strategy (Herman *et al*, 2009; Hollis and Campbell, 1999). It was defined as all patients who were entered into the study, were randomised, issued with a TENS machine, and had on-treatment efficacy data. Per-protocol analysis was also undertaken, but only as a comparison with the ITT analysis as a supporting analysis.

For all efficacy scores (primary outcome measure- the NRS-11, and secondary outcome measures- the BPI, NPS), the change in scores from baseline to end of treatment (completion or withdrawal) was compared between the active and placebo TENS groups using analysis of covariance with the baseline score as the covariate. Efficacy was reported using the adjusted mean difference and its 95% confidence interval.

The proportion of participants to achieve a 30% reduction in mean pain intensity (on the NRS-11) from baseline, was compared between the placebo and TENS groups using a Chi-square test. This was also undertaken for the proportion of participants to achieve a reduction of 2 points on the NRS from baseline.

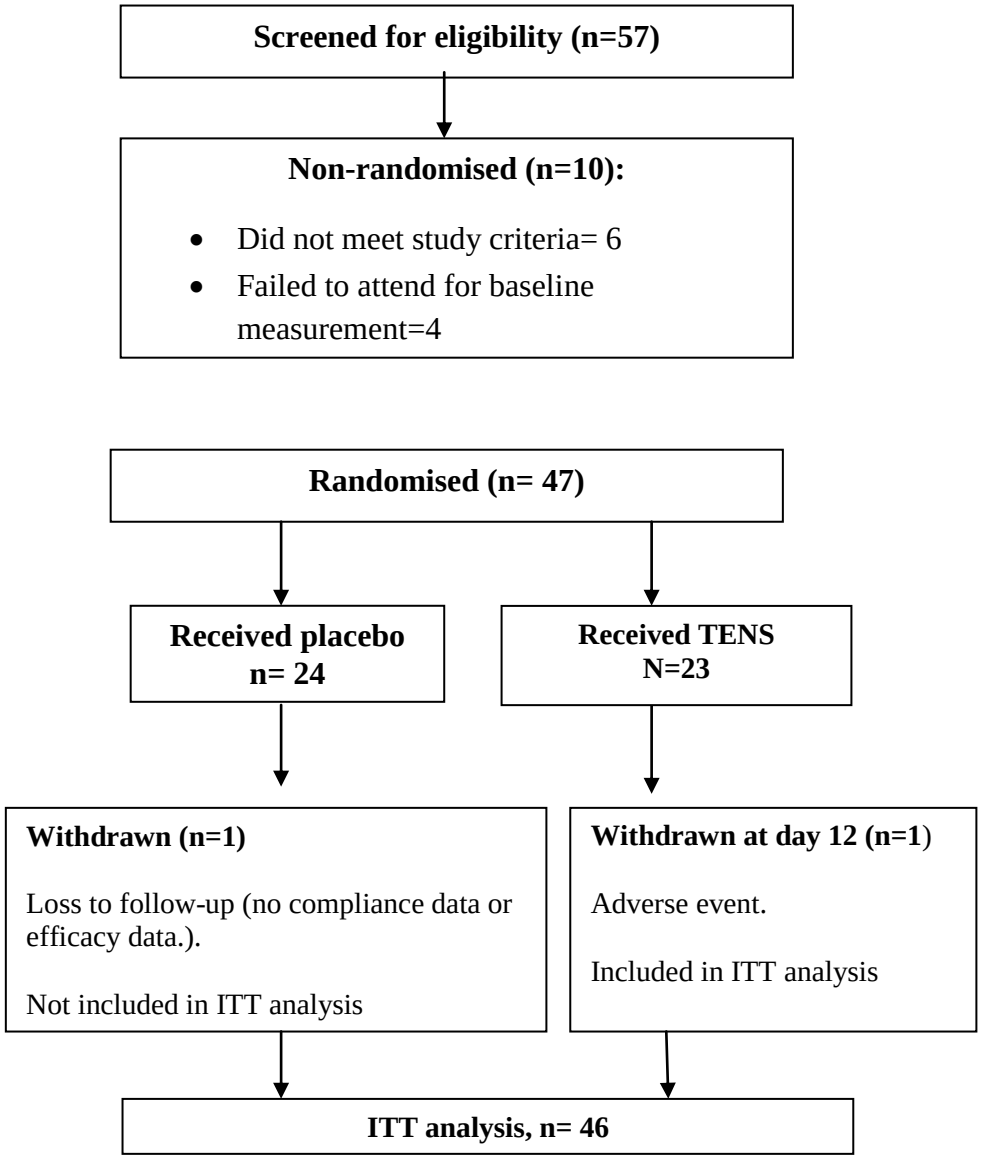
Post TENS PGIC scores and future willingness to use TENS data were also compared between placebo and TENS groups using a Chi-Square test.

11 RESULTS OF TENS STUDY

11.1 Flow of Participants

The flow of participants in the study is shown in Figure 11-1. Of the 57 participants initially screened for eligibility, 47 were randomised and entered into the study. Of the ten participants not entered into the study: six did not meet the study eligibility criteria (i.e. non-neuropathic pain confirmed by PDQ, or contraindications to the use of TENS). Four participants did not proceed to randomisation as they attended for screening but subsequently failed to attend for baseline measurement. Subsequently, 24 participants were randomised into the placebo TENS group and 23 into the active TENS group. For the placebo group, one female participant completed the 7-day baseline run-in period of data, was subsequently issued with a TENS machine, but failed to attend for follow-up measurement, providing no efficacy or compliance data, and was thus withdrawn. This individual was not included within the ITT analysis. In the TENS group one female was withdrawn from the study after suffering an incident of palpitations on day 12 of TENS. There was no evidence that this was directly related to the use of TENS, but treatment was discontinued immediately as a precautionary measure. 12 days of efficacy data was provided and the patient was included within the ITT analyses. Two participants in the active TENS group violated the protocol: one participant was commenced on a new opioid analgesic at the start of the TENS period, the second participant used TENS sporadically during the second intervention week. Both participants provided sufficient efficacy data and were included in the ITT analyses. Thus the ITT population analysed was n=46.

Figure 11-1: Flowchart of participants into the study



11.2 Baseline characteristics of sample

This section presents the baseline characteristics of the sample. It includes demographics, as well as disease and pain-specific variables, such as type of MS and use of concomitant medication. Values are presented firstly for the total sample, followed by the placebo and active TENS groups. Table 11-1 presents these variables for the total sample and compares the active TENS and placebo groups for statistically significant differences at baseline.

11.2.1 Demographics

From Table 11-1 it can be seen that of the 47 participants randomised, 34 had relapsing-remitting MS (72.3%), 11 (23.3%) secondary progressive and 2 (4.3%) primary progressive MS. The mean time since diagnosis (TSD) was 14.9 yrs (SD 8.5, range: 1-45), and a mean age of 47.9 (SD: 9.3, range: 27-69) years. Over three-quarters were female (76.6%) and the sample had a mean disability level (GNDS score) of 19.4 (SD 9.5, range: 4.4-40.4).

Placebo and TENS groups were well matched for the variables gender (*p=0.67),* age (*p=0.94*), type of MS (*p=0.66*) and disability level *(p=0.53),* with no statistically significant differences between them (Table 11-1).

However, there was an observed difference between the TENS and placebo groups for mean TSD, with the TENS group showing a mean TSD of 12.4 (6.7) years, and the placebo group a greater mean TSD of 17.5 (9.5) years. Using a 2-sample t.test, a statistically significant difference of 5.2 (95% CI= 0.31-10.0) years was shown between groups for TSD (*t value= 2.14; p= 0.04).* Although TSD is unlikely to affect the efficacy of TENS, it was felt important to explore whether this difference could have a potential impact on the primary outcome measure, change in average pain intensity from baseline (using the NRS-11 scale). A Pearson's correlation analysis was undertaken between TSD and change from baseline for the average pain intensity. No statistically significant relationship was revealed between TSD and change from baseline for average pain intensity *(p=0.16, r=-0.2)* thus the difference in groups was unlikely to affect TENS effectiveness and did not warrant further formal analysis.

11.2.2 Pain variables

From Table 11-1, it can be seen that the mean duration of pain for the total sample was nine years (SD 6.3, range: 6months- 22), the mean Neuropathic Pain Scale (NPS) score was 48.7 (SD15.2, range: 18.3-73.0), and mean Pain Detect Questionnaire (PD-Q) score 28.8 (5.4: range: 20.0-38.0), with approximately 80% (n=37) describing bilateral lower limb neuropathic pain. Table 1 shows that 34% of the sample (n=16) were currently using opioid analgesic medication. Almost 30% (n=14) of the sample were currently using Tricyclic Antidepressants (TCAs) for pain, and similarly, almost 30 % (n=14) were using anticonvulsant medication for pain. Muscle relaxants were currently used by 21.3% of the sample, whilst 19.1% (n=9) were using NSAIDs, 14.9% (n=7) were using non-opioid analgesics; and 6.45% (n=3) were currently using Benzodiazepines. Almost 40% (38.3%, n=18) of the total sample were currently on a disease modifying therapy (DMT) regime for their MS.

Placebo and TENS groups were well matched for the pain variables: mean duration of pain *(p=0.40),* average baseline pain intensity (NRS-11) *(p=0.38),* Neuropathic Pain Scale (NPS) *(p=0.91)* and Pain Detect Questionnaire (PDQ) scores *(p=0.69*), as well as the proportion of participants with bilateral or unilateral lower limb pain, with no statistically significant differences shown between the groups (Table 11-2).

However, there was a difference between the TENS and placebo groups for the proportion of participants currently using TCAs, with 43.5% (n=10) of participants currently using them in the TENS group, in comparison to only 16.7 % (n=4) taking them in the placebo group. Using a Chi–Square test for trend, a 'borderline' statistically significant difference of 26.8% was shown between groups for the proportion of participants on TCAs (X^2= *4.04; p= 0.05)*. As TCA's, have an effect on pain intensity, it was felt important to explore whether this difference had any potential impact on the primary outcome measure of change in average pain intensity (using NRS-11 scale). A 2-sample t.test illustrated that there were no statistically significant difference in change from baseline for average pain intensity in those currently taking TCAs versus those not taking this medication, with a difference of 0.43 between the two groups (*95% CI: 0.23-1.11*; *t value*=1.3; *p=0.2).* Thus the difference in the percentage of people taking TCAs between groups was unlikely to affect TENS effectiveness and did not warrant further analysis.

Table 11-1: Baseline demographics and pain variables

VARIABLE	Active TENS (n= 23)	Placebo TENS (n=24)	Total (n=47)	P.val ◊
Gender: n (%)				
Female	17 (73.9)	19 (79.2)	36 (76.6)	
Male	6 (26.1)	5 (20.8)	11 (23.4)	0.67
Age, (yrs) mean (SD), range	47.8 (8.4) 36-69	48.0 (10.08) 27-63	47.9 (9.3), 27-69	0.94
Time since MS diagnosis, (yrs) mean (SD), range	12.35 (6.67), 1-24	17.5 (9.5), 3-45	14.9 (8.5), 1-45	0.04*
Disability[1], mean (SD), range	20.5 (8.8) 4.4-40.4	18.2 (10.1), 7.4-24	19.4 (9.5), 4.4-40.4	0.53
Type of MS[2]:				
RRMS	18 (78.3)	16 (66.7)	34 (72.3)	
SPMS	5 (21.7)	6 (25.0)	11 (23.4)	
PPMS	0 (0)	2 (8.3)	2 (4.3)	0.66
Mean duration of pain, (yrs)	8.4 (6.7), 0.5-22	9.9 (5.9), 2-20	9.0 (6.3) 0.5-22	0.40
Mean baseline average pain intensity score[3]	6.7 (1.6), 3.9-9.1	6.3 (1.4), 3.1-9.1	6.5 (1.5), 3.1-9.1	0.38
Neuropathic Pain Scale Total Score	48.9 (16.5)	48.4 (14.1)	48.7 (15.2)	0.91
Baseline PDQ[4] ***score***	29.1 (5.4), 20.0-38.0	28.5 (5.6), 20.0-38.0	28.8 (5.4), 20-38.0	0.69
Neuropathic lower limb pain:				
Bilateral	17 (73.9)	20 (83.3)	37 (78.7)	
Unilateral, n (%)	6 (26.1)	4 (16.7)	10 (21.3)	0.47
Concomitant medication:				
Muscle relaxant	4 (17.4)	6 (25)	10 (21.3)	0.52
Benzodiazepines	1 (4.4)	2(8.3)	3 (6.4)	0.57
NSAIDs	3 (13.0)	6 (25)	9 (19.1)	0.29
Opioid	7 (30.4)	9 (37.5)	16 (34.0)	0.61
Non-opioid analgesics	2 (8.7)	5 (20.8)	7 (14.9)	0.24
Anticonvulsants	7 (30.4)	7 (29.2)	14 (29.8)	0.92
TCAs	10 (43.5)	4 (16.7)	14 (29.8)	0.04*
DMT [5]	8 (34.8)	10 (41.7)	18 (38.3)	0.63

◊statistical analysis of difference between TENS and placebo groups: categorical variables by X^2 analysis, all others by 2-sample t.test of means. * Indicates significant p.value

[1]Disability measured using the GNDS (Guys Neurological Disability Scale). [2]RRMS= Relapsing Remitting MS; SPMS=Secondary Progressive MS; PPMS=Primary Progressive MS.

[3]Based on mean NRS-11 score from 7 day baseline period in relation to neuropathic, lower limb pain (uni/bilat). [4]PDQ score≥19 indicates cases of neuropathic pain. [5]DMT=Disease Modifying Therapy

11.3 Efficacy Analysis

This section begins by presenting the results of the primary outcome measure analysis, the change in *average* pain intensity from baseline. This is followed by the findings of secondary outcome measure analysis, including: the *Neuropathic Pain Scale (NPS), Brief Pain Inventory (BPI), Patient's Global Impression of change (PGIC),* perceived pain relief from TENS, and likelihood of using TENS again for lower limb neuropathic pain. Results presented from this point onwards in the chapter focus on the ITT population only (n=46). A single 'per-protocol analysis' (n=43) for the primary outcome measure of average pain intensity is compared with that of the ITT analysis to strengthen the validity of the conclusions drawn and is presented in the results section.

11.3.1 Primary outcome measure: Average Pain Intensity

This section reports the effect of TENS on average pain intensity (as measured by the NRS-11). The change in mean pain intensity scores from baseline to endpoint is reported for the TENS and placebo groups. Baseline measurement was taken to be the mean of the seven repeated measures of daily pain score, from the seven consecutive days of the base-line period. Endpoint was taken to be the mean of the last seven repeated measures of daily pain score, from the last seven consecutive days of the TENS intervention period. Scores are based on intensity of *average* leg pain within the last 24 hours, using the NRS-11 scale of pain intensity, where a score of '0' indicates no pain and a score of '10' indicates worst pain. In this section '*average'* is used for descriptive purposes as it relates to overall pain experience within the last 24 hours, whereas '*mean*' relates to the arithmetical mean of participant scores.

11.3.1.1 Change in average pain intensity

The mean (SD) change in average pain intensity from baseline to endpoint is presented in Table 11-2 for the TENS and placebo groups. The mean (SD) reduction in pain intensity in the TENS group was 2.1 (0.8) compared to 0.9 (0.8) for the placebo group. This is a mean reduction in pain intensity from baseline of 31.8% (clinically significant) (Haanpää *et al,* 2011) in the TENS group, compared to 14.1% in the placebo group. The change in pain intensity data, from baseline to endpoint, was entered into a one-way analysis of covariance (ANCOVA) (using baseline NRS-11 data as the covariate) to identify any

significant difference between placebo and TENS groups for change in pain intensity. The results of the ANCOVA (Table 11-2) confirmed that the change in pain intensity was greater in the active TENS group compared to that of placebo, with an adjusted difference of means of 1.26 (*95% CI= 0.77-1.75; F=26.86, df= 1; p<0.001).* Thus active TENS was significantly more effective at reducing pain than placebo TENS, during the two week period.

Table 11-2: Mean (SD) change in average pain intensity

	TENS				Placebo				Endpoint comparison TENS-placebo*		
	N	Baseline	Endpoint	Change Baseline-endpoint	N	Baseline	Endpoint	Change Baseline-endpoint	Adjusted difference	95%CI	P.Value
Average level pain Intensity†	23	6.70 (1.6)	4.57 (1.8)	2.13 (0.8)	23	6.31 (1.5)	5.42 (1.7)	0.89 (0.8)	1.26	(0.77-1.75)	<0.001

*TENS-placebo difference in means from the analysis of covariance model, with baseline score as covariate

†PRIMARY EFFICACY MEASURE: Average pain intensity on NRS-11: average of 7 days baseline and last 7 days of TENS period as endpoint score.

11.3.1.2 Proportion of participants to achieve a clinically significant reduction in pain

The proportion of participants to display a clinically significant reduction in pain in presented for each of the groups. Clinically significant pain is defined here in two ways: i) a reduction of at least 2 points in the raw data of the NRS-11, and a 30% reduction from baseline.

Reduction of at least 2 points on NRS-11 scale

The previous section reported a statistically significant (*p<0.00)* mean reduction of 2.13 (0.8) points (on the NRS of pain intensity) for the TENS group, in comparison to the placebo group, which saw a reduction of 0.89 (0.8) points on the NRS, indicating a clinically significant effect of TENS over placebo.

The proportion of participants showing a clinically significant difference in pain intensity (>/=2 on NRS-11 scale) at endpoint was 73.9% (n=17) in the TENS group, compared with 8.7% (n=2) in the placebo group. Thus, almost three-quarters of the active TENs group showed a clinically significant reduction in pain. A chi-square test confirmed that TENS was more effective for providing a clinically significant reduction in pain intensity than compared with placebo (*p<0.001, X^2=20.17).*

30% reduction in pain from baseline

The previous section reported a statistically significant (*p<0.00)* mean reduction in pain intensity (on the NRS of pain intensity) of 31.8% (from baseline), in comparison to a reduction of 14% for the placebo group, indicating a clinically significant effect of TENS over placebo.

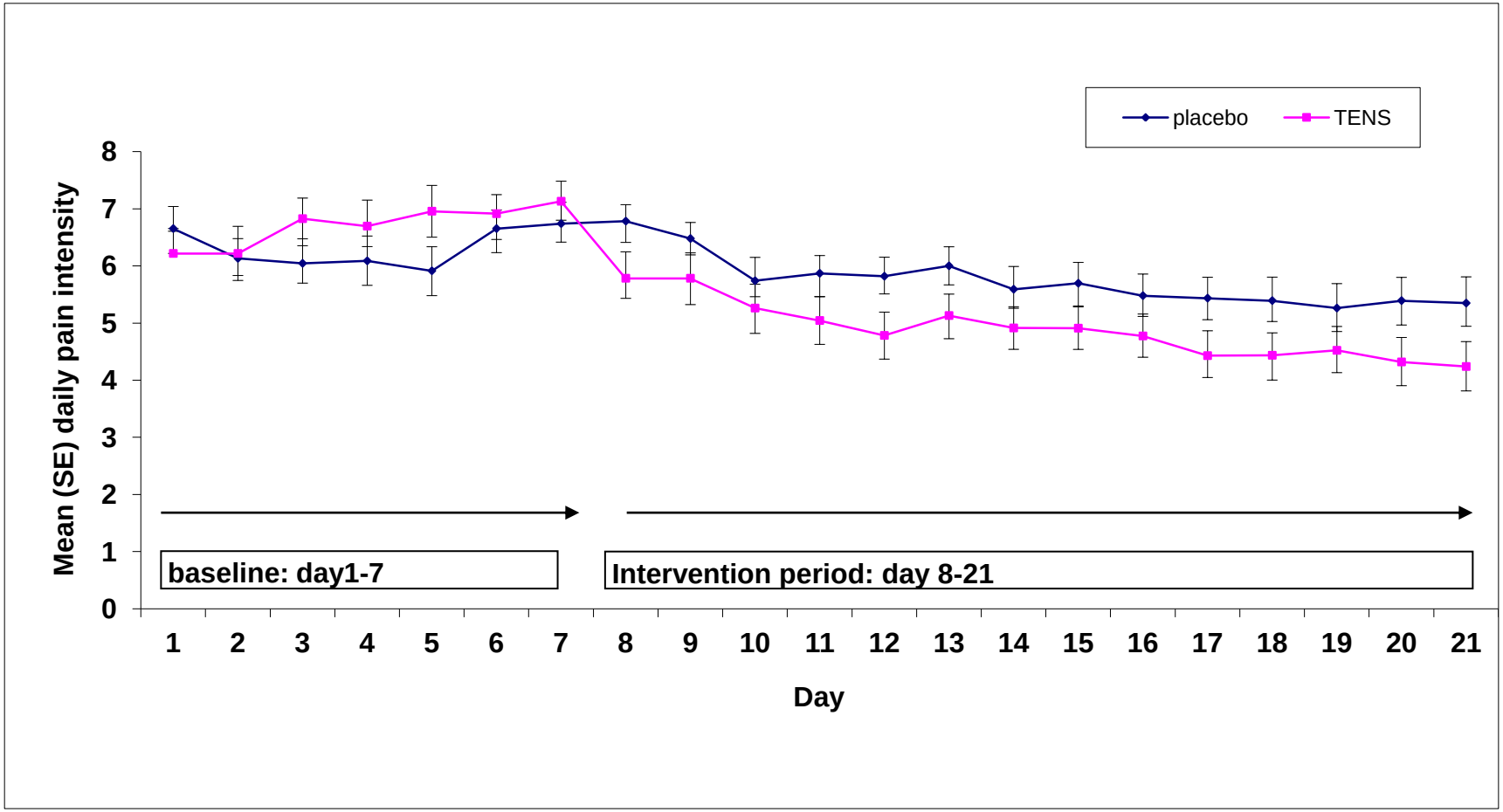
The proportion of participants to show a *30% reduction* in average level pain intensity from baseline in the active TENS group was 56.5%, in comparison to 17.4 % in the placebo group. A chi-square test confirmed that TENS was more effective for providing a clinically significant reduction in pain intensity than compared with placebo (*p=0.005, X^2 = 7.55)*

In summary a clinically significant reduction in pain intensity was found in the active TENS group over placebo.

11.3.1.3 Daily scores of average pain intensity

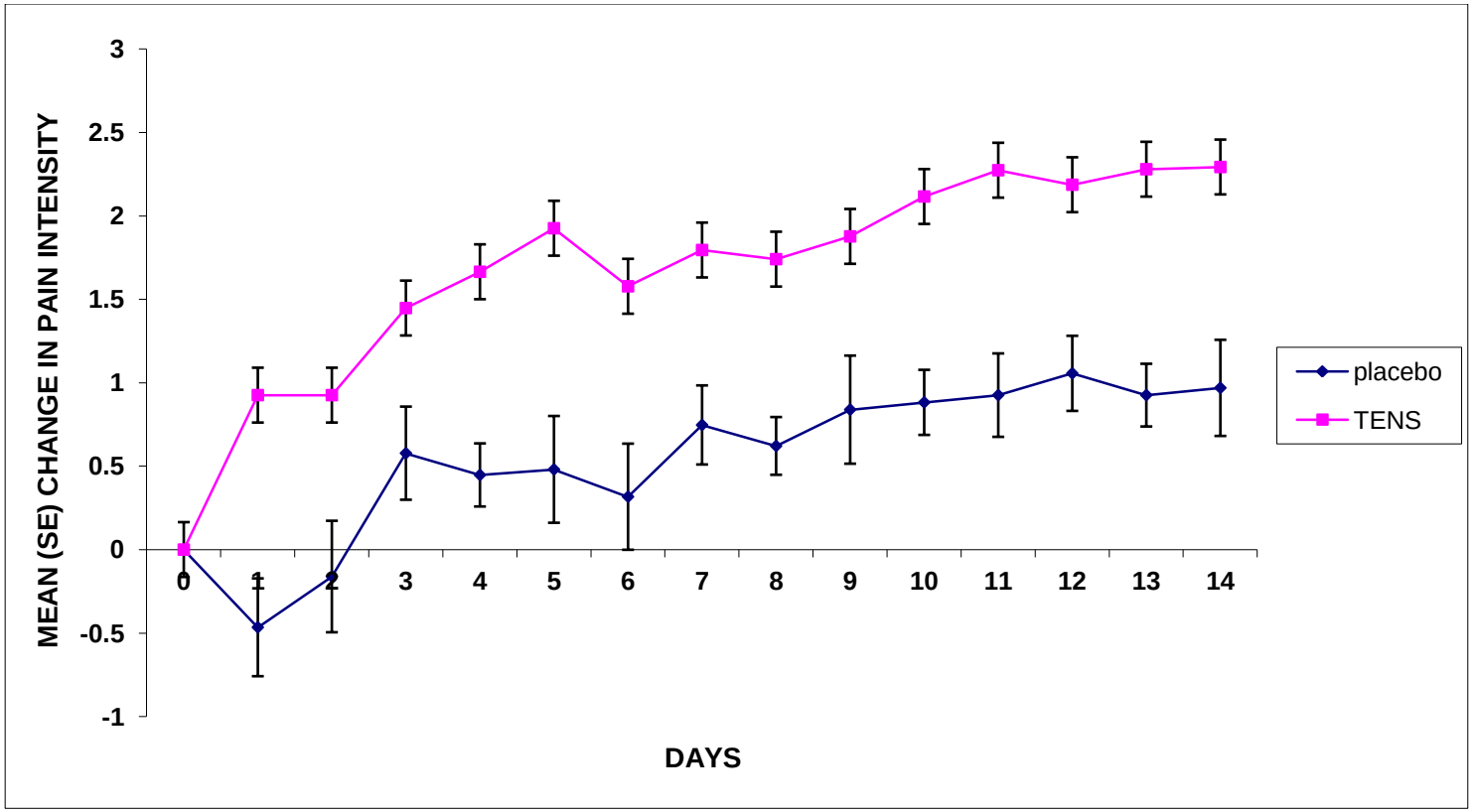
The mean daily pain intensity scores for the placebo and TENS groups are shown in Figure 11-2. The time period includes the 7-day baseline period and 14 days intervention period. Figure 11-3 shows the change in average pain score from baseline for each day of the 14-day intervention period for both the TENS and placebo groups. From Figures 11-2 and 11-3, it can be seen that TENS was more effective over placebo in reducing pain during the 2-weeks period. Figure 11-3 shows a similar separation of the groups throughout treatment time, therefore the effect of TENS is maintained throughout the treatment time. Figure 11-3 also shows that for the TENS group there is a cumulative mean decrease in pain intensity which begins immediately, and continues throughout the intervention period

Figure 11-2: Mean (±SEM) daily pain intensity scores*



*Mean daily pain intensity scores obtained from NRS-11 scale, reported at approx same time daily.
Relates to *average* lower limb, neuropathic pain within last 24 hours. TENS (n=23), placebo (n=23).

Figure 11- 3: Mean (±SEM) change in pain intensity score from baseline*



*Mean change in pain intensity = mean endpoint pain intensity score- mean baseline pain intensity score (mean of the 7 days). (Obtained using NRS-11scale, reported at approx same time daily).
Relates to *average* lower limb, neuropathic pain within last 24 hours, for the 14 day intervention period (1-14)
TENS (n=23), placebo (n=23).

11.3.2 Secondary outcome measure: Neuropathic Pain Scale

This section reports the effect of TENS on Neuropathic Pain Scale (NPS) scores. The changes in mean NPS scores from baseline to endpoint are reported for both the TENS and placebo groups. Firstly, it presents changes in the mean total NPS score (NPS-10), which is the sum of the ten subscales: *intensity, sharp, heat, dull, cold, sensitive, itchy, unpleasant, deep and superficial*. Secondly, the mean change in each of these individual components is also presented. Each individual subscale is rated on a 10-point NRS of intensity for that particular descriptor. For the *heat* subscale, for example: '0' indicates *no heat* and '10' would indicate the *most intense burning feeling imaginable.* Baseline was taken to be the mean NPS score from the three repeated measures of the NPS, completed on the last three consecutive days of the baseline period. Endpoint was the mean score from the three repeated measures of the NPS, completed on the last three consecutive days of the TENS intervention period. As before, scores relate to average leg pain within the last 24 hours.

Figures for a clinically significant reduction in NPS scores have not yet been established in the literature (Farrar, 2004). All changes in NPS scores are presented and statistical analysis used to confirm significant differences between the placebo and TENS groups.

11.3.2.1 Change in NPS-10: total score

The mean (SD) change in NPS-10 score from baseline to endpoint is presented in Table 11-3 for the TENS and placebo groups. The mean (SD) reduction in NPS score in the TENS group was 14.4 (6.6) points, compared to 5.2 (6.0) for the placebo group. The change in NPS-10 score, from baseline to endpoint, was entered into a one-way analysis of covariance (ANCOVA) (using baseline NPS-10 data as the covariate) to identify any significant difference between placebo and TENS groups for change in NPS-10 score. The results of the ANCOVA (Table 11-3) confirmed that the change in NPS-10 score was greater in the active TENS group compared to that of placebo, with an adjusted difference of means of 9.22 (*95% CI=5.48-12.95; F=24.76, df= 1; p<0.001).* Thus active TENS was significantly more effective at reducing neuropathic pain, as measured by the NPS, than placebo TENS, during the two week period.

11.3.2.2 NPS- individual descriptive components scores

The mean (SD) change in score for each of the ten individual components of the NPS, from baseline to endpoint, is presented in Table 11-3, for the TENS and placebo groups. From Table 11-3, changes from baseline can be seen in the TENS group for the individual NPS components: *heat, unpleasantness, intensity* and *deep pain*. For *heat*, the mean (SD) change in the TENS group was 2.07 (1.38), in comparison to 0.58 (0.97) in the placebo group. For *unpleasantness* the mean (SD) change in the TENS group was 1.86 (1.4), in comparison to 0.84 (1.34) in the placebo group. For *intensity*, the mean (SD) change in the TENS group was 1.74 (1.41), in comparison to -0.45 (0.72) in the placebo group. For *deep pain*, the mean (SD) change in the TENS group was 1.72 (1.54), in comparison to 1.05 (1.71) in the placebo group.

Each of the ten individual components of the NPS were analysed similarly, whereby the mean change in the component scores, from baseline to endpoint, was entered into a one-way analysis of covariance (ANCOVA) (using baseline component data as the covariate) to identify any significant difference between placebo and TENS groups for change in each component score. For the *heat* component, for example, the results of the ANCOVA (Table 11-3) confirmed that the change in NPS-*heat* score was greater in the active TENS group compared to that of placebo, with an adjusted difference of means of 1.4 (*95% CI=0.75-2.04; F=, df= 1; p<0.001).* Thus active TENS was significantly more effective at reducing the intensity of *burning pain*, as measured by the NPS, than placebo TENS, during the two week period.

Statistically significant reductions in component scores were also shown in favour of the active TENS group for the following components*: intensity* (*p<0.001), unpleasantness (p=0.016), deep pain (p= 0.009) and sharp pain (p=0.002)* (Table 11-3). However, for the *sharp* pain component, the mean change was a much smaller 0.44 (0.49). Thus, TENS was significantly more effective than placebo at reducing *burning* pain, *deep* pain, the *unpleasantness* of pain, the overall *intensity* of pain, and *sharp* pain, as measured by the NPS, over the two-week period. There was no significant difference between groups for the other five components of the NPS, including: *dull (p=0.31), cold (p=0.84), sensitive (p=0.14), itchy (p=0.42), and superficial pain (p=0.08).*

Table 11-3: Mean (SD) change in Neuropathic Pain Scale (NPS) score

Component	TENS				Placebo				Endpoint comparison TENS-placebo*		
NPS-10 total score¶	N	Baseline	Endpoint	Change Baseline-endpoint	N	Baseline	Endpoint	Change Baseline-endpoint	Adjusted difference	95%CI	P.value
	23	49.26 (16.18)	34.83 (16.91)	14.43 (6.58)	23	48.06 (14.82)	42.93 (14.31)	5.13 (6.02)	9.21	5.5-13.0	<0.001
NPS- Intensity	23	6.04 (1.82)	4.30 (1.91)	1.74 (1.41)	23	5.67 (1.61)	6.12 (1.77)	-0.45	2.09	1.27-2.90	<0.001
NPS-sharp	23	5.10 (3.20)	3.25 (2.55)	0.62 (0.49)	23	4.06 (3.0)	3.78 (2.77)	0.09 (0.53)	0.44	0.17-0.70	0.002*****
NPS-heat	23	5.39 (2.71)	3.32 (2.29)	2.07 (1.38)	23	4.88 (3.33)	4.30 (3.09)	0.58 (0.97)	1.40	0.75-2.04	0.0001*****
NPS-dull	23	4.32 (2.83)	3.16 (2.54)	1.16 (0.80)	23	4.16 (3.00)	3.51 (3.10)	0.7 (0.61)	0.48	-0.47-1.42	0.31
NPS-cold	23	2.94 (3.05)	2.39 (2.48)	0.55 (1.40)	23	2.83 (3.31)	2.23 (2.65)	0.59 (1.79)	-0.08	-0.85-0.69	0.84
NPS-sensitive	23	4.03 (3.09)	3.16 (2.60)	0.87 (2.0)	23	4.41 (2.88)	4.19 (2.62)	0.22 (2.05)	0.78	-0.27-1.83	0.14
NPS- itchy	23	3.74 (3.05)	2.90 (2.51)	0.84 (1.92)	23	4.42 (2.59)	3.75 (2.51)	0.67 (1.85)	0.40	0.60-1.39	0.42
NPS-unpleasant	23	6.87 (1.81)	0.01 (2.19)	1.86 (1.40)	23	6.86 (1.79)	6.01 (1.93)	0.84 (1.34)	1.01	0.20-1.82	0.016*****
NPS-deep	23	6.31 (2.16)	4.59 (2.29)	1.72 (1.54)	23	5.78 (2.44)	5.41 (2.42)	1.05 (1.71)	1.23	0.32-2.14	0.009*****
NPS-superficial	23	3.84 (2.81)	2.74 (2.32)	1.10 (1.26)	23	4.19 (3.2)	3.62 (2.71)	0.57 (1.52)	0.63	-0.073-1.33	0.078

*TENS-placebo comparison in means from the analysis of covariance model, with baseline score as covariate. ¶ NPS-10 total score includes**:** intensity, sharp, heat, dull, cold, sensitive, itchy, unpleasant, deep, superficial.

11.3.3 Secondary outcome measure: Brief Pain Inventory

This section shows the effect of TENS on the scores of the Brief Pain Inventory (BPI). The BPI has two distinct scales: the **Pain Severity** and **Pain Interference** scales and changes in scores are presented for each of these from baseline to endpoint.

For the **Pain Severity** section of the BPI, results will be presented for the total pain severity score (sum of the four subscales of: *worst pain, least pain, average pain and pain right now*), as well as changes in the four individual severity components. For the **Pain Interference** section of the BPI, results will be presented for the total interference score (sum of the seven subscales of: *general activity, mood, walking ability, normal work, relationships, sleep and enjoyment of life*) as well as changes in the seven individual interference components. Baseline score was completed once (one-day prior to beginning TENS). Endpoint score was completed once (post-TENS) at the end of the intervention period. Scores related to the interference of pain, within the previous week.

Figures for a clinically significant reduction in BPI scores have not yet been established in the literature. All changes in BPI scores are presented and statistical analysis used to confirm significant differences between the placebo and TENS groups.

11.3.3.1 Pain Severity

Total Pain Severity Score

The mean (SD) change in total pain severity score from baseline to endpoint is presented in Table 11-4 for the TENS and placebo groups. The mean (SD) reduction in pain severity score in the TENS group was 1.88 (0.68) points, compared to 0.60 (0.85) for the placebo group. The change in pain severity score, from baseline to endpoint, was entered into a one-way analysis of covariance (ANCOVA) (using baseline pain severity score data as the covariate) to identify any significant difference between placebo and TENS groups for change in total pain severity score. The results of the ANCOVA (Table 11-4) confirmed that the change in total pain severity score was greater in the active TENS group compared to that of placebo, with an adjusted difference of means of 1.34 (*95% CI=0.97-1.80; F=, df= 1; p<0.001).* Thus active TENS was significantly more effective at reducing total pain severity score, as measured by the BPI, than placebo TENS, during the two week period.

Individual pain severity components

The mean (SD) change in score for each of the four individual components of total severity score, from baseline to endpoint, are presented in Table 11-4, for the TENS and placebo groups. Changes from baseline can be seen in the TENS group for each of the four individual pain severity components (Table 11-4). For *worst* pain the mean (SD) change in the TENS group was 2.38 (1.36) in comparison to 0.65 (1.15) in the placebo group. For *average* pain, the mean (SD) change was 2.33 (1.53), in comparison to 0.74 (0.96) in the placebo group. For *pain right now*, the mean (SD) change in the TENS group was 1.57 (1.78) in comparison to 0.57 (1.81) in the placebo group. For least pain, the mean (SD) change in the TENS group was 1.24 (1.38), in comparison to 0.44 (0.90) in the placebo group.

Each of the four components were analysed similarly, whereby the mean change in the component score, from baseline to endpoint, was entered into a one-way analysis of covariance (ANCOVA) (using baseline component data as the covariate) to identify any significant difference between placebo and TENS groups for change in component score. For the *worst pain* component, for example, the results of the ANCOVA (Table 11-4), confirmed that the change in score was greater in the active TENS group compared to that of placebo, with an adjusted difference of means of 1.69 (*95% CI=1.01-2.36; F=, df= 1; p<0.001).* Thus active TENS was significantly more effective than placebo TENS at reducing the intensity of the *worst* pain experienced as measured by the BPI, during the two week period.

Statistically significant reductions in component scores were also shown in favour of the active TENS group for the other three pain severity components*: least pain* (*p=0.001), average pain (p=0.001), and pain right now (p=0.015)* (Table 11-4). Thus, active TENS significantly reduced all aspects of pain severity over placebo for the 2-week period.

11.3.3.2 Pain Interference

Total Pain Interference Score

The mean (SD) change in total pain interference score from baseline to endpoint is presented in Table 11-5 for the TENS and placebo groups. The mean (SD) reduction in pain interference score in the TENS group was 0.65 (0.39) compared to 0.47 (0.62) for the

placebo group; neither of which is a noticeable difference from baseline. The change in pain interference score, from baseline to endpoint, was entered into a one-way analysis of covariance (ANCOVA) (using baseline pain interference data as the covariate) to identify any significant difference between placebo and TENS groups for change in total pain interference score. The results of the ANCOVA (Table 11-5) confirmed that there was no significant change in total pain interference score between the TENS and placebo groups, with an adjusted difference of means of 0.18 (*95% CI=-0.13-0.5; F=, df= 1; p=0.2).* Thus active TENS had no greater effect on total pain interference score, as measured by the BPI, than placebo TENS, during the two week period.

Individual Pain interference components

The mean (SD) change in score for each of the seven individual components of total pain interference score, from baseline to endpoint, are presented in Table 11-5, for the TENS and placebo groups. From Table 11-5, a notable change from baseline can be seen in the TENS group for the *sleep* component with a mean (SD) change of 1.62 (1.07) in comparison to 0.91 (1.12) in the placebo group. The change in mean sleep score, from baseline to endpoint, was entered into a one-way analysis of covariance (ANCOVA) (using baseline *sleep* data as the covariate) to identify any significant difference between placebo and TENS groups for change in sleep interference score. The results of the ANCOVA (Table 11-5) confirmed that the change in sleep interference score was greater in the active TENS group compared to that of placebo, with an adjusted difference of means of 1.34 (*95% CI=0.82-1.86; F=, df= 1; p<0.001).*

Each of the seven pain interference components were analysed similarly, whereby the mean change in the component score, from baseline to endpoint, was entered into a one-way analysis of covariance (ANCOVA) (using baseline component data as the covariate) to identify any significant difference between placebo and TENS groups for change in component score. Apart from sleep, none of the other six components of the pain interference score, analysed individually, showed any significant change from baseline over placebo (Table 11-5). There was no significant change for *general activity (p=0.6), mood (p=0.71), walking ability (p=0.52), normal work (p=0.65), relationships (p=0.73), and enjoyment of life (p=0.62).*

This shows that the impact of TENS on sleep must be interpreted with caution, as the *sleep* section is one part of a seven-component pain interference scale, where TENS had no

effect on the other six components. However, with this in mind, it would appear that TENS was significantly more effective at reducing the individual sleep interference score, as measured by the BPI, than placebo TENS, during the two week period.

Table 11-4: Mean (SD) change in pain severity scores from the Brief Pain inventory (BPI)

Variable	TENS				Placebo				Endpoint comparison TENS-placebo*		
	N‡	Baseline	Endpoint	Change: Baseline-Endpoint	N	Baseline	Endpoint	Change: Baseline-Endpoint	Adjusted difference	95%CI	P.Value
†***Total pain severity score***	21	5.56 (1.66)	3.68 (1.55)	1.88 (0.68)	23	5.94 (1.29)	5.34 (1.40)	0.60 (0.85)	1. 34	0.97-1.80	<0.001
Worst pain	21	7.81 (1.97)	5.43 (1.66)	2.38 (1.36)	23	7.70 (1.26)	7.04 (1.30)	0.65 (1.15)	1.69	1.01-2.36	<0.001
Least pain	21	3.19 (2.34)	1.95(1.60)	1.24 (1.38)	23	4.0 (2.09)	3.57 (2.04)	0.44 (0.90)	1.04	0.44-1.64	0.001
Average pain	21	6.14 (1.85)	3.81 (2.02)	2.33 (1.53)	23	6.30 (1.10)	5.57 (1.62)	0.74 (0.96)	1.62	0.85-2.39	<0.001
Pain right now	21	5.10 (2.64)	3.52 (2.14)	1.57 (1.78)	23	5.74 (2.16)	5.17 (2.27)	0.57 (1.81)	1.24	0.26-2.22	0.015

*TENS-placebo difference in means from the analysis of covariance model, with baseline score as covariate

‡ Two missing values in TENS group. †Total pain severity score includes: *worst pain, least pain, average pain and pain right now*, where 0= no pain and 10= worst pain.

Table 11-5: Mean (SD) change in pain interference scores from the Brief Pain inventory (BPI)

Variable	TENS				Placebo				Endpoint comparison TENS-placebo*		
	N ‡	Baseline	Endpoint	Change: Baseline-Endpoint	N	Baseline	Endpoint	Change: Baseline-Endpoint	Adjusted difference	95%CI	P.Value
Total Pain† Interference Score	21	5.31 (2.41)	4.66 (2.29)	0.65 (0.39)	23	5.27 (2.15)	4.8 (2.08)	0.47 (0.62)	0.18	-0.13-0.50	0.20
General activity	21	5.71 (2.49)	5.48 (2.46)	0.24 (0.63)	23	5.39 (2.37)	5.04 (2.33)	0.35 (0.98)	-0.14	-0.64-0.37	0.60
Mood	21	5.19 (3.09)	4.57 (3.04)	0.62 (0.97)	23	5.35 (2.35)	4.57 (2.54)	0.78 (1.59)	-0.15	-0.96-0.66	0.71
Walking ability	21	5.08 (2.77)	4.71 (2.61)	0.37 (0.66)	23	5.36 (2.76)	4.80 (2.62)	0.56 (0.10)	-0.16	-0.66-0.34	0.52
Normal work	21	5.15 (2.81)	4.56 (2.56)	0.59 (0.89)	23	5.50 (2.27)	5.02 (2.23)	0.45 (1.57)	0.17	-0.57-0.91	0.65
Relationship	21	4.75 (3.45)	4.14 (3.20)	0.61 (1.05)	23	4.43 (2.89)	3.96 (3.02)	0.47 (1.17)	0.11	-0.56-0.78	0.73
Sleep	21	6.14 (2.95)	4.52 (2.36)	1.62 (1.07)	23	6.0 (2.83)	5.74 (3.03)	0.91 (1.12)	1.34	0.82-1.86	<0.001
Enjoyment of life	21	5.14 (3.15)	4.62 (2.96)	0.52 (1.03)	23	4.83 (2.59)	4.48 (2.60)	0.35 (0.98)	0.15	-0.45-0.74	0.62

*TENS-placebo difference in means from the analysis of covariance model, with baseline score as covariate

‡ two missing values in TENS group

†Pain interference score= Total score from the Interference scale of the BPI (*mean of general activity, mood, walking ability, normal work, relationships, sleep and enjoyment of life),* where 0= no interference and 10= completely interference. Completed once at baseline and once post TENS

11.3.4 Patients global impression of change (PGIC) scale

This section presents the results of the PGIC scale, where participants indicate the overall change they have felt since beginning TENS in relation to their pain. The scale is from 1-7, where 1= very *'very much improved', and 7= 'very much worse'.* It has previously been shown that scores indicating much or very much improved on the PGIC are clinically significant (Farrar, 2001). Thus the percentage of participants to score a minimum score of 2 on the PGIC (indicating that pain is *much or very much improved*) is shown in this section.

Results showed that 47.6 % (n=10) of participants in the active TENS group scored >/=2 on the PGIC in comparison with 8.7% (n=2) of participants in the placebo TENS group. A chi-square analysis confirmed that there was a statistically significant difference between the placebo and TENS groups of 38.9% (*p= 0.004, X^2= 8.39; df=1).* Thus, those in the active TENS group were significantly more likely to describe a much or very much improvement in overall pain state, than those who received placebo.

11.3.5 Patient's perception of pain relief from TENS

At the end of the intervention period, participants were asked to rate their percentage pain relief since beginning TENS. The 10-point % Pain Relief Scale from the BPI was used as a post-intervention outcome measure, where 0% indicated *no pain relief* and 100% indicated *total pain relief.* The mean percentage pain relief score in the placebo group was 16.5% (SD 13.5%), in comparison to 27.1% (SD of 12.7%), for the TENS group.

A 2-sample t.test was used to confirm whether there was a statistically significant difference between the groups. Results revealed that participants in the active TENS group described significantly more pain relief than those in the placebo group, with a difference of means of 10.6% (*CI: 2.8%-18.5%; t= 2.74; p=0.01).* Thus, those in the TENS group reported 10.6 % more *perceived* pain relief from TENS than that of the placebo group.

11.3.6 Would you use TENS again for this type of pain?

At the end of the intervention period, participants were asked: *Would you use TENS again for this type of pain?* Results revealed that 69.5 % (n=16) of those in the placebo group would use TENS again, in comparison with 81.0% (n=17) in the TENS group, a difference of 12% between groups. Chi-square analysis confirmed that there was no statistically significant difference between the groups (*p=0.38, X^2= 0.76).* Therefore, the efficacy of TENS in relation to pain relief does not appear to predict future willingness for TENS use.

Albeit, the number in the placebo group giving a positive rating was high, making it difficult for the placebo group to do significantly better.

11.4 Success of blinding and compliance

Successful blinding would be indicated by both groups (active TENS and placebo TENS) displaying a similar TENS application time, following the 2-week intervention period.

The total mean TENS application time for the active TENS group (for the 2-week period) was 65.4 hours. The total mean TENS application time for the placebo group for (the 2-week period) was 61.7 hours. The mean (SD) daily TENS application was 4.7 hours (1.2), whilst the mean daily placebo application was 4.4 (1.0) hours. Using a 2-sample t.test, a *non* statistically significant difference of 0.3 (95% CI= -0.4 to 0.9) hours was shown between groups for TENS application time (*t value= 0.80; p= 0.43; df=43).* With similar compliance levels in both groups, it would therefore appear that successful blinding took place in the study.

Participants were instructed to wear the TENS unit for a minimum of 4 hours/day. Thus the results also indicate that compliance was high in both groups.

11.5 Per-protocol analysis

As mentioned, all analysis in this chapter was done on the ITT population (n=46). However, a single 'per-protocol analysis' (PP) (n=43) was undertaken for the primary outcome measure, whereby the individuals who violated protocol were removed from analysis (detailed in Section 11.1, previously in this chapter). As outlined, for the placebo group, one female participant completed the 7-day baseline run-in period of data, was subsequently issued with a TENS machine, but failed to attend for follow-up measurement, providing no efficacy or compliance data, and was thus withdrawn. This individual was not included within the ITT or PP analyses. In the TENS group one female was withdrawn due to an adverse event on day 12 of TENS. 12 days of efficacy data was provided and the patient was included within the ITT analyses, but not in this section for the PP analysis. Two participants in the active TENS group violated the protocol: one participant was commenced on a new opioid analgesic at the start of the TENS period, the second participant used TENS sporadically during the second intervention week. Both participants

provided sufficient efficacy data and were included in the ITT analyses, but again were not included in this section for the PP analysis. Thus a PP analysis of n=33 was undertaken to compare with the findings of the ITT analysis of n=46. A similar ANCOVA analysis of the primary outcome measure (change in NRS-11 pain intensity) for placebo and TENS groups was undertaken for the per-protocol population (n=43). This particular analysis gave similar results to the ITT analysis, presented previously in Table 11-2. The validity of the conclusions based on the analysis of the ITT population in this chapter, are therefore strengthened. A comparison of the ANCOVA analysis for the change in average pain intensity for the ITT and PP populations is shown in Table 11-6.

Table 11-6: Comparison of ANCOVA analysis for primary outcome measure for the Intention to treat (ITT) and Per Protocol (PP) populations of study

Population	Variable	TENS				Placebo				Endpoint comparison TENS-placebo*		
ITT▲ Population	Average pain intensity†	N	Baseline	Endpoint	Change Baseline-endpoint	N	Baseline	Endpoint	Change Baseline-endpoint	Adjusted difference	95%CI	P.Value
		23	6.71 (1.6)	4.57 (1.8)	2.1 (0.8)	23	6.32 (1.5)	5.43 (1.7)	0.9 (0.8)	1.26	(0.75-1.74)	<0.001
PP◊ Population	Average Pain intensity†	20	6.44 (1.5)	4.31 (1.7)	2.1 (0.8)	23	6.32 (1.5)	5.43 (1.7)	0.9 (0.8)	1.26	(0.75-1.74)	<0.001

†PRIMARY EFFICACY MEASURE: Average pain intensity on NRS-11: average of 7 days baseline and last 7 days of TENS period as endpoint score
*****TENS-placebo difference in means from the analysis of covariance model, with baseline score as covariate
▲ ITT= intention to treat population (n=46)
◊ PP = per-protocol population (n=43), where 4 people were removed for protocol violation.

12 DISCUSSION OF TENS STUDY

The previous results chapter showed that **TENS had a hypoalgesic effect over placebo in central neuropathic pain in the MS patient.** This chapter will discuss these findings in relation to MS specifically; in the context of MS as a neuropathic pain condition, and then will consider findings in relation to other chronic pain literature. The chapter will subsequently consider the clinical significance of findings, and implications for practice and future research.

12.1 Efficacy of TENS for central neuropathic pain in MS

This section will discuss the central finding that TENS had a statistically and clinically significant hypoalgesic effect over placebo in central neuropathic pain in the MS patient. It will also discuss the findings that TENS reduced both *average* and *worst* pain intensity, the emotional unpleasantness of pain and was particularly useful for the neuropathic pain qualities *burning* and *shooting pain*.

TENS was effective in decreasing the intensity of pain (NRS-11) in the MS patient with central neuropathic pain, more effectively than placebo ($p<0.001$) (Table 11-2). This is an original finding, not explored in previous literature. Warke *et al,* (2006) reported a non-significant reduction in non-specific low back pain in MS patients, whilst Chitsaz *et al*, (2009) found TENS to be as effective as Nortyriptaline in MS patients with sensory complaints of the upper extremities, which was not confirmed as being of neuropathic pain origin. Miller *et al*, (2007) also noted the hypoalgesic effect of TENS, in MS patients with lower limb spasticity. As a high quality, adequately powered study, this study therefore provides initial evidence to highlight the clinical potential of TENS in the treatment of central neuropathic pain in the MS patient.

TENS was effective in specifically reducing neuropathic pain (Neuropathic Pain Scale (NPS) more effectively than placebo TENS ($p<0.001$) (Table 11-3). Unlike many drug trials of neuropathic pain conditions, including those as a results of MS (Breuer *et al*, 2007; Langford *et al*, 2013), no previous TENS study has used a neuropathic pain-specific measure, making comparison of the current study findings impossible. The NeuPSIG guidelines recommend a neuropathic pain-specific measure in addition to a generic measure of pain intensity (Haanpää *et al*, 2011) as generic measures fail to measure the full neuropathic pain experience, or identify subgroups of patients with neuropathic pain that

may benefit from specific treatments. For the ten individual subscales of the NPS, TENS was significantly more effective than placebo at reducing *burning pain (p<0.001), deep pain (p=0.009),* and *sharp pain (p=0.002)* (Table 11-3), which is a clinically useful finding for MS patients experiencing these sensations. These findings are in contrast to a study which looked at the effect of Levetiracetem (anticonvulsant) on central pain in MS, showing impact on shooting and sensitive pain only (as measured by the NPS) (Falah *et al*, 2012). Although two very different methodologies, the latter a drug trial, this highlights that different interventions may impact on different neuropathic pain qualities, an area of future study.

This is the first study to explore the effect of TENS on the affective component of chronic neuropathic pain. It showed that TENS was also significantly more effective than placebo at reducing the *unpleasantness* of pain, as measured by a sub-score of the NPS (*p=0.016*). The multidimensional nature of pain is understood with pain having both sensory-discriminative and motivational-affective components (Jensen and Karoly, 2011). Thus, the psychological aspects of chronic pain have been acknowledged in recent years, with the emotional response to pain proven to impact on the perceived severity of pain (Fernandez and Milburn, 1994). In turn, it has been shown in MS that the psychological interpretation of pain can impact on pain coping ability and long-term management (Douglas *et al*, 2008a). Thus the impact of TENS in reducing the emotional unpleasantness of chronic neuropathic pain has added clinical benefits. Future studies could explore the potential benefit of TENS in coping and self-management of chronic pain.

Clinically, it may occur that pharmacological intervention impacts only upon the intensity of pain and not on the affective component of pain, as has occurred previously in drug trials. If this situation were to present for the MS patient with neuropathic pain, TENS may be additionally useful in reducing the affective component of pain. Albeit, the effect of TENS in reducing the intensity of neuropathic pain in the MS patient is the main finding of the study.

12.2 Impact of TENS on MS as a neuropathic pain condition

Section 8.4.4.2 highlighted the inconclusive evidence for TENS in general for neuropathic pain, noting that the evidence base included few adequately powered, randomised controlled trails, using IMMPACT recommended outcome measures. Alongside the current study, a recent high-quality, adequately powered study has also emerged

supporting TENS in the treatment of neuropathic pain: Buchmuller *et al,* (2012) highlighted the efficacy of Alternating Frequency TENS (AFT) TENS in chronic low back pain over sham TENS, showing greater pain relief on a VAS of pain intensity for those with a *neuropathic* component to their pain (neuropathic leg pain± low back pain). TENS was applied at a strong (non-noxious) level, for 4 hours/day (as with the current study), which is a much longer application than previous studies of TENS in clinical populations (Moore and Shurman, 1997; Norrbrink, 2009; Warke *et al*, 2006) This was a large-scale, multi-centre study of 236 participants which consolidates the evidence base for the use of TENS in neuropathic pain.

As previously discussed, there is a particular lack of evidence for TENS as a treatment for *central* neuropathic pain, (section 8.4.4.2). Recently a high quality RCT of AL-TENS versus sham TENS was undertaken on 33 patients with central neuropathic pain due to spinal cord injury, showing a significant effect of TENS on a VAS of pain intensity (Celik *et al*, 2013) which is in contrast to a previous study, showing no effect of TENS on the intensity of spinal cord injury pain (Norrbrink, 2009).

From the current study, there is evidence for the efficacy of TENS in central pain in MS, and from other literature, there is conflicting evidence of efficacy for TENS in another central neuropathic pain disorder: spinal cord injury. To-date no studies have explored the effect of TENS on central–stroke-pain, another common manifestation of central pain (Jönsson *et al*, 2006). To conclude upon the efficacy of TENS overall for central neuropathic pain, further adequately powered studies, such as the current study are required. IMMPACT recommended outcome measures should be used, which use neuropathic pain-specific measures, such as the NPS. Hopefully this will be prompted by the awaited Cochrane systematic review on the efficacy of TENS in neuropathic pain (Claydon *et al*, 2010).

At the point of literature review evidence pointed to the use of conventional TENS in the current study over AL-TENS, and the efficacy of AFT over other modes of TENS was inconclusive (Law and Cheing, 2004). However, the findings of these recent studies (Buchmuller *et al*, 2012; Celik *et al*, 2013) calls for further comparison of AFT with AL-TENS and conventional TENS in the treatment of neuropathic pain. Conventional TENS was very effective for the MS patient in the current study, but as different modes of TENS have not been compared in MS this could be an area of further research.

12.2.1 Clinically significant reduction in pain

Although the NRS-11 is accepted as a primary outcome measure in clinical pain trials, the clinical significance of a potential pain reduction must also be interpreted. As already stated, it is recommended that a 30% reduction from baseline be used to determine a clinically significant reduction in pain intensity (Haanpää *et al*, 2011), or a reduction of ≥2 points on the NRS/≥20 mm VAS (Farrar, 1999; Warke *et al*, 2006), with both methods used in the TENS/chronic pain literature (Section 9.3), and the current study to allow comparison.

The current study showed a clinically important mean reduction in pain intensity. The TENS group saw a significant reduction of 2.1(±0.8) points on the NRS-11, in comparison to 0.9 (±0.8) for the placebo group (*p<0.001*). This is a reduction of 31.8% for the TENS group, and 14% for the placebo group from baseline. Furthermore, over half of the TENS group (56.5%) showed a clinically significant reduction in pain (30% reduction from baseline) in contrast to17.4% of the placebo group (*p=0.005*). However, one must remember that this difference of 2.1 for the TENS group is the *within group change* only, and will therefore be a combination of TENS, placebo effects and baseline differences.

Similarly, in other studies of TENS in chronic pain populations, pain intensity decreased on average by 28.5% (Oosterhof *et al*, 2006) and 33.5% (Köke et al, 2004) from baseline after 2-weeks of TENS. Also in line with the current study findings, and specifically in MS populations: Chitsaz *et al*, (2009) reported a clinically significant reduction in pain intensity of 2.0 points (NRS-11) after an eight week period of TENS, for pain of the upper extremities and Warke *et al*, (2006) reported a change of 3.0 (±0.8) points from baseline after 6 weeks of conventional TENS, with 63% showing a clinically significant reduction in pain (>20mm VAS) for low back pain. Conversely, Law and Cheing (2004) reported a higher mean reduction of pain from baseline of 86.5%, with scores reducing from 5.2(±0.7) to 0.7(±0.2) following 10 days of conventional TENS. This size of reduction stands out from previous literature and may reflect the different clinical sample, which was a population with knee OA, with a mean age of 84.3 years. However, as with the current study, an immediate pain reduction was noted, and continued to decease cumulatively to the end of the 10 day intervention period. The length of the intervention period varies in these studies, which may have impacted upon the size of pain reduction reported. This is discussed further in relation to trends in pain reduction (Section 12.3.1).

Historically, a ≥50% reduction in the NRS has been used to classify treatment response. As a 30% reduction is clinically important, many studies risk minimising treatment effects: Recently Buchmuller *et al,* (2012) reported the efficacy of TENS in patients with chronic low back pain, stating that 25% had reported a clinically significant improvement in pain from baseline (in comparison to 6.7% in the placebo group). This is almost half the proportion of participants to achieve a clinically significant reduction in pain in the current sample (56.5%). However, Bunchmuller *et al,* (2012) determined a clinically significant reduction in pain as a ≥50% reduction in VAS from baseline after the 3 month intervention period. As correlated with the PGIC, this translates to "*very much improved",* or a decrease of 4 points (Dworkin *et al,* 2008). The authors do not provide any further data on the proportion of patients who achieved less, such as a ≥30% reduction of pain, which may correlate with a minimum of "*much improved"* from the PGIC, which, from a clinical perspective, is important. Without any further data given on those who scored less, participants who did not achieve a 50% reduction would be counted as a 'non- responder', despite having much improvement from TENS.

Controversy over the definition of a clinically significant reduction in pain may also exist as it is perceived as an arbitrary concept: whether or not a particular change in pain represents an important change can depend on the clinical and situational context. For example, the level of change in pain that is considered important is influenced by baseline pain level, the chronicity of pain, as well as its pattern, i.e. *constant, intermittent, paroxysmal*, and quality, i.e. *burning, stabbing* pain. It may also vary by age, gender, the patient's clinical condition, affective response to pain, and prior treatment response (Dworkin *et al*, 2008). For example, part one of this thesis revealed distinct differences between MS patients with neuropathic and non-neuropathic pain. Those with neuropathic pain experienced more severe, emotionally unpleasant pain that was less likely to be relieved by prescribed pain-relieving medication (Table 6-6). Those with neuropathic pain also experienced lower scores for health-related quality of life (HR-QOL) (Table 6-6). With these differences in mind, would the definition of a clinically significant reduction in pain also vary between the two groups? Future studies are needed to explore the definition of a clinically significant reduction in pain in specific clinical conditions (i.e. those with central neuropathic pain, i.e. MS versus non-neuropathic pain), and other contributory factors mentioned, such as age, and gender.

In summary, the application of TENS lead to a clinically significant reduction in central, neuropathic pain in the MS patient after 2 weeks of treatment, which is in line with the

findings of other chronic pain populations. Future studies may explore the meaning of clinically significant pain in the MS population.

12.2.2 Trends in pain reduction

The current results showed an immediate reduction in pain after the first day of treatment that continued to cumulatively decrease (significantly over placebo) throughout the two-week intervention period (Figure 11-2). Similarly, other studies also reported an immediate and cumulative decrease in pain intensity over 2 weeks (Oosterhof *et al*, 2006; Köke et al, 2004) and 10 days (Law and Cheing, 2004). In MS patients Warke *et al*, (2006) reported a change of 3.0 (±0.8) points from baseline after 6 weeks of conventional TENS; a reduction of 2.6 (±0.7) points after 10 weeks, and a reduction of 1 point after 32 weeks, showing pain reduction to peak within the first six weeks of the study. By contrast, AL-TENS was also used in this previous study, and saw a reduction of 2.0 points (±0.7) from baseline after 6 weeks, 1.3 (±0.5) points after 10 weeks and 2.3 (±0.6) points after 32 weeks, showing the longer term benefits of TENS in pain reduction in MS. However, Chitsaz *et al*, (2009) also highlighted the longer term benefit of conventional TENS for MS patients after the 6-week mark, reporting a clinically significant reduction in pain intensity of 2.0 (±0.5) points after 8 weeks, with mean differences of only 1.0 (±0.3), and 1.5 (±0.4) points at two weeks, and four weeks of TENS respectively. Often studies use a pre/post measure of pain intensity only, without illustrating trends in pain intensity throughout the TENS intervention period, which makes trends in pain reduction over time difficult to evaluate (Buchmuller *et al*, 2012).

Long term pain relief has also been shown in the literature, highlighting the potential clinical usefulness of TENS in managing a chronic condition. Prospective trials of TENS in chronic pain have followed up participants for the period of one year, with approximately 30% of participants still reporting satisfaction (and willing to continue) with TENS after this period (Lampl *et al*, 1998; Oosterhof *et al*, 2012). Retrospectively, a questionnaire of 250 patients with chronic pain, who had participated in a TENS trial, and had initially experienced pain relief was undertaken (Persson *et al*, 2010). After four years, 74% of participants (n=155) continued to use TENS on a regular basis for pain relief, with 32% (n=50) reporting daily use. This is clinically relevant as many MS patients suffer pain intermittently throughout the duration of their disease. However mean pain intensity was not measured in these studies over the longer term, as recommended by the IMMPACT recommendations (Dworkin *et al*, 2005).

In summary, literature shows variability in the effect of TENS over time. As with other studies, the present study saw TENS to be immediately effective, with a cumulative decrease over the 2-week period. There is also evidence that pain reduction may continue for up to 8 (Chitsaz *et al*, 2009) and 32 weeks in the MS patient (Warke *et al*, 2006), although this latter study was not statistically significant over placebo. In other chronic pain conditions, there is some evidence of continued benefit from TENS for years, albeit this is not based on a continued reduction in VAS/NRS of pain intensity. Further research is needed to chart pain intensity using IMMPACT recommended outcome measures, over a longer period of time, in the MS population and other chronic pain conditions.

12.2.3 Impact of TENS on MS pain experience

Impact on pain severity components

The study showed a statistically significant mean reduction (NRS-11) for active TENS, over placebo in all four of the pain severity components of the Brief Pain Inventory (BPI), from baseline: *worst pain* (2.38) (±1.4) points, *average pain* (2.33) (±1.5), *pain right now* (1.57) (±1.8), *and least pain* (1.24) (±1.4) (Table 11-4). The current study has shown that TENS significantly reduced all categories of pain of the BPI, which is clinically significant as it meets with the multi-dimensional nature of the pain experience discussed throughout this thesis. One is most interested in the statistically significant reduction in *average pain*, as that is the most reliable measure of daily typical pain, endorsed by the literature (Jensen and Karoly, 2011). The change in the *average pain* component of the BPI of 2.33 (±1.5) points correlates well with the findings of the primary outcome measure (*average daily pain* in the last 24 hours on the NRS-11) which was a change in 2.13(±0.8) points; further validating the study findings.

The TENS/chronic pain literature has, to-date, not used the Brief Pain Inventory (BPI), so it is not possible to make a direct comparison, however similar trends have been noted in drug trials which have used the BPI. As with the current study, several drug trials of the treatment of neuropathic pain show that successful interventions impact simultaneously on both the level of *average* and *worst* pain components of the BPI, (Gimbel *et al*, 2003; Goldstein *et al*, 2005; Raskin *et al*, 2005). *Wors*t pain as a stand-alone efficacy measure has been criticised as it is more susceptible to catastrophizing behaviour than that of *average* pain level (Jensen and Karoly, 2011; Von Korff, 2011). In MS catastrophizing behaviour has been shown to affect the experience of and adjustment to pain (Osborne *et*

al, 2007). As there is link between pain catastrophizing behaviours and successful self management (Brook *et al*, 2011), TENS may also provide the patient with a coping mechanism for their chronic pain. This is part of the biopsychosocial approach to pain management of recent years, which addresses both the physiological and psychological drivers of the pain experience. Of course, these are only possible explanations for the role of TENS in reducing the level of *worst* pain reported in the current study. The impact of TENS specifically in catastrophizing and other pain behaviours/attitudes need to be formally tested in MS.

Impact on overall change in pain state

Results showed that those who received active TENS were significantly more likely to report that pain was *much or very much improved* (≥2 on the PGIC scale) (*p=0.004*). Almost half of the active TENS group (47.6%) were in this category. Farrar *et al* (2001) examined data from 10 clinical trials in which 2,724 patients with painful diabetic neuropathy, postherpetic neuralgia, low back pain, fibromyalgia, or osteoarthritis in which participants completed a 0 to 10 pain intensity NRS before and after treatment and a 7-point categorical scale of global impression of change (ranging from "*very much improved*" to "*very much worse*") after treatment. In this study (Farrar *et al*, 2001) pre/post-treatment decreases in pain intensity of ≥2 points or 30% were associated with patient ratings of at least "*much improved"* on the PGIC. Similarly, in the current sample, approximately half (56.5%) reported a 30% reduction in pain, *and* reported at minimum of "*much improved"* (47.6%), which further validates the findings of the study.

Although the NRS-11 of pain intensity is recognised as a valid and reliable primary outcome measure in chronic pain clinical trials, there is also a need to give findings clinical meaning. As mentioned, a clinically significant reduction in pain is an arbitrary concept, affected by baseline severity, pain type and duration, as well as the clinical population. Thus secondary outcome measures, such as the PGIC, provide a context for the effect of treatment and can substantiate the primary outcome measure, as with the current study. Unfortunately the chronic pain/ TENS literature does not adopt the PGIC, which is required of future studies.

12.3 Efficacy of TENS in chronic pain

There is a paucity of literature on the effect of TENS specifically in MS, or indeed neuropathic pain. As mentioned previously, there is much literature on the impact of TENS in chronic pain conditions in general, with Chapter 8 outlining the six systematic reviews undertaken on TENS in chronic pain conditions. This section will discuss the current study findings in the context of previous high quality studies of chronic pain and TENS. Each of these studies has been described in detail in Chapters 8 and 9, and includes a variety of chronic pain conditions, including musculoskeletal-related pain, such as osteoarthritis (OA), and low back pain (LBP), as well as pain related to neurological conditions, such as spinal cord injury (SCI). Several of the studies mentioned in this section combine chronic pain conditions of multiple origin, including neuropathic and non-neuropathic aetiologies.

The findings of the current study show that conventional TENS was effective in reducing the intensity of central neuropathic pain in the MS patient, as a chronic pain condition. Conventional TENS has also been effective in the chronic pain conditions: knee OA (Law and Cheing, 2004; Ng *et al*, 2003; Topuz *et al*, 2004), LBP (Moore and Shurman, 1997) and spasticity-related pain in MS (Miller *et al*, 2007) using IMMPACT validated measures. In these studies a standard application of conventional TENS was used: a high frequency, low intensity (strong, but comfortable) (*SBC*), application over the area of pain or within the same neuro-anatomical area for a minimum of *30 minutes*, with a minimum daily application of at least two hours. Section 12.2 also highlighted Alternating Frequency TENS (AFT) as effective in the treatment of chronic LBP, particularly with a neuropathic component. Again, TENS was applied at *SBC* intensity for a minimum daily application time of four hours (as with the current study). These clinical studies are supported by the findings of three adequately powered, high quality studies of experimental pain, where TENS was applied at a *strong but comfortable* (SBC) intensity showing hypoalgesic effects (Chen and Johnson, 2009; Chesterton *et al*, 2002; Simmonds *et al*, 1992)

Conversely, the lack of a statistically significant effect of conventional TENS over placebo in clinical studies of chronic pain has also been reported for the chronic pain conditions: LBP (Deyo *et al*, 1990; Warke *et al*, 2006), knee OA (Cheing *et al*, 2002; Jensen *et al*, 1991a; Lewis *et al*, 1994) SCI (Norrbrink, 2009), and mixed chronic pain (of neuropathic and non-neuropathic aetiology) (Koke *et al*, 2004; Nash *et al*, 1990; Oosterhof *et al*, 2007). Except for Warke *et al,* (2006), these studies do not adopt the advocated "SBC" intensity application. According to the principles of axonal excitation, pulse intensity (alongside

frequency) has a key role in excitation (Howson, 1978). Studies of experimental pain show that strong non-painful TENS is superior to just perceptible TENS (Aarskog *et al*, 2007; Lazarou *et al*, 2009; Moran *et al*, 2011a), implying that clinically patients must learn to titrate current to achieve a *strong but comfortable* (SBC) sensation (Johnson, 2011). It is also important that this intensity is maintained throughout treatment time (Johnson, 2012), which is why participants should be encouraged to turn up the intensity if sensation has reduced due to nerve accommodation (Pantaleao *et al*, 2011). Again, except for Warke *et al*, (2006), it unclear as to whether participants were instructed to do this. Therefore, a suboptimal intensity may have contributed to the inconclusive findings in previous studies.

Furthermore, these studies, which do not show a hypoalgesic effect of TENS over placebo, also show a trend towards shorter daily TENS applications of less than 2 hours/day, as previously outlined in section 9.1.2, highlighting the importance of TENS duration on successful pain relief. Guidelines state that TENS must be applied for a minimum of 30 minutes per episode to elicit therapeutic effects (Bennett *et al*, 2011), however there is no guidance on the minimum *daily* application time to elicit therapeutic effects.
The effect of daily dose of TENS is apparent in the following example: Warke *et al*, (2006) compared conventional TENS to placebo TENS in reducing pain in intensity in MS patients with non-specific low back pain, using a similar application as the current study, including the SBC intensity, and a parapsinal electrode application. However, Warke *et al*, (2006) applied TENS for a minimum of 90 minutes /day (twice daily for 45 minutes) in contrast to the current application of a minimum of four hours/day, which may account for the lack of statistically significant results in the former study.

The current study showed that a minimum dose of four hours was an effective daily dose of TENS. Participants were instructed that these four hours could be broken up throughout the day, as long as it was on for at least one hour per episode. Previously, Section 9.1.2 highlighted that a daily dose of conventional TENS of eight hours is better than one hour for pain relief in MS patients (Miller, 2007), and both 60, and 40 minutes are better than 20 minutes in knee OA patients (Cheing, 2003). Furthermore, in a retrospective questionnaire of long-term TENS users with chronic pain, 40% of the sample used TENS on a daily basis, between 2-4 times/day, with 80% of the sample using TENS for between 30-60 minutes/episode (Persson *et al*, 2010).

However, these studies only generate arbitrary conclusions: there is a lack of research on the optimum daily therapeutic dose, and pattern (i.e. a single daily application or four

hours versus four, one hour applications) of TENS application in the clinical setting, which may relate to specific clinical populations. The exact relationship between duration/pattern of TENS dose, and subsequent pain relief, which may relate to carry-over effects (proposed in relation to endogenous opiate release (Sluka and Walsh, 2003) has not been explored. As with all clinical TENS applications, the optimum treatment time is a balance between therapeutic benefit, and the inconvenience of wearing the unit. It could be postulated that the reason for the lack of evidence on this relationship is due to studies presenting just a pre/post assessment of efficacy, with no trend in mean pain scores throughout the treatment, valuable to determine the pattern of pain relief achieved. For example, Warke *et al*, (2006) reports a reduction in pain intensity of 63% for conventional TENS, after six weeks of TENS, Dayo *et al*, (1990), reported a reduction 21.7% after a four-week intervention period, and Barabrisi *et al*, (2010) a reduction of 40% from baseline, after a three-week TENS intervention. By contrast, the current study showed a cumulative decrease in mean NRS-11 pain intensity for the duration of the 2-week period. It would also have been insightful to explore the carry-over effect of this on a day-to day basis, and whether mean pain reduction has continued following the 2-week intervention period and beyond. Thus future studies must explore the optimum dose/pattern of TENS application in clinical populations. More detailed analysis of trends in pain reduction over time may facilitate this.

From the previous paragraph, it is also interesting that longer periods of TENS intervention time have resulted in larger mean reductions than the current study which applied TENS for only a two week period. Perhaps a longer intervention period would have lead to a larger mean reduction in pain intensity. For example, after 3 months of TENS treatment, (Eriksson *et al*, 1979) found 50% pain relief or more in 72% of the patients with chronic pain, who were satisfied with treatment result and continued to use TENS, whilst (Fishbain *et al*, 1996) reported a statistically significant reduction in pain relief, from baseline, in chronic pain patients with a mean TENS use of 1 year. Osiri *et al*, (2004) found, as a result of reviewing TENS studies in osteoarthritis, that a significant difference in pain relief was achieved in studies with an intervention period of TENS application of at least 4 weeks. However, as almost three-quarters (73.9%) of the TENS group in the present study reported a clinically significant reduction in pain intensity (≥2 points on the NRS-11), a 2-week TENS trial period appears to be an effective starting point for clinicians, managing the MS patient with pain.

12.3.1 Trends in the TENS and chronic pain literature

Recently (Bjordal, 2011) highlighted the anomaly of a non-significant reduction in pain intensity for TENS versus placebo, despite higher patient satisfaction in the active TENS group. Issues, of sub-optimal dosing, inadequate placebo conditions, and inappropriate timing of outcome measures have been responsible for potentially *underestimating* the treatment effect of active TENS over placebo, a common trend in the TENS literature. This concept was introduced by Bennett (2011) who states that poor *TENS implementation fidelity* may have contributed to the underestimation of treatment effects, where fidelity is the degree to which the intervention and control are delivered and assessed as intended(Carroll *et al*, 2007).

As an example of this anomaly, two large-scale RCTs of TENS in chronic pain conditions (of multiple aetiologies) have reported a non-significant reduction in pain intensity for TENS over placebo. This is despite overall satisfaction and willingness continue with TENS being significantly greater in the TENS group (Oosterhof *et al*, 2007; Köke *et al*, 2006). Köke *et al*, (2006) used a 'control situation', which was an active TENS application, the parameters of which were decided by the participant, which were likely to elicit physiological effects. This may account for the reduction in pain intensity in this control group, negating any statistically significant effect with active (conventional) TENS. Oosterhof (2006), by contrast used a sham TENS device, but an inadequate application of the active (conventional) TENS group which may have minimised the potential hypoalgesic effects of TENS. TENS was applied at a frequency of 50Hz, pulse width of 50ms, with an intensity set at a constant 40mA. This does not guarantee that intensity was delivered (or maintained thought the 2-week period) at a strong, but sub-noxious level, as per recent guidelines (Bennett, 2011). Although VAS scores decreased in a cumulative fashion throughout the 2-week period, this effect may had been greater if optimal TENS application had been delivered. Furthermore, both studies measured pain intensity, using a VAS, at a standard point in time each day. VAS scores were based on pain at that specific point in time, which has been criticised as potentially underestimating the true intensity of pain, thus average pain over a defined period of time is much preferred. The current study provided a more accurate assessment of pain intensity, based on average pain intensity (using the NRS) over the previous 24 hrs, which was rated at the same point each day, thus providing a more accurate measurement of the severity of pain as recommended by IMMPACT (Dworkin *et al*, 2005), and frequently used in drug trials.

Based on the findings of several systematic reviews (Section 8.4.4) there is insufficient evidence for the efficacy of TENS in chronic pain, with several authors blaming the lack of adequately powered, high methodological quality studies (Claydon and Chesterton, 2008; Johnson and Walsh, 2010; Nnoaham and Kumbang, 2008). This relates to traditional sources of bias (i.e. lack of/inadequate randomisation, blinding and unaccounted dropouts/withdrawals), and has long been recognised as potentially leading to an overestimation of treatment effects, thus the use of methodological quality scales, such as the Jadad scale (Jadad, 1999), referred to in Chapter 8. However, recently Bennett (2011) highlights that although such scales are important they do not account for the *fidelity* of TENS application, important if bias in *both* directions is to be minimised. Future studies should therefore be guided by the requirements of a clinical TENS study, as set out by Bennett et al (2011), in line with the CONSORT guidelines and IMMPACT recommendations on outcome measurements in chronic pain clinical trials. As mentioned in Chapter 9, these guidelines focus on the three areas of importance in a clinical TENS trial, namely *Allocation, Application and Assessment* (Table 9-1).

The current study aimed to adhere to these criteria (Table 9-1), adding an adequately-powered, randomised, (double-blind), controlled trial of TENS in chronic pain to the existing literature. TENS (and placebo TENS) were applied in the appropriate anatomical area, using an optimal *SBC* intensity, for a sufficient duration, which was maintained through the 2-week intervention period. Furthermore, the placebo used in the current study was unlikely to elicit physiological effects (as with Köke *et al*, 2006), but ensured adequate blinding which has been a concern mentioned by several authors in relation to the use of a sham TENS device (Chakour *et al*, 2000; Claydon and Chesterton, 2008; Johnson, 2012; Johnson and Walsh, 2010; Rakel *et al*, 2010). Unlike much of the previous literature of TENS in chronic pain, the methodological quality and appropriate TENS (and control) application of the current study has therefore provided strong evidence for the efficacy of TENS in the treatment of chronic pain in MS. Future studies which adopt similar methodologies may further add to this evidence base.

12.4 Impact of TENS on pain interference

The results show that active TENS showed no statistically significant effect on overall pain interference score over placebo ($p=0.2$). Total pain interference score of the BPI only reduced by 0.65(0.4) points in the TENS group over the 2-week period, showing no impact

on pain related interference on function (Table 11-5). Pain-related interference with function is not measured in previous TENS/chronic pain literature (as per the BPI). Other functional outcome measures, which do not consider pain-related interference *specifically*, are used, such as the Roland-Morris Disability questionnaire (RMDQ) (Buchmuller *et al*, 2012; Warke *et al*, 2006), the Western Ontario McMaster Osteoarthritis Index, (WOMAC) (Topuz *et al*, 2004), and the Barthel Index (Warke *et al*, 2006) with conflicting findings.

By contrast, IMMPACT recommends use of the physical functioning component of the BPI to measure the effect of pain on physical functioning (Dworkin *et al*, 2005). A recent analysis compared changes in pain (as measured by the NRS-11) with changes in function (as measured by the BPI) in individuals with painful diabetic peripheral neuropathy (DPN), as part of a 12 week placebo-controlled trial of Pregabalin in 401 patients (Hoffman *et al*, 2010). Findings showed that a 30% reduction in NRS-11 score (from baseline) corresponded to a 3-point reduction in the pain interference subscale of the BPI. This does not fit with the current study findings, which although showed a mean reduction of 2.1 (0.8) (31.8%) on the NRS-11, only show a reduction of 0.65(0.4) on the interference component of the BPI. This may be attributed to the short 2-week intervention period of the current study. A longer intervention period may be more likely to impact on pain related interference with function. Fishbain *et al* (1996) surveyed 506 long-term TENS users (mean duration of TENS use of one year) finding statistically significant changes in pain relief ($p=0.001$) as well as reduced pain interference with work ($p=0.001$), home ($p=0.001$), and social activities ($p=0.001$). However this was a retrospective study, where participants had to recall their pre-TENS physical state, which is subject to recall bias. Further prospective work is required to follow up TENS application for a longer period to consider the longer term benefits of TENS for chronic neuropathic pain in the MS population.

Of the seven components of the pain interference scale of the BPI, a statistically significant reduction was found only for the *sleep* component ($p<0.001$). Similarly in a study of TENS and Pregabalin versus Pregabalin and TENS control, in post herpetic neuralgia patients, a significant reduction in the active TENS group was found over control, as measured by an 11-point sleep interference scale, similar to the sleep interference subscale of the BPI (Barbarisi *et al*, 2010). Thus TENS may have an impact on pain-related interference on sleep; future studies are needed to consolidate this finding.

12.5 Clinical Relevance

The results of this study highlight the potential of TENS in the management of central neuropathic pain in MS. TENS may be particularly useful in the management of the neuropathic pain qualities *burning* and *sharp* pain. Participants should expect to see an immediate and cumulative decrease in their pain for at least a 2-week period. TENS involves self-application with no side effects and minimal clinical input, thus is highly useful in the promoting self-management of chronic pain as a long term clinical condition. In recent culture there has been a shift towards promoting self-management for the patient with chronic pain. As TENS was also shown in this study to additionally decrease the emotional unpleasantness of pain, it may also help towards self management of a chronic condition.

Recent NICE guidelines on the pharmacological treatment of neuropathic pain recommend pregabalin, or amitriptyline as first line treatment, or imipramine or nortriptyline if not tolerated, followed by opioids (National Institute for Clinical Excellence (NICE), 2010) and cannabinoids in MS, only if all other treatments fail (Attal *et al*, 2010). Section 6.3.5 showed that over two-thirds (68.5%) of the sample with neuropathic pain were currently taking prescribed pharmacological treatment, but have less pain relief than those with non-neuropathic pain. Furthermore, it has been established that 30-40% of people with chronic neuropathic pain do not achieve adequate pain control with pharmacotherapy (Attal *et al*, 2010), and discontinuation rates are often high. For example, the side effects of the TCA duloxetine include: somnolence, dizziness, nausea, dry mouth, constipation, and hyperhidrosis, which may contribute to the discontinuation rates of 15-20% reported (Gahimer *et al*, 2006; Sultan *et al*, 2008). TENS, with no side-effects, could provide an alternative.

Chitsaz *et al*, (2009) compared TENS and nortyriptaline in 59 MS patients with sensory complaints of the upper extremities, with both showing equal efficacy in decreasing pain intensity (on a VAS) after eight weeks of treatment. Recent randomised controlled trials of the effect of cannabinoids on central pain in MS have shown post treatment differences of between 1.9-2.8 points (adjusted means) on the NRS-11scale of pain intensity (Langford *et al*, 2013; Rog *et al*, 2005; Rog *et al*, 2007b), which is comparable with the difference of 2.1 (0.8) points achieved from TENS in the current study. Despite the fact that these are drug trials with different methodologies, and intervention periods, the potential of TENS

for the effective treatment of central neuropathic pain is clear. Future studies should explore whether TENS is equivalent or even outperforms pharmacological treatments in the management of neuropathic pain. To-date this has not been explored in MS, and would also be useful in other neuropathic pain conditions.

12.6 Success of blinding and compliance

Results indicate that compliance was high, and statistically similar (p=0.43) in the two groups, with a mean daily active TENS application time of 4.7 (1.2) hours and a mean daily placebo TENS application of 4.4 (1.0) hours. This demonstrates that there was successful blinding of the placebo condition, fundamental to the principles of a placebo-controlled trial. Similar compliance rates between active and placebo groups was also reported in previous studies who have used sham TENS applications (Buchmuller *et al*, 2012; Koke *et al*, 2004; Oosterhof *et al*, 2007; Warke *et al*, 2006), unlike the current study which adopted a novel approach to placebo TENS.

As mentioned previously, the issue of a suitable placebo in TENS trials is controversial, with sham TENS being criticised for failing to blind the participant (Chakour et al, 2000). Low frequency, sub-maximal intensity TENS as a potential form of placebo was initially suggested by Chakour and colleagues (Chakour *et al*, 2000), based on the lack of physiological rational for the combination of a low frequency, with a low intensity application. Furthermore, a recent systematic review highlighted the lack of efficacy of low intensity, low frequency (LILF), long pulse duration TENS, based on the findings of seven high quality RCTs (Claydon *et al*, 2011). However, these were experimental pain studies. Future studies would be useful to validate LILF as a form of placebo in the clinical population. Few people today are naive to the sensory stimulus generated by TENS, thus this novel placebo application which still provides a sensory stimulus without physiological effect is highly useful in the TENS studies of the future.

12.7 Merits of the study

The present study succeeded in completing a prospective, randomized, controlled, double-blind clinical trial of TENS treatment for chronic neuropathic pain in MS. By adopting an appropriate placebo TENS situation, participants were adequately blinded and this was maintained for patients, clinicians and researchers throughout the study. The study also showed high fidelity in relation to the optimal TENS application for pain relief, as per

recent guidelines (Bennett, 2011). TENS was applied in the appropriate neuroanatomical area, using the recommended *SBC* intensity (maintained throughout the intervention period), a minimum application time per episode of 30 minutes, and total daily application time of four hours. Participants were confirmed as having neuropathic pain using the PD-Q, a validated screening tool in the diagnosis of neuropathic pain, and IMMPACT recommended outcome measures were adopted. Furthermore data was analysed using the ITT method, as recommended by the recent CONSORT statement(Schulz *et al*, 2010).

12.8 Limitations of the study

In the recent proposed requirements for TENS application in clinical trials an intervention period of a minimum of 6 weeks is recommended in chronic pain clinical trials (Bennett, 2011), which was not possible for practical reasons in the current study, which adopted a two-week intervention period, as a preliminary study. However, as the two-week period was successful, this is undoubtedly an effective starting point for patients new to TENS in the clinical situation. Future studies would be useful to explore the effect of TENS beyond the 2-week period.

Due to time constraints the LILF placebo situation used in this study was not validated in the current MS population, and had only been deemed ineffective in generating physiological effects in the experimental pain setting. However, as compliance was equal in both placebo and active TENS groups in the current study, one is assured that successful blinding took place. The alternative of a sham TENS situation was deemed inappropriate due to the wealth of literature critiquing its blinding capacity.

Lastly the fact that our study did not include a natural history group as well as a placebo might be considered a weak point, because pain improvement during treatment could have been attributed to the natural course of the pain. However, pain reduction started promptly with the beginning of treatment (see Figure 11-2). It should be noted that adding a third natural history group to the study design would have reduced the probability of benefit for the volunteers. This has ethical implications and patients would have entered the study with low expectations, violating the external validity of the study.

12.9 Future recommendations and further research

From the findings of this study, TENS should be offered to the MS patient with chronic, central neuropathic pain. It could be particularly beneficial in those with *burning* and *sharp* neuropathic pain qualities, and those who describe their pain as emotionally unpleasant, and affecting their sleep.

In the context of chronic pain, this study also consolidated TENS as effective in the management of a chronic pain condition.

A summary of future recommendations are provided below as they have been discussed in detail throughout this chapter. From the results of this study, future research is required to:

- Explore the effect of TENS on chronic neuropathic pain in MS beyond the 2-week intervention period, as there is conflicting evidence of its longer term efficacy in MS. No studies have charted TENS efficacy in MS past the 32 week period. This will gauge the long-term efficacy of TENS in the management of chronic neuropathic pain in MS. A pain interference measure would be useful, as would the addition of a HR-QOL measure, which was not used in the current study. In addition to pre/post measures of effect, it would be useful for future studies to map the potential trends in mean pain reduction over time.

- Compare the efficacy of TENS with pharmacological treatment in the management of neuropathic pain. It would be useful to use a neuropathic pain specific measure, such as the NPS used in the current study, to determine which specific neuropathic pain qualities are most responsive to treatment.

- As TENS was shown to significantly reduce the *emotional unpleasantness* of neuropathic pain, future studies could explore the impact of TENS on pain coping skills, self management and attitudes to pain, as part of the psychological approach to pain. This could also cover the attitudes of MS patients towards the use of TENS including the level of inconvenience and trade-off between benefits in relation to pain reduction and self management, which has not been explored. What constitutes a clinically significant reduction in pain for the MS patient should also be investigated, as this may vary for different clinical populations. As this is an

original area, qualitative work would be useful to generate hypotheses in this field, which could subsequently be tested quantitatively for the wider MS population.

- The optimum mode of TENS for central neuropathic pain in MS has not previously been explored. There is evidence for the efficacy of conventional TENS, AL-TENS and alternating Frequency TENS (AFT) in both experimental and other chronic pain conditions. A head to head comparison of these different modes of TENS for pain in MS is indicated. High Intensity TENS (HIT) is controversial for clinical populations with chronic pain.

- Validation of the LFLI form of placebo TENS in a clinical population.

- A small number of studies have looked at the effect of TENS in chronic pain after a one year period, but do not use IMMPACT recommended measures. This is required of future studies to confirm TENS as useful in the long-term management of chronic pain.

12.10 Summary of TENS study

This was the first study to explore the efficacy of TENS in the treatment of chronic neuropathic pain in the MS patient. In this randomised, controlled, double-blind clinical trial, TENS was effective in reducing neuropathic pain intensity over a 2-week intervention period, particularly the *burning* and *sharp* neuropathic pain qualities. TENS was shown to impact on the multi-dimensional nature of pain: reducing *average* and *worst* pain intensity, as well as the *affective* component of pain, which may have implications for its role in the psychological dimension of pain perception. Results indicate a clinically significant reduction in pain intensity which is comparable with that achieved in pharmacological studies of neuropathic pain. Pain intensity immediately reduced in a cumulative fashion, over the two-week period. The lack of effect on pain–related interference on function may be a result of the short TENS intervention period. Future studies may extend the intervention period to explore the longer-term effects of TENS for pain in MS.

13 FINAL DISCUSSION

This chapter begins by discussing the methodological consistencies of the two sections of the thesis. This has allowed integration and interpretation of results from both sections.

13.1 Methodological consistency of thesis

This thesis consisted of two sections: part one an epidemiological study of pain in MS, and part two a trial of TENS on neuropathic pain. Although the two sections of this thesis have different aims, key methodological consistencies have improved the validly of results: the PainDETECT Questionnaire (PD-Q) was used to screen for neuropathic pain in both sections of the thesis. Only participants who scored as '*definite neuropathic pain'* (score of a minimum of 19 points on PD-Q) were included in the prevalence measure of part one of the thesis. Similarly, only those with a score of ≥ 19 were included in the TENS study of part two of the thesis. The same criteria to exclude neuropathic pain, not as a direct result of MS, was also adopted in both sections (detailed in Sections 5.2.2 and 10.4.3). Furthermore, chronic pain was defined as pain of at least 6 months duration in both sections. In this way, the sample with neuropathic pain in the TENS study is representative of the population with neuropathic pain in part one of the thesis. Where possible the same IMMPACT-recommended outcome measures were used in both sections, such as the NRS-11 and scale for emotional unpleasantness. These methodological consistencies have also integrated the two sections, allowing interpretation of findings, which are discussed in the next section.

13.2 Clinical usefulness of TENS for pain in the MS patient

This section aims to combine the key findings of parts one and two of this thesis, highlighting the potential of TENS in the treatment of a neuropathic pain, a common condition in MS.

Chapter 6 highlighted the high prevalence of neuropathic pain and its consequences for the MS population. Almost one third (32.3%) of the study population were currently affected by neuropathic pain (as measured by the PDQ), but this could be potentially as high as 47.4%. Furthermore, dysaesthetic pain (unpleasant, abnormal sensations, such as burning, stinging, stabbing, aching) was experienced by over half (56.2%) the sample at that time, and almost three quarters (74.1%) since diagnosis (Table 6-4). Table 6-6 showed that

those with neuropathic pain describe the affective component of pain (SF-MPQ), as 3 times greater than those with non-neuropathic pain, being significantly more intense, and impacting upon sleep.

Chapter 11 showed that TENS was effective in reducing neuropathic pain intensity over a 2-week intervention period. The mean reduction of 31.8% from baseline after only two weeks of TENS shows great potential for MS patients suffering from this type of pain. TENS worked particularly well for the *burning* and *sharp* neuropathic pain qualities that are common in MS. In fact it was shown that burning pain and sharp pain were amongst the most common descriptors of dysaesthetic pain (Table 6-5). TENS was also shown to impact on the multi-dimensional nature of pain: reducing *average* and *worst* pain intensity, as well as the *emotional unpleasantness* of pain, which may have implications for the role of TENS in the psychological aspect of pain perception. How a person perceives their pain emotionally influences their perception of its intensity, its impact on function and ultimately their ability to self-manage their condition. This is of particular importance in a chronic condition.

The presence of neuropathic pain was associated with reduced Health-Related Quality of Life (HR-QOL) (EQ-5D) (Table 6-7) in the sample. HR-QOL was not measured in the current 2-week TENS trial, however pain reduction has been shown to improve HR-QOL. One may therefore hypothesise that longer–term pain relief by TENS could improve HR-QOL for the MS patient, and is an area of future study. TENS did not affect overall pain-related interference (as measured by the BPI), despite a significant improvement in the subcomponent *sleep,* which is useful as this is affected in those with neuropathic pain. As with HR-QOL, pain related interference may improve with longer–term use of TENS, and is again an area of further study.

As TENS worked immediately, and cumulatively decreased over the intervention period this would provide immediate reassurance for the patient, particularly the patient who has developed a relapse and sudden flare up in their neuropathic pain. Chapter 6 revealed that the presence of the relapse may be associated with a neuropathic pain presentation, with neuropathic pain being most associated with secondary progressive and least associated with primary progressive MS. Although this study has shown TENS to be effective in those with *chronic* neuropathic pain (≥six months), there is no physiological reason why those experiencing a relapse with an acute flare up of neuropathic pain may not also achieve benefit from TENS; an area of future study.

The pharmacological treatment of neuropathic pain is not without its challenges, with high discontinuation rates as previously discussed, and only 30-40% of patients achieving adequate pain control with pharmacotherapy (Attal *et al*, 2010). Furthermore, Chapter 6 revealed that despite over two-thirds (68.5%) of the sample with neuropathic pain currently taking PPRM, pain relief was insufficient, when compared with those with non-neuropathic pain (Table 6-6). Chapter 12 discussed that the magnitude of pain reduction from TENS in the current study was comparable with pharmacological studies of neuropathic pain using identical outcome measures. With this in mind, TENS should be considered alongside the use of pharmacological treatments for neuropathic pain in the MS patient.

13.3 Final conclusion

TENS as an effective, easy to use, inexpensive and non-pharmacological treatment should be considered for the treatment of chronic neuropathic pain, a common problem in people with MS.

14 APPENDICES

Appendix 1: Pain Questionnaire used in epidemiological study

Appendix 2: Ethics and R+D Approval for epidemiological study

Appendix 3: Patient Information Sheet for epidemiological study

Appendix 4: Sensitivity Analysis for PDQ Coding

Appendix 5: Brief Pain Inventory

Appendix 6: Patient Global Impression of Change

Appendix 7: Ethics and R+D Approval for TENS study

Appendix 8: Letter of Invitation for TENS study

Appendix 9: Patient Information Sheet for TENS study

Appendix 10: Neuropathic Pain Scale

Appendix 11: Screening Questionnaire for inclusion into TENS study

Appendix 1: Pain Questionnaire used in epidemiological study

The Pain Experience of People with Multiple Sclerosis

Please complete this questionnaire even if you DO NOT experience pain*

Instructions for completion

1. This study investigates the pain experience of people with Multiple Sclerosis (MS). This experience is different for different people. For example, what some people might think of as 'pain' you may think of as 'unusual' and/or 'unpleasant'. For example, a person may feel pins and needles on the skin as an uncomfortable sensation, but may not think of this as pain in the traditional sense. **If you experience these uncomfortable sensations please consider them as 'pain' for the rest of this questionnaire**.

2. Questions often may be continued over the page, **please make sure that the entire question has been completed.**

3. This form does not have to be completed in one sitting.

4. **It is important that you, the person suffering from Multiple Sclerosis, fills out the questionnaire**. However for some people this will not be possible e.g. those with visual problems or who have problems holding a pen. In these instances it is acceptable for someone else to fill out the questionnaire, but it is imperative that each of the questions are read to the person with MS **word for word** and that responses are recorded as accurately as possible.

5. Section 2 of this questionnaire asks someone **other than yourself** about your disability. This must be someone who can reliably comment on this, such as a friend, carer or family member. Please fill in this section when it is possible to have the assistance of such a person.

6. Completion of Section 2 of this questionnaire requires the assistance of another person. However, please tick the box below if assistance was required to complete **any other** part of this questionnaire: ☐

SECTION 1 – GENERAL

1. Age (in years): _____

2. Gender: male ☐ female☐ (Tick one box)

3. Postcode (in full): _____

4. Employment:
Are you:

A student	☐	
Employed - full time	☐	
Employed - part time	☐	**(Tick one box)**
Unemployed	☐	
Unable to work due to MS	☐	
Retired	☐	

5. Marital Status
Are you:

Single	☐	
Married	☐	
Living with partner	☐	**(Tick one box)**
Widowed	☐	
Divorced	☐	

6. Education
What is your **maximum** level of qualification? Tick one box:

No qualifications ☐

Secondary school qualifications: ☐

Higher education qualifications: i.e. college, university ☐

Other (please state) _____

7. Ethnic Background
Are you?

White: Scottish	☐	
English	☐	
Irish	☐	
Welsh	☐	**(Tick one box)**
Black	☐	
Indian	☐	
Pakistani	☐	
Chinese	☐	
Mixed Race	☐	

Other (please state) _____

8.Time Since Diagnosis:

Please indicate the number of years since you was diagnosed with Multiple Sclerosis.

_____ Years

9. Typical course of your MS:

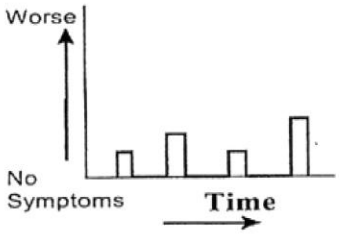
Please check 1 box for the following examples over the page that best describes the course of your MS over time.

Question 9 (Typical course of your MS) continued....

Course of MS

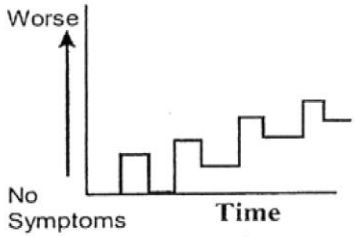
Check one box of the following examples that best describes the course of your MS over time

a.



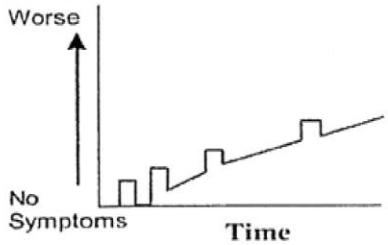
☐ Attacks (exacerbations, relapses) come on over a few hours or days, last from one day to several weeks, but once they are over, you feel the same as you always have.

b.



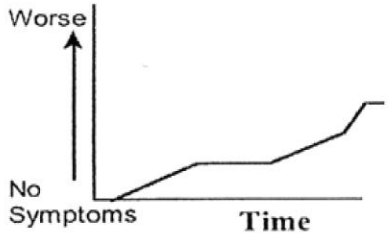
☐ Attacks (exacerbations, relapses) come on over a few hours or days, last from one day to several weeks. After some attacks, your symptoms are worse then before. The symptoms that remain after the attack are stable until a new attack occurs.

c.



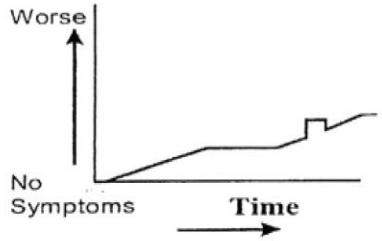
☐ At the start of the disease, attacks (exacerbations, relapses) occur. You may feel your symptoms get worse because of these attacks. Then even between the attacks, you feel you are getting worse. In some cases, attacks cease, yet your symptoms continued to worsen.

d.



☐ Symptoms worsen from the beginning. Your symptoms may be stable for a time, gradually worsen, or deteriorate rapidly, but attacks (exacerbations, relapses) have never occurred.

e.



☐ Symptoms gradually worsen from the beginning. Your symptoms may be stable for a time at the beginning, or may deteriorate rapidly. Attacks (exacerbations, relapses) did not occur at the start, but may occur later in the course of the disease.

SECTION 2 – LEVEL OF DISABILITY

The Guy's Neurological Scale of Disability

The following questions ask about any disability/disabilities you may have in relation to your Multiple Sclerosis. Please consider how you have been affected within the last month:

To the person with the disease (Multiple Sclerosis)

Most of these questions can be answered directly by you. However, as mentioned previously, some questions specifically ask for the opinion of another person. Also, sometimes you may have difficulty in knowing the answer. In this situation it is acceptable for your nominated helper to assist you.

The questions are in boxes. For each question please tick (or ask your helper to tick) the 'yes' or 'no' box.

To the person who helps

Please read the following questions over the page to the patient, and use your judgment

Memory and Concentration

Q	Questions	Yes	No
1	Do you have any problems with your memory or your ability to concentrate and work things out?		
2	*If 'no' to question1:* Do your family or friends think you have such a problem?		
	If *answer to either of the questions (1 or 2) is yes:*		
		Yes	No
3	Do you need to use lists or other aids to help you overcome this problem?		
4	Do you need help from other people to plan your daily affairs or to work out simple finances?		

To the helper or other person:
Is the person fully orientated in time, place and person?

Yes, fully ☐

No, partially ☐

No, totally disorientated ☐

Mood

Q	Questions	Yes	No
1	Have you been feeling anxious, irritable, depressed, or had any mood swings during the last month?		
	To other persons:		
2	Does the person have euphoria (being over happy) or emotional lability (crying or laughing too easily)?		
	If answer to either question (1or 2) is yes:		
3	Have you/ has the person had this problem most days?		
4	Has this problem affected your ability to do any of your usual activities?		
	If yes to question Q4:		
5	Has the problem been severe enough to prevent you from doing all your usual activities?		
6	Have you been admitted to hospital for treatment of your mood problem during the last month?		

Vision

Q	Question	Yes	No
1	Do you have any problems with your vision?		
	If yes to Q1:		
2	Can your read normal newspaper print (with ordinary glasses worn, but not magnifying lenses)?		
	If no to Q2:		
3	Can your read large newspaper print?		
4	Can you count your fingers if you hold your hand out in front of you?		
5	Can you see your hand move in front of you?		

Speech and Communication

Q	Question	Yes	No
1	Do you have any problems with your speech?		
	To other person:		
2	Do you think the person has any problems with their speech?		
	If answer to either of the questions (1 or 2) is yes:		
3	Do you have this problem most days?		
4	Do you have this problem all the time and in every sentence?		
5	Do you need to write things down, use sign language, or use a communication aid?		
	To other person:	Yes	No
6	Is the patient able to communicate effectively?		

Swallowing

Q	Question	Yes	No
1	Do you have to take care when swallowing solids or fluids?		
	If yes to Q1:		
2	Do you have to take care with most meals?		

3	Do you choke during most meals?		
		Yes	No
4	Does your food require special preparation (e.g. mashing) to modify its consistency?		
5	Do you have a feeding tube (nasogastric tube or gastrostomy tube)?		

Arms and Hands

Q	Question	Yes	No
1	Do you have problems with your arms and hands?		
	If yes to Q1:		
2	Do you have any difficulty in doing any of your zips or buttons?		
2a	*If yes to Q2:* Are you able to do all of your zips and buttons?		
3	Do you have any difficulty in washing or brushing your hair?		
3a	*If yes to Q3:* Are you able to wash and brush your hair?		
4	Do you have any difficulty in using a knife and fork together?		
4a	*If yes to Q4:* Are you able to use a knife and fork together?		
5	Do you have any difficulty in handling small coins?		
5a	*If yes to Q5:* Are you able to handle small coins?		
6	If *unable to use hands for any of the above activities:* Can you use your hands for anything at all?		

Mobility

Q	Question	Yes	No
1	Do you have any problems with your walking?		
1a	*To the other person:* Does the person have any problems with their walking?		
	If yes to Q1 or Q1a:		
2	Do you use a walking aid?		
3	How do you usually get around outdoors?		
3a	Without aid?		
3b	Or with one stick or crutch, or holding someone's arm?		
3c	Or with two sticks or crutches, a walking frame, or one stick or crutch and someone's arm?		
3d	Or with a wheelchair?		
4	Can you stand and walk a few steps with help?		

Bladder

Q	Question	Yes	No
1	Do you have any problems with your bladder?		
2	Are you currently on treatment for such problems?		

3	Do you have to rush to the toilet, go frequently, or have difficulty in passing urine?		
4	Have you been incontinent in the past month?		
5	Have you been incontinent every week?		
6	Have you been incontinent every day?		
7	Do you use a catheter (tube) to empty your bladder?		
8	Do you have a permanent catheter (tube) in the bladder, or, if a man, do you use a sheath to catch your urine?		

Bowels

Q	Question	Yes	No
1	Do you have any problems with your bowel movements?		
	If the answer to Q1 was yes:		
1a	Do you suffer from constipation?		
2	Are you on any treatment for your bowels?		
3	Do you take laxatives or use suppositories for constipation?		
4	Do you need to use enemas for constipation?		
5	Do you need to evacuate your bowels by hand?		
6	Do you have to rush to the toilet to open your bowels?		
7	Have you had any bowel accidents (been incontinent of faeces) in the last month?		
8	Have you had bowel accidents every week?		

Fatigue

Q	Questions	Yes	No
1	Have you been feeling tired or getting tired easily during the last month?		
	If yes:		
2	Have you been feeling tired or getting tired easily most days?		
3	Has the tiredness affected your ability to do any of your usual activities?		
4	Has the tiredness been severe enough to prevent you from doing all your usual activities?		
5	Has the tiredness been severe enough to confine you to bed and prevent you from doing all physical and mental activities?		

Sexual Activities

Q	Question	Yes	No
1	Do you have any problems in relation to your sexual function?		
	If yes:		
2	Do you have any problems in finding or satisfying a sexual partner?		
		Yes	No
3	Is your sexual drive (desire) reduced?		
4	Is your sexual function affected by any physical problem such as loss of sensation, pain, weakness, spasms, catheterisation or incontinence?		
5	Do you have any difficulty with: (Men): erection or ejaculation? (Women): vaginal lubrication or orgasm?		

6	Do any of these activities totally prevent any sexual activities?		

Other Disabilities

Do you have any problems due to Multiple Sclerosis (MS), which have not been mentioned so far (such as pain, spasm, dizziness)?

If yes, please answer questions 1-4 below

What is the worst other problem?

Q	Questions	Yes	No
1	Have you had this problem most days during the last month?		
2	Has this problem affected your ability to do any of your usual activities?		
3	Has this problem been severe enough to prevent you from doing all your usual activities, or to make you stay in bed all the time?		
4	Have you been admitted to hospital for this problem in the last year?		

Please continue on to section 3→

SECTION 3- EFFECT OF MULTIPLE SCLEROSIS ON QUALITY OF LIFE

The European, 5-Domain Quality of Life (EQ5D)

The following questions ask about your quality of life. By placing a tick in one box in each group below, please indicate which statements best describe your own average health state within the last month**:**

Mobility

I have no problems in walking about ☐
I have some problems in walking about ☐
I am confined to bed ☐

Self-Care
I have no problems with self-care ☐
I have some problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ☐
I have some problems with performing my usual activities ☐
I am unable to perform my usual activities ☐

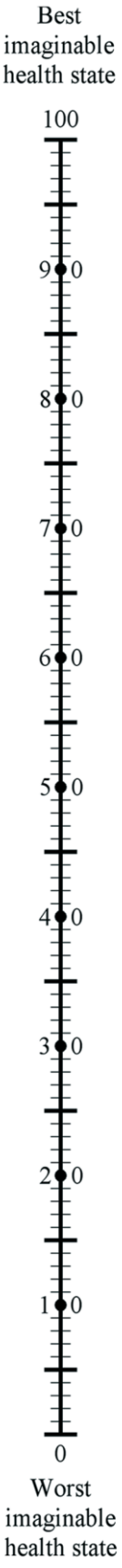
Pain/Discomfort
I have no pain or discomfort ☐
I have moderate pain or discomfort ☐
I have extreme pain or discomfort ☐

Anxiety/Depression
I am not anxious or depressed ☐
I am moderately anxious or depressed ☐
I am extremely anxious or depressed ☐

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

We would like you to indicate on this scale how good or bad your own health has been **within the last month**, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state has been within the last month.

Your own health state in last month.



SECTION 4- YOUR CURRENT MOOD

Hospital Anxiety and Depression Scale (HADS)

This section is designed the help us understand how you feel. Read each item below and underline the reply, which comes closest to how you have been feeling in the past week.

Don't take too long over the replies; your immediate reaction to each item will probably be more accurate than a long, thought-out response. Underline one response only.

I feel tense or wound up: Most of the time A lot of the time From time to time, occasionally Not at all	***I feel as if I am slowed down:*** Nearly all the time Very often Sometimes Not at all
I still enjoy the things I used to enjoy: Definitely as much Not quite so much Only a little Hardly at all	***I get a sort of frightened feeling like 'butterflies' in the stomach:*** Not at all Occasionally Quite often Very often
I get a sort of frightened feeling as if something is going to happen: Very definitely and quite badly Yes, but not too badly A little, but it doesn't worry me Not at all	***I have lost interest in my appearance:*** **14.1 Definitely** I don't take as much care as I should I may not take quite as much care I just take as much care as ever
I can laugh and see the funny side of things: As much as I always could Not quite so much now Definitely not so much now Not at all	***I feel restless as if I have to be on the move:*** Very much indeed Quite a lot Not very much Not at all

Please continue to underline the appropriate response to the statements over the page:

Worrying thoughts go through my mind: A great deal of the time A lot of the time Not too often Very little	***I look forward with enjoyment to things:*** As much as I ever did Rather less than I used to Definitely less than I used to Hardly at all
I feel cheerful: Never Not often Sometimes Most of the time	***I get sudden feelings of panic:*** Very often indeed Quite often Not very often Not at all
I can sit easily and feel relaxed: Definitely Usually Not often Not at all	***I can enjoy a good book or radio or television programme:*** Often Sometimes Not often Very seldom

Please continue on to section 5 over the page→

SECTION 5- MEDICATION

Please list the medication you are currently using, and what you are using medication for. For example, if you are currently taking medication to relieve your pain you would write the name of this medication under the heading ‘medication’. Under the heading ‘purpose of medication’ you could write ‘pain relief’.

Medication ***Purpose of Medication***

SECTION 6- OTHER MEDICAL CONDITIONS

Tick any of the following medical conditions, with which you have ever formally been diagnosed. Tick as many as applies.

Rheumatoid Arthritis ☐
Lupus (or SLE) ☐
Fibromyalgia ☐
Diabetes ☐

Tick any of the following medical conditions, which you have ever experienced. Please detail when and which body area was affected:

Cancer ☐
Accident that damaged a nerve(s) ☐
Spinal cord injury ☐
Surgical operation (within last three months) ☐
Stroke ☐

_____

_____

Tick any of the following medical problems, which you currently experience. The list continues over onto the next page. Tick as many as applies. Where applicable detail where on your body you are affected over the page:

Limb ulceration ☐
Pressure sores ☐
Shingles ☐
Severe back problems (where you have been formally diagnosed with slipped disc, sciatica or trapped nerve). This does not include common backache that we all experience from time to time, depending on our activities. ☐
Recent back surgery ☐

If you have any other medical conditions, which you feel may be relevant, please detail below:

_____

_____

_____

Please continue on to section 7

SECTION 7-PAIN

This section asks about your experience of pain in relation to your Multiple Sclerosis.

Throughout our lives, most of us experience everyday types of pain, from time to time (such as minor headaches, sprains, and toothaches). We also may experience pain as a result of a recent injury. **Other** than these types of pain, **at present, or within the last month,** have you experienced **ongoing, bothersome pain? (**This pain may be constant or 'off and on'). Please tick ONE of the following:

No: ☐ Go to section 7A over the page.
Yes: ☐ If yes:

How long have you had **this** pain? (You may have more than one type of pain that is ongoing- please consider **your most bothersome pain only.**

Please tick one box below:

I have had this pain for:

Less than 6 months ☐

At least 6 months and more ☐

Please indicate for exactly how long you have had this pain

---------- (use months/and or years as appropriate)

In your opinion, is **any** of **this** pain due to stiffness, changes in your walking, or the way you sit or stand, **as a result of your MS**? Please tick ONE of the following:

Yes: ☐
No: ☐

Now go to section 8

Section 7A

Have you **ever** experienced bothersome pain, since you were diagnosed with MS?

☐ Yes: I have experienced bothersome pain: please go to section 8

☐ No: I have never experienced bothersome pain:

If you have never experienced bothersome pain since you were diagnosed with MS, you should not complete the rest of the questionnaire. Please read the instructions on page 30 regards the return of the questionnaire to the researcher.

Thank you for taking the time to complete this questionnaire.

SECTION 8- TYPES OF PAIN

This section asks if you have experienced certain types of pain. If you have experienced a particular type of pain, please continue to answer each of the questions in that section.

Have you **ever** suffered from any of the following types of pain due to your MS? Tick as many as applies, taking care to answer numbers 1-7:

1) Lhermitte's' Sign: *(The sudden sensation of an electric shock that spreads up the body on bending the neck. It normally lasts a few seconds).*

No ☐ If no, go to question 2
Yes ☐ If yes**:**

Have you experinced this pain within the last month ? (tick one box only)

Yes ☐
No ☐

2) Optic Neuritis: *(sudden loss of vision (partial or complete), or sudden blurred or "foggy" vision, and pain on movement of the affected eye)*

No ☐ If no, go to question
Yes ☐ If yes:

Have you experinced this pain within the last month ?(tick one box only)

Yes ☐
No ☐

3) Trigeminal Neuralgia: (*severe facial pain that comes on suddenly and can be sharp, shooting or electric- shock- like. This type of pain may come on after chewing or touching the face.)*

No ☐ If no, go to question 4
Yes ☐ If yes:

Have you experinced this pain within the last month ? (tick one box only)

Yes ☐
No ☐

4) Have you **ever** experienced any of the following ***unusual, unpleasant sensations*****?**

These sensations can come on without warning, or can come on due to factors, such as movement, touch, pressure, chewing, heat, stress, or pain.

Tick as many boxes as applies**:**

Burning, stinging, nipping, searing (heat-like sensations) ☐
Pins and needles/tingling/prickling/crawling, which are unpleasant ☐
Aching ☐
Sharp, stabbing, shooting, electric shock-like ☐
Cold, freezing, ice-like burn ☐
Tightness, tight band-like, squeezing, cramping, vice-like ☐
Itching, nettle sting ☐
Dull, numbness ☐
Wetness, liquid on the skin ☐
Other, please specify_____ ☐

If you have never experienced any of the above sensations please now go to question 5.

Have you experinced any of these unusual, unplesant sensations above within the last month ? (tick one box only)

Yes ☐
No ☐

Where do/ (did) you experience these sensations? Tick all boxes that apply:

Head ☐
Neck ☐
Face ☐
Trunk ☐
Back ☐

Limb (arm or leg) ☐
Limbs ☐
Foot ☐
Feet ☐
Hand ☐
Hands ☐

5) ***Migraine Headache:*** *(usually a severe one-sided headache, often described as pulsating. Many people experience nausea and vomiting, and a heightened sensitivity to bright lights and noise.)*

No ☐ If no, go to question 6
Yes ☐ If yes**:**

Have you experinced this pain within the last month ? (tick one box only)

Yes ☐
No ☐

6) Painful Spasms: *(sudden involuntary muscle spasms that can be uncomfortable or painful)*

No ☐ If no, go to question 7
Yes ☐ If yes:

Have you experinced this pain within the last month ? (tick one box only**)**

Yes ☐
No ☐

7) Bladder or Bowel Pain: *pain that you feel comes from the bladder or bowel*

No ☐ If no, please read instrcutions (in bold) at bottom of page.
Yes ☐ If yes:

Have you experinced this pain within the last month ? (tick one box only)

Yes ☐
No ☐

Only those who have experienced <u>ongoing, bothersome pain within the last month</u> should continue with the questionnaire on the next page. If you have not experienced ongoing, bothersome pain within the last month you should not fill in the rest of this questionnaire. Please read the instructions on page *regarding the return of the questionnaire to the researcher. Thank you for taking the time to complete the questionnaire.

SECTION 10- DESCRIPTION AND AREA OF YOUR PAIN

This section asks more detailed questions about your pain. Please consider only **ongoing, bothersome** pain that you have experienced, **at present, or within the last month** when completing this section. Remember, this does not include everyday types of pain; it may be constant or 'off and on' and must not be pain from a recent injury. If you experience unpleasant, and/ or unusual, sensations, please consider them as 'pain' when completing this section.

Pain Description: The Short Form McGill Questionnaire (SF-MPQ)

The following table includes a list of possible words to describe this pain and a rating of how severe this type of pain is for you. This intensity is rated from 1- 3, where 1= mild pain, 2= moderate pain and 3= severe pain. It is important to work your way down all the descriptors of pain on the list. For each word that describes your pain place a tick in the correct numbered box to describe how intense this pain is. It is possible to tick more than one type of pain description. For example, a person may experience both burning leg pain and shooting back pain. If you do not have a description of pain please leave this section blank. *Please complete the table below:*

	Intensity		
Pain description	1	2	3
Throbbing			
Shooting			
Stabbing			
Sharp			
Cramping			
Gnawing			
Hot-Burning			
Aching			
Heavy			
Tender			
Splitting			
Tiring-Exhausting			
Sickening			
Fearful			
Punishing-Cruel			

This section continues to ask questions about your pain. Please consider only **ongoing, bothersome** pain that you have experienced, **at present or within the last month.** Remember, this does not include everyday types of pain; it may be constant or 'off and on' and must not be pain from a recent injury.

The following list shows possible body areas where you may have experienced this pain. Working your way down all the body areas on the list, place a tick in the correct box for each body area that you have experienced this pain. In this list, *Arm* and *leg* refer to pain in the limbs. They **do not** refer to pain that you feel comes from within or around the joints in these areas. The section *joint pain* specifically refers to pain that you feel comes from within or around the joints. *Abdomen or pelvis* refers to pain that you feel comes from the bladder, stomach or bowel.

Please tick all body areas that you have pain:

Neck	☐
Head	☐
Face	☐
Back	☐
Trunk	☐
Abdomen or pelvis	☐
Arm (NOT joint pain)	☐
Hand	☐
Hands	☐
Leg (NOT joint pain)	☐
Foot	☐
Feet	☐
Joint Pain	☐

If you ticked joint pain above, which joint(s) are affected?

_____

Section 11- Pain Behaviour

This section asks further questions which will help us to understand your pain. Please consider only **ongoing, bothersome** pain that you have experienced, **at present or within the last month** when filling in this section. Remember, this does not include everyday types of pain; it may be constant or 'off and on' and must not be pain from a recent injury. Please complete each of the questions 1- 3 below:

Question 1): Unpleasantness

Pain can have a low intensity, but still feel extremely unpleasant, and some pain can have a high intensity, but be very tolerable. The following scale, from 0 to 10, represents the level of **unpleasantness of pain**. On this scale, 0 indicates **not unpleasant**, and 10 indicates **most unpleasant**. By circling the appropriate number on the scale below, please indicate how **unpleasant** your pain feels. Currently, you may experience pain in more than one area, with different levels of unpleasantness. When completing this section, please consider your **most bothersome pain only.**

Not unpleasant **Most unpleasant**

0	1	2	3	4	5	6	7	8	9	10

Question 2): Sleep

Within the last month, has your pain affected your usual sleep pattern? Please tick one of the following boxes:

Never ☐
Occasionally ☐
Frequently ☐
Every night ☐

Question 3): Pain Relieving Treatments

The following table asks what treatments you may have used for pain relief. Place a tick in the appropriate box if you have used a treatment within the **last month**, or, if it has **ever** been used. Tick all treatments that you have used:

Treatment	**Used Within the last month**	**Used Ever**
Pain-relieving Medication: Prescribed		
Non-Prescribed		
Homeopathic Medicine		
Physiotherapy		
TENS		
Reflexology		
Cannabis (Non-Prescribed)		

Other, please specify_____
_____
_____

If you have used prescribed pain- relieving medication within the last month, answer the section below. If you have not used prescribed pain-relieving medication within the last month, please go to section 11 over the page.

The scale below represents the percentage pain relief that you have had from **prescribed, pain-relieving medication**. On this scale, 0% indicates no pain relief, and 100% indicates total pain relief. By circling the appropriate number on the scale below, please indicate the percentage relief you have had from pain relieving medication within the **last month**:

No pain relief **Complete pain relief**

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

SECTION 12- TYPE OF PAIN

The PainDETECT Questionnaire (PDQ)

Over the page is the 'PainDETECT' questionnaire. This asks further, more detailed questions about your pain. This allows us to assess the possible type of pain that you may be experiencing.

The first section asks you to describe how intense your pain is on scale of 0 to 10, where 0 indicates no pain and 10 indicates maximum pain intensity. Please circle the number which best describes your pain on this scale. Currently, you may experience pain in more than one area, with different levels of intensity. When completing this section on intensity, please consider your **most bothersome pain only.**

When completing the rest of this section, please consider only **ongoing, bothersome** pain that you have experienced within the **last month**. Remember, this does not include everyday types of pain; it may be constant or 'off and on' and must **not** be from a recent injury.

Do not complete the scoring section at the bottom of the page. (This section reads, "**To be filled out by physician").**

Please complete this whole section over the page:

painDETECT™

PAIN QUESTIONNAIRE

How would you assess your pain now, at this moment?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the strongest pain during the past 4 weeks?

0 1 2 3 4 5 6 7 8 9 10

none max.

How strong was the pain during the past 4 weeks on average?

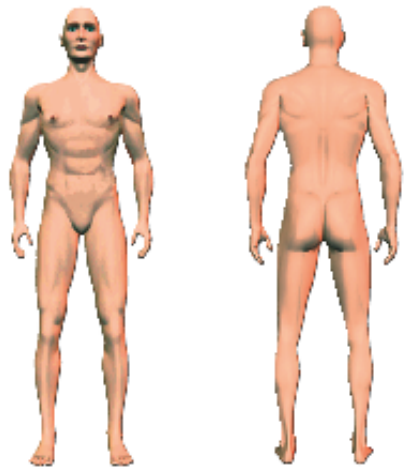
0 1 2 3 4 5 6 7 8 9 10

none max.

Mark the picture that best describes the course of your pain:

- Persistent pain with slight fluctuations ☐
- Persistent pain with pain attacks ☐
- Pain attacks without pain between them ☐
- Pain attacks with pain between them ☐

Please mark your main area of pain



Does your pain radiate to other regions of your body? yes ☐ no ☐

If yes, please draw the direction in which the pain radiates.

Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is light touching (clothing, a blanket) in this area painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you have sudden pain attacks in the area of your pain, like electric shocks?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Is cold or heat (bath water) in this area occasionally painful?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Do you suffer from a sensation of numbness in the areas that you marked?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

Does slight pressure in this area, e.g., with a finger, trigger pain?

never ☐ hardly noticed ☐ slightly ☐ moderately ☐ strongly ☐ very strongly ☐

(To be filled out by the physician)

never	hardly noticed	slightly	moderately	strongly	very strongly
☐ x 0 = 0	☐ x 1 = ☐	☐ x 2 = ☐☐	☐ x 3 = ☐☐	☐ x 4 = ☐☐	☐ x 5 = ☐☐

Total score ☐☐ out of 35

End of Questionnaire

Thank you for taking the time to complete this questionnaire.
Please return the completed questionnaire, in the enclosed stamp, addressed envelope, to:

Gayle Connolly
MS research project (Dr Mattison)
Douglas Grant Rehabilitation Centre, NHS Ayrshire & Arran,
Ayrshire Central Hospital,
Kilwinning Road,
Irvine
KA12 8SS

Appendix 2: NHS Research and Development and Ethics Approval: Epidemiological Study

Research and Development
58 Lister Street
Crosshouse Hospital
Kilmarnock
KA2 0BB

Tel: (01563) 825856
Fax: (01563) 825806

NHS Ayrshire & Arran

Ms Gayle Connolly
7 Cowan Crescent
Barrhead
Glasgow
G78 2SP

Date: 6th April 2009
Your Ref:
Our Ref: KF/KLB/AM 2008AA084

Enquiries to: Karen Bell
Extension: 25850
Direct Line: 01563 825850
Email: Karen.bell@aaaht.scot.nhs.uk

www.nhsayrshireandarran.com

Dear Gayle

The prevalence and experience of pain in people with Multiple Sclerosis (MS) in NHS Ayrshire and Arran

I confirm that NHS Ayrshire and Arran have reviewed the undernoted documents and approve the above study.

Approved documents:

Document	Version	Date
Participant Information Sheet	3	28 February 2009
Letter of invitation to participant	2	28 February 2009
Questionnaire	2	8 January 2009
Application	1	18 November 2008

The terms of approval state that the investigator authorised to undertake this study within NHS Ayrshire & Arran is: -

- Ms Gayle Connolly, Physiotherapist ,NHS Ayrshire and Arran

With additional investigators : -

- Dr Paul Mattison, Consultant, NHS Ayrshire and Arran
- Ms Linda Miller, Physiotherapist, NHS Ayrshire and Arran

The sponsors for this study are: University of Glasgow

This approval letter is valid until: 6th October 2010

Regular reports of the study require to be submitted. Your first report should be submitted to Dr K Bell, Research & Development Manager in 12 months time and subsequently at yearly intervals until the work is completed.

In addition approval is granted subject to the following conditions: -

- All research activity must comply with the standards detailed in the Research Governance Framework for Health and Community Care and appropriate statutory legislation.

- If any amendments are to be made to the study protocol and or the Research Team the Researcher must seek Ethical and Management Approval for the changes before they can be implemented.

- The Researcher and NHS Ayrshire and Arran must permit and assist with any monitoring, auditing or inspection of the project by the relevant authorities.

- The NHS Ayrshire and Arran Complaints Department should be informed if any complaints arise regarding the project and the R&D Department must be copied into this correspondence.

- The outcome and lessons learnt from complaints must be communicated to funders, sponsors and other partners associated with the project.

- As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collated, until the destruction of these data. Under no circumstances should personal data be stored on any unencrypted removable media e.g. laptop, USB or mobile device (for further information and guidance please contact the Information Governance Team based at Ailsa Hospital 01292 513693 or 513694).

If I can be of any further assistance please do not hesitate to contact me. On behalf of the department, I wish you every success with the project.

Yours sincerely

Dr Ken Ferguson
Associate Medical Director for Integrated Care & Partner Services

cc Dr Lorna Paul, Dr Paul Mattison, Ms Linda Miller, Hugh Hunter,
Jillian Neilson, Information Governance, Ailsa Hospital,
Lesley Douglas, Finance, Ailsa Hospital.

Ayrshire & Arran Local Research Ethics Committee
NHS Ayrshire & Arran
Ayr Hospital
Dalmellington Road
Ayr
KA6 6DX

Telephone: 01292 614553
Facsimile: 01292 513655

31 March 2009

Dr Lorna Paul
Reader in Nursing and Healthcare
University of Glasgow
Division of Nursing & Healthcare
Faculty of Medicine, University of
Glasgow, 59 Oakfield Avenue
G128LW

Dear Dr Paul

Full title of study:	**The prevalence and experience of pain in people with Multiple Sclerosis (MS) in NHS Ayrshire and Arran.**
REC reference number:	**08/S0201/48**
Protocol number:	**1**
EudraCT number:	

Thank you for responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Committee held on 25 March 2009. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research

Application System or at http://www.rdforum.nhs.uk.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
letter from funder		20 November 2008
indemnity arrangements		20 November 2008
cv for supervisor		20 November 2008
Participant Information Sheet	3	28 February 2009
Letter of invitation to participant	2	28 February 2009
Questionnaire	2	14 January 2009
Letter from Sponsor		20 November 2008
Protocol	2	14 January 2009
Investigator CV		18 November 2008
Application	1	18 November 2008
Response to Request for Further Information		28 February 2009
Response to Request for Further Information		March 2009

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review –guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments

- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/S0201/48	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Fr Matthew McManus
Chair

Email: susan.dillon@aaaht.scot.nhs.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
"After ethical review – guidance for researchers"
Site approval form

Copy to: *Dr K Bell, R&D Manager, Crosshouse Hospital*

Appendix 3: Patient Information Sheet for Epidemiological Study

INFORMATION SHEET

Pain in Multiple Sclerosis: The prevalence and experience of pain in people with Multiple Sclerosis (MS) in NHS Ayrshire and Arran.

Recently you were contacted about the above research study that is currently being undertaken on MS. You are now invited to take part in this study, which aims to measure the prevalence (frequency) and experience of pain in people with MS, who live in the Ayrshire and Arran area. It is a joint project between NHS Ayrshire and Arran and the University of Glasgow and is funded by the Multiple Sclerosis Society.

Although pain is recognised as a disabling symptom of Multiple Sclerosis (MS), the number of people affected is still unknown. Previous research was done on much smaller, more specific groups of people with MS, making it harder to gain a true picture of the frequency and pattern of pain for the rest of the MS population. The current research study therefore aims to recruit as many people with MS in Ayrshire and Arran as possible so as to accurately estimate the frequency and experience of pain for the wider MS population. It aims to be as far-reaching as possible, by including a variety of groups of people, i.e. people at different stages of their disease, with different types of MS, and different levels of disability.

Why have I been chosen?

As the study aims to assess the pain experience in people with Multiple Sclerosis, you have been chosen as a person who has been diagnosed with Multiple Sclerosis, and are known by the MS service at the Douglas Grant Rehabilitation Centre.

What does taking part involve?

If you decide to take part you will be required to complete the enclosed questionnaire, entitled ‘The Pain Experience of People with Multiple Sclerosis’. The questionnaire mainly includes questions on pain that you may have experienced. Sections are also included which ask about any disability you may have, your current mood, level of function and quality of life. The questionnaire is fairly detailed and may take up to one hour to complete but it does not have to be completed in one sitting and assistance from another person is permitted, if required. When you have completed the questionnaire, we ask that you return it in the stamp-addressed-envelope provided. It is possible medical records may be accessed to clarify responses from completed questionnaires.

How will the information I provide be used?

Information from completed questionnaires will be pooled together to make conclusions about pain in MS.

Do I have to take part?

It is up to you to decide whether or not to take part. If, after reading this you do decide to take part, you will be given this sheet to keep. You will not sign a consent form, but by completing and returning the questionnaire enclosed, the researcher will assume that you have provided your consent.

Will my taking part in this study be kept confidential?

All information, which is collected about you during the course of the research, will be kept strictly confidential. You will be identified by an ID number only and any information about you will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

On completion of the research, the results will form part of a PhD thesis, which will be marked. It is hoped that the findings will be published, but the results of individual participants will not be identified within the publication.

We will be holding a session in late 2009, when you will be invited along to hear the results of the study and to discuss any of the findings with the team. This event will be held locally and details will be advertised nearer the time. A written summary of the study results will also be available and can be sent to people unable to attend the feedback session.

Thank you very much for your time. If you require any further information or have any questions about completing the questionnaire please contact:

Douglas Grant Rehabilitation Centre
01294322112

Appendix 4: Sensitivity Analysis

Sensitivity Analysis for the PainDETECT Scoring Method

A sensitivity analysis was undertaken to compare outputs in two scenarios: scenario 1) when cases of *possible* neuropathic pain (indicated by PD-Q score of 13-18) was coded as *actual* cases of neuropathic pain; scenario 2) when cases of *possible* neuropathic pain (indicated by PD-Q score of 13-18) were coded as cases of *non*-neuropathic pain.

As outlined in section 5.5.5.2, backward, stepwise logistic regression was used to obtain a parsimonious model that included the variables independently associated with neuropathic pain. Outputs from the final model of the two scenarios are shown as follows

Table 1) Logistic regression model of predictors of neuropathic pain (n=263):

Possible cases coded as actual cases

PREDICTOR	P value	Odds Ratio	95% CI
TYPE OF MS[a]			
Relapsing Remitting	0.005	2.87	1.37-6.00
Secondary Progressive	0.001	5.52	2.07-14.7
Progressive Relapsing	0.075	2.45	0.91-6.57
DISABILITY (GNDS)	<0.001	1.07	1.04-1.10
Hosmer-Lemeshow goodness of Fit p=0.55			

[a] primary progressive as reference category

Table 2) Logistic regression model of predictors of neuropathic pain (n=263):

Possible cases coded as cases of non-neuropathic pain

PREDICTOR	P value	Odds Ratio	95% CI
TYPE OF MS[a]			
Relapsing Remitting	0.012	2.31	1.27-5.61
Secondary Progressive	0.003	4.91	1.91-13.65
Progressive Relapsing	0.081	2.13	0.89-5.31
DISABILITY (GNDS)	<0.001	1.08	1.05-1.11
Hosmer-Lemeshow goodness of Fit p=0.57			

[a] primary progressive as reference category

In each of the two scenarios, both show type of MS and disability level (GNDS) as independent predictors of pain. Both showed goodness of Fit (using the Hosmer-

Lemeshow Goodness of Fit Test).Thus from the sensitivity analysis it would seem that either method of coding is appropriate for the purpose of multivariate analysis of the predictors of neuropathic pain.

Appendix 5: The Brief Pain Inventory

The Brief Pain Inventory

Pain severity

1) Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 2 weeks:

0	1	2	3	4	5	6	7	8	9	10

No pain — worst pain imaginable

2) Please rate your pain by circling the one number that best describes your pain at its **least in** the last 2 weeks:

0	1	2	3	4	5	6	7	8	9	10

No pain — worst pain imaginable

3) Please rate your pain by circling the one number that best describes your pain on **average** in the last 2 weeks:

0	1	2	3	4	5	6	7	8	9	10

No pain — worst pain imaginable

4) Please rate your pain by circling the one number that best describes your pain **right now**:

0	1	2	3	4	5	6	7	8	9	10

No pain — worst pain imaginable

5) In the last week how much relief has TENS provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%

Complete pain relief — Total Pain relief

Pain-related Interference

Circle the one number that describes how during the past week pain has interfered with your:

A) General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										completely interferes

B) Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										completely interferes

C) Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										completely interferes

D) Normal work (includes work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										completely interferes

E) Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										completely interferes

F) Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										completely interferes

G) Enjoyment of Life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										completely interferes

Appendix 6:

Patient Global Impression of Change (PGIC)

Since beginning TENS treatment, how would you rate the **overall change** in your pain? Please tick one of the boxes below:

1. Very much improved ☐
2. Much improved ☐
3. Minimally improved ☐
4. No change ☐
5. Minimally worse ☐
6. Much worse ☐
7. Very much worse ☐

Appendix7: NHS Research and Development and Ethics Approval for TENS study

Healthcare Quality, Governance and Standards Unit
Research, Development & Evaluation Office
58 Lister Street
Crosshouse Hospital
Kilmarnock
KA2 0BB

NHS Ayrshire & Arran

Tel: (01563) 825856
Fax: (01563) 825806

Mrs Gayle Connolly
University of Glasgow
Nursing & Health Care
59 Oakfield Avenue
Glasgow
G12 8LL

Date: 6 June 2011
Your Ref:
Our Ref: CAW/KLB/AMK 2011AA026

Enquiries to: Karen Bell
Extension: 25850
Direct Line: 01563 825850
Email: Karen.bell@aaaht.scot.nhs.uk

www.nhsayrshireandarran.com

Dear Mrs Connolly

R&D 2011AA026 The effect of Transcutaneous Electrical Nerve Stimulation (TENS) on neuropathic pain in Multiple Sclerosis

I confirm that NHS Ayrshire and Arran have reviewed the undernoted documents and grant R&D Management approval for the above study.

Approved documents:

Document	Version	Date
IRAS R&D Form	3.1	19 April 2011
Protocol	1.0	19 April 2011
Initial Screening Questionnaire	1.0	19 April 2011
Pain detect Questionnaire	/	/
PGIC Scale	/	/
Neuropathic pain Scale	/	/
Brief Pain Inventory	/	/
Primary Outcome measure	/	/
Mini Mental State Exam Instructions	/	/
Invitation letter	2.0	16 May 2011
GP Letter	1.0	19 April 2011
Reminder Letter	1.0	19 April 2011
Flowchart	1.0	19 April 2011
Participant Consent form	2.0	16 May 2011
Participant Information Sheet	1.0	19 April 2011

The terms of approval state that the investigator authorised to undertake this study within NHS Ayrshire & Arran is: -

- Mrs Gayle Connolly, NHS Ayrshire & Arran

With additional investigator(s): -

- Dr Paul Mattison, NHS Ayrshire & Arran
- Ms Linda Miller, NHS Ayrshire & Arran

The sponsors for this study are NHS Ayrshire & Arran.

This approval letter is valid until 30 June 2012.

Regular reports of the study require to be submitted. Your first report should be submitted to Dr K Bell, Research & Development Manager in 12 months time and subsequently at yearly intervals until the work is completed.

Please note that as a requirement of this type of study your name, designation, work address, work telephone number, work e-mail address, work related qualifications and whole time equivalent will be held on the Scottish National Research Database so that NHS R&D staff in Scotland can access this information for purposes related to project management and report monitoring.

In addition approval is granted subject to the following conditions: -

- All research activity must comply with the standards detailed in the Research Governance Framework for Health and Community Care www.cso.scot.nhs.uk/publications/ResGov/Framework/RGFEdTwo.pdf and appropriate statutory legislation. It is your responsibility to ensure that you are familiar with these, however please do not hesitate to seek further advice if you are unsure.

- You are required to comply with Good Clinical Practice (ICH-GCP guidelines may be found at www.ich.org/LOB/media/MEDIA482.pdf), Ethics Guidelines, Health & Safety Act 1999 and Data Protection Act 1998.

- If any amendments are to be made to the study protocol and or the Research Team the Researcher must seek Ethical and Management Approval for the changes before they can be implemented.

- The Researcher and NHS Ayrshire and Arran must permit and assist with any monitoring, auditing or inspection of the project by the relevant authorities.

- The NHS Ayrshire and Arran Complaints Department should be informed if any complaints arise regarding the project and the R&D Department must be copied into this correspondence.

- The outcome and lessons learnt from complaints must be communicated to funders, sponsors and other partners associated with the project.

- As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collated in line with NHS Scotland IT Security Policies, until the destruction of these data. Under no circumstances should personal data be stored on any unencrypted removable media e.g. laptop, USB or mobile device (for further information and guidance please contact the Information Governance Team based at Ailsa Hospital 01292 513693 or 513694).

If I can be of any further assistance please do not hesitate to contact me. On behalf of the department, I wish you every success with the project.

Yours sincerely

Professor Craig A White
Assistant Director Healthcare Quality, Governance and Standards

cc R&D Office, NHS Ayrshire & Arran (sponsor)

cc via email
Dr Paul Mattison, NHS Ayrshire & Arran
Linda Miller, NHS Ayrshire & Arran
Information Governance, NHS Ayrshire & Arran
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Mrs Gayle W Connolly
University of Glasgow
Nursing and Health Care
59 Oakfield Avenue
Glasgow G12 8LW

Date 24th May 2011
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Mrs Connolly

Full title of study: **The effect of Transcutaneous Electrical Nerve Stimulation (TENS)on neuropathic pain in Multiple Sclerosis**
REC reference number: **11/AL/0248**

Thank you for your letter of 16th May 2011. I can confirm the REC has received the documents listed below as evidence of compliance with the approval conditions detailed in our letter dated 05 May 2011. Please note these documents are for information only and have not been reviewed by the committee.

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Covering Letter		16 May 2011
Letter of invitation to participant	2	16 May 2011
Participant Consent Form	2	16 May 2011

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

11/AL/0248 **Please quote this number on all correspondence**

Yours sincerely

Liz Jamieson

Mrs Liz Jamieson
Committee Co-ordinator

Copy to: Dr Karen Bell, NHS Ayrshire and Arran Research and Development

Delivering better health

Appendix 8: Letter of Invitation: TENS study

Douglas Grant Rehabilitation Centre
Ayrshire Central Hospital
Kilwinning Road
Irvine
KA12 8SS

Dear Sir/ Madam,

The effect of TENS on neuropathic pain in people with Multiple Sclerosis

I am writing to inform you of a study taking place on the effect of Transcutaneous Electrical Nerve Stimulation (TENS) on pain in people with Multiple Sclerosis (MS). TENS is a small unit, which delivers electrical impulses to the skin producing a comfortable, tingling sensation. TENS is a common treatment that has been shown to be effective in the relief of pain in many medical conditions however few studies have looked at the effect of TENS on MS-related pain.

The study focuses on a particular type of pain, known as neuropathic pain, which is caused by damage to the nervous system. Neuropathic pain is very common in MS and it is hoped that TENS may be helpful in managing this condition. Many people with this condition describe having pain, but some would describe it as unusual, unpleasant sensations. Examples of this include burning, cold, itching, prickling, tingling or squeezing. The study particularly focuses on those people with neuropathic pain in the lower limb(s). However, **anyone with pain (or unpleasant sensations) in the lower limb(s)** may be eligible to participate even if you are unsure whether you have neuropathic pain, as this will be established at an initial assessment.

The study will involve the application of TENS at intervals each day for a two-week period and pain levels will be recorded during this time. All participants will be randomly allocated to one of two groups. Each group will receive a different form of TENS, one of which is a placebo TENS application. Both TENS applications will be completely comfortable. In either situation, all patients will continue to receive normal clinical care as before. After the study period, participants are welcome to continue with TENS treatment if they find it is beneficial.

The study is a joint project between NHS Ayrshire and Arran, and the University of Glasgow, and is being supervised by myself, at the Douglas Grant Centre. The research, which is funded by the MS Society, is undertaken by Gayle Connolly, a Physiotherapist, currently working in NHS Ayrshire and Arran. Please take the time to read the enclosed patient information sheet attached. If you have questions and are interested in taking part please contact Gayle Connolly. She can be contacted on:

Gayle Connolly
Phd student
School of nursing & healthcare
The university of Glasgow
59 Oakfield avenue
Glasgow
G12 8lw
Telephone: 0141 330 4053
Email: g.connolly.1@research.gla.ac.uk

Alternatively if you have any further queries related to the study please do not hesitate to contact me. Yours Sincerely, Dr Paul Mattison

Appendix 9: Patient Information Sheet for TENS study

Participant Information Sheet

The effect of TENS on neuropathic pain in people with Multiple Sclerosis

Before you decide whether or not to take part it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

Part 1: Basic Study Information

What is the purpose of the study?

The purpose of this study is to determine whether Transcutaneous Electrical Nerve Stimulation (TENS) is effective in the treatment of neuropathic pain in people with MS.

TENS is used in the healthcare setting for pain relief. TENS is a small unit, which delivers electrical impulses to the skin, producing a comfortable, tingling sensation. It has been shown to be effective in the relief of pain in many medical conditions, such as low back pain and osteoarthritis. However, the effect of TENS on MS-related pain is not yet clear. If proven to be successful in the treatment of pain, TENS, as a simple, portable, non-invasive treatment, may be beneficial as pain management for people MS.

The study focuses on a particular type of pain, known as neuropathic pain, which is caused by damage to the nervous system. Neuropathic pain is very common in MS and TENS may be helpful in managing this condition. As neuropathic pain often affects the lower limbs, this study will focus solely on lower limb pain. To assess whether TENS is an effective treatment, all eligible participants will wear a TENS unit for a set period of time and the intensity and impact of their pain will be recoded at intervals.

Why have I been chosen?

The study aims to assess the effect of TENS on pain in people with Multiple Sclerosis. You have been identified by Dr Mattison as a person with MS and are known by the MS Service at the Douglas Grant Rehabilitation Centre.

What does taking part involve?

i) TENS Application

If you decide to take part you will be asked to wear a TENS machine every day for a period of two weeks. You will be asked to use the machine for a minimum of four hours per day (this can be broken down, i.e. 4x1-hour blocks of TENS). You can choose the time of day that it is suitable for

you to use the TENS machine, but it would be helpful if you would apply the TENS unit when you experience pain.

TENS application involves placing two self-adhesive electrodes (which are connected to the TENS machine) over your lower back. The nerves that affect your lower limbs come from your spine at this point. You will initially be reviewed by a Physiotherapist, who will apply the TENS machine and instruct you on the specific application to be continued for the two-week period. Many people describe TENS as a tingling type sensation, but it can vary slightly for different people. TENS application will always be comfortable.

You will be randomly allocated to one of two groups. Each group will receive a different form of TENS, one of which is a placebo TENS application.

ii) Daily Pain Recording

For the week before you start using the TENS you will be asked to record each day how intense you pain is on the Numerical Rating Scale (NRS-11) of pain intensity from 0-10, where 0= no pain and 10= the worst pain you could imagine. You will also be asked to do this throughout the two-week TENS treatment period in a pain diary. This simply involves marking a number on a scale and should take no more than one minute. You will also be asked to complete a short questionnaire, the Neuropathic Pain Scale (NPS) which measures the level of neuropathic pain you experience, on three consecutive days before you start TENS treatment and towards the end of TENS treatment. This will also be completed at home and should take no more than 5 minutes.

ii) Appointment at Douglas Grant Centre

You will be asked to attend the Douglas Grant Centre on three occasions: The first visit will be for an initial eligibility assessment, where the researcher (a physiotherapist) will assess whether you have neuropathic pain affecting your lower limb/s and whether you have any medical conditions in which TENS may not be right for you. At this initial assessment, you will be given instructions on how to record your pain at home during the seven day period before TENS application. This appointment will last approximately 30 minutes.

A second appointment will involve an initial assessment of your pain and then the application of the TENS unit by a physiotherapist, who will instruct you on its use for the two-week period. This appointment will last approximately one hour. A third appointment will involve return of the TENS unit and a further assessment of your pain, this will last approximately 30 minutes. Pain measures taken at appointments two and three include the Neuropathic Pain Scale (previously mentioned) and the Brief Pain Inventory, a short questionnaire, which measures the impact of your pain on your life. At the end of treatment you will be asked how effective you felt your experience of TENS was in relieving your pain and whether you would consider continuing with it as a treatment.

Disadvantages of taking part

There are no expected risks, side effects or disadvantages expected from taking part in the study. Wearing the TENS machine on a daily basis may be perceived as an inconvenience. However, as the device is small, portable and comfortable during application, this will be of minimal inconvenience.

What are the potential benefits of taking part?

The information you provide will help us understand whether TENS is effective in the treatment of neuropathic pain for people with MS. It is possible that the application of a TENS unit may be beneficial in providing pain relief.

Expenses and Payment

Participants will be compensated for the costs of travel to the Douglas Grant Centre, Irvine. Patient transport may be organised if you are unable to make your own way to the centre.

Do I have to take part?

Participation in the research is entirely voluntary. If you decide to take part you are still free to withdraw at any time and without giving reason. A decision to withdraw at any time, or a decision not to take part, will not have any effect on the standard of care you receive.

How do I go about participating in the study?

If you do wish to participate, **you should contact the researcher, Gayle Connolly (contact details at the end of this sheet)** who will explain the study in further detail, go through the information sheet with you and answer any questions you may have. An initial screening visit will then be made for you at the Douglas Grant Centre in order to determine if you are eligible to be included in the study. At this point, the researcher will be happy to answer any further questions and you will then be asked to sign a consent form to show that you are happy to participate.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential. All information that you provide will be identifiable by an ID number only. All personal details will be removed so that you cannot be recognised in any way. We will ask your permission to notify your GP that you have participated in the study. If you are happy for this, a letter will be sent to your GP, which will be kept in your medical notes.

Part 2: Additional Information

What happens if new information becomes available?

Sometimes new treatment information becomes available. Although this is unlikely, should this happen during the study the researcher will inform you of any new treatments.

What will happen if I don't want to continue in the study?

You can withdraw at any time. With your permission the information collected from you to this point will still be included within the study results.

What if there is a problem?

Should you have a concern about any aspect of the study you should contact the main researcher (see contact details at the end) in the first instance. If this does not resolve the issue, and you would like to formally complain you can do this through the NHS Complaints Procedure. Details can be obtained from the Patients, Relations and Complaints Office (Tel: 01292 513620). Independent advice about the study can be obtained from MS specialist nurse Alan Izat or Anne Thomson (Tel: 01294 323030).

What will happen to the results of the research study?

On completion of the research, the results will form part of a PhD thesis, which will be marked. It is hoped that the findings will be published, but the results of individual participants will not be identified within the publication.

We will be holding a session in the summer of 2012, when you will be invited along to hear the results of the study and to discuss any of the findings with the team. This event will be held locally and details will be advertised nearer the time. A written summary of the study results will also be available and can be sent to people unable to attend the feedback session.

Who is sponsoring and funding the research?

The study is funded by the Multiple Sclerosis Society UK. The study is sponsored by NHS Ayrshire and Arran and is audited by the University of Glasgow.

Who is undertaking the research?

The research will be undertaken by Gayle Connolly, a Physiotherapist within NHS Ayrshire and Arran, and PhD student at the University of Glasgow. Gayle is undertaking the research as part of her PhD qualification into the field of pain in MS.

Who has reviewed this study?

All research in the NHS is looked at by the Research Ethics committee, an independent group of people who aim to protect patient safety, rights, well being and dignity. This study has been reviewed and given a favourable opinion by the West of Scotland Research Ethics Committee.

Participation, further information and contact details.

Should you wish to participate or if you require any further information about this research study please contact the main researcher on the number below:

Gayle Connolly
PhD Student
School of Nursing & Healthcare
The University of Glasgow
59 Oakfield Avenue
Glasgow
G12 8LW

Tel: 0141 330 4053
Mobile:07908730152
Please leave a message if there is no one to answer your call.

Email: g.connolly.1@research.gla.ac.uk

Appendix 10: The Neuropathic Pain Scale

Neuropathic Pain Scale

1) Please use the scale below to tell us how **intense** your pain is. Place an 'X' through the number that best describes the intensity of your pain.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most **intense** pain sensation imaginable

2) Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include: "like a knife", "like a spike", "jabbing" or "like jolts".

Not sharp	0	1	2	3	4	5	6	7	8	9	10	The most **sharp** sensation imaginable ("like a knife")

3) Please use the scale below to tell us how **hot** your pain feels. Words to describe very hot pain include "burning and "on fire".

Not hot	0	1	2	3	4	5	6	7	8	9	10	The most **hot** sensation imaginable ("on fire")

4) Please use the scale below to tell us how **dull** your pain feels. Words used to describe very dull pain include "like a dull toothache", "dull pain", "aching" and "like a bruise".

Not dull	0	1	2	3	4	5	6	7	8	9	10	The most **dull** sensation imaginable

5) Please use the scale below to tell us how **cold** your pain feels. Words used to describe very cold pain include "like ice", and "freezing".

Not cold	0	1	2	3	4	5	6	7	8	9	10	The most **cold** sensation imaginable ("freezing")

6) Please use the scale below to describe how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin", and "raw skin".

0	1	2	3	4	5	6	7	8	9	10

Not Sensitive

The most sensitive sensation imaginable ("raw skin")

7) Please use the scale below to tell us how **itchy** your pain feels. Words used to describe itchy pain include, "like nettle skin" and "like a mosquito bite".

Not itchy

0	1	2	3	4	5	6	7	8	9	10

The most itchy sensation imaginable ("like a nettle skin")

8) Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how **unpleasant** your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable". Remember pain can have a low intensity, but still feel extremely unpleasant and some kinds of pain can have a high intensity but be very tolerable. With this scale please tell us how **unpleasant** your pain feels.

Not un-pleasant

0	1	2	3	4	5	6	7	8	9	10

The most **unpleasant** sensation imaginable ("intolerable")

9) Lastly, we want you to give us an estimate of the severity of your deep versus surface pain. We want you to rate each location of pain separately. We realise that it can be difficult to make these estimates, and most likely it will be a "best guess", but please give us your best estimate.

HOW INTENSE IS YOUR *DEEP* PAIN?

No deep pain

0	1	2	3	4	5	6	7	8	9	10

The most intense **deep** pain sensation imaginable

HOW INTENSE IS YOUR *SURFACE* PAIN?

No surface pain

0	1	2	3	4	5	6	7	8	9	10

The most Intense sensation imaginable

Appendix 10: Screening Questionnaire for Inclusion into TENS study

ID NO

INITIAL SCREENING QUESTIONNAIRE

1) Demographic details:

i) Age:
ii) Sex:

Employment category:

Student ☐
Employed- full time ☐
Employed- part time ☐
Unemployed ☐
Unable to work due to MS ☐

Marital status:

Single ☐
Married ☐
Living with Partner ☐
Widowed ☐
Divorced ☐

2) MS Information:

i) When were you first diagnosed with MS?

ii) What Type of MS do you have? Please tick one box:

Relapsing–Remitting: ☐

Primary Progressive: ☐

Secondary Progressive: ☐

Progressive Relapsing: ☐

Unsure: ☐

iii) When did you last have a relapse in your condition?.....

3) Other information

i) Are you **currently** involved in any other research study?

Please tick one box: Yes: ☐

No: ☐

ii) Have you **ever** been involved in a research study?

Please tick one box: Yes: ☐

No: ☐

If so, when?

Please give details of the study:

iii) Have you ever used TENS before?

Please tick one box: Yes: ☐

No: ☐

If so, when?

What body area (s) did you apply it to?.....

Did you find it helped your pain?.....

4) Other Medical conditions:

Please tick if you have, or have had, any of the following medical conditions:

□Stroke
□Spinal cord injury
□Nerve damage
□Lupus (SLE),
□Fibromyalgia
□Rheumatoid Arthritis
□Cancer
□Diabetes
□Shingles
□Surgical operation (within last 3 months):
□Any areas of decreased sensation or numbness
□Pregnancy
□Epilepsy
□Pacemaker
□Percutaneous central venous catheter
□Skin problems
□Heart Problems

If yes, please give details:----------

Do you have any other medical conditions, not mentioned above?----------
---

---

4) Pain:

i) Throughout our lives, most of us experience every-day types of pain, such as minor headaches, sprains and toothaches. Other than these every-day types of pain, have you experienced **on-going, bothersome pain** within the last two weeks?

Please tick one box: Yes: ☐

No: ☐

ii) Where is this pain? (Please give details of all body areas): ----------
---

---

iii) Please rate your pain by circling the one number that best describes your pain on **average**:

0	1	2	3	4	5	6	7	8	9	10

No pain **Pain as bad As you Can imagine**

iv) How long have you had this pain?

v) What medication are you currently taking for pain? Please list (and provide dose):

---

vi) When was this prescribed?

vii) Has there been any recent change in the amount (or dose) of pain medication you have been prescribed or are taking?

If so, when?

NOW COMPLETE:
PAIN DETECT
MMSE

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