Investigating the impact of a spinal mobilisation intervention in people with multiple sclerosis.

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Abstract

Investigating the impact of a spinal mobilisation intervention in people with multiple sclerosis.

Background: Multiple Sclerosis (MS) has many disabling symptoms due to weakened signal propagation in the central nervous system. Manual therapeutics are often seen to have a positive effect on these symptoms with limited information as to why. The purpose of this project was to investigate a spinal mobilisation intervention, objectively measuring the changes it may be causing to muscle quality and movement patterns as a contribution to research in MS therapeutics.

Methods: A series of 3 studies were designed to investigate the effects of a spinal mobilisation intervention on muscle quality and movement patterns. Study 1 tested people with lower back pain (LBP) as a pilot population (n=40), testing for an immediate effect on muscle quality. Study 2 replicated this with MS patients (n=20) assessing muscle quality, balance, and pain. Study 3 tested the intervention in a longer-term 4 bout study (n=20), assessing muscle quality, balance, pain, and fatigue.

Results: Significant muscle stiffness reductions were seen in the LBP population post the intervention ($p = 0.01$, $\eta^2_{partial} = 0.15$). Baseline stiffness was found as a significant contributor ($p = 0.002$, $R^2 = 0.22$). These muscular results were not replicated with the MS population. However, significant improvements in self-reported pain as a result of the intervention were revealed ($p = 0.008$, $\eta^2_{partial} = 0.33$). Study 3 findings demonstrated significant improvements from baseline in balance and fatigue measures as a result of the intervention. High variability in the data are seen within the MS population.

Conclusions: Four sessions were not sufficient to elicit a significant response in muscle quality as a result of the intervention in an MS population. However, significant improvements in balance and fatigue were revealed. Given the variability from the MS population, it is necessary to undertake a longer-term study and normalise baseline muscle quality values.

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List of Abbreviations

AEA	Anandamide
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AP	Anterior-posterior
APC	Antigen presenting cell
BBB	Blood brain barrier
BMI	Body mass index
BW	Body weights
CNS	Central nervous system
CoG	Centre of gravity
CoP	Centre of pressure
CPR	Clinical prediction rule
CV	Coefficient of variation
dPAG	dorsal peri-acqueductal grey area
DMT	Disease modifying therapy
EDSS	Expanded Disability Status Scale
EMG	Electromyography
FIS	Fatigue Impact Scale
GP	General Practitioner
GRF	Ground reaction force
Hz	Hertz
LBP	Lower back pain
ML	Mediolateral
MS	Multiple sclerosis
MSIS	Multiple Sclerosis Impact Scale
N	Newtons
NICE	National Institute for Health and Clinical Excellence
ODI	Oswestry Disability Index
PEA	ß-endorphins N-palmitoylethanolamide
PA	Posterior-anterior
PNS	Peripheral nervous system
PPMS	Primary progressive multiple sclerosis
PPT	Pain pressure threshold
QoL	Quality of life
RA	Rheumatoid arthritis
RoM	Range of motion
RRMS	Relapse-remitting multiple sclerosis
SD	Standard deviation
SEM	Standard error of mean
SF	Short Form
SNS	Sympathetic nervous system
SPMS	Secondary-progressive multiple sclerosis
UTI	Urinary tract infection
VAS	Visual Analogue Scale

Declaration

I hereby declare that:

1. the research contained in this thesis has not been submitted for any other degree or professional qualification.

2. the thesis is a result of original work from the author, while the investigation rationale was in collaboration with Pacla Medical Ltd. and the project funded by Medical Research Scotland.
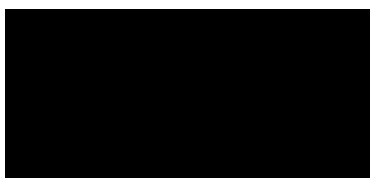
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Chapter One

Introduction

1.0 An Introduction to Multiple Sclerosis

As a chronic and inflammatory disease of the central nervous system (CNS) and affecting millions of people across the globe, the impact of multiple sclerosis (MS) as a condition is substantial and a critical area to research (Backus et al., 2016). Although known to be caused by autoimmune demyelination of the CNS, there are many complexities around the specifics of why this occurs (Compston & Coles, 2008; O'Gorman et al., 2012; Ziemann et al., 2011). MS is the most common cause of neurological disability in young adults not including traumatic injury worldwide and highly prevalent in Scotland (Dimitrov & Turner, 2014; Mackenzie et al., 2014; Wallin et al., 2019b).

The manifestation of symptoms in the individual are dependent on the affected pathways of the CNS (Langdon et al., 2012; Sumowski et al., 2018). There is a large degree of variation between patients in terms of the symptoms they experience and therefore, the required treatment to address these symptoms. Therapeutics aimed to help within the management of the range of symptoms experienced by patients can vary amongst oxygen therapy, manual therapy, exercise therapy, orthosis, speech and language therapy, and others (Feinstein et al., 2015; Khan et al., 2007; Langdon & Thompson, 1999; Patti et al., 2002). Key practitioners in decision making around the management and care are General Practitioners (GPs), neurological consultants and MS nurses.

1.0.1 Symptom Management

Many symptoms can persist that lead to limited function and disability, even with pharmacological treatment (Crabtree-Hartman, 2018). Although symptoms can manifest very differently in every individual, mobility is often affected in many different ways and is highly important to quality of life (QoL) due to its association with independence and physical health, and the harmful effects of physical deconditioning (Langdon & Thompson, 1999; McCullagh et al., 2008; Ottenbacher et al., 1996; Sebastião et al., 2016). Symptom management often requires a patient

centred approach, as well as regular monitoring due to the individual and progressive nature of the disease (Dimitrov & Turner, 2014; Khan et al., 2007; Kehoe et al., 2015).

1.0.2 Physiotherapy Measurement

Physiotherapy is a therapeutic treatment tool that has been recommended for MS patients due to specific functions it can target while also focussing on whole-body mobility. The wide range of potential therapeutics involved aim to maintain function within the musculoskeletal system. However, the subjective nature of the application and assessment of these treatments have resulted in limited information for the mechanism and effectiveness (Etoom et al., 2018b). The effectiveness of an intervention can be measured by performance tasks such as muscle strength ability, speed of walking and joint range of motion (RoM). Elements that are sometimes subjectively assessed are pain and stiffness; key contributors to functional movement and independence (Giovannelli et al., 2007; Gordon et al., 2015). The following chapters will describe the biomechanical measurement forms that are used to define and analyse physiotherapy interventions in literature, with focus on objective muscle response and movement patterns.

Due to the multifactorial nature of MS symptoms and their effect on an individual's life, symptom management plans may constantly change. The following chapters examine the literature on symptom management investigations and the outcomes that have resulted. The analysis adopted in this investigation used both objective and self-reported measures, due to their contributions to a fuller analysis. This will help to examine specific benefits in muscle and movement response. This also contributes to the formation of patient centred therapeutic treatment, and addressing the most critically disruptive symptoms that are reported by MS patients: stiffness, pain and fatigue (Backus et al., 2016).

1.1 Thesis Aims

The aim of this thesis was to provide a thorough investigation of a spinal mobilisation intervention within the context of MS symptom management and rehabilitation. The findings from the investigation will provide novel data characterising and investigating a manual therapeutic tool used for MS symptom management and the potential to improve QoL. This was with the intention of contributing to the

knowledge around physiotherapy research and the measurement of intervention impact.

1.2 Rationale Development

The rationale for this investigation was developed by Pacla Medical Ltd. and the physiotherapy work they have been carrying out for several years, largely with MS patients. They developed an intervention using spinal mobilisations in a specific manner for a 30-minute treatment period. This works at a slower rate, and for a longer time than any spinal mobilisation intervention described in the literature (Chiradejnant et al., 2003; Jowsey & Perry, 2010; Pecos-Martín et al., 2017; Pentelka et al., 2012; Thomson et al., 2009; Willett et al., 2010). Anecdotally patients reported reduced experiences of pain and stiffness after receiving this spinal mobilisation intervention. Both the patients and the physiotherapist reported improvements in whole-body mobility as well as motor refined movements, which could be connected to a reduced experience in pain and stiffness.

In a collaboration formed between Pacla Medical Ltd., Medical Research Scotland and Edinburgh Napier University, the project was developed to investigate this intervention scientifically, and the impact that it may be have on people with MS and their overall symptoms management.

1.3 Thesis Outline

The six chapters of this thesis outline the course of this investigation over a four-year period. The literature around MS pathophysiology, risk factors, diagnosis, symptoms, interventions, spinal therapeutics, and biomechanical measurement methods are described in chapter two. This literature provided validated methods for measurement of physiotherapy interventions, their impact and their importance.

The following three chapters report on the series of studies that were designed, to investigate the effects of the spinal mobilisation intervention on an MS population. This includes a pilot study (n = 40) reported in chapter three which was completed in the first year of the PhD. This was completed with a lower back pain (LBP) population rather than an MS population for ethical reasons, due to the lack of MS data and mobilisation interventions. This pilot study tested the efficacy and feasibility of the intervention enabling data for sample size calculations before working directly with

people with MS. This was based on the similarities described between the populations of increased levels of spinal stiffness and decreased levels of spinal mobility (Giesser et al., 2007; Shum et al., 2013).

Two MS studies (study two: n = 20, study three: n = 20) were carried out over the remaining time on the PhD and are reported in chapters four and five. Study two was designed as an MS feasibility study with information based on the pilot study and study three was designed as a randomised control trial based on the information from both previous studies. A summary of these results combined from all three studies is reported in chapter six with recommendations for future research. This incorporates results discussed in objective muscle response, objective balance movement patterns, self-reported pain, and self-reported fatigue.

Chapter Two

Literature Review

2.0 Introduction

This chapter provides an overview of the literature covering an overview of MS as a condition, symptoms and symptom management interventions; an aspect that is repeatedly reported as a key element for treatment in people with MS (Backus et al., 2016; Crabtree-Hartman, 2018; Visaria et al., 2018). The literature review will also cover the measurement and possible effects of physiotherapy-based interventions, with focus on lumbar spinal mobilisations. The research around MS rehabilitation is extensive and involves many different treatments and therapies. However, due to a person's individual needs, specific benefits and the efficacy of these treatments are difficult to determine (Donzé, 2015). Research to better this knowledge is ongoing, therefore this chapter will provide an updated review of physical interventions, spinal mobilisations, and their relationship to MS symptom management. An overview of methodological factors and biomechanical measurements concerned with the project are also included.

A large body of evidence demonstrates the collective acceptance of a general benefit from manual therapy for a wide variation of people groups. This is particularly relevant in conditions affecting the musculoskeletal system with reported improvements in pain, mobility and overall wellbeing (Krouwel et al., 2010; Nougarou et al., 2016; Willett et al., 2010). Much of this evidence stems from anecdotal and observational evidence over the years, supporting its use around the globe, particularly for the lumbar back (Clark & Horton, 2018; Hartvigsen et al., 2018; Hoy et al., 2010). However, there remains a lack of understanding in the scientific mechanism underlying the benefit of manual therapy (Chiradejnant et al., 2003; Pickar, 2002; Nougarou et al., 2016; Triano, 2001; Willet et al., 2010).

The review of this literature was based around searches from databases, PubMed, Science Direct, Ovid, Medline, Google Scholar and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) using only publications that were peer reviewed

and in the English language. Keywords were searched under the following 3 fields and using a variety of combinations:

- 'Multiple Sclerosis' AND, OR, 'rehabilitation', 'therapeutics', 'intervention', 'physiotherapy', 'symptom management', 'quality of life', 'gait', 'mobility', 'disability', 'balance', 'assessment', 'gender'.
- 'Manual therapy' AND, OR, 'spinal', 'manipulation', 'mobilisation', 'lumbar', 'lower back', 'stiffness', 'pain'.
- 'Biomechanical analysis' AND, OR, 'forward lunge', 'force plate', 'stability', 'body sway', 'sit-to-stand', 'kinetics', 'myometer', 'myoton pro', 'muscle stiffness', 'muscle tone', 'muscle elasticity'.

The articles were hand searched and chosen based on their subject relevance to the project from the information in the abstract. Citations used within relevant chosen articles were also included if they contributed viable content to the gathering of knowledge for the literature review. This was an ongoing process throughout the PhD project with the intention of keeping up with new peer reviewed research, particularly within the field of MS therapeutic interventions as an evolving field of study.

This chapter aims to consolidate information from the investigations already carried out in spinal physiotherapy and MS rehabilitation. The following chapters will provide a thorough overview of the methodologies used in this investigation with due consideration of the feasibility of working with an MS clinical population and gathering objective and accurate information on such a population. In doing so, this investigation aims to provide information on the areas where there is minimal literature, or insufficient scientific integrity or validity and which need more clarity requiring further investigations.

2.1 Multiple Sclerosis Overview

Multiple Sclerosis is known to be a chronic complex autoimmune condition that results in inflammatory damage to the CNS causing demyelination and potentially long-term neurodegeneration. There are over 2 million people around the world estimated to be suffering with the condition, with uneven prevalence distributions

globally and between sexes. The cause of the condition is likely to be multifactorial and may even represent a spectrum of diseases that result in inflammation of nerve tissue and demyelination. A combination of genetic, environmental, and life-style factors are said to contribute to the susceptibility of the condition, though none are the definitive cause and the condition has no cure. Treatments are based around management of symptoms and of the inflammatory attacks. The symptoms caused by neural degeneration are widespread and clinically present in many ways including physical, mental, visual, and emotional disabilities. The result of this condition has a high social cost (greater than stroke and Alzheimer's) due to the longevity of the disease and the varied age groups to which it can affect (Compston & Coles, 2008; Huang et al., 2017; Lassmann, 2018).

2.1.1 Pathophysiology

As a chronic autoimmune disorder, MS is characterised by degradation of myelin sheaths and neurons in the CNS due to a malfunction in the immune system targeting healthy nerve tissue. Immune cells infiltrate the CNS by crossing the blood brain barrier (BBB) through tight junctions they should not normally be able to permeate. Their activation leads to a cascade of events causing neural inflammation, demyelination, gliosis, and neural degradation. The most important aspect of these events is demyelination due to the destruction and loss of oligodendrocytes. Myelin sheaths are formed by oligodendrocytes from a mix of proteins and phospholipids, acting as an insulator covering the nerve axons. The sheaths protect the neuron and aid the conduction of impulses travelling down the nerve axon. This assists the process of signal transmission from one neuron to another, between peripheral nerves, the brain, and the spinal cord.

T-cell (immune system lymphocytes that fight harmful elements) infiltration induces a secretion of cytokines that promote further degradation of the BBB, making it more permeable, and recruit other immune cells (B-cells and macrophages). These cells degrade the myelin sheaths by antibody secretion and phagocytosis. The cytokine secretion causes damage to oligodendrocytes also amplified by the binding of Fas ligands produced that promote apoptosis (demonstrated in fig. 2.1). During the initial stages of inflammation, oligodendrocyte activity can promote remyelination to aid

damage recovery. However, the degradation of oligodendrocytes causes remyelination reduction and a proliferation of astrocytes causes the build up of scarred plaques. Remyelination is then overpowered by the immune system in a process that is perpetuated from recruiting additional cells, resulting in neural inflammation, demyelination and disruption of neural signalling (Ghasemi et al., 2017; Huang et al., 2017; Lassmann, 2018).
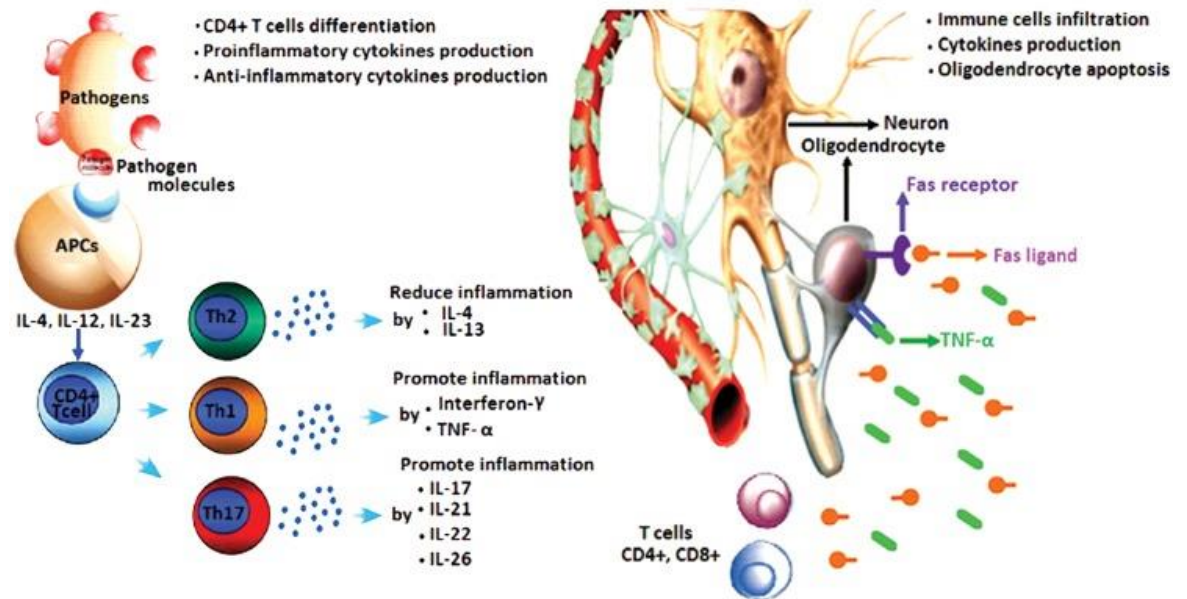
Figure 2. 1 Immune cell infiltration into CNS demonstrating an antigen presenting cell (APC) and potential pathogen interaction, resulting in T-cell activation and secretion of cytokines involved in demyelination. The result is oligodendrocyte degradation, demyelination and neural inflammation (Ghasemi et al., 2017).

The resultant disruption can affect signalling in the CNS and subsequently the mediation through to the peripheral nervous system (PNS), responsible for peripheral tissue communication to the brain and spinal cord. A below normal functioning of the sympathetic nervous system (SNS) has been revealed within the MS condition, which could alter the body's state of alertness. As part of the autonomic nervous system, the release of noradrenaline from peripheral neurons causes a cascade of events responsible for the fight or flight response and includes regulation of blood flow, heart rate and respiratory rate (Sternberg, 2012). The potential symptoms because of disruption in CNS signalling and PNS communication can vary widely from person to person, however, can often be clinically manifested as muscle weakness, loss of balance, speech loss, vision loss and sensory loss (Visaria et al., 2018).

2.1.2 Research Development

Since many MS symptoms are shared with other conditions, early cases of the condition were attributed to nervousness, stress, pain or fatigue (Weiner, 2005). Medical historians have found reports of possible MS cases dating back to the early 19th century based on clinical similarity and progression from modern MS case reports (Compston & Coles, 2008; Thompson et al., 2018; Weiner, 2005). Then in 1868, Dr Jean-Martin Charcot gave the definitive description of the disease and related the clinical symptoms to plaque like scarring on the brain because of inflammation (Vollmer, 2007). Much of his published works are still referred to today in the characterisation of the disease (Compston & Coles, 2008; Dimitrov & Turner, 2014; Weiner, 2005).

Fuelled by advances in microscope technology, further associations between MS and the fatty protein, myelin, were then identified in the early 20th century. This was due to the increased number of studies on human brains, focusing on the effects of damage to myelin structures. It was then identified as an autoimmune disease in the mid-20th century and prevalence data for different global regions started to develop (Rosati, 2001; Weiner, 2005).

2.1.3 Risk Factors and Epidemiology

For many years, the cause of MS has been investigated and research continues looking into genetic susceptibility, viral infections, environmental triggers, deficiencies and hormonal influences among others (Harbo et al., 2013; Wallin et al., 2019b). The exact cause of the condition is not known despite being one of the most common neurological disorders in the Western Hemisphere (Bishop & Rumrill, 2015).

The discrepancies in global prevalence of the condition reveal that people in countries further from the equator have a higher likelihood of developing MS. The continents with the highest prevalence (per 100, 000) are North America (140) and Europe (108), and regions with the lowest prevalence are South East Asia (2.2) and sub-Saharan Africa (2.1). Though part of the reason for these differences may be due to lack of data reported, the large discrepancy between these numbers is indicative of the geographical and genetic risk factors of the condition (Leray et al., 2016).

Within Europe, the UK has the highest prevalence of the condition, and within the UK, Scotland has the highest prevalence. The disease prevalence number in Scotland is constantly changing however the most recently published by Public Health England is 290 per 100, 000. Even within Scotland, the prevalence number doubles in the northerly part of the country in Orkney (Szczepaniak et al., 2018). These numbers have led to investigations into vitamin D deficiencies and ancestry likelihood of the condition (Leray et al., 2016; Mackenzie et al., 2014; Pugliatti et al., 2006; Thompson & Banek, 2013).

Vitamin D has an important role within the body particularly in gene expression and regulation of immunity. It's essential for B-cell and cytokine regulation, important factors within the pathogenesis of MS. Vitamin D is produced by the skin in ultraviolet radiation and is therefore produced more in areas with greater sun exposure. Low levels of vitamin D in the blood stream has been associated with high incidence of MS, also linked with the geographical prevalence distribution (Ghasemi et al., 2017; Munger & Ascherio, 2012). Trials for Vitamin D supplementation as a therapeutic benefit are under way and may help to regulate the relapses due to regulation of the immune system malfunction. However, the metabolic processes concerning Vitamin D may also be under an element of genetic control and less effective for therapeutic benefits in some (Jagannath et al., 2010; Munger & Ascherio, 2012; Smolders et al., 2008).

The geographical distribution of the disease is also linked to disease genetic susceptibility with over 200 genes with identified associations with MS. One of the most recent studies investigating genetic likelihoods used a meta-analysis of familial risk studies with a total of 18 family and twin studies on genetic prevalence of MS. The reported risk of someone from the general population developing the condition is approximately 0.1%, the risk of a child who has a parent with MS is 2%, the risk of the condition with a sibling with MS is 2.7%, and the risk of the condition with an identical twin is 20% (O'Gorman et al., 2012). Since identical twins share 100% of their genetic material, the resulting 20% genetic contribution of MS is likely required to be combined with environmental risk factors in order for the condition to develop (Multiple Sclerosis Genetics Consortium et al., 2018). The identified genes still have a

small risk associated with the development of MS, but continued research into these genes and relative risk of MS can help to identify further risk factors and potentially a cause (Multiple Sclerosis Genetics Consortium et al., 2018).

The resulting cause of the condition appears due to complex interactions with potential environmental or lifestyle risk factors. Several viruses have been investigated as potential triggers for development of MS with interest in the Epstein-Barr Virus (EBV), commonly known as the cause of glandular fever. High numbers of people with MS have also been revealed to have previously had the EBV, though it may have been non-symptomatic (O'Gorman et al., 2012). Potential lifestyle risk factors include smoking and obesity, which has been linked to CNS vulnerability to attack from immune cells (O'Gorman et al., 2012; Westerlind et al., 2014). Although none of these have proven theories, development in their research is ongoing and a lot more is known now around the combination of risk factors that are likely to be involved in the development of MS (Compston & Coles, 2008; Ghasemi et al., 2017).

A lot of literature exists on gender differences in MS for disease prevalence, type of disease, type of symptoms and response to interventions (Harbo et al., 2013; Houtchens & Bove, 2018; Mackenzie et al., 2014; O'Gorman et al., 2012; Pugliatti et al., 2006). Males present a higher prevalence of more progressive forms of the disease compared to women (Tremlett et al., 2010; Wallin et al., 2019a). The female-to-male MS prevalence ratios vary across the world. However, globally and locally in the UK, the trend tends to stay around 2.4:1 (Ahlgren et al., 2011; Harbo et al., 2013; Mackenzie et al., 2014). This implies that the disease can manifest differently with regards to sex, as well as develop differently. The variation in outcomes according to gender suggest that there are still further investigations possible in this area to decipher the role and predictive nature of gender on both symptom manifestation and response to interventions.

2.1.4 Diagnosis and Prognosis

Technological developments in the late 20th century allowed for the characterisation, diagnosis, and progression of the disease to be better investigated. For example, lumbar punctures facilitate the collection of spinal fluid which can be analysed for proteins associated with nerve inflammation. Computerised tomography images

then allowed the development and progression of plaques to be visualised, providing information on the rate of disease progression alongside clinical symptoms. However magnetic resonance imaging now provides more clear visuals with markers that help identify where scarring has occurred (Donzé, 2015; Weiner, 2005). With this technology also came developments in the Macdonald criteria for MS patients, allowing accurate clinical guidelines for efficient diagnosis (Gafson et al., 2012; Polman et al., 2011). These criteria, most recently updated in 2017, now state that evidence must be present for CNS damage over a recorded period, indicating the development of lesions over time, for MS diagnosis to be applicable. This means that MRI scans are heavily relied upon for efficient diagnosis and upkeep of the Macdonald criteria (Bove & Hauser, 2018; Thompson et al., 2018).

The requirements for both clinical symptom manifestation and visible lesions means that the diagnosis process can be prolonged. If an MS diagnosis is confirmed, a patient can then be classified into different MS types, describing the different forms of disease progression. For patients who are diagnosed with relapse-remitting MS (RRMS), neurological symptoms tend to be manifested in an inflammatory attack, with a period of recovery in between. These attacks are defined by symptoms associated with an inflammatory response and dependent on the nervous system pathway affected (Compston & Coles, 2008). A relapse can be entirely random or can be triggered by stress or other stimuli such as heat. These are referred to as a pseudo-relapse where triggers can also worsen symptoms (Vollmer et al., 2002). People with MS can be in this stage for many years with attacks such as numbness, tingling, blurry vision, or severe fatigue occurring spontaneously or in a triggered manner. Symptom management strategies then become important both to micro manage the symptom, and macro manage to maintain a good QoL (Visaria et al., 2018; Wallin et al., 2019b).

Progressive MS describes the stage of the disease where neurological deterioration is constant, resulting in a progressive increase of disability (Dimitrov & Turner, 2014). This is often seen clinically with worsening symptoms and less recovery time between relapses. These relapses can manifest as increasing problems in the whole body and refined motor function as well as other areas such as memory, continence, and speech. Progressive MS can be categorised as primary or secondary and describes

different stages of neurological deterioration. Primary progressive MS (PPMS) is a form of the disease progressive from the point of diagnosis, whereas secondary progressive (SPMS) develops as a progressive condition after initial diagnosis with the relapse-remitting form of the disease. Around 10-15% of people with MS are diagnosed PPMS, the rest are diagnosed RRMS. Around 50% of those diagnosed with RRMS go on to develop SPMS after approximately 10 years from point of diagnosis (Dimitrov & Turner, 2014; Visaria et al., 2018).

2.2 Multiple Sclerosis Symptoms

Due to the debilitating nature of MS symptoms, rehabilitative interventions will span the lifetime of a patient post-diagnosis. MS symptoms are both broad in nature and unpredictable, posing challenges for rehabilitation interventions aimed to suit the whole MS population. Certain symptoms may be triggered, some may be affected indirectly, and some may appear randomly. Many functions can be affected such as muscle strength, coordination, vision, cognition, balance, stability and mobility (Feinstein et al., 2015; Wallin et al., 2019b). To improve all of these, a combination of intervention types can be utilised, as well as providing advice for family and friends involved in the life of the patient. Multidisciplinary programmes have shown beneficial results for improvements in level of activity participation and good satisfaction rates. However, they require more investigation and constant re-evaluation due to the complex and multifactorial elements they entail (Khan et al., 2007; Langdon & Thompson, 1999; Sumowski et al., 2018).

2.2.1 Symptom Variation

Though the variation of clinical symptoms presented in patients is vast, commonalities have been shown in initial symptoms such as weakness of the limbs, blurred vision, numbness, tingling, double vision, and vertigo. These are likely to be some of the most noticeable neurological symptoms when first experiencing demyelinating episodes (Vollmer et al., 2002). Walking difficulties is reported as one of the most common symptoms and can affect many aspects of daily life with subsequent effects on cardiovascular health, muscle and joint health and mental health (Crenshaw et al., 2006; Halabchi et al., 2017). Problems in gait often arise as an issue related to muscle stiffness and weakness from atrophy and can create a

damaging cycle of muscle and joint disuse, as well as reduction in independent function ability (Patti et al., 2002).

Fatigue is a common symptom with around 90% of patients reporting this (Crenshaw et al., 2006; Dimitrov & Turner, 2014; Vollmer et al., 2002). This can cause severe tiredness, mental blocking and has a substantial effect on many people's daily activities, social activities, and relationships. Despite a large effect on QoL, there are no drugs licenced to treat MS fatigue and people are often recommended treatment based on avoidance of potential fatigue triggers. These can range from sleep deprivation, hot environments, medication side effects, infections, high stress levels and low mood levels. However, some of these may be unavoidable with an MS diagnosis and may therefore perpetuate each other (D'Arcy, 2007; Heine et al., 2015; Rumrill et al., 2004).

Other highly disabling symptoms reported are painful sensations, loss of sensation, and loss of proprioception, all affecting mobility and subsequently QoL (Crenshaw et al., 2006; Halabchi et al., 2017; Patti et al., 2002). These are caused by nerve damage and can lead to various manifestations of neuropathic pain such as pins and needles, burning, hypersensitivity, numbness, or tightness. Although drugs to treat neuropathic pain are available, they often have undesirable side effects that can negatively influence QoL.

Disruption to upper motor neurons can also lead to the motor disorder, spasticity. The motor nerve disruption can cause an imbalance in inhibitory and excitatory signals to muscles, and result in intermittent or sustained involuntary muscle activity (Pandyan et al., 2005). Over time this can lead to abnormally high levels of muscle stiffness and tone, uncontrolled and painful spasms, reduced RoM and reduced control of voluntary movement. This not only affects muscles, but also ligaments and other soft tissues, impacting overall mobility and QoL (D'Arcy, 2007; Losseff et al., 1996).

Loss of the ability for small and intricate movements as well as whole body movements have vast consequences on functional independence and can affect aspects such as self-esteem, self-worth, mood and motivation (Jarret, 2010). The treatment and management of musculoskeletal pain and spasticity can be

pharmacological as well as physically based. Although, the side effects associated with drugs for spasticity are often undesirable (drowsiness, dizziness, nausea). Therefore effective physiotherapy management is highly beneficial due to the reduced risk of side effects (D'Arcy, 2007).

A range of cognitive symptoms experienced by people with MS can be seen in a decline of memory, reduced processing speed, reduced attention, efficiency of information processing and executive functioning. There are associations between higher levels of cognitive disability and lower levels of social and vocational activity, employment, and household tasks (Compston & Coles, 2008; Demaree et al., 1999). Kalmar et al. (2008) found a correlation between objective assessment of everyday activities and cognitive performance, and subjective assessment of functional activity was correlated with emotionally distressing symptoms. Patients with greater cerebellar symptoms (such as tremors) have shown less progression in recovery, particularly in daily activities and can affect the level of the individual's independence (Langdon & Thompson, 1999). The most common cognitive symptom reported is short-term memory problems, which can also be affected by fatigue. Cognitive problems can alter someone's ability to learn something new, quality and speed of information processing, attention, and concentration. Symptoms of this kind can affect someone's ability to take on information about their condition and about interventions to manage symptoms. Therefore, cognitive symptoms are important to be aware of for the individuals symptom management (O'Brien et al., 2008).

Around 30% of people with MS develop speech and swallowing difficulties and can impact both the mental health of someone with MS as well as their physical safety in terms of eating and drinking (Poorjavad et al., 2010). Other symptoms include bladder and bowel incontinence which can also affect someone physically, socially and psychologically and often requires a specialist in this area for an assessment (Griffith, 2002). Evidence has previously suggested that urinary tract infections (UTIs) are the most common admittance in hospital for people with MS. UTIs can often be avoided by completing a programme of pelvic floor exercises and lifestyle health advice. QoL could then be improved reducing pain and discomfort for the individual as well as reducing time spent in hospital (Dimitrov & Turner, 2014).

Demyelination in brain regions can contribute to depressive symptoms in some patients. Depressive symptoms have been linked to a 7-fold increase of suicide rates (Compston & Coles, 2008; Vollmer et al., 2002) and therefore a key factor to be aware of and incorporate into a rehabilitative programme (Chiaravalloti & Deluca, 2008). An Intervention to monitor and treat MS related depression has previously revealed significant improvements after 6 months. Though fatigue and anxiety were not significantly affected, this study demonstrated significant impact on a large aspect of mental health by using a mental health evaluation service (Askey-Jones et al., 2012).

Visual problems and optic neuritis can be a problematic symptom if optic nerves are damaged in the individual. People can experience vision blurring, reduced vision, double vision, vision pain, colour blindness and can contribute to balance problems and nausea (National Institute for Health and Clinical Excellence, 2003). Sexual dysfunction can be problematic for people with MS and has a substantial effect on QoL. It is also a symptom that individuals can find difficult to discuss and therefore has limited information on management and treatments that can help individuals (National Institute for Health and Clinical Excellence, 2003).

2.2.2 Symptom Measurement

Since there is not only variation in the symptoms experienced, but also in the type of MS condition, the individual experience of MS lies on a broad spectrum and requires further detailed definition. For this reason, the Expanded Disability Status Scale (EDSS) was developed in the 1980s (Kurtzke, 1983) and has been used as part of MS diagnosis, treatment and research since. (Benedetti et al., 1999; Boes et al., 2012; Caminero & Bartolomé, 2011; Comi et al., 2017; Freeman et al., 1997; Jagannath et al., 2010). The EDSS has been used extensively throughout studies to categorise level of disability of patients (Benedetti et al., 1999; Boes et al., 2012; Caminero & Bartolomé, 2011; Comi et al., 2017; Crenshaw et al., 2006; Demaree et al., 1999; Freeman et al., 1997; Kobelt et al., 2017; Martin et al., 2006). This quantifies disabling symptoms and their effects on aspects of daily life and certain physical capabilities. This is done on a scale from 0 to 10, using several categories called 'functional systems' as the main descriptor. The scale spans from 0 (no clinical disability and normal, healthy neurological status), to 10 (death due to MS complications). The

EDSS was reviewed by Meyer-Moock et al., (2014) assessing 120 publications on the assessment tools of MS. They determined the scale as suitable and the most preferred tool for measuring the effectiveness of clinical interventions and monitoring of disease progression. Though it has some limitations in reliability and sensitivity to change, its international acceptance as a measurement tool and wide use amongst clinical trials in MS research, allows for cross study comparisons (Meyer-Moock et al., 2014).

With the development of the EDSS scale, came further advancements in the measurement of clinical symptoms. Level of spinal activity has been linked to clinical disability in MS patients, specifically correlated to spinal atrophy using medical imaging. Spinal cord atrophy has also been correlated with duration of MS condition (Evangelou et al., 2005). The manifestation of spinal cord atrophy is seen clinically in symptoms such as leg weakness, movement difficulties and refined motor function difficulty, all contributing heavily to impaired functional independence and daily activity competency (Yamout et al., 2013). Bernitsas et al. (2015) showed a significant correlation between spinal atrophy and disability based on EDSS. This was seen for both progressive and relapsing MS. They investigated the cross-sectional area at C2 level of the spinal cord and found this to be significantly correlated with EDSS ($r = -0.75$, $p < 0.0001$). This was a significant predictor of disability, irrespective of disease duration or disease type. These studies suggest that spinal health in a person with MS is a major element in their level of disability and subsequently their QoL. Other variables such as disease duration and type were less significant. This then tends to be related to symptoms relating to lower extremity weakness, tingling, numbness, coordination, and balance. Gender and age were not significant factors in EDSS rating (Bernitsas et al., 2015).

2.3 Multiple Sclerosis Treatment Interventions

With developments over the years in MS diagnostics and the use of neuroimaging, early diagnosis can allow for early preventative treatment to prevent neurological decline (Compston & Coles, 2008). This includes the use of disease modifying therapies (DMTs) available for patients and can alter the course of the disease if taken early enough. They specifically target inflammation within the CNS by interacting with the immune system, decreasing the severity and number of neurological relapses.

DMTs however are only helpful for early stages of the condition, and not administered for progressive patients. Treatments for progressive patients are mainly aimed to minimise and manage symptoms (Sumowski et al., 2018; Wingerchuk & Carter, 2014).

While rehabilitation is important for the management of symptoms for many conditions, for MS this is particularly crucial because of the magnitude of disabling and fatiguing symptoms and the longevity of the disease. It requires an individualised approach to address the person's needs (Dimitrov & Turner, 2014; Khan et al., 2007). A systematic approach for treatment structure can be beneficial to the MS population to an extent. However, due to the wide range of symptoms experienced, each individual may have to address specific symptoms and a multi-disciplinary approach is often recommended (D'Arcy, 2007).

2.3.1 Exercise Interventions

Physical rehabilitation has been part of the MS treatment journey from early descriptions of the condition. However, the first randomised controlled trial was published as recently as 1996. This concluded that physical activity posed no risk to patients and had positive effects on their overall well-being (Petajan et al., 1996). The variables with positive results included maximal aerobic capacity (VO_2max), isometric strength, body composition, blood lipids, daily activities, mood, fatigue, social interaction, home management and emotional behaviour disease status. Following this, other studies have displayed similar results revealing improvements in aspects of physical health, fatigue and overall QoL, implying there is a considerable potential benefit for MS patients from exercise-based interventions (Cruickshank et al., 2015; Freeman et al., 1997; Garrett et al., 2013; Kehoe et al., 2015; Patti et al., 2002). These study results have not shown improvement in EDSS or neurological impairment, but rather significant improvements in a wide range of health outcomes, involving physical functioning, general health, social functioning, and mental health. Particular focus on walking ability is often placed on these interventions due to its significant contribution to MS QoL results (Kehoe et al., 2015).

Though exercise and movement therapy has been shown to be successful in MS populations as well as others, adherence to the full intervention has been an issue in

previous studies (Feinstein et al., 2015; Heine et al., 1996; McCullagh et al., 2008). Community-based exercise interventions have had success in improving this element. Indeed, results support these as being a predictor of the physical impact of the MS condition. Results have shown that community-based group activities were successful and led to significant improvements, regardless of the type of exercise activity. This implies the type of exercise is not a key component in results, however, a community focus is (Garrett et al., 2013; Kehoe et al., 2015). This is supported by the systematic review results on different forms of exercise treatments with MS patients with neither strength, aerobic, stretching, endurance or mixed exercise interventions showing more benefit than the other (Heine et al., 2015; Rietberg et al., 2005). The success of community-based group exercises and the impact on MS symptoms could imply that the community focus may be more important than the type of exercise.

The overall improvements in both physical and psychological factors from simple exercise routines have considerable benefit for people with MS. This has opened potential for further research to develop physical interventions with this group of people with a vast number of studies reporting positive outcomes in similar variables. Exercise interventions can be manageable with little side effects compared to pharmacological interventions (Rietberg et al., 2005), therefore further research in this area as a treatment for the variables above could have great benefit for symptom management in people with MS.

2.3.2 Balance and Gait Interventions

Abnormal balance control is a common symptom in people with MS, leading to an overall reduction in physical activity and affecting various aspects of daily life (Motl, 2014; Van Emmerik et al., 2010). Interventions based on balance focussed activity have demonstrated positive results for improvement in these areas (Cattaneo et al., 2006; Gandolfi et al., 2015; Kanekar et al., 2013). Abnormal balance is likely to increase risk of falling and can lead to further injuries and lack of confidence in movement (Soyuer et al., 2006). Therefore, it's important to decipher and try to prevent the risk, which can be done through balance tests also (Cattaneo et al., 2006).

Significant differences have been found between people with MS and healthy controls for slower walking speed, weaker leg strength and more gait variability (Bowser et al., 2015; Cattaneo et al., 2006; Martin et al., 2006; Soyuer et al., 2006). Even within the MS population, there are significant differences in leg strength indicating that varying degrees of disability can manifest within the condition and should be accounted for within gait investigations. Bowser et al. (2015) revealed a significant correlation between leg strength and EDSS score, with a weaker leg strength group reporting an average of 2.5 times higher in EDSS than the MS group with better leg strength. The results of reduced leg strength led to compensation in other movements when performing important daily tasks such as walking, turning and moving from sitting to standing (Bowser et al., 2015; Hansen et al., 2014). Therefore, MS programmes promoting leg extensor strength and power, may lead to improved performance in key functional activities for patients (Cameron & Wagner, 2011; Stevens et al., 2013).

Balance differences between MS patients have been found based on their disease type and severity, with progressive forms of MS revealing significantly greater levels of impairment compared to RRMS, demonstrating a greater risk of falling as a consequence (Soyuer et al., 2006). However, even in the less impaired MS population (EDSS 2 or below), muscle recruitment abnormalities have been revealed through electromyographic (EMG) recordings with early recruitment and late relaxation of leg muscles (Benedetti et al., 1999). The balance and gait abnormalities for not only MS patients compared to a healthy population but within the condition are therefore important to recognise and their impact on daily movements. This could be important to incorporate from early on in the condition (Bernardi et al., 2004; Büla et al., 2011; Cruickshank et al., 2015).

As well as the breakdown in neurological processes, gait and balance can be affected by psychological state and heavily influenced by fatigue. As well as significant differences in gait abnormalities, MS patients have shown greater fatigue measures compared to healthy controls (Crenshaw et al., 2006). Therefore, fatigue could play a part in the variability seen within MS gait measures and could also affect variables measured after an intervention and important to monitor. Fatigue could be an

indicator of other psychological factors affecting gait and balance such as mobility confidence as well as physical factors. Understanding the relationship between fatigue and the effect it will have on gait and balance outcome measures will aid the interpretation of changes that may be occurring due to an intervention.

Neural plasticity is the adaptive process in the CNS to re-organise neural connections, responding to other neural inputs or influences, according to the surrounding environment. To maximise this process within rehabilitation interventions, balance specific exercises can help neural re-organisation of sensory integration within the CNS and lead towards improved muscle recruitment pathways for small movements as well as motor learning (Morgen et al., 2004; Tomassini et al., 2011). Although neuroplasticity is believed to be more beneficial in people at earlier stages of their MS condition, evidence has shown there is still capacity for neural plasticity in later stages of the condition also and therefore an essential element for their balance rehabilitation (Feinstein et al., 2015). Task-orientated therapeutic approaches involve practicing certain movements that can subsequently lead to their improvement, with a common aim to improve movements used in a person's daily routine. Application of both external and internal stimuli help to reinforce the specific neural pathways associated with these movements and potentially improve muscle memory. Therefore, someone can learn by repeating a certain task in changed environments and under changed conditions (Heine et al., 2015; Stevens et al., 2013; Straudi et al., 2014). This is helpful for movements not only associated with postural sway and balance, but other aspects of daily life. The learning process in performing these tasks in different environments and improving awareness, may be more important than the actual quality of the task (Sumowski et al., 2018).

Proprioceptive interventions have revealed improvements in stability and posture with varying levels of intervention (Stevens et al., 2013). Improvements in body sway, stability and posture have been demonstrated from a basic intervention with finger touch application (Kanekar et al., 2013). Equine-based therapy using horse riding has shown benefits in MS therapy showing muscle strengthening, balance and mobility measures and psycho-emotional benefits with improved QoL (Bronson et al., 2010; Silkwood-Sherer & Warmbier, 2007). Benefits could be seen from both the

proprioceptive and sensory feedback as well as the psychological benefits seen from animal interaction (Hammer et al., 2005). The use of activities with proprioceptive feedback appear to have good outcome results for balance deficits and could even be combined with animal-based therapy for greater impact on QoL.

The variety of therapeutics available for balance and gait is vast and the use of combining rehabilitation therapy types can not only help to improve balance, mobility and coordination but also to build tolerance for activities through improved cardiovascular fitness and reduction in stiffness and spasticity (Khan et al., 2007; Rietberg et al., 2005). New therapeutics with use of robotics, tele-rehabilitation, virtual reality and games are areas under development for modern forms of therapy and could be useful tools for the future of MS rehabilitation (Donzé, 2015). Some of these new forms of therapeutic interventions have not been in standard practice for long, or long enough to be part of MS based therapeutic investigations, therefore information about their specific benefits are limited. However, the studies that have reported on these task-based exercises in combination with standard physical based exercises are very promising (Feinstein et al., 2015; Freeman et al., 2012; Khan et al., 2007). Many of the benefits seen in exercise-based interventions, could also be brought into balance and gait improvements, given the strength and muscle recruitment memory they can instil. These results are particularly strong in lower limb strength exercises due to the muscle work necessary in many aspects of gait and balance.

2.3.3 Quality of Life Impact

The concept of physical rehabilitation and its connection with QoL has not always been part of MS treatment. Knowledge around this has been improving with the understanding of the individualised nature of the condition and the effect this has on an individual's QoL. Developments for health and well-being and improving QoL for MS patients became more prevalent in the 1990s (Freeman et al., 1997; Langdon & Thompson, 1999; Patti et al., 2002; Petajan et al., 1996; Schapiro et al., 1988). The measurement of QoL has also been developed in terms of how best to describe the many different contributing factors. This includes all areas around general health and well-being, social and psychological functions, as well as physical functioning.

However, clinical assessments for this are still limited and the need for more methods around this area are becoming apparent and QoL assessments are said to be a standard element of all MS based trials. In order to get a complete view of QoL, more than one of these scales will be required (Halabchi et al., 2017; Kobelt et al., 2017; McCullagh et al., 2008; Patti et al., 2002).

Many authors report effects of intervention on QoL, even though this is not the main outcome of the investigation (Bernitsas et al., 2015; Cattaneo et al., 2006; Kehoe et al., 2015; Petajan et al., 1996), giving an insight into the importance of this aspect within various types of MS research. The multifactorial nature of QoL means that this can be difficult to quantify whilst still being completely represented. Measures for lifestyle, physical function, psychological state and social function are often represented using complex scales, some of which have been described below in table 2.1, as well as other scales and questionnaires used within MS research to assess health and well-being (Gandolfi et al., 2015; Langdon & Thompson, 1999; McCullagh et al., 2008; Yamout et al., 2013).

Table 2. 1 Health and well-being scales and questionnaires previously used in multiple sclerosis research.

Scale	Outcome Measures	Reference
Beck Depression Inventory	Level of depression based on mood and emotion.	(Cruickshank et al., 2015)
Brief Pain Inventory	Level of pain based on physical symptoms.	(Kean et al., 2016)
Expanded Disability Status Scale (EDSS)	Level of disability based on physical function.	(Meyer-Moock et al., 2014)
Fatigue Impact Scale (FIS)	Level of fatigue based on physical tiredness.	(Kawada, 2017)
Functional Assessment of Multiple Sclerosis	General QoL assessment based on physical symptoms, emotional well-being and social well-being.	(McCullagh et al., 2008)
Functional Independence Measure	Level of independent function based on physical, psychological and social components.	(Barnes et al., 2010)
Fatigue Severity Scale	Level of fatigue based on physical symptoms.	(Petajan et al., 1996)
Hamilton Depression Rating Scale	Emotional well-being assessment based on mood and fatigue.	(Yamout et al., 2013)

Health Related Quality of Life	Health and well-being assessment based on physical, mental, emotional and social functioning.	(Hadgkiss et al., 2013)
London Handicap Scale	Level of functional ability based on physical, social and economic elements.	(Rietberg et al., 2005)
Multiple Sclerosis Impact Scale (MSIS-29)	Physical and psychological impact of MS symptoms.	(Garrett et al., 2013)
Multiple Sclerosis Quality of Life -54	Health and well-being assessment, based on SF-36 incorporating MS specific issues.	(Negahban et al., 2013)
Short Form-36 Questionnaire (SF-36)	Health and well-being assessment based on physical, psychological and social components.	(Khan et al., 2007)
Tempelaar Social Experience Checklist	Measure of social experience based on daily function.	(Patti et al., 2002)
Visual Analogue Scale (VAS)	Self-perceived measurement of pain (global or local).	(Vucic et al., 2010)

The SF-36 survey has excellent reliability from previous studies including those investigating interventions with MS patients and is highly used for this reason (Backus et al., 2016; Garrett et al., 2013; Laucis et al., 2015; Rietberg et al., 2005; Savigny et al., 2009). However, due to the number of questions used in the form, it can often be too time consuming for some studies to incorporate and can result in a low response rate. Therefore, analysis of these results is often limited. Shorter versions of the form also exist which can be more appropriate for some studies, though would not give the full general health assessment it is known for (Farinotti et al., 2007; Khan et al., 2007; Patti et al., 2002).

As two commonly reported symptoms, fatigue and pain are very important to monitor within MS therapeutic interventions. They are also known to be very difficult to monitor due to the subjective nature of their experience as well as their complexity and their influence on other symptoms. Fatigue is not only poorly understood but has very high associations with QoL and therefore requires further development and monitoring (Crenshaw et al., 2006; Kawada, 2017; Kehoe et al., 2015; Polman et al., 2011; Vucic et al., 2010). Though pain is also a very complex neurological process, its main method for measurement within therapeutic setting is in a self-perceived scale. Along with fatigue, pain is highly associated with QoL outcomes and other physical

symptoms. Although information is known about nociceptive pathways that cause pain, monitoring this during therapeutic treatment and its potential mechanism is lacking (Feinstein et al., 2015; Patti et al., 2002; Smith et al., 2016).

A rehabilitation intervention was assessed by Patti et al. (2002) and demonstrated significant improvements in several aspects contributing to QoL, by allocating therapies based on their individual needs from a baseline assessment. This incorporated specific needs for symptom management and QoL. These included therapies such as physiotherapy, occupational, speech, music, mirror, video, group, and goal orientated therapies. Compared to a control group, MS patients allocated to a therapy intervention showed significant improvements in physical functioning, body pain, general health, and social functioning, all contributing to their overall QoL score with an analysis using several different QoL scales. In a similar manner to other study results, the EDSS levels were unchanged (Patti et al., 2002). Therefore, addressing potential benefits in specific aspects of symptom management, can help with long-term improvements in QoL, regardless of their MS neurological impairments.

2.3.4 Gender Differences in Intervention Response

Gender differences in muscle mass and composition are well established and have been identified in some physiotherapy-based studies. They have been well reported in injury prevention literature, with differences found in muscle mass production, muscle to fat ratio, muscle distribution, joint anatomy, joint kinematics as well as pain thresholds (Granata et al., 2002a; Granata et al., 2002b; Kristianslund et al., 2012; Pruyn et al., 2015). However, gender differences for biomechanical analysis of muscle in relation to active and passive stiffness has been less well researched and reported (Bailey et al., 2013; Granata et al., 2002a; Granata et al., 2002b; Mauvais-Jarvis, 2015). These well-known gender differences in musculoskeletal injuries could provide further insight in passive and active states of muscle tissue.

Where active muscle stiffness is because of the sarcomere unit in muscle tissue contracting and creating a forceful tension in order to move skeletal muscles, passive muscle stiffness is created by resistance stretching. This allows muscle fibres to elongate through proteins that have been activated without a forceful contraction

generated (Naraoka et al., 2017). Granata et al. (2002a and 2002b) revealed gender to be a significant factor in active muscle stiffness outcomes. The study also found males to have significantly higher levels of agonist and antagonist activity, relating to active muscle stiffness. As expected, greater levels of muscle activation, would be likely to arise from greater muscle mass and create greater levels of active muscle stiffness (Granata et al., 2002a; Granata et al., 2002b).

The differences between sexes and how they phenotypically present with MS and respond to therapeutics has led to studies investigating this more thoroughly. There was a suggestion by Kehoe et al. (2015) that female gender explained 57% of the variance in results testing a 10-week exercise intervention. They found gender to be a significant predictor in the physical impact outcomes using MSIS-29 (table 2.1) specifically looking at daily activities, mobility, refined movements, fatigue and walking ability. Females in the study had a lower physical impact of MS score and longer walking distance compared to males. Although gender was found to be a poor predictor of walking ability, females were found to have gained more psychologically from the intervention support and better disease management strategies, which may have influenced these results to show the significant differences between gender results. This is also supported by other studies suggesting gender differences in treatment response (Garrett et al., 2013; McCullagh et al., 2008). The results from this study indicate psychological benefit from the intervention and the support they provide, may lead to significant differences in physical outcomes, and that males and females may then respond differently because of this.

The differences between males and females investigated in previous studies (Bailey et al., 2013; Granata et al., 2002b; Harbo et al., 2013; Kehoe et al., 2015) indicate the importance around the gender differences and how this affects their intervention response. Awareness of these differences could be essential depending on how tailored they are required to be for the individual and of this effect on results. Gender specific interventions may not be possible in every therapeutic scenario; however, these results imply they are important to be aware of.

2.4 Manual Therapeutic Interventions

Manual therapy is often used for people with MS as a relief for symptoms connected with stiffness and pain, aiding symptom management. This type of physiotherapy involves use of manual touch in either a massage, manipulation, mobilisation or joint movement, in order to restore muscle and joint mobility to a more improved form of movement with less pain (Carnes et al., 2010; Olson, 2009). This type of therapeutic has been used for many years due to its simple and effective results in terms of pain and stiffness release and is a well-known therapeutic in clinical practice (Millan et al., 2012; Voogt et al., 2015). Although manual therapy is commonly used in clinical practice, there is limited understanding of the specific mechanisms responsible for the benefits seen (Goertz et al., 2016; Voogt et al., 2015).

Manual therapies which target para-spinal muscles are suggested to act on various components of vertebrae, separating facet joints and passively allowing the para-spinal muscles to be mechanically stretched (Maigne & Vautravers, 2003). Results from spinal therapy are both positive (Chiradejnant et al., 2003; George et al., 2006; Haas et al., 2014; Sterling et al., 2001) and conflicting (Assendelft et al., 2003; Childs et al., 2004; Goodsell et al., 2000; Stamos-Papastamos et al., 2011; Thomson et al., 2009). There is therefore a robust rationale to establish the efficacy of such treatments given their low risk side effects (back pain, trigger of other pain, minor bruises) and potential economic savings. The National Institute for Health and Clinical Excellence (NICE) guidelines have recommended using manual therapy for these reasons (Carnes et al., 2010; Powers et al., 2008; Savigny et al., 2009; Shum et al., 2013; Stamos-Papastamos et al., 2011; Wong et al., 2016).

The unknown mechanisms of action of manual therapeutics means that deciphering whom they benefit, what type of intervention is most beneficial for a specific patient, and how long or often they should be receiving this treatment, is challenging. Investigations around spinal therapeutics and those most likely to respond positively have resulted in a clinical prediction rule (CPR) specifically for back pain sufferers (Childs et al., 2004; Fritz et al., 2005; Fritz et al., 2011). The results from these CPR studies indicate use of symptom severity, symptom location, symptom duration and symptom root cause to be predictors in therapy response, depending on type and dosage of treatment. With similar pain and stiffness symptom similarities in MS

patients, a third of people with MS claim that they use a form of manual therapy as an alleviation of these symptoms with success (Backus et al., 2016; Brouwer & Andrade, 2009). A similar predictive protocol based on symptom features may be an informative tool for manual therapy within MS physiotherapy.

A systematic review by Zoogt et al. (2015), investigated 13 studies on the effects of spinal manual therapy on pain thresholds, with 10 of these studies revealing significantly improved immediate results. These results were for pressure pain thresholds (PPTs), with no studies showing any significant results for thermal pain thresholds. No conclusions were drawn for location or intensity of the manual therapeutic, therefore information on these aspects may help to draw conclusions around benefits for symptom type of the therapy receiver. Manual therapy is said to mechanically alter the neurophysiological triggers affecting the nociceptive pathways for pain, with many pieces of evidence showing that PPT can be altered with mechanical stimulation (Chaitow, 2015; Olson, 2009). However, the lack of results for thermal pain thresholds, could signify a different mechanism for these different types of pain. Zoogt et al. (2015) claim no conclusions were drawn from a central or spinal mechanism for manual therapy, therefore information about these specifics does not appear to be available. Similar results were also seen in Lascurain-Agiurrebeña et al. (2016) in their systematic review of studies using spinal mobilisation treatment. This review revealed consistent results in studies with hypoalgesia, spinal stiffness reduction, improved muscle function, however no effect on thermal pain thresholds. Though they conclude very little about the lack of effect in thermal pain mechanisms, their review displays consistent results suggesting endogenous pain inhibition through mechanical stimulation.

Schmid et al. (2008) found results based on 15 studies in a systematic review, revealing consistent results for hypoalgesia, activation of the SNS and changes to motor function, after receiving manual therapy. With their combined data, they concluded joint mobility improved by 20% along with reductions in pain or stiffness. The main outcome in results from these reviewed studies were outcomes for improved functional movements important in daily tasks, signifying its importance throughout manual therapy literature. The suggested mechanisms reported are

limited, due to their complex and multi-factorial nature. However, they offer similar suggestions as the Lascurain- Agiurrebeña et al. (2016) and Zoogt et al. (2015) reviews around release of pain modulating neurotransmitters due to mechanical stimulation.

2.4.1 Lumbar Spine and Lower Back Pain

The lumbar spine is the lower back region and consists of the 5 spinal vertebrae from L1 to L5. These are the largest of the vertebral column and help to provide support for the lumbar spine to bear the weight of that person. Large muscles that support the back also allow for movement of the trunk and the body as a whole and important in maintaining healthy lumbar vertebral movement (Balderston & Auerbach, 2005; Berry et al., 2018).

Healthy spinal mobility is crucial in a general population for whole body movement. The importance of spinal cord health within MS has been demonstrated with significant results of spinal deterioration affecting disease status. Spinal cord function in MS patients is often used to define clinical disability. Spinal mobility can then be an issue for people with MS struggling with mobility, pain, and muscle stiffness. The manifestations of the disease in lower extremities, core strength and balance symptoms are often related to spinal cord atrophy and reduced spinal mobility emphasising the need for continued spinal mobility within the condition (Bernitsas et al., 2015; Evangelou et al., 2005).

Reduced spinal mobility is often associated with an increase in lower back stiffness and pain, which can lead to longer-term lower back pain (LBP). This has shown to be common and become debilitating for daily life in various musculoskeletal conditions including the MS population (Compston & Coles, 2008; Hartvigsen et al., 2018; Hoy et al., 2010). This can however be as a result of different contributing factors, such as spasticity in some of the para-spinal muscles, and other physical symptoms that are affecting mobility, fatigue, mental health, kinesiophobia as well as symptoms directly causing pain to that area. Mobility related symptoms may also lead to an uneven distribution of weight that can subsequently put pressure on the lower back and contribute to pain in this area. LBP can cause a deviation from the normal posture in the static spine and often results in deviation of normal function of the spine (Maigne & Vautravers, 2003). Along with reduced spinal mobility, LBP sufferers can present

with altered loading patterns in the spine, an increase in spinal stiffness and spasticity and greater risk of injury (Powers et al., 2008; Shum et al., 2013). Patients often show limited flexibility and tenderness in lumbar muscles because of LBP, a possible connection between pain and stiffness. Para-spinal muscles can be the main limiting factor for movement when highly tense and stiff, particularly within the lumbar region (Maigne & Vautravers, 2003). Vertebral support from attaching muscles is also said to be important for prevention of spinal buckling during loading of the spine, by decreasing direct mechanical stress (Triano, 2001). Functionality of para-spinal muscles is crucial for mobility of the lumbar spine and consequently on the effect of someone's whole body mobility and management of their condition.

The severity of LBP is generally differentiated by the duration of symptoms, acute (0-12 weeks) and chronic (over 12 weeks). However, further classifications can be made on the cause of pain (musculoskeletal, inflammatory, neuropathic) (Hartvigsen et al., 2018; Maigne & Vautravers, 2003). Furthermore, the factors influencing LBP can go beyond biomedical explanations, and developments have been in place to investigate these further including the psychological and social factors that can contribute to the LBP experience (Pincus et al., 2013). This can have a substantial effect on someone's response to treatment and deciphering individual needs will therefore be beneficial.

Treatment of the spine and para-spinal regions can have significant impact on mobility of the whole body due to its influence both structurally and physiologically on body movement initiated in the torso area (Bernitsas et al., 2015; Maigne & Vautravers, 2003). When muscles are highly tense and stiff, they lack the ability to respond to changes in shape that would allow contraction for movement. This can make voluntary movements more difficult and painful and create more likelihood for involuntary spasm reactions. Results from a systematic review suggested both manipulation and mobilisation as an effective therapeutic for LBP with many improvements in RoM, reductions in stiffness and relief of pain (Bronfort et al., 2004). Chronic back pain patients have shown a higher liklihood of response to spinal manual therapy compared to acute sufferers and could be an important element in deciphering the most appropriate treatment for the indivual (Chou & Huffman, 2007).

2.4.2 Spinal Mobilisations

Introduced in the 1960s by Geoffrey Maitland, mobilisations is a manual therapy technique still used today. It is particularly common for treatment of back pain, stiffness and to improve spinal RoM (Chansirinukor et al., 2003; Maitland et al., 2013; Piekarz & Perry, 2015). It consists of low-velocity and high amplitude oscillatory force, separating facet joints and stretching para-spinal muscles, differing from a manipulation thrusting and more forceful technique (Maigne & Vautravers, 2003; Pickar & Bolton, 2012; Stamos-Papastamos et al., 2011). The spine experiences movement by rotation of pelvis and thoracic cage, compression of skin and tissues, and movement of spinal joints (Chansirinukor et al., 2003; Lee & Evans, 2000; Powers et al., 2008; Shum et al., 2013). Mobilisation treatments can differ in level of force applied, rate of mobilisation oscillations, length of mobilisation treatment time and direction of the mobilisations. These are generally in the following categories: Anterior-Posterior (AP), Posterior-Anterior (PA), Longitudinal Caudad (towards the tail), Longitudinal Cephalad (towards the head), Medial Glide and Lateral Glide. Together the force, velocity, and direction of this manual treatment, dictate the way in which vertebrae and paraspinal muscles are influenced. The most used mobilisation technique is the PA (Chiradejnant et al., 2003; Snodgrass et al. 2005).

Though objective research has been growing in recent years, more development is needed, particularly within spinal mobilisation efficacy to determine the specificities of what and how is most beneficial (Piekarz & Perry, 2016). Although a large body of research exists in mobilisations as a treatment for LBP, little exists on this treatment within MS rehabilitation. Advancements in this research area will contribute to the knowledge in MS therapeutics (Bronfort et al., 2004; Chiradejnant et al., 2003; Perry & Green, 2008; Piekarz & Perry, 2015, 2016; Stamos-Papastamos et al., 2011).

The duration of mobilisations and number of repetitions can be used to regulate mobilisation treatment dose. The different dosages included in studies of spinal mobilisations often result in different findings as seen by differing methods within spinal mobilisation investigations. The 15 mobilisation studies reviewed in this section are summarised in table 2.2 and identified as regularly cited within spinal mobilisation literature and therefore have high level of impact in the research area.

Also included were studies with high degree of relevance to the study design, despite having less impact through number of citations.

The most common response seen in these spinal mobilisations studies is the reduction of pain (Ferreira et al., 2009; Goodsell et al., 2000; Lopez-Lopez et al., 2015; Powers et al., 2008; Shum et al., 2013; Sterling et al., 2001; Willett et al., 2010). This is suggested to be associated with reduction in stiffness in results from Shum et al. (2013) due to their potential similar mechanistic response as well as associations with improvements in RoM which known to be affected by both pain and stiffness (Lopez-Lopez et al., 2015). Many study results also show results with increased activity from the SNS and is suggested to be an area of further development for the potential mechanistic influence of spinal mobilisation (Jowsey & Perry, 2010; Perry & Green, 2008; Piekarz & Perry, 2016; Sterling et al., 2001). Though several studies investigate the optimal dose of mobilisations that are most beneficial in terms of these effects, there is no consensus on the number of sessions, length of time, or specific spinal location for the most beneficial outcomes (table 2.2).

Table 2. 2 Results from previous spinal mobilisation investigations.

Study Aim	Mobilisation Method	Findings	Reference
Treatment of LBP using either therapist selected or randomly selected spinal mobilisation technique.	5 different mobilisation techniques, each applied for 2 minutes, using different directions and locations.	No significant difference in pain and RoM measures compared to baseline or between groups.	(Chiradejnant et al., 2003)
Treatment of LBP investigating stiffness and pain.	12 sessions in 8 weeks of either spinal mobilisations or manipulation, compared to control exercise group.	All groups had significant reduction in stiffness compared to baseline, no significant difference between groups.	(Ferreira et al., 2009)

Treatment of LBP investigating pain and RoM.	Single 3-minute mobilisation session compared to control.	Significant pain reduction in mobilisation group compared to control.	(Goodsell et al., 2000)
Treatment of upper-mid back pain investigating SNS.	Single 3-minute 0.5Hz mobilisation applied to thoracic spine compared to a placebo.	Significant difference between groups for skin conductance in the hand.	(Jowsey & Perry, 2010)
Treatment of neck pain investigating pain and RoM	Single 2 Hz mobilisation, manipulation and apophyseal natural glide group.	Mobilisation and manipulation groups significantly reduced RoM and pain compared to baseline.	(Lopez-Lopez et al., 2015)
Treatment of upper-mid back pain investigating muscle activity and pain.	Single 3-minute mobilisation applied to thoracic spine compared to placebo.	Significantly reduced thoracic muscle activation in mobilisation group compared to placebo.	(Pecos-Martín et al., 2017)
Treatment of musculoskeletal pain investigating PPTs.	5 mobilisation bouts of either 30 or 60 seconds on lumbar spine.	No significant difference between 30 or 60 second sessions for PPT compared to baseline. Significant improvement after 4 sessions compared to single session.	(Pentelka et al., 2012)
Treatment of lumbar disorders investigating SNS.	Single 5-minute 2Hz mobilisation session compared to placebo and control.	Significant difference in skin conductance compared to control and placebo.	(Perry & Green, 2008)
Treatment of LBP investigating SNS.	3Hz and 2Hz mobilisation group compared to placebo and control, applied for 3 minutes.	3Hz mobilisation group had significantly greater skin conductance compared to 2Hz, placebo and control.	(Piekarz & Perry, 2016)

Treatment of LBP investigating pain and RoM.	Single 10-minute session with several bouts of 40 second mobilisations compared to exercise group.	Significant decrease in pain compared to baseline in both groups.	(Powers et al., 2008)
Treatment of LBP investigating pain and stiffness.	Single 3-minute session applied to lumbar spine.	Significant immediate reduction in pain and stiffness compared to baseline. Significant correlation between pain and stiffness.	(Shum et al., 2013)
Treatment of lumbar stiffness investigating stiffness and RoM.	Single 3-minute mobilisation at 2Hz and 3-minute manipulative thrust, both applied to lumbar spine.	No significant results for stiffness or RoM.	(Stamos-Papastamos et al., 2011)
Treatment of general back pain investigating SNS.	Single 6-minute mobilisations applied to cervical spine compared to placebo and control.	Significant increase in PPT, increase in skin conductance, decrease in skin temperature, and decrease in VAS compared to baseline and between groups.	(Sterling et al., 2001)
Treatment of LBP investigating pain.	Single manipulation, mobilisation, or control group.	No significant differences in PPT.	(Thomson et al., 2009)
Treatment of LBP investigating pain.	Single mobilisation applied to lumbar spine at 2Hz, 1Hz and quasi-static.	Significant immediate improvement in PPT compared to baseline, no significant difference	(Willett et al., 2010)

		between mobilisation groups.	

2.5 Proposed Treatment Mechanisms

2.5.1 Sympathetic Nervous System

Reasons for the benefits of mobilisation therapy could lie at the neuro-physiological level with results showing an activation of the SNS and an increase in body alertness. Many studies have recorded some of these effects such as increased blood flow, increased heart rate, increased respiratory rate, pupil dilation, increased sweating, and increased skin temperature occurring as an outcome of mobilisation therapy (Kingston et al., 2014; Lascurain-Aguirrebena et al., 2016; Perry & Green, 2008; Piekarz & Perry, 2016; Sterling et al., 2001). However, these suggestions are mainly based on physical outcomes seen and could also be affected by other internal physiological systems (Lascurain-Aguirrebena et al., 2016; Schmid et al., 2008; Triano, 2001).

Skin conductance and skin temperature increase were seen in significant results from Sterling et al. (2001) after methodically applied mobilisations in participants with spinal pain. These SNS skin-based outcomes were also associated with pain reductions measured using Visual Analogue Scale (VAS) and PPTs when compared to a control intervention. Perry and Green (2008) also found significant changes in skin conductance and temperature in lower limbs after lumbar mobilisation treatment. The significant responses were specific to the side treated, indicating that mechanical stimulation in the lumbar spine, can elicit a neurophysiological response in the lower limbs. This investigation was continued by Piekarz and Perry (2016) to further analyse the rate of mobilisations used, and whether this affected the level of SNS response. Their results indicated mobilisations at 3Hz had significantly greater response compared to slower rate treatments. These results overall therefore imply that a faster rate of oscillatory movements, may have a greater effect on SNS activation. Therefore, faster mobilisations could be important for some of the more commonly reported reductions in pain and stiffness (table 2.2).

A systematic review by Schmid et al. (2008) found results from several studies suggesting SNS activation with results in increased skin conductance, increased blood pressure, heart rate and respiratory rate. These results are over several different studies, and some of these effects extended beyond the body part that was being treated. Since the SNS is activated because of a stress trigger, the mechanical stimulation during mobilisation therapy could induce chemical release that initiate this stress trigger. A review by Kingston et al. (2014) similarly shows results from a range of studies demonstrating SNS-excitatory effects, irrespective of the location of the mobilisations on the spine. Along with other studies showing effects on body parts that were not manually treated, this suggests neural centralised influence. The main theory suggested for these effects is mediation by the mid brain (dorsal peri-acqueductal grey area, dPAG). Mobilisation of a spinal segment stimulates receptors in joints, tendons and connective tissue that can directly or indirectly activate dPAG mechanisms in the mid brain. This subsequently affects neural descending pathways that can trigger the outcomes of the SNS such as increased heart and respiratory rate. This is also the primary control centre for descending pain mediation which may then be an interconnected stimulus response (Kingston et al., 2014; Schmid et al., 2008; Vicenzino et al., 2001). Since SNS activity has been found at lower levels in people with MS, this could be a key area of benefit from mobilisation therapy and could be associated with the stiffness and pain reductions referred to from other people groups (Sternberg, 2012).

2.5.2 Analgesia

Analgesia or hypoalgesia are the terms referred to when the feeling of pain is reduced or absent, algesia meaning a sensitivity to pain. Several study results have referred to pain reduction after mobilisation treatment, along with results in SNS activation, with suggestions that their descending pathway regulation could be mediated in the same centralised location (Kingston et al., 2014; Schmid et al., 2008). The VAS is a standard and simple way of measuring pain, often before and after an intervention to analyse potential effects. It is a self-reported scale used regularly as standard practice for pain measurement (Lopez-Lopez et al., 2015; Shum et al., 2013). When this measure is used alongside objective or functional outcomes, this can help to get

a better overview of intervention effects and results, particularly with a clinical population (Rabey et al., 2017).

The result of an experience of pain is a complex interaction of physiological and psychological interactions, and manual therapeutics have the potential to influence both (Voogt et al., 2015). The previously mentioned immediate results in improved PPTs suggest increased pain tolerance from mechanical stimulation (Millan et al., 2012; Voogt et al., 2015). Neurophysiological theories are often used to explain the analgesic effects from manual therapies, such as peripheral nerve receptor stimulation that activates a centralised mechanism that mediate pain pathways. There is also said to be a psychosocial aspect of therapeutic exercises that induces relaxation (Lopez-Lopez et al., 2015; Voogt et al., 2015).

George et al. (2006) found a hypoalgesic effect in lumbar areas where manual treatment was occurring, however, no correlations were found alongside psychological variables. Therefore, the suggestion of these results imply that physiological processes were responsible for the hypoalgesia effect. Though many claims of a placebo effect of manual therapeutics have been made (Goodsell et al., 2000; Pecos-Martín et al., 2017; Ruddock et al., 2016) there is more to be investigated in neurophysiological mechanisms. However, Lopez-Lopez et al. (2015) demonstrated improvements in self-reported VAS pain levels with significant interactions between intervention type and anxiety traits, meaning that these elements may influence each other. This suggests that psychological factors, such as anxiety, depression, kinesiophobia, and catastrophizing can play an important role in some of the pain and RoM outcome measures. Goodsell et al. (2000) also investigated the effect of pain, stiffness and RoM, by testing a mobilisation treatment versus a control treatment. Their results did not show any significant changes in outcome measures for stiffness or RoM in either groups. However, significantly greater improvements for levels of pain on lumbar areas treated for mobilisations compared to controls was found (Goodsell et al., 2000). This potentially indicates greater effects on pain compared to stiffness and RoM are possible.

Fritz et al (2011) also reported an immediate decrease in self-reported pain that was correlated with levels of stiffness. This is contrary to findings of Haas et al. (2014) who

demonstrated that 12 sessions were necessary to see these kinds of effects. Although this study did not use a placebo or a control, therefore results could be less reliable. This implies long-term interventions are more likely to show significantly beneficial results than short-term immediate results. Pentelka et al. (2012) investigated in their study treatment time periods and number of treatment sets, to establish whether there is an optimum number of sets and time of treatment to achieve an analgesic effect. They showed no difference between 30 second and 60 second mobilisation sets but did however show that four sets were necessary to achieve the analgesic effect. These results could suggest that a certain number of sets is necessary in order for an analgesic effect to occur (Pentelka et al., 2012, table 2.2).

The review by Lascurain-Agiurrebeña et al. (2016) collated some results for neurophysiological effects after spinal mobilisation treatments. They reported studies with results in mechanical algesia reduction along with improved muscle function. The relationship between these is unclear, though suggested to be associated with an excitation of the SNS inducing longer lasting effects, previously discussed due to activation of dPAG mechanisms in the mid brain. They also revealed results of an immediate increase in nociceptive flexion reflex (NFR) threshold. Used as a measure of spinal excitability, this is a spinal reflex elicited after activation of nociceptive A-delta afferent fibres. The magnitude of this reflex response is then related to the intensity of perceived pain. Therefore, mobilisation treatment may be affecting this pathway. Thermal pain threshold was unaffected by the treatment, like other study results. Pathways for this type of pain may be affected differently and less likely to be altered when mechanically stimulated.

Other theories arose from an *in-vivo* experiment by Langevin et al. (2005) based on mechanically stretching fibroblasts, replicating what happens *in-situ* in a controlled cellular environment. Results showed a modification of interstitial osmotic pressure, increasing blood flow and reducing concentrations of pro-inflammatory cytokines, with the suggestion that this could cause a reduction in pain due to the reduction in cytokines (Langevin et al., 2005). Degenhardt et al. (2007) describe altered levels of pain biomarkers after manual treatment which was greater in people with chronic LBP compared to healthy controls. They found immediate increases in ß-endorphins

N-palmitoylethanolamide (PEA) and a decrease in anandamide (AEA) (Degenhardt et al., 2007). A similar decrease in AEA was also found by McPartland et al. (2005) after spinal therapy and found changes in AEA correlated with changes in experience of pain (McPartland et al., 2005). These theories are contributions to potential explanations as to what the underlying mechanisms are for the hypoalgesic responses that occur with countless reports in pain reduction post spinal manual therapy.

The main summary of the biochemical theories of CNS-mediated pain pathways are based on the elicitation of primary afferent neurons, altering afferent inputs into the CNS. High frequency discharge from central neurons is associated with high levels of pain (Chaitow, 2015; Pickar, 2002; Reed et al., 2014). Though the specifics of these remain unclear, the concept of modifying proprioceptive afferent inputs to the CNS remains a common theme within literature (Chaitow, 2015; Pickar & Bolton, 2012; Pickar, 2002; Voogt et al., 2015). The regular reports of reduction in pain from mobilisation mean this is an important area to investigate. Though pain is an experience with physiological and psychological complexities, neurophysiological explanations for pain reductions, providing further physiological explanations for the hypoalgesic effect will be beneficial for the understanding of how to elicit this response through manual therapy.

2.5.3 Stiffness Reduction

Muscle stiffness is described as a stretch resistance in tissue, resulting in difficulty of change of length in muscle tissue and subsequently movement difficulties (Marusiak et al., 2012; Zinder & Padua, 2011). As previously described, this can be a result of an active forceful contraction creating the resistance to muscle change in length or shape, and can also be passive when no active force is being generated by the muscle and resistance to change of shape or length still occurs. The capacity of a muscle to resist deformation, either by contraction or external force can be measured to show stiffness, the opposite is termed compliance (Granata et al., 2002; Shum et al., 2013). Muscle stiffness is often referred to as a factor that affects localised movements, whole body movement and connected to pain and function of daily activities. The biomechanical characterisation of stiffness is a research area that is growing rapidly with high reliability in many studies (Bizzini & Mannion, 2003; Nair et al., 2016; Pruyn

et al., 2014) though the reliability has been higher for stiffness and tone, and less for elasticity (Fröhlich-Zwahlen et al., 2014).

Spinal stiffness values have previously been shown to have potential demographic characteristics based on age, sex, level of pain and lifestyle. With an element of active muscle stiffness required for the maintenance of stability in a joint, a heavier body mass is then likely to require a greater level of stiffness to maintain stability (Granata et al., 2002a; Granata et al., 2002b). Results from Granata et al. (2002a) revealed females have less than 57% active muscle stiffness compared to males in leg muscles and there was a significant difference in lumbar spinal stiffness between sexes in a study by Owens et al. (2007). This study also revealed L5 to have the highest values for stiffness (Owens et al., 2007). These results suggest that the lower lumbar regions are more likely to have greater stiffness and males tend to have higher stiffness values compared to females in both the lumbar spine and lower extremities. This could mean that males have a higher level of response to spinal therapy than females, supported by the proposal from Kehoe et al. (2015) that gender specific interventions are necessary for MS rehabilitation programmes.

Studies have previously reported improvements in RoM, pain relief and stiffness however, the methods for measuring these improvements are often subjectively assessed and therefore can result in false positives due to the effects of bias (Chiradejnant et al., 2003; Edgecombe et al., 2013; Ferreira et al., 2009; George et al., 2006; Lopez-Lopez et al., 2015). A significant relationship between pain and stiffness reductions has been previously reported by Shum et al. (2013), emphasising the importance of baseline symptom correlating with reduction levels. The implication of this relationship is that people with greater levels of stiffness and pain, may be more likely to show a reduction.

Ferreira et al. (2009) did a thorough investigation with many lifestyles and performance-based outcome variables looking at the effects of a specific manipulation intervention. Their study showed a significant correlation between baseline stiffness and stiffness reduction levels. Pain measures were recorded using self-reported scales and showed a significant correlation with change in stiffness (table 2.2). Therefore, as previously mentioned in Fritz et al. (2011) and Ferreira et al.

(2009) stiffness and pain are closely interlinked and can affect each other. Self-reported functional status for daily activities also showed a change that was significantly correlated against change in stiffness. Stiffness reduction may also affect other areas associated with pain, muscle recruitment for mobility and therefore functional independence. Tissue stiffness therefore appears to be impactful, potentially affecting other areas within whole-body function. Consequently, a treatment that can successfully reduce stiffness, could potentially influence other areas also. This could impact whole body health and the physical activity needed for functional independence.

Owens et al. (2007) demonstrated that subjects with a higher body mass index (BMI) score tended to have lower stiffness and attributed this to a thicker level of overlying soft tissue at the contact point of stiffness measurement (Owens et al., 2007). High BMI levels could therefore create inaccuracies within the stiffness measurements and could be an area for further development in muscle stiffness measurement. Lee et al. (1998) determined a low average BMI for subjects in their study but did not find any correlation between BMI and stiffness values in their study (Lee et al., 1998). There could therefore be an association between BMI, levels of activity, level of stiffness and pain. Since previous studies have not found a pattern in this response for spinal therapy, there could be other anthropometric measures that could be better associated with spinal therapy and level of response.

The notion of mechanical influence of spinal mobilisations encompasses altering receptors within para-spinal muscle tissue ultimately leading to a reduction in pain and stiffness. Mechanical manipulation of the tissue may have the potential to trigger primary afferent neurons, affecting muscle spindle response and the muscle fibre ability to change shape (Reed et al., 2013). This equates to the concept of mechanically stretching the muscle, allowing the muscle spindle (stretch receptors) to respond, which is the primary proprioceptor of the muscle, and allows adaptive signalling to reduce the resistance to the shape change (equating to muscle stiffness). The cascade of events in mechanical stretching may therefore assist in the reduction of stiffness (Pickar & Bolton, 2012; Reed et al., 2014; Reed et al., 2013). An element of this said to be attributed to the adaptable nature of muscle is the protein tintin,

working within the sliding filament of the sarcomere structure, and acts as a muscle spring structure. This protein has the appropriate structural characteristics to allow plasticity within the skeletal muscle fibres to respond structurally and functionally according to the demands being placed on the muscle (Janecki et al., 2011; Lindstedt, 2016; Viir et al., 2006). Therefore, passive stretching of the muscle during manual therapy can provide this adjustment, causing structural changes both in adaptive signalling in afferent nerve fibres and adaptive sarcomere structuring. The communication between peripheral sensory nerve fibres and the CNS is crucial for this process and the process of adaptive signalling may also be connected to altering pain biomarker concentration (Pickar & Bolton, 2012; Pickar, 2002; Piekarz & Perry, 2015; Reed et al., 2015).

2.6 Spinal Mobilisations as a Treatment for Multiple Sclerosis

The literature around spinal mobilisations referred to within the literature review and found in literature searches (table 2.2), all referred to this treatment for people with LBP, neck pain, upper back pain, mid back pain and musculoskeletal pain; none were in the context of people with MS. However, many cross overs can be made in terms of symptoms experienced and ways in which these symptoms can be alleviated and therefore alter lifestyle factors. This also implies that research in this area has not been published and could therefore be novel within MS therapeutic literature.

As previously discussed, many studies have shown effective results after spinal mobilisation treatment, with the main benefits consisting of reductions in pain and stiffness. Due to the symptoms experienced by MS patients, reductions in both could have large impacts on their daily life, as fatigue and walking difficulties are two of the most experienced symptoms. This can either directly or indirectly affect aspects such as muscle strength, muscle coordination, balance, stability, walking ability and daily functional activities. Direct influence would indicate that the mechanical stimulation affecting afferent pathways for pain, stiffness, and aspects of sympathetic excitation, could be counteracting the result of disrupted neural pathways resulting in these symptoms. Indirectly, reductions in pain and stiffness can subsequently affect symptoms such as fatigue, anxiety, depression, and daily functional activities, due to improved body movement. Previous mobilisation studies on developing a CPR and symptomatic level studies have suggested that a greater level of symptom, whether

pain or stiffness, results in a greater level of response (Fritz et al., 2011; Shum et al., 2013). Therefore, some of the people who benefit the most from mobilisation therapy, may be the people who have greater level of symptoms, and struggle with other forms of therapeutics such as exercise interventions.

Exercise interventions have shown to be very helpful in MS therapeutics to aid improvement in body movement. However, movement limitations may be a barrier for some people to participate. Therefore, a manual intervention that involves passive work on muscles, with successful results from previous studies in people with similar symptoms, may contribute to MS therapeutic knowledge. Since MS is a chronic condition, and symptom management is a long-term feat, a sustainable management strategy incorporating therapeutics that are most helpful for individuals, will also be necessary to decipher in the long-term feasible plans for the individual.

2.7 Biomechanical Measures
2.7.1 Muscle Biomechanics
There is value in the objective measurement in muscle changes due to methodology differences that arise when comparing intervention application and analysis. An objective form of measuring muscle tissue quality not only helps to remove some of these issues but can also aid diagnosis of conditions based on muscle tissue quality abnormalities, and help assess their progression (Bizzini & Mannion, 2003; Fröhlich-Zwahlen et al., 2014).

Developments in recent years have been made in the mechanical measurement of muscle stiffness, using biomechanical principles. Owens et al. (2007) developed a system measuring PA spinal stiffness where stiffness measurements were recorded over the lumbar spine using electronic sensors recording displacement and force. This is a measurement for bending stiffness, which is often referred to in stiffness measurement literature (Lee et al., 2005; Shum et al., 2013; Stamos-Papastamos et al., 2011). The spine is measured as a bending beam, that is fixed at two points: the pelvis, and the ribcage. A known level of force is applied to a third point on the beam, and the displacement recorded. There are differing methods that have been used in literature for this measurement. Therefore, development and standardisation of this

measure has been required (Lee et al., 2005; Owens et al., 2007; Shum et al., 2013; Stamos-Papastamos et al., 2011). Over time, the development of this method has led to a small hand-held indenter, for non-invasive stiffness measurement called myometry.

A myometer is now a form of indenter and the main form of measuring viscoelastic properties of tissue. An indenter is placed above the desired tissue and produces a series of short force impulses from the electromagnetically activated device. This causes small deformations in the tissue for a predetermined period, to which the tissue responds with damped oscillations determined by the viscoelastic properties of the tissue. These oscillations are recorded by an accelerometer on the testing end of the indenter, recording the muscle deformation characteristics. Stiffness is then calculated as the ratio of resisting force response and the change in length of the tissue (mechanical stretch) (Bizzini & Mannion, 2003; Pruyn et al., 2015; Viir et al., 2006). Studies that have been part of the development of these objective measurements with the use of a PA force-displacement indenter have become more prevalent in the past twenty years (Chansirinukor et al., 2003; Edgecombe et al., 2013; Goodsell et al., 2000; Lee et al., 1998; Owens et al., 2007; Wong et al., 2015). This has become foundational work for biomechanically measuring muscle stiffness. The main way of working with these devices have remained broadly the same, with only changes in style and in size.

A handheld myometer, MyotonPRO, has previously been validated with reliable results from investigations into stiffness, elasticity, and tone of soft tissue; characteristics said to be key elements of the biomechanical make up and functionality of muscles. The measurements from muscle mechanics can characterise muscle abnormality symptoms and monitor mobility and rehabilitation developments (Bizzini & Mannion, 2003; Schneider et al., 2014). Myometry has been used to assess results in interventions with Parkinson's disease patients (Marusiak et al., 2012; Rätsep & Asser, 2011) that helped not only to assess the stage at which a patient was at in terms of stiffness and rigidity of muscles, but also the efficacy progression of anti-parkinsonian medication.

Alongside muscle stiffness, measuring the change in tone and elasticity can contribute towards knowledge of the effectiveness of an intervention and muscle quality (Kelly et al., 2018; Nair et al., 2016). Though muscle tone is necessary for background tension in resting state, hyper-tonality can cause high intramuscular pressure and have a harmful effect on muscle recovery. Elasticity of a muscle describes its ability to return to original shape after deformation and can be a used as a measure for mechanical stability and tissue changes (Kelly et al., 2018; Schneider et al., 2014). Investigation into tonality and elasticity of muscles can aid with diagnosis of musculoskeletal disorders as well helping to monitor the functional state of the muscle.

2.7.2 Stability Measures
The use of self-reporting scales and objective measures are both used within stability measures with differing benefits in terms of feasibility, accessibility, and performance outcomes (Bernardi et al., 2004; Cattaneo et al., 2006; Crenshaw et al., 2006; Kehoe et al., 2015). The measures that relate to daily activities, have a high value for QoL impact and used regularly within physiotherapy analysis (Rome et al., 2009; Shum et al., 2007).

The use of force plates has previously been used to help evaluate stability, balance, and posture measures. Testing body sway variables is an aspect of mobility heavily associated with gait and daily activities. Measuring these variables can help to determine how they may be directly or indirectly influenced by an intervention. Body sway measures have previously been investigated with elderly population (Jonsson et al., 2004), LBP population (Goertz et al., 2016), rheumatoid arthritis (RA) population (Rome et al., 2009), investigating the effects of weightless environment (Treffel et al., 2016), determining balance disorders (Mancini & Horak, 2010) as well as MS patient rehabilitation (Kanekar et al., 2013; Ramdharry et al., 2006). This has helped to determine the influence of an intervention and improved outcomes have shown to have a high relation to improved functioning in daily activities. Other force plate measures allow analysis in force exertion as well as the level of body sway within movements associated with daily tasks and include movements from seated to standing, lunging, balancing, walking, and turning. These have been tested in conditions such as motor impairment in elderly populations (Bernardi et al., 2004;

Jonsson et al., 2004), stroke patients (Karlsson & Frykberg, 2000), musculoskeletal injuries (Alkjær et al., 2009), LBP (Reza et al., 2018) as well as MS (Bowser et al., 2015; Soyuer et al., 2006). These are all movements that are associated with functional independence and many of these mobility measures contribute to the basis of the EDSS scale (Mancini & Horak, 2010; Meyer-Moock et al., 2014).

Assessment of balance and stability can help to process risk of falls and even determine some of the underlying causes for why balance disorders may occur. The suggestion has been made that this type of objective testing for balance could be useful for further investigation of potential sensorimotor mechanisms and how this could affect balance. However their use for investigating patient rehabilitation progression or the effects of an intervention are well warranted (Mancini & Horak, 2010).

2.8 Methodological Factors

2.8.1 Spinal Mobilisation Measurement

Investigations of spinal manual treatments often involve the subjective analysis of a practitioner, to decipher the range and force level of manual treatment. This will normally involve different grades (1-4) and techniques, and performed by an experienced practitioner (Chiradejnant et al., 2003; Jowsey & Perry, 2010). Objective measurement of treatment can help to standardise interventions and determine specific aspects of the treatment that may be beneficial to analyse.

The specific information given from measuring the force of an intervention, helps to monitor its repeatability over different testing sessions. This can add an element of accuracy to an intervention that has a great deal of heterogeneity. The reliability studies based on these testing measures, help to determine a level of confidence in the repeatability of testing. The mounting of a plinth onto force plates has been used successfully to decipher vertical ground reaction forces (GRF) elicited, particularly to decipher the force threshold reached (Goodsell et al., 2000; Pentelka et al., 2012; Stamos-Papastamos et al., 2011). Goodsell et al. (2000) used a custom-made treatment couch mounted on force plates for threshold assessment. They found the force loads to be between 60N and 230N, with a mean of 137N during mobilisation treatment and a maximum error of 2.7%, which was equal to 7N. However, the study

does not specify whether the force information was evaluated in real time or retrospectively. Similarly, Pentelka et al. (2012), Stamos-Papastamos et al. (2011), and Lee et al. (2005) used this method to measure force during mobilisation therapy, to decipher the threshold reached, as well as using a metronome to standardise the rate of mobilisations. Shum et al. (2013) appear to be the only study to display the force loads exerted in real time, with a maximum force of 250N exerted in their treatments, as is deemed to be the force tolerable for people with LBP.

None of these studies specify any dampening effect from indirect measurement of force exertion, going through 2 systems before being recorded by the force plates. However, it seems to still be a very useful and valid description of force loads exerted during treatment assuming additional loads of plinth and participant remain consistent. Although none of these studies measure force loads over time and frequency of mobilisations, this is mainly monitored using a metronome. If recorded on force plates measures, this would indicate the total length of time someone is experiencing the force load for and not just the threshold or mean values. Therefore, methods to successfully determine forces applied during treatment are in development and could help to further research into specifics of who responds to what treatment and dosage response. Overall, these studies seem to justify the feasibility of using a plinth mounted on force plates to measure vertical GRF, though different methods have been used to determine peak forces during the treatment.

2.8.2 Participant Testing

Testing with humans has many feasibility implications due to factors that cannot be controlled. Limitations for clinical studies with an MS population not only include time and funding restraints, previous studies have shown that lack of blinding, lack of follow-up evaluation, heterogeneity of the disease, medication variety as well as lifestyle differences that affect aspects of diet, activities and symptom management can create limitations (Gandolfi et al., 2015; Jagannath et al., 2010; Langdon et al., 2012). Inclusion and exclusion criteria are essential to ensure the well-being of participants, while study design must also be developed to ensure scientific integrity of the investigation and manage as many influencing factors as possible.

Most MS rehabilitation studies involve people with an EDSS score of 6 and below due to the feasibility and ethical problems with testing more disabled people. Thus most of the results from these interventions are only applicable to people who still have a good degree of mobility (Benedetti et al., 1999; Bernitsas et al., 2015; Cruickshank et al., 2015; Rietberg et al., 2005). This is generally the relapse-remitting type and not the progressive type who also have far less pharmacological medication available to them (Kehoe et al., 2015). Even within this range of EDSS mobility, there is a vast spectrum of physical capabilities, and response to interventions could vary depending on certain types of strengths and weaknesses.

Short-term investigations come under these restraints to a higher degree. In addition to this, the lack of spinal mobilisations literature on people with MS means that no criteria can be drawn for the participants for this intervention. Before testing a new intervention on an MS population ethically, the feasibility and efficacy of the intervention should be tested. The LBP population have symptoms that cross over with the MS population such as spasticity, pain, fatigue, depression, and movement difficulties. These are all symptoms that may be alleviated from spinal mobilisation treatment and could therefore provide useful pilot data where MS data are not available (Ahmad & Al-Sayed, 2018; Birkett & Day, 1994; Julious, 2005; Leon et al., 2012). Since LBP is not only common in the general population but also within the MS population, pilot data with this population will be beneficial before recruiting for an MS clinical population.

LBP as a musculoskeletal disorder is very common within the general population, with around 80% of people experiencing it at some point in their lives. It is one of the biggest costs for the national health service in the UK and often successfully treated with manual therapeutics. NICE have stated that manual therapy is recommended for LBP sufferers to help manage absences from work and mild disabilities (Chiradejnant et al., 2003; Maniadakis & Gray, 2000; Stamos-Papastamos et al., 2011). There is therefore added value in investigating the effects of the intervention in the LBP population as well as the MS population.

2.9 Summary

The development of research around MS, for diagnosis, cause and management has been rapidly growing for years, with still many areas to develop. The challenge with good quality research in MS rehabilitation and symptom management is both the individual nature of the condition and the heterogeneity of rehabilitative interventions. Though a lot of development has been done, conflicting results have also meant that there are many gaps still in literature and in clinical practice.

Symptom management has huge importance for anyone suffering from MS, therefore good quality research appropriate for patients at all stages of disease is necessary. Objective forms of measuring manual therapeutics can assist in providing a comprehensive overview of intervention efficacy: an aspect crucial to assessing what is best for the symptom management of a patient. Manual therapeutics are often used in clinical settings for treatment of MS symptoms, therefore more knowledge about the effects they may be having will be beneficial to the development of MS and physiotherapy research.

2.10 Project Aims and Research Questions

The aim of this project was to provide a thorough investigation of a particular intervention, using spinal mobilisation techniques in a non—typical format. The project aimed to provide objective and novel data to characterise and analyse the intervention within the context of MS symptom management and rehabilitation. This is due to the observational and anecdotal success of the intervention along with the lack of spinal mobilisation investigations within MS literature. Given mobilisation therapy success in reduction of pain and stiffness in other rehabilitative contexts, there is good rationale for a scientific investigation of this within MS rehabilitation. There is a need for MS physiotherapy research development in deciphering the types of treatment and dosages most appropriate for individuals based on their symptoms experienced. This project aimed to provide a meaningful contribution to MS and physiotherapy research and provide rationale for future study.

1. What data can be used to objectively characterise the spinal mobilisation using force produced by the therapist as well as the rate and timings of the mobilisation oscillations?

2. How can the impact of the intervention be objectively measured on muscular response and whole-body movement patterns?

3. How can a myometer device and force plate measurement provide objective data to analyse the impact of the intervention.

4. Does the intervention have an immediate impact on a myometer measured muscle response in people with LBP?

5. Does this intervention have an immediate impact on myometer measured muscle response and force plate measured movement patterns in people with MS?

6. Does this intervention have a longer-term impact on myometer muscle response and force plate measured movement patterns in people with MS?

7. Is there a gender-specific response?

8. What is the importance in change of stiffness (myometry measured) to balance measures (force plate measured) and other lifestyle measures (questionnaire measured)?

Chapter Three

Study One: Intervention pilot study.

Analysis of a spinal mobilisation intervention in people with lower back pain.

3.0 Introduction

The focus of this pilot study was to investigate and consider the feasibility and efficacy of a new spinal mobilisation intervention with no current scientific data or validation to support it. This together with the lack of MS data in mobilisation therapy and myometer muscle response data indicate that a pilot with MS participants was deemed unethical for new intervention feasibility testing. The intention of the pilot study was also to assess equipment usage and reliability within the testing situation, to pilot recruitment strategies, data collection, data management and scheduling of testing.

Spinal mobilisation therapeutics are well documented with reports suggesting benefits from both single and multiple sessions (Ferreira et al., 2009; Goodsell et al., 2000; Powers et al., 2008). Spinal mobilisation research for MS rehabilitation is lacking and therefore previous data cannot be used to forecast likely outcomes in this population. However, pilot data are still required for the intervention and myometer results which will support the development of an appropriate methodology for working with MS patients. This also helps to identify study design modifications that may be necessary (Hertzog, 2008; Leon et al., 2012).

3.0.1 Study Aims

The aim of this study was to provide data on the specifics of the intervention being investigated, given its novel status working at a specific rate, location, and pressure consistently over 30 minutes. Mobilisation treatments are generally given in smaller dosages, therefore data on longer mobilisation treatments does not exist. The study aims to gather data on muscle response values using a myometer as an objective form of analysis for treatment efficacy, as well as anthropometric data to investigate potential influencing factors in results. The data collected in this study will be used as

pilot data for the intervention feasibility and efficacy. Besides ethical requirements for testing new interventions with clinical populations, the feasibility of protocols often evolve and change according to the needs of the study and the participants. This is not only to retain adherence to the Declaration of Helsinki (Ahmad & Al-Sayed, 2018) but to ensure that research integrity is maintained so that both vulnerable clinical populations receive the most benefit from the research outcome and the researcher does not use time and resources on issues that may arise during piloting that may negate some of the data collected.

The study was also exploratory and aimed to investigate anthropometric measures and how they may influence results. The researcher hypothesised that there would be a reduction in para-spinal stiffness and tone due to the intervention compared to a control, and an increase in elasticity, and that these would be related to baseline values and gender as this has been previously seen in literature also. The null hypothesis stated that the intervention did not have any effect on these measures.

3.0.2 Lower Back Pain Pilot Population

The lack of scientific data for the intervention and mobilisations in an MS population led to the decision to recruit a population that share some symptoms with the MS population, and would potentially still benefit from a lumbar manual therapeutic. Many factors can contribute to LBP that are also experienced by people with MS such as muscle spasticity, pain, fatigue, depression, cognitive deficits, reduced mobility, reduced fitness, muscle weakness, ataxia; all known as risk factors for LBP and commonly experienced by people with MS also (Bishop & Rumrill, 2015; Dimitrov & Turner, 2014; Feinstein et al., 2015; Patti et al., 2002). It can appear as a direct consequence of a physical condition, however is most common as a side effect symptom of conditions affecting mobility (Hartvigsen et al., 2018). Although the two different conditions equate to two different populations, the cross over in symptoms, and treatment at a symptomatic level could result in benefits to both population groups.

With several potential factors contributing to either acute or chronic LBP, the generator of pain can be difficult to identify. LBP pain can be derived from nerve roots, muscle, fascia, bones, joints, and intervertebral discs. Due to the complexity of

pain, nerve pathway abnormal activities can also contribute to neuropathic pain. Psychological influences can contribute to pain with factors such as stress, depression and anxiety. These factors can contribute either directly or due to the side effects of these conditions and result in lower levels of back care. Psychosocial factors that can influence likelihood or levels of pain can include work conditions, economic status and family support and lifestyle factors such as smoking, hours of sitting and obesity. These are potential factors influencing pain as described in the biopsychosocial model previously described (Hartvigsen et al., 2018; Hoy et al., 2010; Naraoka et al., 2017).

As previously described, pain is a result of nociceptor mediation. Nociceptors are the sensory peripheral neurons and when triggered by a chemical, mechanical or thermal harmful stimulation is then transduced into an electrical signal that is communicated to higher brain centres. This signal is projected to the somatosensory cortex that processes this sensory information, subsequently signalling descending pathways resulting in a painful sensation. If this harmful stimulation persists, then these processes of peripheral and central sensitisation can occur. This stimulation can be fired off without a trigger, and can cause the pain to change from acute to chronic (Allegri et al., 2016; Pincus et al., 2013). This can result in people with MS more readily because of axonal degeneration and potentially damaged signalling process that characterises their condition. This can also occur in people with LBP due to abnormal signalling, though not necessarily due to an inflammation reaction of the nervous system. In both conditions pain can be as a result of spasticity contribution which can also occur due to disrupted descending motor pathways (Feinstein et al., 2015).

Many people who have their mobility restricted by LBP are most likely to have recurring forms of LBP, making it more debilitating in many aspects of life (Hoy et al., 2010). The likely consequences of lower levels of mobility for LBP sufferers are reduced function of the lumbar spine, reduced spine mobility, altered spine kinematics and increased stiffness (Ferreira et al., 2009; Goertz et al., 2016; Powers et al., 2008). This can have an impact on body movement capability, limited flexibility and lead to the development of chronic problems with posture, coordination and RoM (Fritz et al., 2011; Haas et al., 2014; Vicenzino et al., 2001).

Since a high number of people in the UK experience back pain at some point in their lives, it's a common problem for workplaces and disability management (Hartvigsen et al., 2018; Maniadakis & Gray, 2000). Therefore, with such a high number of people experiencing back pain, and many people incorporating management of LBP into their lifestyles, the availability of people within this group should be high to recruit for a pilot study.

3.0.3 Spinal Mobilisations Summary

Since spinal mobilisation treatments in MS studies are lacking, most literature reviewed for this treatment is based on LBP. Immediate reductions in pain have been found regardless of the type of mobilisation (pressure, rate and location differences) (Chiradejnant et al., 2003; Willett et al., 2010). Improvements in pain and RoM were found specifically after grade 3, 2Hz mobilisations on the spine by Lopez-Lopez et al. (2015), and their results revealed an association with anxiety level outcomes. Studies by Piekarz and Perry (2016) after investigating different rates of mobilisations, found that faster rates elicited a greater response in SNS activation. A collection of results have indicated that baseline symptomatic level of stiffness and pain has an effect on the level of response (Childs et al., 2004; Fritz et al., 2011; Shum et al., 2013). Results have also indicated that mobilisation treatment cannot be differentiated from other manual therapeutics in terms of these benefits (Stamos-Papastamos et al., 2011; Thomson et al., 2009). The range of results on spinal mobilisations are due to the different methods in studies investigating rate of application, location, time of mobilisation set, number of sets, and combination of other therapy types involved throughout treatment. Therefore, although there is a clear collation of results that demonstrate improvements in pain, stiffness and RoM from mobilisations, there is still no definitive specifications for what dosage is most beneficial for different population groups, depending on the symptoms they experience. Since these results differ in the benefit of their outcomes, analysing mobilisations with an MS population will be necessary to draw accurate conclusions for that separate population.

While other mobilisation interventions have been scientifically tested, they have been generally tested in 1 to 6 minute bouts (Goodsell et al., 2000; Jowsey & Perry, 2010; Krouwel et al., 2010; Pecos-Martín et al., 2017; Pentelka et al., 2012; Shum et al., 2013). Mobilisations are often administered in a clinical setting alongside another

form of treatment such as manipulation thrusts, stretches or exercises (Maitland et al., 2013). Therefore, to the author's knowledge, this is the first intervention of its kind to use consistent mobilisations for a full 30 minutes in scientific testing. Knowledge around dosage, rate and timings of mobilisations will help to carry research in this area forward, particularly for types of responders. Since testing on mobilisations for this length of time has not previously been reported in scientific literature, this information can help develop mobilisation therapeutic research.

The differences in these results may stem from methodological differences and the heterogeneity of participants. However, they still imply that further research around the specific benefits of mobilisations is necessary. Specifically investigating the benefit of spinal mobilisations either together with or in place of other types of therapies, can help in the management of LBP, affecting a large percent of the population.

3.1 Methods

3.1.1 Participants

40 LBP participants were recruited for this study (male: n = 18, female: n = 22) in a repeated-measures cross-over study design. Inclusion criteria was based on testing with LBP participants to test the feasibility of the intervention. Therefore, participants were recruited with any level of LBP for recruitment to comply within timings of the study period. Exclusion criteria was based on safety of the participant to receive spinal treatment and retaining scientific integrity of the study.

Inclusion criteria included:

- suffering from LBP which could be acute, chronic, diagnosed, undiagnosed as long as pain has been experienced in the region between 12th rib and gluteal folds reaching the buttock within the time of recruitment and testing.
- within the age range of 18 to 80.

Exclusion criteria included, must not respond to any spinal therapy absolute contraindications including:

- bone tumour
- inflammatory/infectious/metabolic disease affecting the spine

- dysplasia

- healing fractures/dislocations

- spinal cord damage

- cauda equine syndrome

- aortic dysfunction

- severe haemophilia

- must not have a connection with Point One Clinic (previous name of Pacla Medical and practicing physiotherapy clinic collaborating on the project)

- must not be taking any pain medication other than paracetamol

Must not respond to any relative contra-indications including:

- spinal disc prolapse

- spondylosis

- spondylolisthesis

- inflammatory arthritides

- osteoporosis

- hypermobile syndrome

- pregnancy

- cancer

- cardiovascular disease

- respiratory disease

- healing injury

- adverse reaction to previous spinal treatment

Ethical approval was obtained from the University Research and Integrity Committee, following the ethical guidelines stated by the Declaration of Helsinki (Appendix 1).

3.1.2 Procedure
Recruitment for the study was carried out via poster advertisement, social media (Facebook and Twitter) and word of mouth. The poster and information sheet were used either in hard copy or electronically when a participant showed interest in response to advertisement, no coercion was added when speaking face to face. Participants were encouraged to read through the information sheet and ask

questions regarding the study. Participants were involved in both a control and spinal therapy intervention session. All participants were informed about details of the study and all provided written informed consent to take part. Participants were randomly allocated into one of two groups via a random group generator on Microsoft Excel. All data collection took place in the same treatment room on the same standard physiotherapy plinth, and as close to the same time of day as possible to avoid additional environmental influences. Ambient room temperature was controlled (between 20 and 25° Celsius) for all sessions.

All participants completed the Oswestry Disability Index (ODI) questionnaire and an ODI scoring sheet prior to their first session. The ODI was used to categorise level of LBP (Chou & Huffman, 2007; Fairbank & Pynsent, 2000; Fritz et al., 2011; Kamali & Shokri, 2012, Appendix 6). Anthropometric measures for height, mass, waist circumference and gender were also recorded.

The chartered physiotherapist performing the treatment worked under their own liability. They had a Master of Science qualification in Physiotherapy, registration with the Health and Care Professions Council and 7 years of experience working as a physiotherapist in practice at the time of the study. The physiotherapist performed a 30-minute session for the spinal mobilisation intervention, working at a specific rate (0.37 Hz) maintained by a metronome set to the equivalent 22 beats per minute in their view. The physiotherapist worked at a grade lower than grade 1 and at a specific location (L1-L5), using PA mobilisations, oscillating the lumbar vertebra, with both hands working on the lumbar spine. Contact remained consistent over the 30-minute period. This was a pre-set setting of the intervention based on what had been used by the physiotherapist themselves for several years. Although in practice the physiotherapist worked on parts of the upper spine also, for the study the intervention was performed only on the lumbar spine to focus on this area in testing. Force analysis of the intervention had not been set up at this stage of the project and was one of the elements that was taken forward as a feasibility factor for following studies. During the intervention treatment the physiotherapist's manual contact was constant and not removed from the participant's spine.

Outcome measures for muscle stiffness, tone and elasticity were taken before and after both sessions. The pre intervention stiffness measure determined which side the therapy was applied to, based on the greatest mean value for stiffness following 3 repeated measures. The control session involved no physical touch. The participant lay either prone or supine on the same plinth, with no manual touch, and encouraged to relax for 30 minutes. These measures were taken by the researcher for the project who had research experience based on a Bachelor of Science in Biomechanics involving a research project and worked as a research assistant on two separate projects. All projects had involved working with participants and biomechanics-based equipment usage.

3.1.3 Outcome Measures

Measurements for para-spinal muscle stiffness, tone and elasticity were taken using a myometer palpation device (MyotonPRO, Myoton Ltd., London UK, fig. 3.1). This previously validated handheld device has been documented to give reliable results for muscle stiffness, tone and elasticity (Bizzini & Mannion, 2003; Marusiak et al., 2012; Pruyn et al., 2014; Schneider et al., 2014; Sohirad et al., 2017; Viir et al., 2006; Zinder & Padua, 2011). The myometer uses a series of low force mechanical impulses (0.4N) registered as an oscillation in the form of an acceleration signal. The stiffness, tone and elasticity parameters are reported as a mean of these impulses along with the coefficient of variation (CV) (Andonian et al., 2015; Little et al., 2014; Schneider et al., 2014; Viir et al., 2006). The manufacturer recommends acceptance of values that have a CV of <3%, complying with the findings of Schneider et al. (2014).

Measures were repeated 3 times on each side of the spine, to determine which side had higher levels of stiffness. The location for measurements were identified on both sides of the spine on erector spinae (longissimus). The myometer is held perpendicular to the identified spot and oscillations are sent through to the corresponding muscle. The participant was asked to lift their head and feet at the same time to contract their lower back muscles so the researcher could define the central belly of this muscle on either side of the spine. This spot was then marked to ensure pre and post measures were taken at the same location. The distance and width from the base of the spine was measured to locate the same spot for their second session.
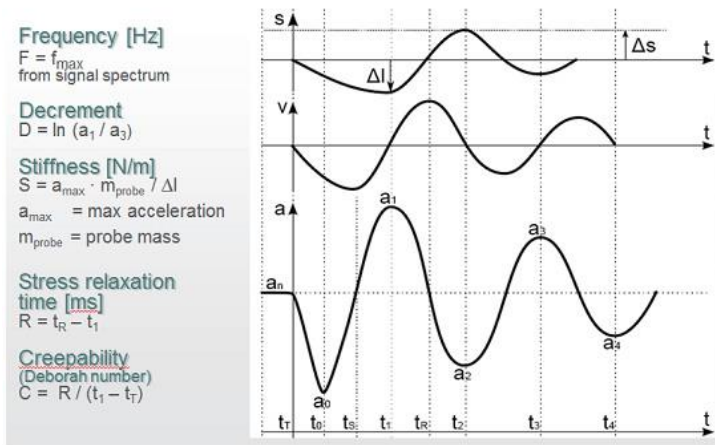
Figure 3. 1 *MyotonPRO device with active probe and calculations automatically used to produce variables for stiffness, tone and elasticity (image from myoton.com, acceleration graph image).*

3.1.4 Analysis

Data were collected for outcome measures from MyotonPro (Desktop Software v5.0.0.177) and exported into Microsoft Excel spreadsheets for stiffness, tone, and elasticity pre and post each session. The mean was calculated for each variable and used in statistical analysis with SPSS (version 23), alpha level set at 0.05. Results from the ODI questionnaire and anthropometric measures were imported into an excel spreadsheet for covariate analysis. Analysis was carried out on each dependent variable (muscle stiffness, tone, and elasticity) in separate 2-way repeated measure within participant ANOVAs. This was to determine any significant differences that occurred due to the independent variables (condition and time). Covariates were also assessed in separate ANCOVAs to determine any significant factors contributing to their changes. Due to differences previously displayed in muscle characteristics between males and females (Granata et al., 2002a; Granata et al., 2002b; Owens et

al., 2007), gender was investigated further with independent t-tests and Pearson correlations, as well as within the ANCOVA analysis as a covariate.

3.2 Results

Results in this chapter are based on 40 LBP participants.

Table 3. 1 Anthropometric and pain participant data collected before study testing.

	Male Data Mean ± SEM (n=18)	Female Data Mean ± SEM (n=22)	All Data Mean ± SEM (n =40)	All Data Range
Height (m)	1.79 ± 0	1.66 ± 0	1.72 ± 0	1.6 – 1.9
Mass (kg)	81.2 ± 1.6	69.3 ± 2.9	74.7 ± 1.9	52.5 – 95.7
BMI	22.3 ± 0.6	25.2 ± 0.9	25.2 ± 0.6	18.3 – 33.7
Age (years)	31.6 ± 3	30.7 ± 2.3	31.1 ± 1.8	22 - 66
Waist circumference (cm)	88.6 ± 8.3	82.8 ± 12.7	84.8 ± 1.6	71 - 113
ODI score (%) Minimal 0 – 20% Moderate 20 – 40%	14.8 ± 10.8 Minimal = 15 Moderate = 3	13.5 ± 9.5 Minimal = 18 Moderate = 4	14 ± 1.5 Minimal = 34 Moderate = 6	1 - 38

3.2.1 Muscle Stiffness

A 2-way repeated measures ANOVA revealed a significant interaction between condition and time, $F(1, 39) = 12.411$, $p = 0.001$, $\eta^2_{partial} = 0.241$. Pairwise comparisons were then used to determine where specific differences lie, showing a significant increase within the control from pre to post ($p = 0.004$, $\eta^2_{partial} = 0.19$) and a significant decrease within the intervention condition ($p = 0.012$, $\eta^2_{partial} = 0.15$, fig. 3.2). There was no significant difference between pre control and pre intervention values. Significance differences ($p < 0.05$) in the figures are denoted (*). Data variation shown in the error bars are represented using standard error of mean (SEM).
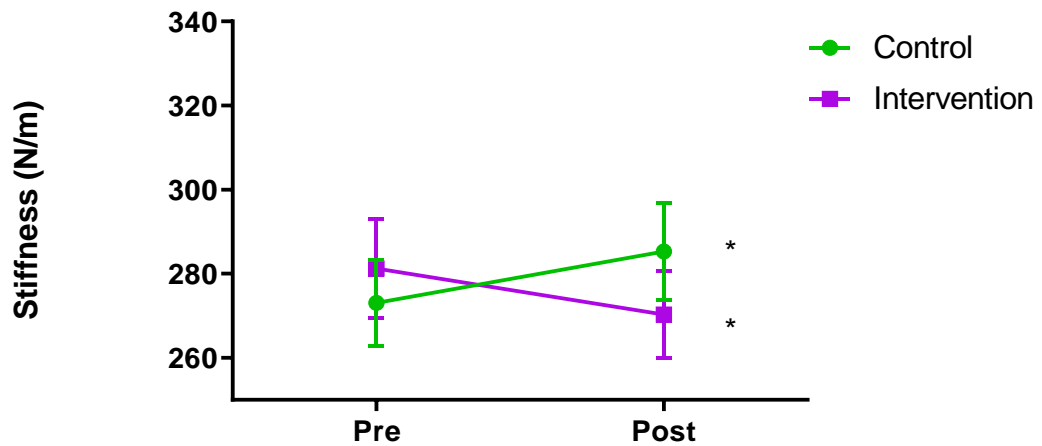
Figure 3. 2 Muscle stiffness change for mobilisation intervention from pre (281.24Nm ± 11.68) to post (270.28Nm ± 10.4) and control condition from pre (273.07Nm ± 10.22) to post (285.26Nm ± 11.45). 2-way repeated measures ANOVA data presented with SEM error bars.
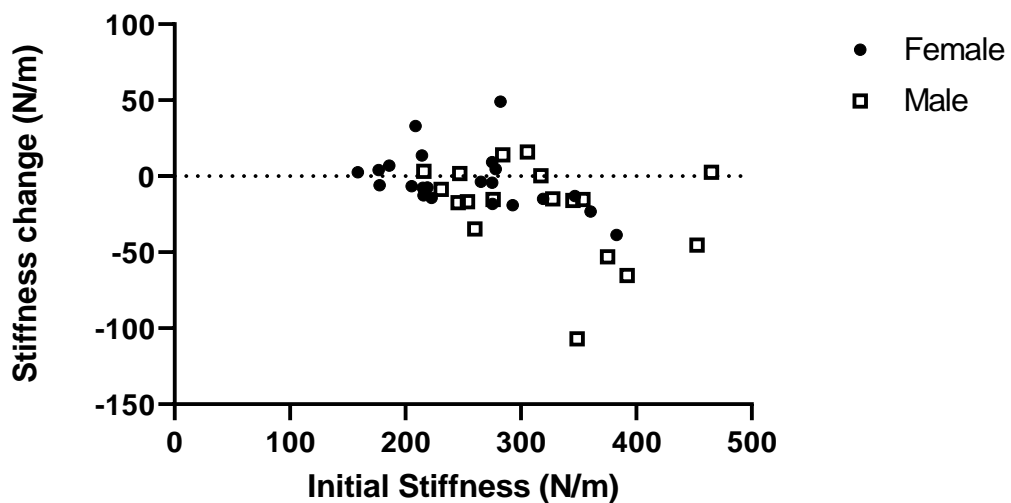
Figure 3. 3 Muscle stiffness significant bivariate correlation between pre-intervention stiffness and stiffness change.

ANCOVA was performed using all covariates to explore their interaction with the change in stiffness post intervention. Change in stiffness was used as the dependent variable. Pre intervention stiffness, BMI, ODI, waist circumference, height and gender were added as covariates. A backward elimination was conducted based on highest p-value. The only covariate remaining with significant influence was pre-intervention stiffness ($p = 0.002$) with resultant model $R^2 = 0.22$ (adjusted = 0.2). There was a significant bivariate correlation between pre intervention stiffness and change in

stiffness (p = 0.002, r = -0.47, fig. 3.4, table 3.2). This results in a negative correlation due to the reduction in stiffness seen in figure 3.2.

Table 3. 2 *Muscle stiffness bivariate correlations between pre-intervention stiffness and stiffness change values.*

	p value	r value
Male	0.137	-0.37
Female	0.057	-0.41
All Data	0.002 *	-0.47 *

A significant difference was found between male and female stiffness change ($p = 0.032$), however gender was not a significant contributor to the ANCOVA model. Bivariate correlations for pre-intervention stiffness and stiffness change carried out separately with male and female data showed a similar pattern (table 3.2) suggesting that initial stiffness rather than gender alone was the contributing factor.

3.2.2 Muscle Tone

A 2-way repeated measures ANOVA revealed a significant main difference for condition, $F(1, 39) = 4.942$, $p = 0.034$, $\eta^2_{partial} = 0.11$, and the interaction between condition and time, $F(1, 39) = 20.908$, $p < 0.001$, $\eta^2_{partial} = 0.349$. Pairwise comparisons were then used to determine where specific differences lie, showing a significant increase in tone within the control condition from pre to post ($p = 0.006$, $\eta^2_{partial} = 0.18$) and a significant decrease within the intervention ($p = 0.001$, $\eta^2_{partial} = 0.25$, fig. 3.4). There was no significant difference between pre-control and pre-intervention values.

ANCOVA was performed using muscle tone as the dependent variable and in the same way as above. BMI ($p = 0.048$), waist circumference ($p = 0.01$) and gender ($p = 0.005$) were found as significant contributors to tone change with resultant model $R^2 = 0.253$ (adjusted = 0.19). There was a significant bivariate correlation between pre intervention tone and change of tone ($p = 0.044$, $r = -0.32$, fig. 3.5, table 3.3). This results in a negative correlation due to the reduction in tone seen (fig. 3.4).
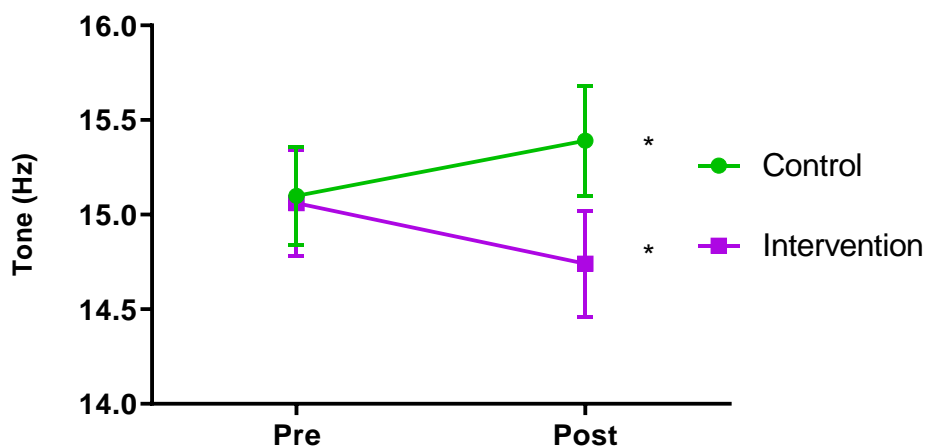
Figure 3. 4 *Muscle tone change for mobilisation intervention from pre (15.06Hz ± 0.29) to post (14.74Hz ± 0.28) and control condition from pre (15.1Hz ± 0.26) to post (15.39Hz ± 0.28). 2-way repeated ANOVA data presented with SEM error bars.*
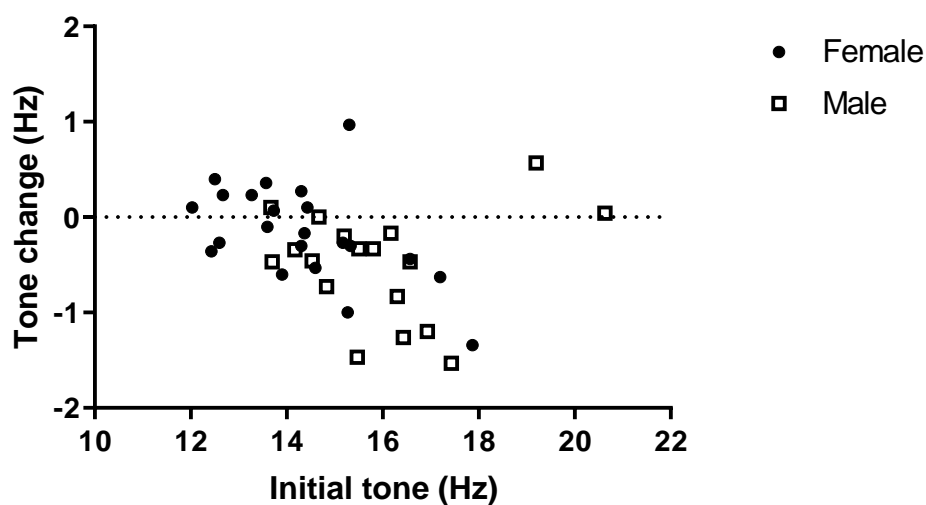
Figure 3. 5 *Muscle tone significant bivariate correlation between pre-intervention tone and tone change.*

Table 3. 3 *Muscle tone bivariate correlations between pre-intervention tone and tone change values.*

	p value	r value
Male	0.756	0.079
Female	0.012 *	-0.528 *
All Data	0.044 *	-0.32 *

There was no significant difference between male and female tone change (p =0.052), however gender was a significant contributor to the ANCOVA model as a contributor to muscle tone change. Bivariate correlations for pre intervention tone and tone change conducted separately with male and female data show different patterns, accounting for the differences in male and females (fig. 3.5, table 3.3).

3.2.3 Muscle Elasticity

A 2-way repeated measures ANOVA revealed a significant main difference for time, $F(1, 39) = 30.913$, $p = 0.000$, $\eta^2_{partial} = 0.442$. Pairwise comparisons were then used to determine where specific differences lie, showing a significant increase in the post muscle decrement values within the control condition from pre to post ($p = 0.000$, $\eta^2_{partial} = 0.3$) and a significant increase in post muscle decrement values within the intervention ($p = 0.001$, $\eta^2_{partial} = 0.24$, fig. 3.6). There were no significant differences between pre control and pre intervention values.
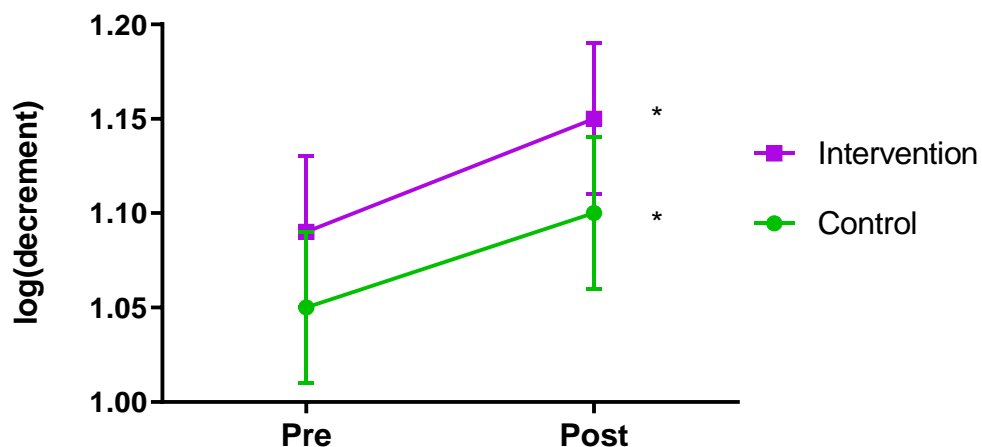
Figure 3. 6 *Muscle elasticity change for mobilisation intervention from pre (1.09 ± 0.04) to post (1.15 ± 0.04) and control condition from pre (1.05 ± 0.04) to post (1.1 ± 0.04). 2-way repeated measures ANOVA data presented with SEM error bars.*

ANCOVA was performed using changes in decrement as the dependent variable as above. There were no covariates with a significant influence on decrement change. Determination of change in decrement in elasticity is therefore likely linked to other variables not measured. A bivariate correlation between pre-intervention decrement and decrement change was not significant (fig. 3.7, table 3.4).
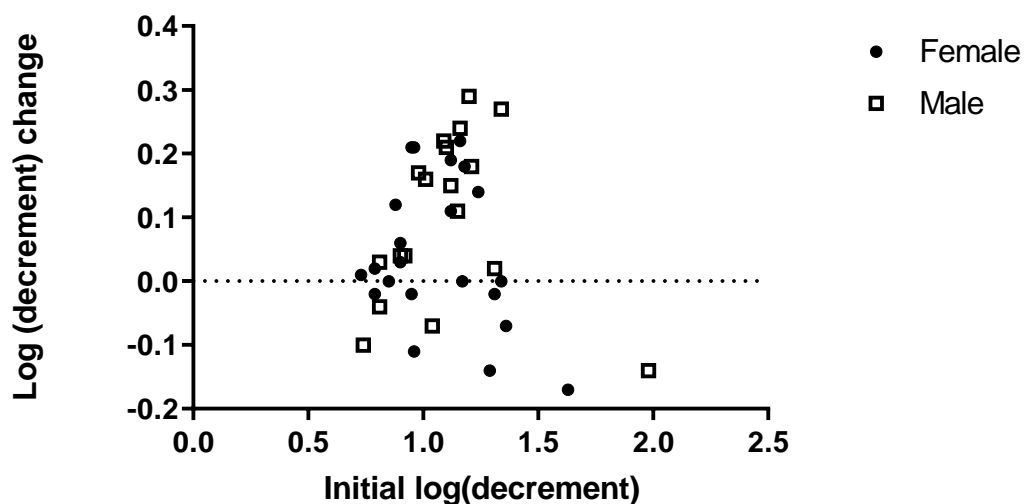
Figure 3. 7 *Muscle elasticity non-significant bivariate correlation between pre-intervention elasticity and elasticity change.*

There was no significant difference between male and female elasticity change (p = 0.162) and bivariate correlations for pre intervention decrement and decrement change conducted for male and female data showed no pattern (table 3.4).

Table 3. 4 *Muscle elasticity bivariate correlations between pre-intervention elasticity and elasticity change values.*

	p value	r value
Male	0.992	0.002
Female	0.228	-0.268
All Data	0.508	-0.108

3.3 Discussion

Though the premise of the study was a pilot investigation, the implications for objective results are relevant to the LBP population as well as other chronic conditions affecting mobility. Since reports of LBP as a common symptom have been increasing, addressing this in public health has potential for high impact in society including one the main reasons for work absence (Clark & Horton, 2018; Hartvigsen et al., 2018). Results for an intervention to improve aspects associated with LBP such as spinal stiffness, work towards not only benefiting this area of research but also associated conditions.

3.3.1 Muscle Stiffness

A significant reduction in para-spinal stiffness due to the intervention (fig. 3.2), signify that these results support the study hypothesis alongside other literature (Ferreira et al., 2009; Fritz et al., 2011; Shum et al., 2013; Wong et al., 2015). The results from this pilot study therefore imply that the spinal mobilisation intervention can have a significant effect on reduction of para-spinal stiffness. This provides an objective finding on reduction of muscular stiffness surrounding the spine after a 30-minute specific manual therapy treatment. Since stiffness characterises the muscle's ability to resist change in shape, and is known to be associated with pain and reduced mobility (Fritz et al., 2011; Haas et al., 2014; Lopez-Lopez et al., 2015; Vicenzino et al., 2001), a reduction in stiffness of these muscles may allow greater compliance and agility, potentially allowing better fluidity of movement (Ferreira et al., 2009; Shum et al., 2013). The theory discussed in the previous chapter referred to mechanical stretching of the muscle, affecting the signalling for muscle spindles (the muscle stretch receptors) and adapting this signalling, in turn affecting the muscle fibre's ability to respond to change in shape (Pickar & Bolton, 2012; Reed et al., 2014). This provides potential for further adaptations to take place with more sessions, which may lead to longer-term adaptations, and not just the immediate ones seen in this study.

Where previous results have reported 12 as the optimum number of treatment sessions (Haas et al., 2014), this study demonstrates an immediate stiffness reduction similar to Fritz et al. (2011), Childs et al. (2004) and Flynn et al. (2004). These studies also demonstrated immediate stiffness reductions in their studies but did not state the force and time of the oscillations used, an important variable for deciphering optimum dosage and strength of the treatment. Therefore, this is an important element to analyse in current and future studies.

The control condition resulted in a significant increase in stiffness after 30 minutes of lying still, showing stiffness levels can accumulate within a small period. Sedentary behaviour has been identified as one of the risk factors for developing LBP and stiffness (Hartvigsen et al., 2018; Naraoka et al., 2017) and this study shows the impact that lying sedentary for just 30 minutes can have. This supports the notion

that movement, or avoidance of stationary positions, is beneficial for decreasing stiffness (Shum et al., 2013).

The involvement of other factors influencing these levels of stiffness is partly explained in this study with significant correlations revealing baseline stiffness as a significant contributor (p = 0.002, r = -0.47, fig. 3.3, table 3.2). While this study demonstrates the benefit of a single mobilisation session in terms of stiffness reduction, it does not fully describe the influencing factors. More information on level, type, cause, and potential lifestyle contributors to pain could give more indication on potential contributors to stiffness also. While previous studies have found significant correlations with pain and stiffness (Ferreira et al., 2009; Fritz et al., 2011; Shum et al., 2013), no significant connection was found in this study between pain and stiffness. This could indicate that either pain was not a factor involved in baseline stiffness or level of stiffness change. However, previous studies show a strong correlation for this (Shum et al., 2013, pre intervention correlation r = 0.89, post intervention stiffness r = 0.98), with similar significantly correlated findings from Fritz et al. (2011), suggesting an association. This supports the notion that back pain can contribute to muscular stiffness and is related to reduced mobility. Due to the lack of correlation found in our study between ODI pain score and baseline stiffness levels, it is likely that there was not enough variation in pain severity to show this. Most participants reported mild levels of LBP (no participants scored over 40%; minimally disabled: n = 34, moderately disabled: n = 6, table 3.1). This was expected due to the exclusion criteria for pain medication no other than paracetamol, included in the criteria as a safety measure. However, a recruitment strategy that allowed a larger variation of back pain sufferers to participate, may have revealed more informative results for the association between baseline stiffness and level of pain.

This study did not collect pain data post intervention, which could have provided more data to investigate this association. The study aim was focussed on the muscle response aspect and therefore not the changes in levels of pain. The ODI was used as a measure of baseline levels of pain to investigate this as a potential influencing factor. The ODI categorises level of pain based on several lifestyle factors and to what degree their LBP affect these. Therefore, a pre and post measure of pain using this

questionnaire, would not have been suitable. However, the researcher acknowledges this information could have added benefit to the study given the previous reports on the relationship between pain and stiffness. This information could add a level of understanding on how stiffness is reduced and if pain is reduced in a related capacity. This was an aspect of the study design that was revised in the next study.

Other literature suggests that the influence of pain is a significant factor on stiffness and on subsequent mobility factors involving many aspects of daily life and heavily involved in functional independence affecting QoL. Pain, BMI, waist circumference, height or gender were not found to be influencing factors in this study. These could therefore be investigated more with higher numbers of participants, or more effective ways of measuring these to get a better picture as to the influencing factors both of stiffness development and reduction.

Given the subjective nature of pain, posture differences and daily environments, future research could consider additional measures that would affect initial levels of pain and stiffness. Aspects such as activity levels and sleep quality can affect either of these. Although the ODI questionnaire deals with these aspects in relation to pain, further information on these could reveal trends for baseline stiffness. Further insight into other influencing factors caused by daily activities that play a role in muscle stiffness could help to gain a more complete picture of the role stiffness plays in daily life. These could all be counted as prior environmental influences. As no significant differences were found between the control and intervention pre-stiffness levels, it was concluded that the protocol design had been successful in controlling for prior environmental influences. The study found that baseline stiffness is related to level of stiffness change, which corresponds with previous study findings also. This not only determines that higher levels of stiffness are more likely to show a change with regards to mobilisation therapy, but is also indicative of a relationship, changing one can alter the other. This correlation would indicate that an increase in sedentary time, could also increase muscle stiffness and increase the level of stiffness reduction in response to manual therapy, and vice versa.

With the comparison to a control condition, the results indicate that the intervention had a greater improvement on para-spinal muscles than inactivity. To investigate

specifically the benefits of the intervention, the intervention should be tested against a placebo therapy, investigating the effects of the consistency of the pressure, location, and rate of the mobilisations, compared to a placebo treatment. This will help to determine if any type of manual therapy is best or if these mobilisations specifically are most efficient. Differences in pain, stiffness and RoM can often be attributed to placebo effects regularly referred to in manual therapeutics. The concept of receiving a therapeutic, and a therapist manually treating an area of pain or stiffness, being encouraged to relax, can all influence psychological well-being. The benefit of therapy sessions often encourage recipients to feel and move better regardless of the mechanisms behind manual therapy (Goodsell et al., 2000; Shum et al., 2013). However, since this study was investigating objective muscle response values, this effect should have been reduced, though would be more robust with a placebo trial comparator.

Although the ANCOVA results showed that initial stiffness was a significant contributor to stiffness response (also supported by a significant correlation, fig. 3.3), results for gender as a covariate were more complex. Gender did not account for the variance in stiffness within the ANCOVA model, however a significant difference in the ANOVA suggests that stiffness response have pooled results that can be attributed to their levels of pre intervention stiffness. This result would mean that male and female correlations separately were expected to show a similar pattern, which was the case (fig. 3.3). Therefore, the difference in baseline levels of stiffness accounted for differences in their level of response, however the relationship between baseline and reduction, appears to be the same. Specifically, males displayed greater levels of baseline stiffness compared to females, and significantly greater stiffness reduction ($p = 0.032$). This indicates males are more likely to show a stiffness reduction after treatment due to a higher likelihood of greater baseline levels. The lack of significant contribution from ODI, BMI, waist or height measurements suggest that if these factors were to contribute to stiffness response, any significant effect would likely be influenced by the initial stiffness values as the main contributor.

Previous studies also describe baseline stiffness correlation with response levels but did not find a connection with clinically important outcomes. Therefore, relating these results to functional daily activities and QoL is still important to investigate (Ferreira et al., 2009; Shum et al., 2013). The development of a CPR by Childs et al. (2004) indicated that symptom severity was an important predictor for therapy response, however, this is in relation to pain rather than stiffness. Combining these findings with baseline stiffness measurements in further investigation, and the use of further biomechanical factors as diagnostic tools can help to determine the likelihood of responders to this type of therapy.

Knowledge around muscle health and how to measure this can help to monitor changes within neurophysiological conditions and prevention of further injury for risk populations. Stiffness specifically is referred to in literature as one of these important factors to learn about (Bailey et al., 2013; Kelly et al., 2018). From first thing in the morning to last thing before sleeping, efficient use of muscles, whole body movements, and refined movements are crucial for daily activities. This helps to retain not only good QoL, but also aspects of good mental health due to the association of mobility with functional independence. Better knowledge on these specific factors such as muscle stiffness and how they affect whole body mobility, as well as psychosocial factors on QoL will work towards better care to people most in need.

3.3.2 Muscle Tone
Results for muscle tone (fig. 3.4) were similar to results for muscle stiffness (fig. 3.2) which has also been seen in previous studies (Fröhlich-Zwahlen et al., 2014; Schneider et al., 2014; Wang et al., 2016). This indicates a potential similarity between stiffness and tone response to manual therapeutics. Although stiffness and tone are muscle characteristics used within a similar context, they describe different aspects of muscle quality. The myometry form of muscle tone is describing resting muscle tension and is described mechanically by the acceleration frequency of the oscillations induced and recorded. This is based on intrinsic skeletal electrical activity of the muscle cells (Bizzini & Mannion, 2003; Viir et al., 2006). Whereas stiffness is based on the resistance to the change of shape induced, it is a responding value (Rätsep & Asser, 2011; Schneider et al., 2014). Since stiffness is describing a response

value and tone is describing a resting value, knowledge on both these characteristics is useful.

Similar results for muscle tone and stiffness indicate that both variables respond to the intervention in a similar way. Pre-intervention tone values for the control and intervention groups were very similar, and although pre intervention stiffness (between control and intervention) was not significantly different, they showed more variation than baseline tone. Since tone is an intrinsic muscle cell characteristic required for resting muscle tension, this may be a reason as to why there is less variation in baseline values. Tone revealed a similar response to stiffness measurements, only with less variation (smaller SEM values) and less difference between baseline values for the 2 different groups. Therefore, the difference in their intrinsic and responding nature, may be a factor in terms of their level of variation.

Factors contributing to the response were different in the ANCOVA results. This showed BMI, waist circumference and gender to have a significant influence, with no contribution from baseline tone. Though similarity in stiffness and tone results are shown in previous studies (Gervasi et al., 2017; Kelly et al., 2018; Schneider et al., 2014; Wang et al., 2016), the difference in contributing factors may indicate some potentially key underlying differences in the mechanism of response. Since tone relates to the underlying electrical activity, these electrical signals may be mechanically altered, in a similar manner described in analgesia effects and stiffness reduction produced in previous studies. These outcomes seem to be connected, however underlying differences in electrical signalling may be responsible for the slight differences in pain, stiffness, and tone results.

The contributors influencing results for change in tone showed different results compared to those seen with stiffness. Where baseline stiffness was the only contributor to change in stiffness, tone showed to have differences, gender being a significant factor for this. Again, possibly the difference between these is the ways in which the concepts are described. Since tone is based on an intrinsic value, male and female differences could be more prominent and therefore show more of a significant difference between them. Males and females showed different trend lines in their response correlations (fig. 3.5) suggesting that gender could be a contributing

factor for tone also shown by the ANCOVA model. Fröhlich-Zwahlen et al. (2014) showed gender to be a significant contributor to tone values in their study, but also for stiffness which was not the case in this study (Fröhlich-Zwahlen et al., 2014).

The ANCOVA model also described other contributors including BMI and waist circumference. Both these measures are associated with body weight and health measures. Both BMI and waist circumference give indication of body weight and fat distribution, however adipose tissue was not directly measured in this study, which is a known limiting factor for the MyotonPRO, despite having excellent reliability (Fröhlich-Zwahlen et al., 2014). There could therefore be a connection between the intrinsic tone value and health measures such as BMI and waist circumference, and how they may affect changes in tone.

Though differences are seen between the changes in tone and stiffness, they seem to be affected by different factors, and dependent on different aspects within the body. Baseline level of stiffness is the main important factor to show that level of change of stiffness is affected by. However, baseline stiffness tends to differentiate between males and females, with males showing higher levels than females and therefore showing more likelihood of response. Tone however, showed to be influenced by both gender, and health measures such as BMI and waist circumference from the ANCOVA results (fig. 3.4), which may represent a greater dependence on intrinsic health factors.

Although an aspect of background resting muscle tension is necessary (Rätsep & Asser, 2011), high muscle tone has been associated with pain and discomfort during injury rehabilitation studies (Ortega-Cebrian et al., 2016). Hypertonia is also associated with conditions known to have symptoms in rigidity and muscle spasms, restricting movement such as stroke and Parkinson's disease (Fröhlich-Zwahlen et al., 2014; Schneider et al., 2014). Monitoring levels of hypertonia and when they are related to pain and discomfort of these conditions, will be useful knowledge for measuring the effects of rehabilitation and deciphering a healthy measurement for the individual.

3.3.3 Muscle Elasticity

Elasticity results show a higher degree of variance compared to stiffness and tone (fig. 3.6) also shown previously (Gervasi et al., 2017). An increase in decrement relates to a higher dissipation of mechanical energy, and a lower level of elasticity (Schneider et al., 2014), therefore the results show that both control and intervention conditions resulted in decreased elasticity due to an increase in dissipated energy. This suggests that both relaxing in the same position and manual therapy affected the elasticity of para-spinal muscles in a similar way. Schneider et al. (2014) and Rätsep and Asser (2011) reported a decrease in stiffness and tone and an increase in decrement and Viir et al. (2006) showed elasticity to have wide variation in their results (Rätsep & Asser, 2011; Viir et al., 2006). Whereas the study by Gordon et al. (2015) saw a decrease in stiffness and increase in elasticity due to a manual therapy intervention (Gordon et al., 2015). The reason for this is unclear and was suggested by Schneider et al. (2014) to be the result of the muscle relaxed state. The passive nature of the therapy may have resulted in an elasticity decrease because of the participant lying still with no active movements. Consequently, muscles may require active movements to have any effect on elasticity. With no covariates showing to be significant contributor to the level of change this supports that a higher level of variation seen in these results.

Muscle elasticity seems to clearly be an area worth investigating more as results from studies so far show a varied response, but the implications of what the benefits to increased elasticity are include many areas within muscle health that will undoubtedly include muscle recovery (Gordon et al., 2015; Schneider et al., 2014). Since elasticity describes a muscle's ability to return to original shape after deformation, a high value of elasticity therefore indicates a lower level of dampening and release of mechanical energy, this could also be a crucial element to muscle fibres recovering from injury.

3.3.4 Gender Differences and Potential Explanations

Gender differences described in this study have arisen in both stiffness and tone but not with elasticity. Though differences in stiffness results were due to initial levels, gender was found to be a significant contributor to differences in tone. These gender differences are important because they can describe innate differences that males

and females are likely to have in terms of muscles. This then affects how they respond to treatments, both to isolated muscles and the whole body, and can influence chosen treatments. Similar results were found by Zinder and Pauda (2011) and Nair et al. (2016) with significant differences found between gender and stiffness. Therefore, further confirmation of gender differences in muscle response characteristics could add knowledge to differences in treatment responses (Nair et al., 2016; Zinder & Padua, 2011).

Knowledge of gender differences is important because of the difference in response to treatment, different dosages, timings or pressure may be necessary and also shows a difference in their risk of injury (Granata et al., 2002a; Granata et al., 2002b). With gender differences in neuromuscular affected conditions such as MS, the suggestion for gender-specific physiotherapy has been made due to its influence as a significant contributor (Kehoe et al., 2015). Gender assumptions should however be avoided, as it is one of the factors involved in muscle response, there may still be other influencing factors other than the ones this study has identified. Therefore, despite results in gender differences, treatment should have an individual assessment regardless of gender, and use these findings to enhance treatment plans.

3.3.5 Study Limitations

MyotonPRO manufacturers state that measurements beyond 20mm of subcutaneous fat limit results; a variable not measured in this study. BMI and subcutaneous fat layer have also been factors in previous studies. Owens et al. (2007) showed that subjects with a higher BMI tended to have lower stiffness, attributing this to a thicker layer of adipose tissue at the point of stiffness measurement. BMI itself as a measurement of a person's physical condition does not consider muscle to fat ratio and may therefore not be an accurate description. This could mean that high levels of adipose tissue can affect measurements, and this is difficult to determine with BMI. The cross-over design and within participant analysis will to some degree reduce this effect.

The lack of myometer data in MS investigations means that these results cannot be compared to data with MS participants, and therefore only act as data for intervention feasibility and efficacy. The intervention was also tested against a control treatment, not a placebo trial or another form of manual treatment. This

signifies that any benefits seen from the intervention could be due to any form of passive treatment or any form of activity since the comparison level was sedentary stillness. More meaningful comparisons would allow for specific information about treatment to be analysed. As LBP data analysis was not the main focus of this project and due to time constraints on the project, further analysis on these comparisons were not completed.

The inclusion criteria for LBP participants indicated any level of LBP as well as only taking paracetamol as a form of medication. This resulted in many participants with mild levels of LBP and a large degree of heterogeneity between participants and lifestyle factors. A specification of chronic diagnosed LBP and even restricting to specific type of LBP or related side effect symptoms would potentially allow for further analysis contributing factors. Post-intervention measurement for pain would have allowed for stiffness and pain change comparisons, and analysis into their interaction with each other and how they can potentially influence each other. However, as described above, this was not the main aim of this study.

Participants were all recruited from a University working environment and time of day for each condition were consistent to reduce the chances of variance in pre-assessment activity levels. Physical activity levels were not controlled and could be a factor in baseline levels of stiffness, tone and elasticity.

3.4 Study Conclusions

The 30-minute spinal mobilisation intervention had a significant immediate effect on muscle quality showing a stiffness and tone reduction in sufferers of LBP when compared to a control. Initial levels of stiffness contributed to reduction levels post intervention and there was more variance in contributing factors for tone. Although significant differences exist between male and female stiffness results, gender was not a significant contributor and was likely due to initial baseline levels. Gender was however a significant contributor to reduction levels of tone.

Results show the intervention had an immediate effect and improved stiffness and tone outcomes. Further study will need to investigate the use of the intervention against a placebo therapy rather than a control to find if there are specific benefits to the consistent movements of the mobilisations. These results relate to the

feasibility and efficacy of the intervention and may need more investigation time to decipher the effects in an MS population.

Chapter Four

Study Two: Multiple sclerosis immediate effect study.

Analysis of a spinal mobilisation intervention in people with multiple sclerosis.

4.0 Introduction

The aim of the PhD project is to contribute to physiotherapy research for MS patients. Therefore, the results from study one with LBP participants demonstrate that it is feasible and safe and testing can continue to ethically test with an MS population. The shared symptoms between the LBP and MS population means that the level of response may show similarities. The implication of para-spinal stiffness reduction could be connected to reduced spinal pain and improve whole-body mobility (Barnes et al., 2010; Donzé, 2015; Stevens et al., 2013). However, the complications of the MS condition and how it is manifested in individuals may introduce differences in their response.

4.0.1 Introducing Multiple Sclerosis as a Population Group

As previously discussed, MS is the most common non-traumatic neurological disease in young adults affecting millions of people around the globe (Giovannoni et al., 2016). There is a high social cost for the individual because of the duration of the disease and also a high cost of health care necessities, correlating with the disease severity (Mackenzie et al., 2014; Pugliatti et al., 2006). There is great humanistic benefit to investigating MS with results that are relevant for the MS individual, family members and carers making decisions for this people group.

Though substantial progress has been made in MS research including diagnosis, treatment and symptom management, there are still many unknown elements of the condition. There is difficulty in diagnosis of MS phenotype and monitoring symptoms due to the large array in clinical presentation of the disease. The development of the McDonald Criteria evidenced how research with MS patient centred approach along

with MRI development can provide an improved representation of the condition. This helped to categorise patients into MS phenotypes as well as distinguishing it from other neurological conditions (Dimitrov & Turner, 2014; Gafson et al., 2012; Giovannoni et al., 2016). A patient centred approach is an important element to retain while developing study design and managing feasibility, particularly with the complex nature of this condition. Re-evaluation of interventions and rehabilitation programmes are also said to be crucial for both the recipient patient, and the efficacy of the intervention (Khan et al., 2007).

This systematic categorisation of patients with the EDSS has highlighted areas of research to enable analysis that can put MS patients on a rating system, helping with grading level of disability in interventional studies. As well as categorising overall degree of disability, it also categorises symptoms into functional system groups, in order to distinguish between the different types of symptoms experienced. The scale has helped to progress MS research and has since been used in countless research studies with MS patients (Barnes et al., 2010; Benedetti et al., 1999; Bernitsas et al., 2015; Crenshaw et al., 2006; Freeman et al., 1997; Khan et al., 2007; Kobelt et al., 2017; Patti et al., 2002). It is used widely in MS physiotherapy studies as a categorical tool, but not an outcome that is likely to change as an outcome measure (Freeman et al., 1997; Khan et al., 2007; Patti et al., 2002).

Symptom management can involve both pharmacological and non-invasive treatments. Although steroids can provide relief in some symptom areas and help to improve QoL, they can also be the source of negative side effects (Dimitrov & Turner, 2014; Jagannath et al., 2010). The benefit of investigating non-invasive physiotherapy-based interventions is the lack of potential side effects compared to drug treatments. However, there is a lack of evidence and understanding of their efficacy and scientific basis for their effectiveness. Further investigation into the objective analysis of their effects on the musculoskeletal system may help to bridge this gap (Campbell et al., 2016; Etoom et al., 2018a; Garrett et al., 2013).

4.0.2 Multiple Sclerosis and Physiotherapy

Physiotherapy interventions have been previously reported as having beneficial outcomes for symptom management, and the maintenance of a good QoL in people

with MS (Bellanti et al., 2018; Donzé, 2015; Patti et al., 2002). The progressive and debilitating nature of MS means emphasis on retaining functional movement is important. Physiotherapy can be adaptable to individual needs of the patient depending on their specific symptomatic areas, while maintaining whole body movement as an overall focus. They can also involve treatments including manual therapies, exercise treatments and stretches, which all aim to improve efficiency of musculoskeletal movements (Campbell et al., 2016).

The pilot study in the previous chapter reported that a single session of spinal treatment had a significant effect on an LBP population in terms of muscle response. Better efficiency of muscle tissue function is also likely to improve movement patterns and whole-body mobility (Pickar & Bolton, 2012). Stevens et al. (2013) reported that nerve dysfunction in MS patients is greatest over the longest pathways due to the accumulation of lesion impact on the CNS. This results in nerve dysfunction between the cortex and lumbo-sacral roots, leading to dysfunction in nerve pathways that affect muscle recruitment in the lower extremities. Gait impairments often experienced by MS patients could be due to lesions in these long nerve pathways, leading to weakened muscle recruitment and coordination, numbness, muscle spasticity and fatigue, all contributing to gait abnormalities. As well as gait disturbance, other symptoms commonly reported that can affect mobility and functional independence are depression, osteoporosis, falls, spasticity, pain and sleep disorders, all highly associated with QoL and have been influenced by physiotherapy interventions previously (Dimitrov & Turner, 2014; Kehoe et al., 2015; Stevens et al., 2013; Yamout et al., 2013).

It has been reported that around 33% of surveyed MS patients use massage therapy as a form of treatment for their MS symptoms with significant improvements in fatigue, pain and health perception (Backus et al., 2016). Their results revealed a significant correlation between fatigue and pain, and between perception of health and QoL, showing how these outcomes can influence each other. The significant correlation between spinal atrophy and clinical disability also signifies the importance of spinal health for both RRMS and progressive MS (Bernitsas et al., 2015). The involvement of the spine is a major element of whole-body mobility and overall

clinical disability. This can significantly impact the disability outcome of patients (Losseff et al., 1996; Shum et al., 2013). Therefore, physiotherapy interventions facilitating spinal mobility and function, can play a positive influential role in maintaining whole body mobility and clinical disability status in the long term for MS patients.

The lack of consistency in testing manual therapeutics has led to conflicting results in objective measures. However, similarities exist in outcomes directly related to more subjective measures of QoL with improvements in self-esteem, self-perception, fatigue, anxiety, depressed mood, body image and social participation (Finch & Bessonnette, 2014; Hernandez-Reif et al., 1998; Porcari et al., 2019). Therefore, these appear to be common outcomes for manual therapy interventions and important to recognise as elements of the treatment. A review by Namjooyen et al. (2014) around complementary and alternative medicine in MS found the management of functional independence and fatigue to be a key factor in symptom management-based therapeutics (Namjooyan et al., 2014). Several studies have reported improvements in pain reduction. Though difficulties around the measurement of pain has meant that the clinical significance of some study results is low (Backus et al., 2016; Bronfort et al., 2004; Reid et al., 2014; Shum et al., 2013; Thomson et al., 2009; Voogt et al., 2015).

Better understanding of biomechanical and biochemical changes induced by spinal therapeutics would add to the knowledge around pain and stiffness reductions found in investigations. Theories around pain mediation stem in altering primary afferent neurons through chemicals triggered by the mechanical manipulation as described in the literature review (Pickar & Bolton, 2012; Voogt et al., 2015). Manipulating the para-spinal tissues by mechanical stretching, would then lead to a response from muscle spindles as the stretch receptors for the muscle fibres. By detecting the change in length of the muscle and conveying this information to the CNS by afferent nerve fibres allows adaptive signalling in descending pathways contributing to chemical signals involved in the experience of pain and stiffness in muscle tissue (Pickar & Bolton, 2012; Reed et al., 2014). The adaptable nature of the protein titin works as a structural element of the sarcomere to allow stretching and elasticity back

to the original muscle shape, and could be a key element in this signal adaptation during mechanical stretching of muscles (Janecki et al., 2011; Lindstedt, 2016).

Spinal mobilisations have been reported to be helpful for other chronically ill populations suffering from back pain, dizziness and stroke recovery, with immediate effects seen in short-term intervention (Bronfort et al., 2004). The common theme around these interventional studies is the improvement of symptoms such as pain, stiffness, and RoM, which are often shared symptoms for people with MS. This bears impact on the quality of movement on not only daily tasks, but participation in other forms of physical activity that are potentially beneficial for the individual also.

In addition to pain symptoms, spasticity is commonly seen in MS patients, and is a disorder as well as a symptom for many other conditions. This motor disorder is caused by an imbalance of signals in the CNS and characterised by sporadic increased levels of tone and stiffness. This leads to exaggerated tendon jerks due to hyperexcitability from the stretch reflex. It is associated with higher levels of disability, causing issues in whole-body mobility, and contributes to muscle spasms and weakness. It is experienced by approximately 60% of people with MS (Barnes et al., 2010; Etoom et al., 2018a; Shakespeare et al., 2010). A study by Barnes et al. (2010) found that 97% of their MS study participants showed spasticity and out of those, 47% had spasticity at a clinically significant level. The individuals with spasticity had significantly higher levels of disability than those without spasticity in this study. With its high prevalence, the authors of this study recommended treatment of spasticity as a priority for a large proportion of the MS population.

The spinal mobilisation intervention introduced in the last chapter uses an oscillatory force, at a low force and velocity. Spinal mobilisations have been used within physiotherapy for a number of years often as a treatment for back pain (Maitland et al., 2013; Perry & Green, 2008; Piekarz & Perry, 2016; Shum et al., 2013). Immediate benefits have been demonstrated in reduced levels of pain, stiffness and RoM (Chiradejnant et al., 2003; Pecos-Martín et al., 2017; Willett et al., 2010) similar to the results reported in study one of this thesis. Researchers have previously investigated the effect of different forces and rates of mobilisation with equivocal results (Chiradejnant et al., 2003; Pentelka et al., 2012; Willett et al., 2010). The

specific differences seen between these study results lie in whether location, force, oscillation rate or number of sets make a difference as to the magnitude of pain relief, with no clear answers for any of these factors (Chiradejnant et al., 2003; Pecos-Martín et al., 2017; Shum et al., 2013; Willett et al., 2010).

4.0.3 Multiple Sclerosis and Myometry

The development of myometry now allows objective analysis of interventions and their effect on superficial muscles. As mentioned in chapter two (section 2.7.1), myometry has been used to analyse muscle quality in conditions that have similar neuromuscular issues as MS. Marusiak et al. (2012) revealed a significant reduction in resting muscle stiffness when on medication compared to the medication off-phase for Parkinson's patients. This information has then helped to inform medication prescription for Parkinson's patients with rigidity through an objective and reliable assessment. Frölich-Zwahlen et al. (2014) investigated bilateral differences in muscle characteristics for stroke patients. Using objective analysis, these muscle response results gave good test-retest reliability. Since myometry is a relatively new way of measuring muscle quality, studies in this area with MS patients are limited, but those involving other neurological conditions such as Parkinson's and Stroke indicate reliable results that have informed treatment of the condition.

MyotonPro has some limitations including detecting deep layer muscles under other tissue structures, analysis of muscle groups rather than a single muscle and detecting muscles that aren't palpable. However, the feasibility and reliability has been tested and approved in previous literature and study one of this project. Schneider et al. (2014) reported positive results for feasibility, ease of use, non-invasive assessment and for real-time assessment. The MyotonPRO reliability has been shown in several studies, with moderate to high test-retest reliability and good validity (Bailey et al., 2013; Fröhlich-Zwahlen et al., 2014; Kelly et al., 2018; Pruyn et al., 2014; Viir et al., 2006). The method for establishing the side of the lumbar back with a higher magnitude of stiffness and use of palpation to determine measurement location had good feasibility in the pilot study with LBP participants and was not anticipated to cause any issues with MS patients either.

4.0.4 Multiple Sclerosis and Balance Measures

The use of balance measures with MS patients can be particularly useful to identify differences in balance and gait, which are seen in a large percentage of patients. Information gathered can help monitor movement patterns and establish how they may or be not be improving, particularly with balance and stability as main outcomes, and how they relate to QoL (Mancini & Horak, 2010; Panuccio et al., 2015; Stevens et al., 2013).

Mobility issues related to balance and stability can affect many aspects of gait with patients experiencing balance problems, a higher number of falls and altered step cadence. These can lead to reduced endurance and increased metabolic cost, affecting many areas of mobility and functional independence. Even in people with minimal disability, analysis has shown them to still walk slower, with fewer, shorter, wider and increased variability between steps when compared to healthy controls (Sosnoff et al., 2012; Stevens et al., 2013). If muscles pertaining to gait are not functioning to full potential, they can impact limb movements, impairments such as foot drop, hyperextension, hyperflexion around the knees, leaning towards anterior, posterior, or either lateral side, and hip drop (Crenshaw et al., 2006; Sosnoff et al., 2012; Stevens et al., 2013). Balance requires integration from all sensory systems; visual, somatosensory and vestibular to inform the brain and the body of its position in the environment, and elements of this can be measured by the force and pressure exerted by the body in some of these movements (Cameron & Wagner, 2011; Stevens et al., 2013). Analysis of these balance and stability issues can help determine some of the underlying causes of why falls occur, how to help develop exercises to prevent them, and improve the endurance and metabolic cost of walking and daily activities (Mancini & Horak, 2010; Panuccio et al., 2015).

Analysis of some of these movement patterns may help to stabilise some basic everyday movements, in particular walking gait (Cameron & Wagner, 2011; Sosnoff et al., 2012; Stevens et al., 2013). The overall muscle activity generated by MS patients is a lower level of contraction compared to healthy controls due to a reduced central motor drive and reduced muscle recruitment. Muscle atrophy can then result as a consequence (Cameron & Wagner, 2011; Stevens et al., 2013).

Static balance is an aspect of human balance characterising the ability to maintain certain postures requiring neuromuscular control and refined movement to stay in a stable position. Lack of refined movements can often lead to increased levels of body sway which can be magnified in neuromuscular disorders, including MS. Measurements of body sway characteristics can be influenced by many factors including levels of concentration, proprioception, and neuromuscular activity (Borg & Laxaback, 2010; Karlsson & Frykberg, 2000; Mancini & Horak, 2010).

The use of force plates as balance measures also has numerous reliability studies within literature, including MS rehabilitation (Bowser et al., 2015; Kanekar et al., 2013; Ramdharry et al., 2006). Le Clair and Riach (1996) analysed the use of force plates as a means of investigating postural stability, finding that centre of pressure (CoP) measures and GRFs had good reliability for differentiating between mechanical and sensory conditions, and can detect postural differences, either between conditions or between interventions (Le Clair & Riach, 1996).

CoP measurements give a summary of the forces exerted on a force plate, the position of this will change as the body on the force plate moves. CoP measures the pressure below the participant's feet, and the resultant force on the force plates. Though centre of gravity (CoG) represents the point within the body where all forces are equally dispersed, this point within the body will change as the body moves. However, this may not be the same as the resultant force that is applied to the supporting surface. Though both measures are related to body balance and represent body movement to maintain an equilibrium of forces, CoP can be measured directly with force plates as the supporting structure and used as an analysis for how these movements represent balance and stability. Several parameters can be assessed from this including direction of body sway, determining whether sway is more common in one direction compared to another (Karlsson & Frykberg, 2000). Rome et al. (2009) investigated its use with an RA population in an eyes open and eyes closed task for body sway CoP measures, finding that AP body sway was significantly different to healthy controls, but not for mediolateral (ML) body sway. This result meant that the RA group had more CoP excursions within the AP direction (Rome et al., 2009). Raymakers et al. (2005) also tested body sway parameters with an elderly

population, looking at displacement velocity range of movement along both ML and AP planes. Displacement velocity was found to be the most consistent difference between all their testing situations of elderly compared to young healthy controls (Raymakers et al., 2005).

Although body sway is commonly investigated for both MS patients and other populations, there are multiple activities that are part of a daily routine are essential for functional independence. For example, DeBolt and McCubbin (2004) incorporated forward lunges, leg curls and step ups as part of an exercise intervention with MS patients. They found significant benefits for leg extensor power, however not for mobility and balance measures (DeBolt & McCubbin, 2004). These are activities that can also be measured objectively on force plates and analysed for body sway and efficiency of movement. It may be that the exercise intervention helped to improve strength, but to apply that strength into activities requires its incorporation into the intervention.

Forward lunge is not generally used as a daily task in isolation, however used as part of other activities. The stepping forward motion involves control and pushing off from the back leg to the returning position and requiring strength, balance, and control. Although strength benefits have been seen from the use of forward lunge as an intervention (Alkjær et al., 2009; DeBolt & McCubbin, 2004; Rietberg et al., 2005) there is limited evidence for interventions and balance improvements with the MS population. The objective analysis from force and body sway measures using force plates will help to contribute to this area of knowledge.

While these tests have the potential to give useful information for MS patients and symptom management, it does require participants with reasonable walking ability in order to obtain valid measures. These measures were not piloted with the LBP population in study one and must therefore be chosen carefully to be appropriate and beneficial to the MS population. Therefore, these tests are not beneficial for patients who are EDSS at 6 or above with higher levels of disability.

4.0.5 Pilot Study Result Implications

The improved muscle stiffness and tone results from study one support the notion it is worth investigating in an MS population. The feasibility and practicality of the

intervention has been tested and although some aspects of this second study have not been piloted, a large part of the protocol has been successfully carried out. Ethically, the researcher has a better understanding of what testing sessions will look like for the participants.

The gender-based differences in the muscle response results led to the recruitment decision of a single gender. With a higher prevalence for females compared to males with MS as previously described, it was deemed appropriate to recruit female participants only for this study to control for gender as a possible factor, to contribute to potential gender specific intervention and remain relevant to current MS prevalence.

To allow analysis on differentiation or otherwise because of the nature of the manual therapy intervention and to avoid worsening symptoms, this study will use an alternative manual therapy treatment session to compare to the intervention rather than a controlled environment. This is anticipated to increase the internal validity of the findings and improve ethical integrity of the study.

4.0.6 Study Aims

The aim of this study was to investigate the efficacy of the intervention on acute muscle response and movement patterns within the MS population. The study design was informed by results from the pilot. The study therefore recruited females with MS for a repeated-measures cross-over, single intervention study, where all participants received both the mobilisation intervention and an alternative therapy session. The study was investigating the intervention treatment in comparison to a general manual therapy session to investigate the specificities that may be beneficial in terms of the forces, oscillation rate and consistency used. Though this cannot be used as a placebo comparison due to the therapeutic elements involved, the comparison will be more beneficial than a control session of sedentary lying still.

The researcher hypothesised that there would be a reduction in muscle stiffness, tone, body sway and pain measures because of the intervention compared to the general massage. The null hypothesis stated that the intervention would have no effect on these measures compared to the general massage treatment.

4.1 Methods

4.1.1 Participants

20 female participants were recruited for this study. The recommended number of participants for repeated measures, within factors ANOVA was 24. This was established from a G-power calculation with a large effect size using partial eta squared (0.25) from the pilot study results, a power of 0.95 and an alpha significance level of 0.05. There was no MS mobilisation data available for estimation of a clinically meaningful effect size, therefore this was based on study 1 results with LBP data. Due to time constraints and participant availability, recruitment was completed with 20 participants.

Inclusion criteria included:

- must be female
- must have an MS diagnosis, must be able to walk independently with an EDSS of 6 or below
- must be within the ages of 18-80

Exclusion criteria included that participants must not respond positive to spinal therapy absolute contraindications including:

- bone tumour
- inflammatory/infectious/metabolic disease affecting the spine
- dysplasia
- healing fractures/dislocations
- spinal cord damage
- cauda equine syndrome
- aortic dysfunction
- severe haemophilia
- must not have a connection with Point One Clinic

In addition, participants must not respond to any relative contra-indications including:

- spinal disc prolapse

- spondylosis

- spondylolisthesis

- inflammatory arthritides

- osteoporosis

- hypermobile syndrome

- pregnancy

- cancer

- cardiovascular disease

- respiratory disease

- healing injury

- adverse reaction to previous spinal treatment

Participants who responded positively to any relative contraindications were excluded based on severity and GP recommendation. If participants responded positively to relative contraindications, they were asked to request permission from their GP for their opinion as to whether it was safe for them to take part.

The physiotherapist was made aware of all relative contraindications before any treatment and all treatments were considered gentle and low grade. Participants were told to inform the therapist or researcher if they felt in pain or discomfort at any point during the treatment.

Ethical approval was obtained from the University Research and Integrity Committee, following the ethical guidelines stated by the Declaration of Helsinki (Appendix 9).

4.1.2 Procedure

Recruitment for the study was carried out via poster advertisement, social media (Facebook and Twitter) and word of mouth. Contacts were made to private or charity-based physiotherapy centres and MS therapy centres. Initial contact was made in accordance with ethical approval and information days were organised with two MS therapy centres in Edinburgh and Glasgow.

The poster and information sheet were used either in hard copy or electronically when a participant showed interest in response to advertisement and no coercion was added when speaking face to face. Participants were encouraged to read through

the information sheet and ask questions regarding the study. Participants were offered to be accompanied by a friend or family member to make them more comfortable during the testing if they wished.

Once participants had shown interest in taking part, they were sent a link to a Novi Survey (Appendix 11). This was created to collect basic information about their MS condition and ask about any contraindications they may respond positively to. They were given a participant number to fill this out, so all information was pseudonymised to maintain security of their personal and medical information. This also ensured that the information was received before the participant began the protocol, meaning knowledge of their eligibility was received beforehand and avoiding any unnecessary journeys for someone who was not eligible. Only the researcher had access to this information on the Novi Survey. One password protected document was kept with the participant name and number code, to which only the researcher had access to, and which will be destroyed after completion of the PhD, as per General Data Protection Regulation guidelines. All other information was then pseudonymised according to their participant number. If the participant was eligible, they were randomly allocated to group A or group B by a random group generator on Microsoft Excel^{TM}, to organise suitable times for their sessions. Group A received the placebo massage first and then the intervention treatment, and vice versa for group B.

Participants were required to attend on two separate occasions for the intervention treatment and general massage. These sessions were requested to be one week apart and at the same time of day for both their sessions, however this was not possible for a small number of participants. The order of the treatments they received were based on their randomly allocated group. The participants were blind to which treatment they were receiving. Though they were aware that one session was a general treatment and one was a specific intervention treatment and were therefore likely to be able to decipher which was which. All testing took place at the Edinburgh Napier University Sighthill campus Engage building with the room maintained at standard room temperature (20-25°).

Participants again had the opportunity to read through the information sheet and the researcher ran through the protocol with each upon arrival on both occasions.

Participants were invited to ask any questions about the study before consent forms were given and encouraged to ask throughout the sessions if they wanted. They were also informed they could withdraw from the study at any point and it would not affect their treatment. Their data could be removed up until the point of dissemination of summarised results. Once written informed consent was given, anthropometric measures were taken for age, weight and height. Information was also taken regarding their most prominent symptoms and location of symptoms. Results from their Novi Survey were reviewed to go through their MS condition and EDSS.

The same chartered physiotherapist who performed the intervention in the previous study performed the same intervention for participants in this study (same details from chapter three, section 3.1.2). The physiotherapist was involved in the rationale development for the study. However, all data collection and analysis were done by the researcher guided by academic supervisors without input from the physiotherapist. During the intervention treatment the physiotherapist's manual contact was constant and not removed from the participant's spine. The massage therapy was conducted by a different qualified massage therapist also working under their own liability and performed a 30-minute general massage applied on mid-lower back, with no specificities or consistencies; physical contact, rate and force magnitude was not constant. This treatment acted as an alternative therapy, allowing comparison of the specificities of the intervention. The use of a non-consistent massage therapy ethically allowed MS participants to still receive a form of treatment that may be beneficial to them on their alternate session. The use of objective criteria for force, rate and location, allowed for the differentiation between the treatment protocols. This is similar to placebo therapeutics from previous studies testing mobilisations (Haas et al., 2014; Perry and Green, 2008). The use of different therapists for the two treatments was due to practicality issues and allowed for the analysis of two different therapy treatments and their comparison. However, this results in different therapists who may already have different techniques and therefore result in differences due to this factor alone and is a study limitation to be aware of.

Figure 4. 1 *Plinth mounted onto 2 portable force plates to record vertical GRF.*

The force of both the intervention and the massage treatment was measured by monitoring vertical GRF profiles using two force plates (Kistler Instruments Ltd., Hampshire, UK, Force Plate Type 2875A) placed underneath the plinth. These were placed securely on the ground ensuring the floor surface was even and the force plate did not wobble. The plinth legs were placed on top of each force plate and secured with the breaks (example is demonstrated in figure 4.1). Only vertical GRF was measured. To ensure standardisation between participants of differing mass, a zero force was generated once each participant was lying supine and still on the plinth and recordings were taken during treatment every 3 minutes in 30-second samples periods (Kistler Ltd., BioWare). The summation of the vertical GRFs from the force plates were graphed and monitored during the treatment sessions to check the consistency of the force. The same process was carried out for the massage session (sample graphs in Appendix 16).

The researcher conducted myometer tests for muscle quality, balance tests with the force plates and VAS tests with lumbar movements before and after the treatment sessions, completing a total of 4 separate set of tests. The participants could practice each of the balance tests on the force plates before testing began, however no separate familiarisation session took place. Once both testing sessions were complete, participants were thanked for their contribution and given a debrief sheet with further information and contact details to give to their GP or carer as required.

4.1.3 Outcome Measures

Participants started with VAS tests measuring lumbar movements during flexion, extension, lateral flexion and rotation. They rated their pain during these movements on a scale of 0 to 10, 0 equating to no pain and 10 equating to worst pain felt. The researcher also completed the lumbar movements to provide a demonstration and instruction continued through the measurement process. Visual images for each lumbar movement and the pain scale were given to the participants (Appendix 15).

Myometer tests were completed with participants lying in a prone position on a plinth and using a myometer digital palpation device (MyotonPRO, Myoton Ltd., London, UK). This is the same device used in study one, and collected the measurements in the same way, for the same muscle. The measurement collection was the same protocol as study one (section 3.1.3), collecting values on both sides of erector spinae muscle and using the higher mean value to determine the stiffer side of the spine. The same location was then palpated using the measurements from the base of the spine recorded from the first session and remarked.

The participants then performed two balance tests positioned on the force plates. These were performed on force plates (Kistler Instruments Ltd., Force Plate Type 2875A) using MARS performance analysis software which allows for body sway data extraction, including directional body sway. The first test involved the single leg stance where the participant was asked to balance on a single leg for 10 seconds. This test was performed with the leg corresponding to the side of the body with higher stiffness results. For example, if a participant showed the left side of their lower back had higher levels of stiffness compared to their right, the balance tests were performed on the left leg, and vice versa (fig. 4.2). The participant was asked to place their balancing leg in the middle of the force plate, with the front of their foot facing the anterior direction of the force plate. The test lasted for 10 seconds and they were instructed when this started and finished. The participant was asked to stand on their single leg with their other leg lifted while holding onto a chair placed beside them. They were counted into the test before letting go of the chair and visually focussing on a spot in the room to aid their balance. If their lifted leg touched the force plate,

the test automatically stopped and was not counted. The chair placed beside them was an aid to help them re-stabilise if necessary and stop them from falling.

The full 10-second period was used for analysis using the CoP measurements produced by the MARS software (fig. 4.3). The variables extracted for analysis were total path length, AP path length, ML path length and path length velocity automatically produced by the software. The participant repeated this test 5 times if they were able. Any tests where the participant stepped off the force plate was deleted, and the test re-started.

The second test used was the forward lunge test which required normalisation to the participant's body weight. The force plate was set to zero and the participant then instructed to step on and stand still. The plate was then calibrated by the researcher and the participant could step off. Participants were asked to lunge forward on the same leg that performed the single stance test. They stepped forward until they reached approximately a 90° angle with their front leg, as directed by the researcher, and then step back to normal position (fig. 4.4). The distance at which the participant was stepping onto the force plate from their back leg was marked on the floor, to allow the test to be repeated from the same distance in the post therapy protocol. This was determined in a practice test based on where the participant felt most comfortable to step forward. A chair was placed beside them again to assist stabilisation if needed and recorded if used. The participant was asked to have their arms by their side while lunging forward onto the force plate and the test recording was initiated automatically when their foot was placed on the force plate. Therefore, they were not counted into this test and could lunge forward when they felt ready to do so and the researcher affirmed the test was ready.

The researcher was available to help at any time if participants felt uncomfortable or unstable during the tests or therapy session. Participants were encouraged to rest between the balance tests and at any time they felt tired. Once the participant stepped onto the plate the test automatically recorded all phases of the test (stepping forward, bending to a 90° angle, stepping up and stepping off the plate). The variables extracted for analysis were CoP ML displacement, impact force normalised to body weight, and contact time on the plate (fig. 4.5-4.6). The

participant repeated this test 5 times if they were able. All tests were repeated after the treatment session to collect pre and post data for both conditions.
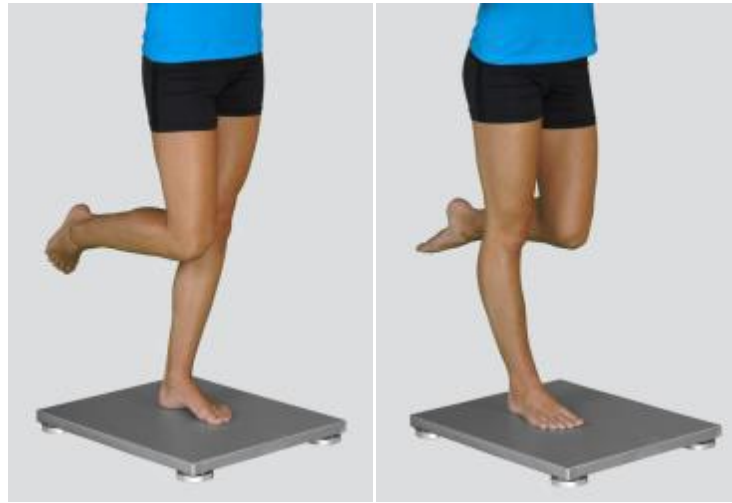
Figure 4. 2 *The single leg stance test, on either left or right foot placed in the centre of the plate with normal upright position (image from Kistler MARS Software v2.1 Manual).*
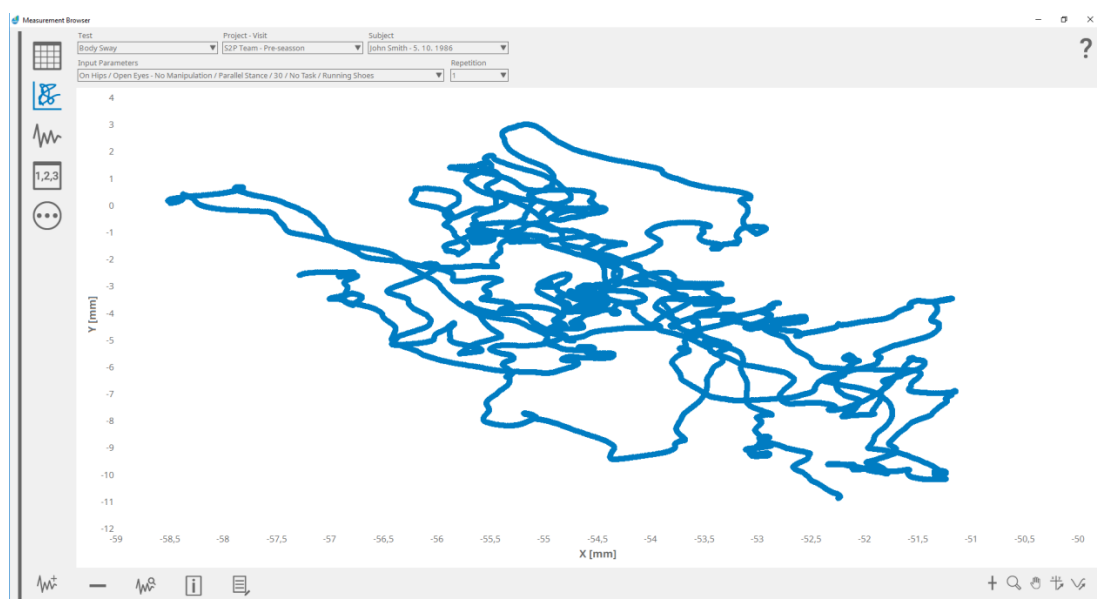
Figure 4. 3 *The CoP path length result from which body sway measures were analysed (image from Kistler MARS Software v2.1 Manual).*
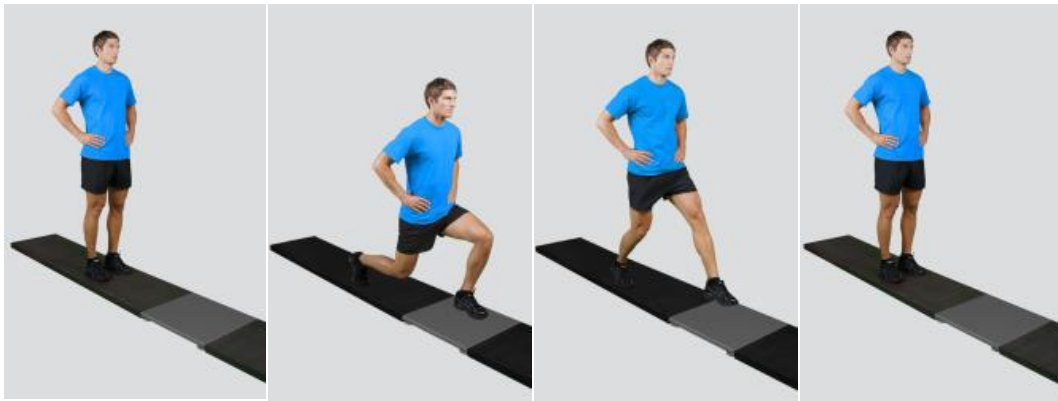
Figure 4. 4 *The forward lunge test with participant stepping forward onto the force plate and stepping back to same position (image from Kistler MARS Software v2.1 Manual).*
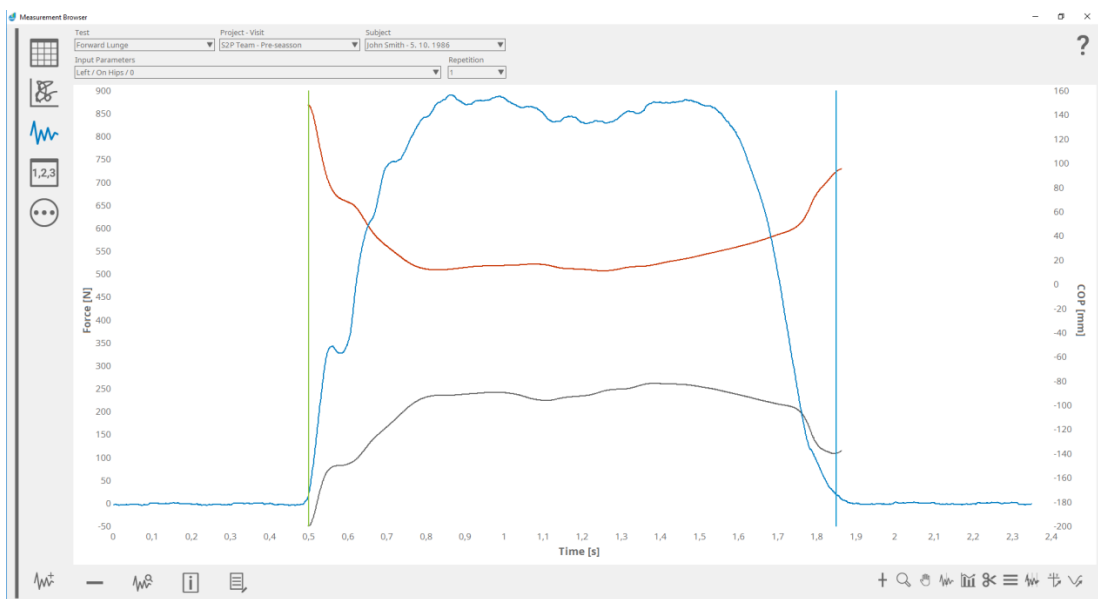
Figure 4. 5 *The force result measurements from which impact force and contact time were analysed from (image from Kistler MARS Software v2.1 Manual).*
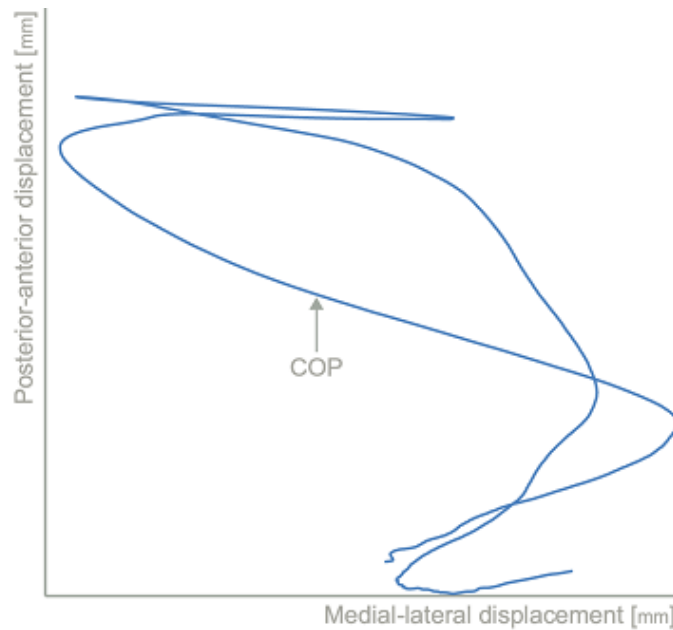
Figure 4. 6 *The CoP result measurements from which CoP ML displacement was analysed from (image from Kistler MARS Software v2.1 Manual).*

4.1.4 Analysis

Data were collected for outcome measures from MyotonPro (Desktop Software v5.0.0.177) and Kistler MARS Software (v2.1) and exported into Microsoft Excel spreadsheets. Both MyotonPro and MARS software produced the variables used for analysis from the recorded tests. The mean was calculated for each variable of viable tests for pre and post in both testing sessions of each participant. VAS score was recorded as a number for pre and post in both testing sessions. Each participant then had a mean value for each variable pre and post for both testing sessions. Patient's data were kept on their own file and then the mean values were brought together for each variable and each participant into a summary data file. Statistical analysis was then carried out on these mean values for all dependent variables on SPSS (version 23). The mean for all tests were gathered with standard error dispersion values. 2-way repeated measures ANOVAs were used to determine differences pre and post treatment, and between the intervention and massage trials with an alpha level set < 0.05.

4.2 Results

Results in this chapter are based on 20 female participants diagnosed with MS.

Table 4. 1 Patient anthropometric data displayed with mean and SEM and range values. Data gathered in Novi survey and in their first session.

	Mean ± SEM	Range
Height (m)	1.66 ± 0	1.55 – 1.7
Mass (kg)	76.7 ± 5.4	52 – 140.4
BMI	27.7 ± 1.9	19.7 – 46.9
Age (years)	46.5 ± 3	23 - 70
EDSS	3.3 ± 0.4	1 – 6

Table 4. 2 Patient MS information with regards to their condition. Data gathered in Novi survey and in their first session.

MS Type	RRMS = 16
	PPMS = 1
	SPMS = 3
Most Symptomatic Functional System	Pyramidal = 8
	Sensory = 7
	Bowel and Bladder = 3
	Cerebral = 2
Most Symptomatic Side	Right = 10
	Left = 8
	Both = 2
Dominant Side	Right = 17
	Left = 1
	Both = 2

4.2.1 Muscle Stiffness

All three tests on muscle quality data had Shapiro Wilk normality violations due to outliers within the data. These data were not removed as they did not seem to be inaccurate and represented the level of variation within the population muscle quality data. These values could have been represented as percentage change to minimise the variation and would also change the normality violations. However, this did not alter any of the findings in terms of significance, therefore these were left as

absolute values. To best represent the data and test for an effect between pre and post, parametric tests were chosen due to the ability to detect an effect if there is one. If non-parametric tests are used, a larger sample size is required to test for this effect.

A 2-way repeated measures ANOVA revealed no significant main effect for time ($F_{(1, 19)}$ = 0.397, p = 0.536), condition ($F_{(1, 19)}$ = 0.047, p = 0.83) or their interaction ($F_{(1, 19)}$ = 0.176, p = 0.680) for either treatments in stiffness. There was no significant difference between the mobilisation intervention and the massage baseline values pre-treatment. Both conditions revealed an increase in stiffness after treatment. The increase after the intervention treatment was less than the increase for the massage treatment, however not significantly (fig. 4.7).
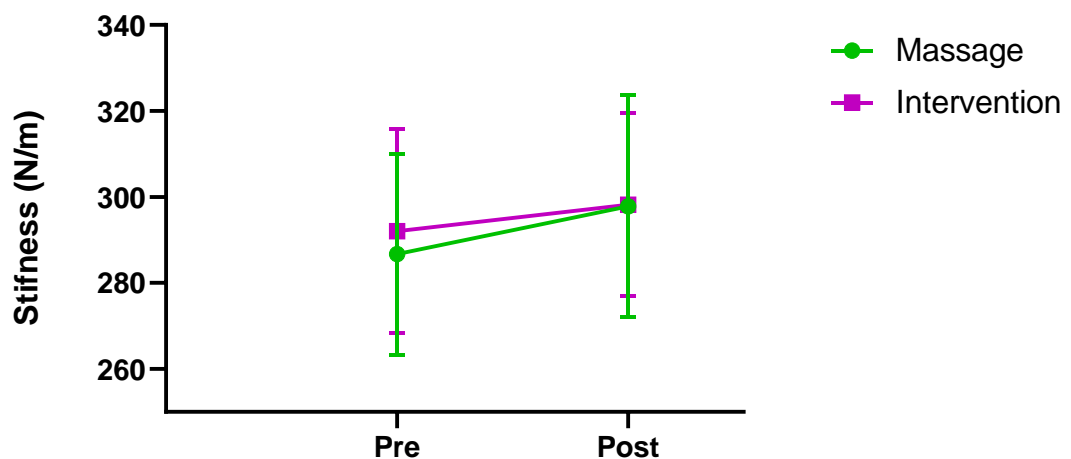
Figure 4. 7 Muscle Stiffness change for intervention from pre (292.05Nm ± 23.69) to post (298.17Nm ± 21.32) and massage from pre (286.68Nm ± 23.38) to post (297.82Nm ± 25.78) in a 2-way repeated measures ANOVA data presented with SEM error bars.

A bivariate correlation was carried out on the stiffness data comparing baseline stiffness with the degree of stiffness change. With data from both treatments together, this was a non-significant correlation with a similar pattern to study one data and a p-value close to the alpha level (r = -0.31, p = 0.05, fig. 4.8). Separately the treatments had non-significant correlations (massage: r = -0.23, p = 0.34, mobilisation: r = -0.27, p = 0.25).
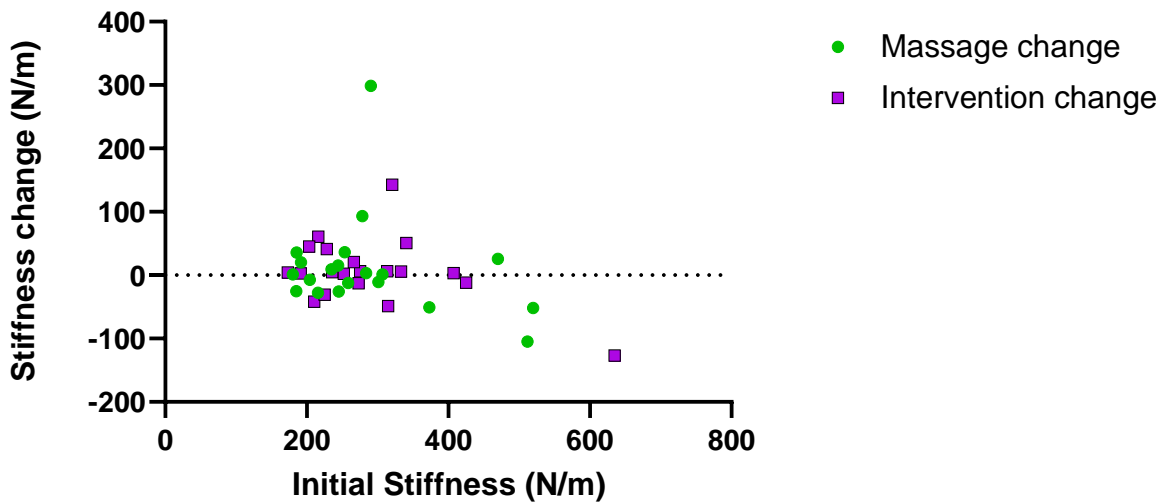
Figure 4. 8 Muscle stiffness non-significant bivariate correlation between pre-treatment stiffness and stiffness change.

4.2.2 Muscle Tone
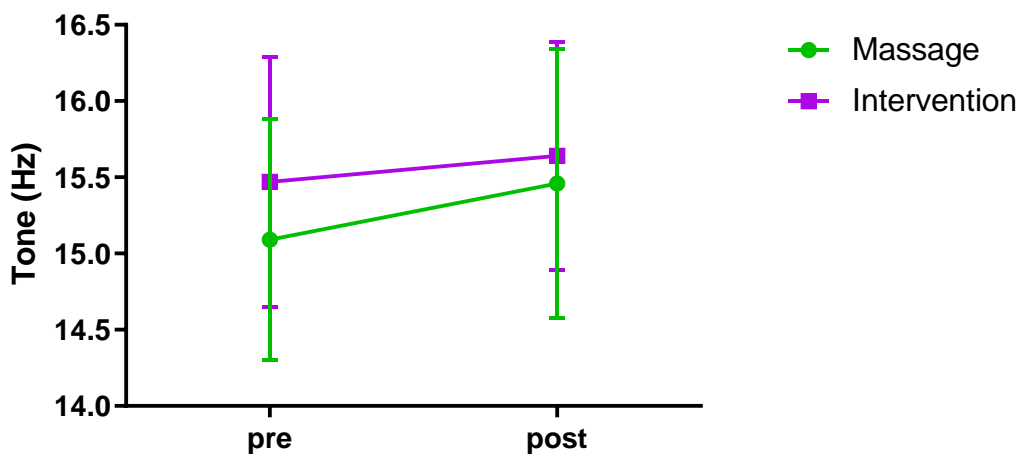
Figure 4. 9 Muscle tone change for intervention from pre (15.47Hz ± 0.82) to post (15.64Hz ± 0.75) and massage from pre (15.09Hz ± 0.79) to post (15.46Hz ± 0.88) in a 2-way repeated measures ANOVA data presented with SEM error bars.

A 2-way repeated measures ANOVA revealed no significant main effect for time ($F_{(1, 19)}$ = 0.44, p = 0.515), condition ($F_{(1, 19)}$ = 0.328, p = 0.573) or their interaction ($F_{(1, 19)}$ = 0.368, p = 0.551) for either treatments in tone. There was no significant difference between the massage and intervention baseline values pre-treatment. Both conditions report an increase in tone after treatment (fig. 4.9). The increase

after the intervention treatment was less than the increase for the massage treatment, however not significantly. A bivariate correlation was carried out on the tone data comparing baseline tone with the degree of tone change. With data from both treatments together the correlation was non-significant (p = 0.12, r = -0.25, fig. 4.10) and non-significant correlations for treatment data separately (massage: p = 0.66, r= -0.11, mobilisation: p = 0.07, r = -0.41) however with a similar pattern to study one.
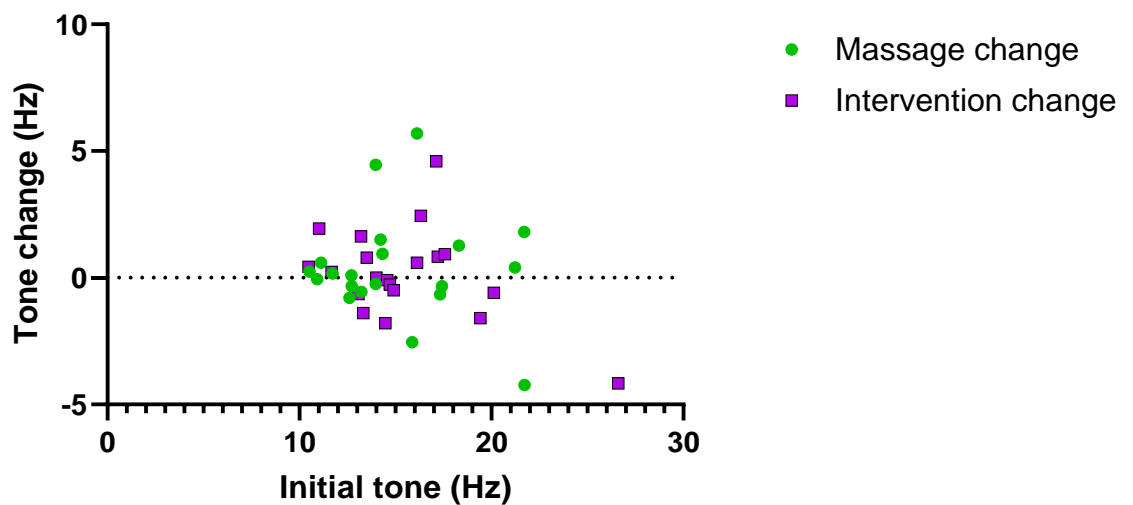
Figure 4. 10 *Muscle tone non-significant bivariate correlation between pre-treatment tone and tone change.*

4.2.3 Muscle Elasticity

A 2-way repeated measures ANOVA revealed no significant main effect for time ($F_{(1, 19)}$ = 0.001, p = 0.98), condition ($F_{(1, 19)}$ = 0.125, p = 0.727, or their interaction ($F_{(1, 19)}$ = 2.404, p = 0.138) in elasticity. There was no significant difference between the intervention and massage baseline values pre-treatment. A decrease in the decrement equates to an increase in elasticity. Therefore, figure 4.11 demonstrates the intervention treatment resulting in an increase in elasticity and the massage in a decrease in elasticity.
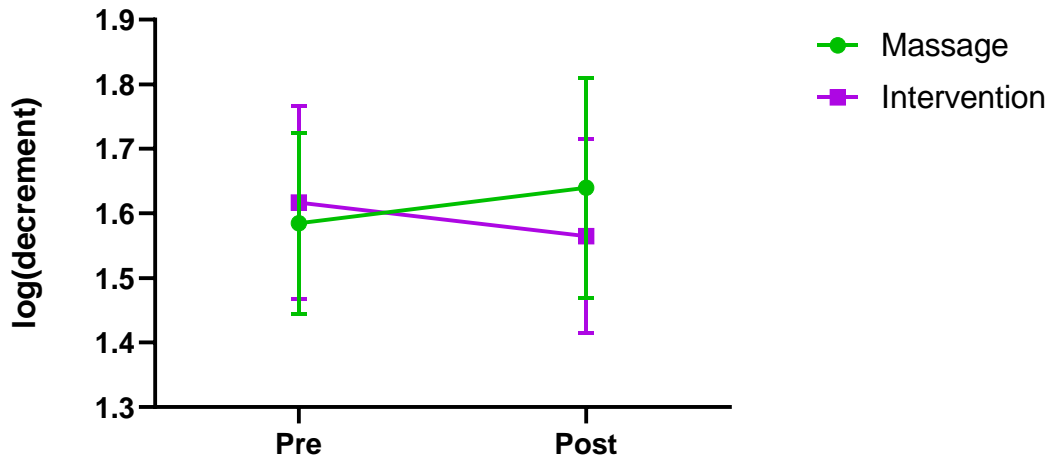
Figure 4. 11 *Muscle elasticity change for intervention from pre (1.62 ± 0.15) to post (1.57 ± 0.15) and massage from pre (1.59 ± 0.14) to post (1.64 ± 0.17) in a 2-way repeated measures ANOVA data presented with SEM error bars.*
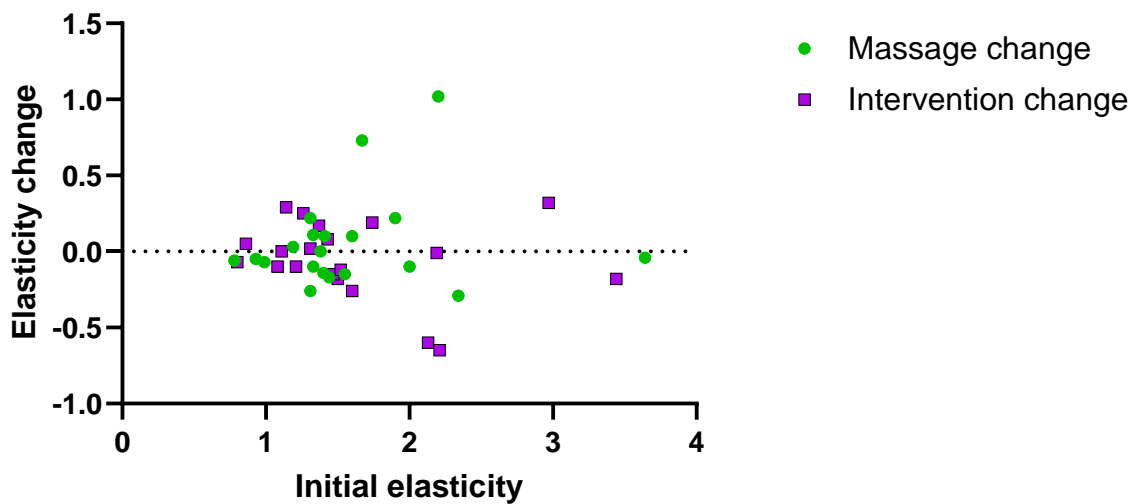
Figure 4. 12 *Muscle elasticity non-significant bivariate correlation between pre-treatment elasticity and elasticity change.*

A bivariate correlation was carried out on the elasticity data comparing baseline elasticity with the degree of elasticity change. With data from both treatments together the correlation was non-significant (p = 0.99, r = -0.02, fig. 4.12) and separately also non-significant (massage: p = 0.52, r = 0.15, mobilisation: p = 0.37, r = -0.21).

4.2.4 Single Stance Test Results

A 2-way repeated measures ANOVA revealed no significant main effect for time ($F(1, 19) = 4.318$, $p = 0.05$), condition ($F(1, 19) = 0.149$, $p = 0.703$) or their interaction ($F(1, 19) = 1.37$, $p = 0.256$) for either treatment in body sway total path length. Both treatments showed a decrease and the mobilisation decrease was greater than the massage decrease (fig. 4.13). Significance differences ($p < 0.05$) in the figures are denoted (*). Effect sizes are reported as partial eta squared values (0.01 = small, 0.09 = medium, 0.25 = large).

The same analysis displayed for AP path length revealed a main significant difference for time ($F(1, 19) = 5.823$, $p = 0.026$, $n^2_{partial} = 0.235$) and no significant difference for condition ($F(1, 19) = 0.384$, $p = 0.543$) and no significant interaction ($F(1, 19) = 0.657$, $p = 0.428$, fig. 4.14) in AP body sway path length. Pairwise comparisons with a Bonferroni adjustment were then used to determine where specific differences lie, revealing a significant reduction in the massage treatment between pre and post and large partial eta squared effect size ($p = 0.0015$, $\eta^2_{partial} = 0.273$). The same analysis for ML body sway path length did not show any significant main effect for time ($F(1, 19) = 1.173$, $p = 0.292$), condition ($F(1, 19) = 0.11$, $p = 0.744$) or their interaction ($F(1, 19) = 0.7$, $p = 0.413$) (fig 4.15). The same analysis displayed for velocity of body sway movements had no significant main effect for time ($F1, 19) = 4.398$, $p = 0.052$), condition ($F(1, 19) = 1.814$, $p = 0.194$), or their interaction ($F(1, 19) = 1.453$, $p = 0.243$) (fig. 4.16).

All 4 variables analysed for this test had Shapiro Wilk normality violations due to outliers within the data. If the outliers are removed, normality was not violated, and some reductions become significant. However, outliers were not removed as they did not seem to be inaccurate and represented the level of variation within the population balance data.
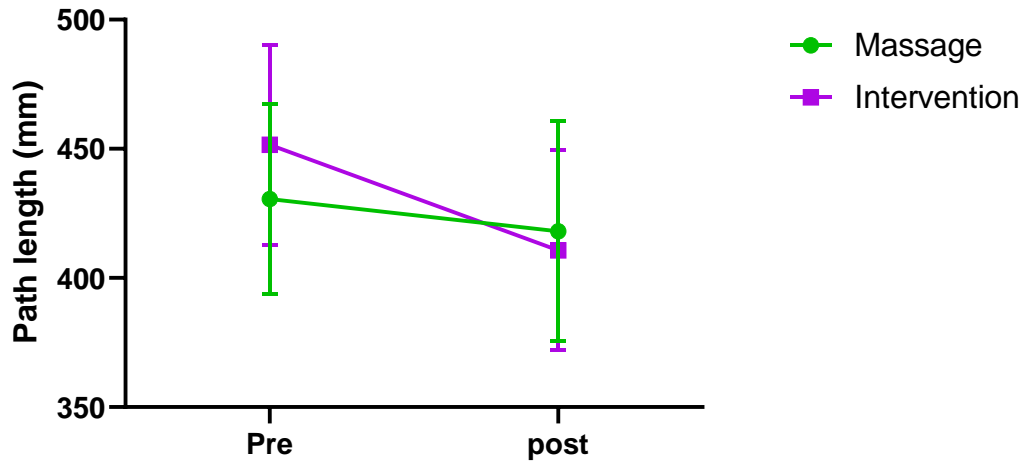
Figure 4. 13 *Body sway, total path length change for intervention from pre (451.54mm ± 38.55) to post (410.66mm ± 38.72) and massage from pre (430.54mm ± 36.84) to post (418.06mm ± 42.63) in a 2-way repeated measures ANOVA data presented with SEM error bars.*
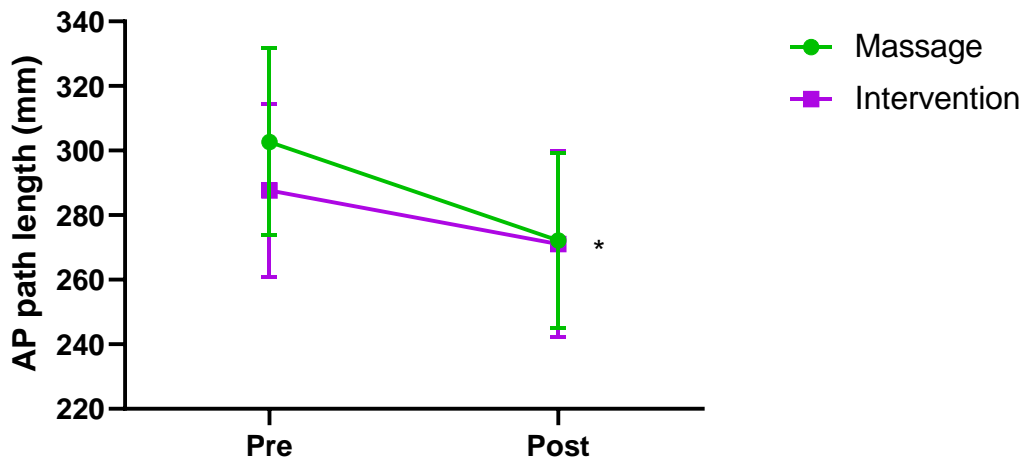
Figure 4. 14 *Body sway, AP path length change for intervention from pre (287.65mm ± 26.9) to post (271.06mm ± 28.68) and massage from pre (302.69mm ± 28.93) to post (272.14mm ± 27.2) in a 2-way repeated measures ANOVA data presented with SEM error bars.*
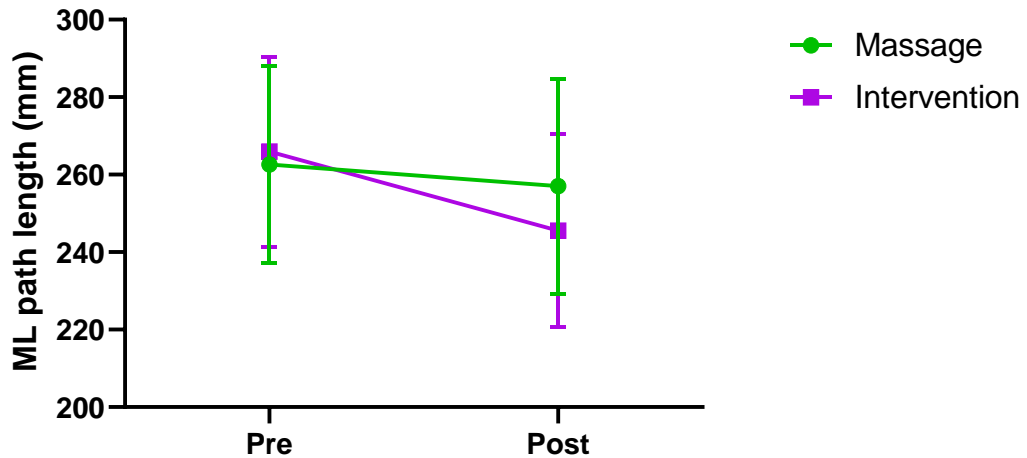
Figure 4. 15 *Body sway, ML path length for intervention from pre (265.93mm ± 24.46) to post (245.55mm ± 24.93) and massage from pre (262.63mm ± 25.32) to post (257.01mm ± 27.8) in a 2-way repeated measures ANOVA data presented with SEM error bars.*
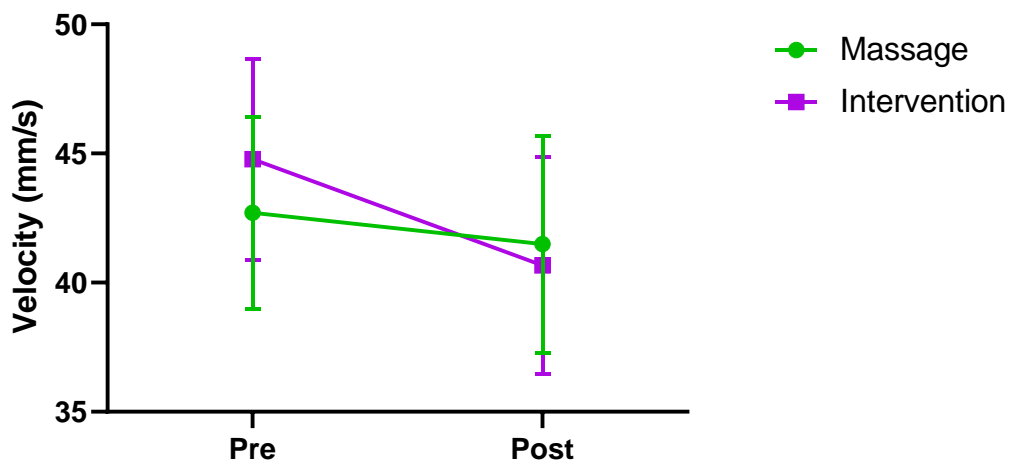
Figure 4. 16 *Body sway velocity change for intervention from pre (44.78mm/s ± 3.82) to post (40.67mm/s ± 3.83) and massage from pre (42.71mm/s ± 3.65) to post (41.49mm/s ± 4.21) in a 2-way repeated measures ANOVA data presented with SEM error bars.*

4.2.5 Forward Lunge Test Results

A 2-way repeated measures ANOVA revealed no significant main effect for time $F_{(1, 19)} = 0.934$, $p = 0.346$), condition ($F_{(1, 19)} = 1.814$, $p = 0.194$) or their interaction ($F_{(1, 19)} = 0.625$, $p = 0.439$) in CoP ML displacement during the forward lunge (fig. 4.17). The same analysis was conducted on impact force of the forward lunge (percentage of body weight used when leaning into the forward lunge). This also revealed no significant main effect for time $F_{(1, 19)} = 1.630$, $p = 0.217$), condition ($F_{(1, 19)} = 0.918$,

p = 0.35) or their interaction (F(1, 19) = 0.771, p = 0.391, fig. 4.18). The same analysis on contact time, representing the time the participants took on the forward lunge, revealed no significant main effect for time (F(1, 19) = 1.102, p = 0.307), condition (F(1, 19) = 3.43, p = 0.08) or their interaction (F(1, 19) = 0.573, p = 0.458, fig. 4.19).
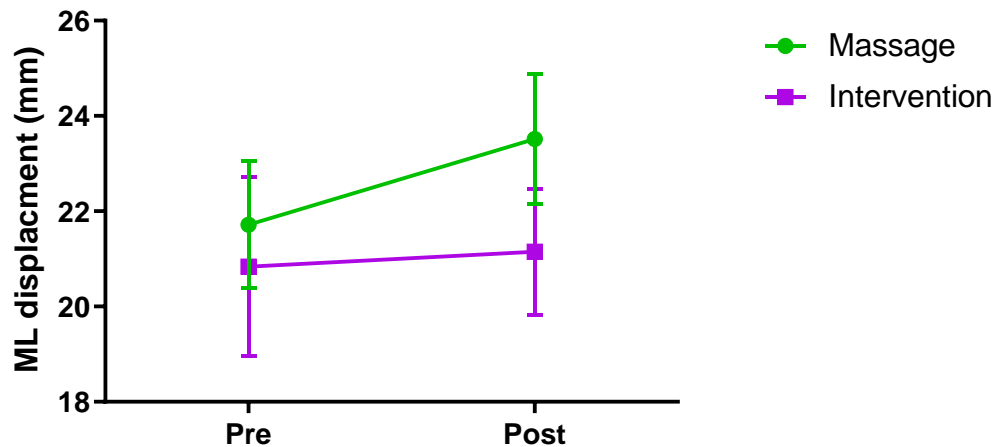
Figure 4. 17 *Forward lunge body sway, ML displacement for intervention from pre (20.84mm ± 1.87) to post (21.15mm ± 1.15) and massage from pre (21.72mm ± 1.33) to post (23.52mm ± 1.37) in a 2-way repeated measures ANOVA data presented with SEM error bars.*
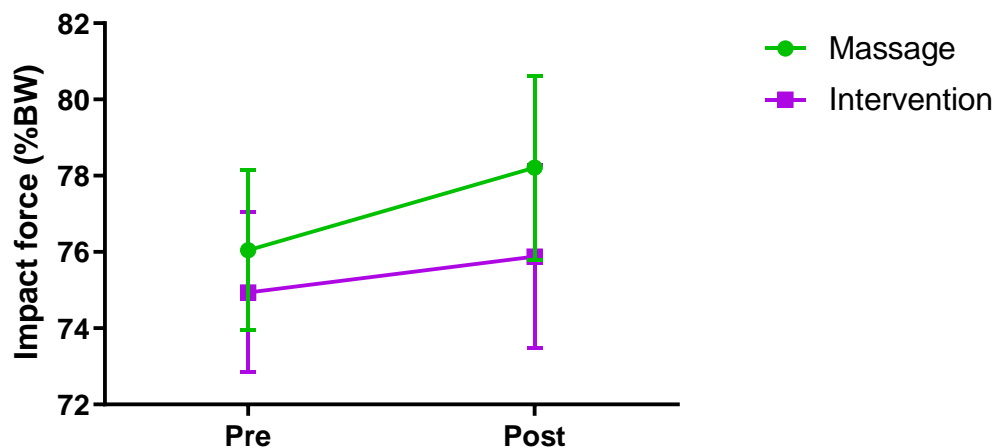
Figure 4. 18 *Forward lunge relative impact force change for intervention from pre (74.94%BW ± 2.1) to post (75.88%BW ± 2.41) and massage from pre (76.05%BW ± 2.1) to post (78.21%BW ± 2.42) in a 2-way repeated measures ANOVA data presented with SEM error bars.*
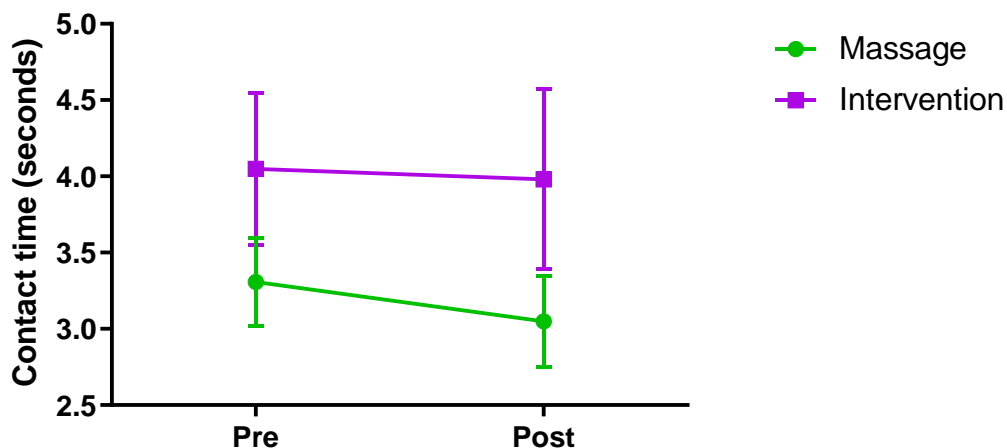
Figure 4. 19 *Forward lunge contact time change for intervention from pre (4.05sec ± 0.5) to post (3.98sec ± 0.59) and massage from pre (3.31sec ± 0.29) to post (3.05sec ± 0.3) in a 2-way repeated measures ANOVA data presented with SEM error bars.*

All three variables analysed for this test had Shapiro Wilk normality violations due to outliers within the data. However, outliers were not removed as they did not seem to be inaccurate and represent the level of variation within the population balance data. If the outliers were removed, normality was still violated, and these differences are still non-significant.

4.2.6 Visual Analogue Scale Results

A 2-way repeated measures ANOVA revealed a significant main effect for time ($F_{(1, 19)} = 5.817$, $p = 0.026$, $n^2_{partial} = 0.234$), no significant main effect for condition ($F_{(1, 19)} = 0.597$, $p = 0.449$) and no significant interaction ($F_{(1, 19)} = 0.318$, $p = 0.58$). Pairwise comparisons with a Bonferroni adjustment were then used to determine where specific differences were, revealing a significant difference in the intervention condition from pre to post with a large partial eta squared effect size ($p = 0.008$, $n^2_{partial} = 0.333$, fig. 4. 20). Both conditions revealed reductions for this self-reported measure. However, these results violated Shapiro Wilk's normality with several outliers due to a large variation in pain scores. Since there was no indication that these pain scores were a poor representation of the participant's level of pain, these were not removed.
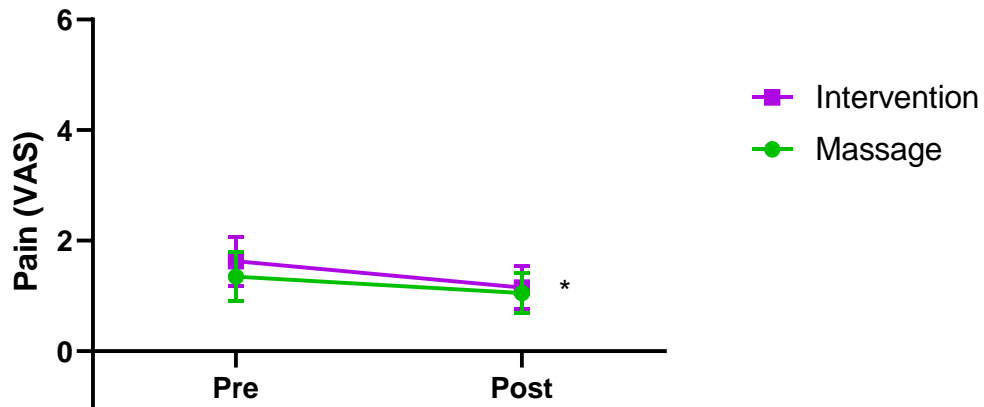
Figure 4. 20 *Self-perceived pain change for intervention from pre (1.63 ± 0.44) to post (1.15 ± 0.39) and massage from pre (1.35 ± 0.45) to post (1.05 ± 0.37) in a 2-way repeated measures data presented with SEM error bars.*

4.3 Discussion

4.3.1 Myometer Results

Muscle stiffness immediately increased following treatment for both conditions (fig. 4.7). This was an unexpected result due to stiffness reductions in previous studies within literature (Ferreira et al., 2009; Fritz et al., 2011; Shum et al., 2013; Stamos-Papastamos et al., 2011; Wong et al., 2015) as well as the results from study one within this project (chapter 3, fig. 3.2). However, all but one of these stiffness reductions listed in the literature above (Shum et al., 2013), are from interventions with more than 1 session. Less evidence exists for an immediate effect on stiffness with manual therapeutics on the lumbar spine. These findings could therefore be important in determining how many sessions are necessary to elicit a muscular stiffness response, since no immediate response was found for this outcome. Other studies within this area of muscle dosage response, investigate the optimal number of sets with results ranging from 4 to 12 (Haas et al., 2014; Pentelka et al., 2012; Xia et al., 2014).

Both conditions resulted in an increase of stiffness post treatment, which was also found post the control sessions in study one (chapter 3, fig. 3.2). This could be an important finding in terms of the formation of stiffness in muscles during inactivity. The increase post intervention (2.1%) was less than the massage increase in stiffness (3.9%) by almost half, therefore may be slightly more effective at minimising the rise

in stiffness that may occur while stationary (Ferreira et al., 2009; Janecki et al., 2011, chapter 3, fig. 3.2). However, due to no significant changes in these results, both treatments were found to have no effect on muscle stiffness and therefore ineffective as an immediate form of treatment for muscle stiffness within this MS group.

The proposed theory of mechanical stretching, creating a cascade of events that ultimately lead to a physiological reduction in pain and stiffness may not happen immediately. Since an immediate stiffness reduction was seen in the LBP pilot population, this could in fact be due to physiological differences between the two groups. Afferent neurons respond to a sensory stimulus and alter signalling to the CNS and the brain (Pickar & Bolton, 2012; Reed et al., 2013). The muscle spindle that controls the muscle's ability to change shape due to adaptive signalling from afferent neurons, may have a delayed response because of inflammatory damage. These muscles would therefore not respond to this immediate stimulus in the same way that someone from the general population would. Due to potential altering of this sensory response in MS patients, they are likely to require more than a single session for this stiffness reduction to be mechanically shown. This is supported by the high level of sensory symptoms in the study participants (table 4.2), likely a representation of CNS sensory disruption. The individualisation of inflammatory attacks on the CNS in MS patients may also result in a greater variability in response depending on CNS pathways affected and therefore require more numbers to show this response if it is occurring.

A significant association in change of stiffness relative to baseline stiffness has been previously found in literature (Ferreira et al., 2009) as well as the previous study result (chapter 3, fig. 3.3). A similar pattern in the correlation was found in this study results, however without significance (fig. 4.8, $r = -0.31$, $p = 0.05$). These results along with study one imply that baseline level of stiffness is an important factor. The higher someone presents with muscle stiffness, the more likely they are to respond to treatment, regardless of the type of treatment. This suggests that someone struggling with movement due to a build-up of muscle stiffness, is more likely to respond with stiffness reductions after manual treatment. The implication of reductions in muscle

stiffness can ultimately mean better movement and improve QoL, particularly due to its association with reductions in pain, implying that these are connected within muscle and movement pathways (Shum et al., 2013) and particularly with MS patients (Backus et al., 2016; Compston & Coles, 2008; McCullagh et al., 2008; Stevens et al., 2013).

The results for tone (fig. 4.9) had a very similar pattern to stiffness which was expected due to previous results (Bailey et al., 2013; Fröhlich-Zwahlen et al., 2014; Ortega-Cebrian et al., 2016; Schneider et al., 2014) and the results from study one (chapter three, section 3.2). This consistency in their pattern of response again shows how they are related in function and can show similarity in results despite their differences in function description (Bailey et al., 2013). Some studies record only stiffness and elasticity with myometry, due to the relatedness in results for stiffness and tone (Kelly et al., 2018; Rätsep & Asser, 2011). Though a level of tone is required for muscle and body stability, hypertonality is seen in neuromuscular conditions, and can contribute to some symptoms such as spasticity, pain and fatigue (Fröhlich-Zwahlen et al., 2014; Marusiak et al., 2012). A reduction in tone may help to ease some of these symptoms in MS patients, and improve the efficiency of movement. Similar to the stiffness results for this study, since there were no significant changes after either treatment, both were ineffective as an immediate form of treatment for muscle tone.

The results for elasticity (fig. 4.11) had a higher level of variability, similar to previous studies (Schneider et al., 2014). As previously discussed in the biomechanical description of muscle elasticity, it may require active movement rather than passive to make a consistent difference. There have also been reports of elasticity decrease while in relaxed state, and could be result of periodic tremors in patients with neuromuscular disorders (Rätsep & Asser, 2011). This again implies that active movement may be required for improvements in elasticity. This would mean that mechanical energy is released more efficiently also allowing for more efficiency in plastic change of the muscle shape. Again, due to non-significant changes, both treatments were ineffective for muscle elasticity.

Neither treatments therefore had a significant impact on the muscle quality measured by the myometer, which articulates an element of the MS condition and the variation they are likely to show in terms of their muscle response data. MS patients report a high degree of spasticity, pain, fatigue and sensorimotor symptoms, depending on the location of lesions within the CNS, which can be a large factor in how their muscles respond to manual therapy (Backus et al., 2016; Stevens et al., 2013). The difference in location of lesions may be a factor in the variation seen within the data, highlighted by the difference in study one results. Although there was a difference in sample size, this emphasizes the likely element of variability seen in the MS data, and is therefore likely to require multiple sessions to see any longer-term effect in the muscle data.

4.3.2 Force Plate and Body Sway Results

Analysis of body sway parameters help to characterise body stability and ability to keep control of muscle function. Body sway parameters represent body movement to recover body balance equilibrium. Objective measurements to represent these movements can aid the analysis of sensorimotor mechanisms that manage postural control. A reduction in body sway parameters has been reported to signify an improvement in stability and control of the movement performance (Karlsson & Frykberg, 2000; Mancini & Horak, 2010; Raymakers et al., 2005). Reductions in all body sway variables were displayed in this study, however most were not a significant level of change. Therefore, with more data or more consistent sessions continuing to have the same effect (like the myometer results), these results would possibly become significant.

Within the body sway path length data, total path length reduced three times more in the mobilisation intervention with a 9.1% decrease compared to the massage intervention with a 2.9% decrease (fig. 4.13). However, when split into the path directions, the massage intervention shows a larger significant decrease in the AP direction (fig. 4.14, 10.1% decrease) and the mobilisation intervention trial showed a larger decrease in the ML direction (fig. 4.15, 7.7% decrease), though not significant. This potentially implies that stabilising movements could originate from the AP plane more so than the ML plane. Kanekar et al. (2013) found improved proprioception

with MS patients in both AP and ML planes in their study. Due to a similar trend in the reductions for all path length variables in this study (fig. 4.13 - 4.15), proprioceptive improvements for both planes of movement may still be occurring and would therefore show improvements in both planes of motion. However, the previous results from Rome et al. (2009) suggest that improvements are more likely in the AP plane because of higher initial body sway movements in this direction and more falls in this direction. Improvement in this plane may therefore have an important implication on likelihood of falls.

Similarly, Raymakers et al. (2005) reported that ML sway showed more variation than AP in body sway measurements when comparing young and elderly patients. Karlsson and Frykberg, (2000) suggested two different strategies for maintaining posture in those two planes, with ML controlled by a load-unload strategy, and AP by an ankle stabilising strategy. These results suggest that the ankle stabilising strategy proposed by Karlsson and Frykberg (2000) may be responsible for improvements in AP directional body sway. Therefore, body sway may be more common and more variable in the ML direction, and easier to stabilise in the AP direction. Potential influences from the intervention could be multivariate. There could be better efficiency from muscles working to stabilise the body, these could be concentrated on ankle muscles according to the theory suggested by Karlsson and Frykberg (2000). These could also be improved from higher levels of concentration and a learned effect in performance (Büla et al., 2011; Mancini & Horak, 2010).

Balance tests can often show a conditioning effect, meaning that stability performance improves with practice, and therefore body sway measures would be improving due to practice rather than a stabilising effect from the intervention. This is an aspect of neural reorganisation, beneficial for motor learning in many conditions with mobility difficulties, such as stroke patients (Arya et al., 2011). A separate familiarisation session with the stability exercises, could have reduced this effect to an extent. The participant would have learned the stability movements required in the initial session and therefore this learned effect may not carry over into the testing sessions. However, improvements in neural organisation and muscles required for these balance activities, may still occur regardless. A familiarisation session was not

included in this study to reduce unnecessary travel for the participants and was therefore a practical consideration.

If reductions in stiffness and tone were seen, a degree of assumption could be made that this reduction contributes to improved stability, due to the complex nature of balance coordination, combining functional skills, and muscle quality contributing to posture and stability (Mancini & Horak, 2010). However, since this synergy of symptom improvements was not seen in the results, our data results cannot contribute to the association of reduced stiffness and improved stability.

Evidence exists on improved balance confidence after practice for better posture and less likelihood of falling (Büla et al., 2011). This may have been useful data in a self-reported confidence interview to see if this influenced their performance improvement. These balance data with improvements for a single stance movements can have positive implications for many aspects of daily living (Jonsson et al., 2004; Karlsson & Frykberg, 2000; Mancini & Horak, 2010). However, they cannot be attributed to reduced stiffness in this study, though both treatment conditions may have still influenced this.

The forward lunge body sway results did not show reductions, indicating improved stability. In fact, both conditions revealed an increase, with the intervention treatment showing less of an increase than the massage treatment (fig. 4.17). Better efficiency in this movement would lead to less body sway, and less impact force in the front leg, which also revealed an increase (fig. 4.18). Therefore, this movement did not show noticeable improvement through body sway reduction in this study, whereas the single stance balance movement did. To improve forward lunge as a movement is likely to require a combination of postural control, balance and stability and may therefore require more work to improve. This could be both through practice and a manual intervention (Alkjær et al., 2009).

The contact time for forward lunge decreased non-significantly for both treatments (fig. 4.19). However, the participants were not directed to try and perform the forward lunge in a quick time, therefore this decrease in time used appears to be self-motivated from the participants. This decrease in contact time could also be connected to the increase in impact force (fig. 4.18), due to the increase in force

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utilised for faster movement (Raymakers et al., 2005). Due to the body sway stability increasing and increased impact force in these sessions, the reduced contact time for the forward lunge could therefore also be an indicator of reduced stability due to the faster movement.

4.3.3 Visual Analogue Scale Results

To help get an overview of the experience from the patient, a self-reported measurement of pain was taken, specifically after and during spinal stretches as part of the session. This is regular practice within manual therapy research (Kamali & Shokri, 2012; Owens et al., 2007; Powers et al., 2008; Xia et al., 2014) as well as allowing the participant to respond themselves. Previous literature has also shown a large number of studies resulting in a hypoalgesic effect from manual therapy interventions (George et al., 2006; Pentelka et al., 2012; Thomson et al., 2009; Vicenzino et al., 2001; Willett et al., 2010; Yeo & Wright, 2011). Due to the association between stiffness and pain (Fritz et al., 2011; Wong et al., 2016) a reduction in stiffness would be expected to also show a reduction in pain. The VAS was used as it complied well with feasibility and ethical considerations, though it added an element of a subjective pain measure. Pain was unofficially, anecdotally reported through the researchers initial PhD interviews with patients that helped to gather the rationale for the project.

This measurement showed a significant difference in the mobilisation intervention treatment, with a reduction in self-reported pain (29.5%) and a large effect size. The massage intervention also revealed a similar reduction with 22.2% decrease however this was not significant (fig. 4.20). The intervention may have a larger effect on pain relief in comparison to other more general manual treatments. This could be to do with the specifics of the mobilisations and location and consistent movement resulting in pain relief. However, although the reduction in pain is statistically significant, the initial levels of pain in participants was already low and therefore this difference is still marginal. Kelly (2001) studied different groups in pain severity and their difference in levels of pain dependent on their initial pain. They found that to be clinically meaningful, this resulted in pain difference that was between 1-1.4 on

the VAS regardless of the initial levels of pain (Kelly, 2001). Therefore, the differences in the levels of pain in fig. 4.20 do not reach this degree of clinical significance.

This could also be one of the indicators that more than one session is necessary to show objective difference in results, but self-perceived pain can still be reduced after a single session. A reduction in perceived pain, even if based around a psychological effect can influence movement confidence, which has previously shown to improve balance and reduce falls in other populations such as the elderly (Büla et al., 2011) as well as MS (Cattaneo et al., 2006; Donzé, 2015; Negahban et al., 2018). Therefore, reduced perception of pain could possibly influence balance measures, but would be unable to influence the muscle response measures unless there is also a physiological effect occurring.

4.3.4 General Discussion

The lack of significance in the study results is likely to be due to the variability seen in the MS population and the complex nature of the condition. The difference in outcome measure results in relation to each other highlights the difficulty in defining the beneficial mechanisms of manual therapeutics. Finding a significant result in a subjective measure could be more common than objective measures such as self-reported pain, due to the benefits already associated with manual therapy. This therefore provides a possible confirmation bias in the participants, encouraging the results of a placebo effect. This highlights some of the importance of why the objective measures are necessary alongside the subjective. Since most participants in the study reported pyramidal and sensory based symptoms as their most common, improvements in pain and stability are likely to be of great benefit to their functional living. Therefore, investigating the degree to which these can be affected is valuable for this population.

Outliers were not removed from the results as it did not change any significance level for the measures and there was no indication of any of the data being a poor representation of that movement or response. Given the level of variability seen within the MS patient data in these results as well as other studies (Boes et al., 2012; Crenshaw et al., 2006), outlier data seems to be a crucial element for the full picture of how this population could be responding. The outlier data is likely to be a

quantitative representation of less consistent response, showing greater degrees of fluctuation when compared to the response of a healthy population.

The combined results for this study informed us that there was a significant improvement in participant's experience of pain because of the intervention. However, this is unlikely to be clinically significant and there is not enough evidence to discount a placebo effect. Therefore, further investigation, with repeated sessions and data to help determine the specifics of this, is the next step within the research.

4.3.4 Study Limitations

The design for this study controlled for gender as a factor that could contribute to a difference in responses between participants, and therefore the study only recruited females due to the higher prevalence of the condition. The result of this meant that there was a cofounding factor removed, but that recruitment was reduced. However, higher number of participants is likely to be more beneficial for insight into measure outcomes. Much higher number of participants is likely needed to show gender differences in response to manual therapy. Therefore, recruitment was limited with a female only study, as well as limited in time and resources for large scale recruitment. This then had bearing on decisions made for the next study, whether reducing recruitment to a single sex is best for the outcomes of the study with the limited time-periods of these studies.

The study was also based on pilot data from the LBP study in the previous chapter due to the lack of myometer data for the MS population. Although the sample size recommended for this study was 24, it is likely for an MS population to experience an immediate effect this would be much higher.

Although the intervention and the myometer tests had been piloted in the previous study, the balance tests had not, and five repeated successful trials of each exercise could become strenuous for some participants. Therefore, the combination of the single leg stance and forward lunge tests may not be suitable for all MS participants. The forward lunge did not show to be improving in the same way as the single stance test and could be replaced with a more meaningful stability test.

The use of two different therapist for the two treatments means that any differences found, could already be attributed to inter-therapist differences. The intervention was compared to a general massage manual therapy session to investigate potential benefits from the intervention specificities. This was based on previous study designs with similar type placebo trials. However, since this was still a form of therapy, the analysis could not provide a placebo type comparison. This meant that when attending both trials, participants were still receiving a type of therapy and could explore themselves if they found benefit in either one.

4.4 Study Conclusions

In conclusion, the main aim of this study was to investigate the effects of the intervention with an MS population. Results revealed no significant differences in any of the muscle quality measurements, with stiffness and tone even reporting increases for both conditions. Movement pattern results for balance and stability did show reductions, with a significant reduction in the AP direction, indicating that both treatments may influence balance that reduces body sway. However, without similar results in muscle response, this can still be attributed to a learned or placebo effect. The MS population is therefore likely not to show an immediate effect and need more sessions to show or have an effect for muscle quality response.

Due to lack of significant results between the two treatments, the specificities of the intervention and their potential benefits could not be determined. This leads to the next step in the project in collecting more data with a longer testing time, to see if there is a cumulative effect occurring. Repeated sessions could be more likely to be beneficial for the participants, creating a cumulative effect. Therefore, the next study will aim to analyse similar outcome measures, only testing people for more sessions, to analyse a longer-term effect.

Chapter Five

Study Three: Multiple sclerosis cumulative effect study.

Analysis of a spinal mobilisation intervention in people with multiple sclerosis – continued.

5.0 Introduction

The lack of significant results from study two demonstrate that the intervention did not have an immediate effect with an MS population, despite some reductions in body sway measures and pain measures. Results also revealed an abnormal distribution and large variance. Therefore, with inconclusive results for a single session, investigating a cumulative effect after repeated sessions may have greater value, based on results from some previous studies with MS and other conditions (Backus et al., 2016; Bronfort et al., 2004; Naraoka et al., 2017).

To make the most use of the remaining time for data collection on the PhD, this study was developed to test for a longer-term intervention, rather than the continuation of data collection for a single session response. This is also more likely to be beneficial for the participants taking part in the study, receiving multiple treatment sessions and potentially having a longer-term effect, since it is a long-term condition (Etoom et al., 2018b).

5.0.1 Multiple Sclerosis and Long-Term Interventions

There is evidence to suggest that long-term therapeutics can have cumulative effects that last longer than a short-term intervention (Backus et al., 2016). Short-term interventions are beneficial due to a lower cost and resources required to carry them out. Therefore, if a beneficial result is seen in a short-term intervention, this is resource efficient. Short-term interventions can be useful for short-term relief of symptoms, such as pain and muscle spasms shown in some previous studies (Goodsell et al., 2000; Pentelka et al., 2012; Powers et al., 2008; Shum et al., 2013).

However, since MS is a chronic condition, incorporating interventions that help to manage symptoms in the long-term is critical.

A physiotherapy intervention aims to restore function and well-being of the whole-body while concentrating on areas where function has been disrupted and focussing on mechanical properties of the musculoskeletal system (Etoom et al., 2018b; Pentelka et al., 2012). For MS patients this will be due to symptoms that arise from their condition, which can result in sensory and motor dysfunction such as pain, muscle weakness, spasticity, poor balance leading to secondary symptoms such as depression and fatigue. The management of these symptoms can then have knock-on effects including areas such as cardiovascular health, mental health, sleep quality, fatigue and functional independence, all affecting QoL (Kobelt et al., 2017). Given the previously discussed importance of symptom management for MS patients, a long-term intervention that can address these will benefit the patient in their routine management. Additionally, information on the specific areas of symptom improvement will be beneficial. Long-term follow up analysis will ultimately help to determine how the intervention is helping to sustain elements of their symptom management as a long-term lifestyle.

Objective results, and aspects around biomechanical methods for measurement help to give added information in terms of physiotherapy intervention efficacy. By monitoring different areas within functional independence and aspects of daily life, the areas that would benefit from physiotherapy can be distinguished. This can also contribute towards creating individualised rehabilitation based on specific needs and symptoms. Exercise has shown particularly to improve symptoms for MS patients when it comes to aerobic endurance, balance and stretching as treatment of MS related fatigue (Dimitrov & Turner, 2014; Garrett et al., 2013; Rietberg et al., 2005). Many studies state the importance of exercise, movement, and healthy living as long-term therapeutics for management of MS symptoms (Campbell et al., 2016; DeBolt & McCubbin, 2004; Garrett et al., 2013; Rietberg et al., 2005). However, long-term manual therapeutics for MS symptom management is less prevalent within current literature. This is a simple form of treatment, with little need for equipment and is adaptable to location. Therefore, specifying the benefits it may have for symptoms

with objective information will help to further not only MS therapeutics, but also physiotherapy research.

The individual nature of MS often requires re-evaluation of disease progression and therefore how it is symptomatically affecting the patient. In a systematic review by Khan et al. (2007), studies were reviewed which investigated multidisciplinary rehabilitation for the management of MS symptoms. The overall outcome from their review suggested that levels of impairment were unchanged, however experience of the condition and functionality of daily activities improved, including social participation and activities. This multidisciplinary technique was found to adapt well to the specific and individual needs of the patients, however required a lot of re-evaluation and assessment. They also found that studies of low intensity over a longer period had a greater impact on QoL than high intensity programmes over a short period. This was attributed to better self-efficacy and health promoting behaviours in a sustainable manner (Khan et al., 2007).

5.0.2 Quality of Life Measures

Side effects experienced due to reduced mobility can affect various elements of daily life. MS patients are known to have more difficulties with mobility leading to physical deconditioning, greater likelihood of fatigue, depression, and poor health. These can lead to long-term consequences in other areas of general health with potential risk of cardiovascular disease, obesity, osteoporosis, diabetes and hypertension (McCullagh et al., 2008). The goal of a physiotherapy-based intervention is to enhance movements, return them to functionality, with an end goal that relates to improved QoL. However, there are many aspects encompassed into QoL, as it is a multifaceted concept. Physically it involves movement, as well as psychological and emotional factors. These can be a secondary consequence of certain MS symptoms, and can be improved through aspects within an intervention such as pain reduction and positive emotional affects that improved movement capability can have. There are also social factors involved in QoL that encompass areas such as employment and social participation, which influence QoL (Kobelt et al., 2017; Yamout et al., 2013). It is therefore appropriate to measure an aspect of this to give a more complete view of the full effect of an intervention.

Forms of measuring QoL can be quite complex. Many scales and questionnaires exist, some of which have been listed in chapter two (section 2.3.3, table 2.1). These can span a wide range of areas that contribute to QoL, and some of these are specifically used for an MS population. Examples of these are; Multiple Sclerosis Quality of Life-54, EDSS, Multiple Sclerosis Impact Scale-29, Functional Assessment of Multiple Sclerosis (McCullagh et al., 2008; Patti et al., 2002; Porcari et al., 2019; Yamout et al., 2013). All these scales can be time consuming for patients and for medical staff interpreting these data. Since the main aspect of this project does not revolve around these concepts, but recognises the importance of QoL measurement, a more concise version is appropriate for this study. Pain and fatigue measurements are elements that influence a QoL score, and used in previous studies (Backus et al., 2016; Heine et al., 1996; Kamali & Shokri, 2012; Kobelt et al., 2017; Reid et al., 2014; van den Akker et al., 2016). These measures can therefore be incorporated into study outcomes, without it being the focus. QoL is a complex concept to measure, however literature and the results previously from studies one and two would indicate that this is an important concept to acknowledge and incorporate.

Rehabilitation programmes can consider many aspects of people's lives. This may consider care received from family and friends, socialising outside of home, ability to get outside and employment ability. It may also consider aspects in overall care for oneself such as the ability to dress themselves, to wash themselves, to cook and to feed themselves (Caminero & Bartolomé, 2011; Kesselring & Beer, 2005; van den Akker et al., 2016; Vucic et al., 2010). Knowledge of these aspects influencing QoL, can help with the management of symptoms within rehabilition and develop a full picture that individual measures would not be enough to decipher (Kobelt et al., 2017).

The reduction of pain and fatigue has a large implication on overall QoL (Yamout et al., 2013). Collecting measures for this is not only common practice within these studies, but allows the participant to feedback on this aspect of their experience (Kamali & Shokri, 2012; Owens et al., 2007; Powers et al., 2008; Xia et al., 2014). It can help identify the important aspects of the patient's experience for improvment, as well as allowing a reflective process for the participant to decipher themsleves

whether they feel better (Ontaneda et al., 2017; Patti et al., 2002). With some of the previous results revealing improvements in pain and stability, this could indirectly influence aspects that contribute to fatigue that can be measured in a long-term intervention. Many aspects can contribute to fatigue in both a physical and mental capacity and reduction in muscle pain, stiffness and improved movement efficiency are all aspects that may help to reduce this symptom (Backus et al., 2016). Since this is a variable that is highly linked to QoL and highly experienced by people with MS, results in this area will help to inform the overall effect of the intervention.

A mixed method design would allow both these elements to be investigated fully. This would allow both quantitative and qualitative measures based on interviews to be analysed and would help to cover all potential areas of effect. However, study design must encompass all aspects of feasibility, and qualitative based interview data were not possible for this study. Therefore, these aspects can be recognised and brought into the analysis using a quick and easy to use self-reported measure, for pain and fatigue, the two most likely aspects to affect parts of QoL (Yamout et al., 2013).

5.0.3 Studies One and Two Results

Aspects learned from the previous study were incorporated into this study design to aid the continuity of the studies.

The likelihood of difference between sexes in their response to treatment has been established in previous studies and supported in study one results. This could be due to differences in muscle composition, level of stiffness, hormonal differences and other physiological traits (Granata et al., 2002; Houtchens & Bove, 2018). However, large numbers of the same sex would be necessary to show this. Due to time constraints on the PhD project and findings in study two, it was deemed most appropriate to recruit both male and females to have larger number of participants.

Non-significant reductions in body sway for balance tests are worth investigating further, as these reductions may increase with the accumulation of treatment sessions. Without improvements in the forward lunge tests, it was important to make best use of the participants' time and therefore use a functional stability test that may provide more value to the thesis. For this reason, the sit-to-stand test was

incorporated into the study. This is a test that can apply to many aspects of daily movement, such as getting out of bed, standing up from a chair, and getting up off a toilet; all largely associated with movements and QoL (Agrawal et al., 2011; Reza et al., 2018; Vosoughi & Freedman, 2010). This is an important movement to maintain function in and could therefore have informative value to as an outcome measure. This test has been used in previous literature with chronically ill populations using force plate data (Bernardi et al., 2004; Bowser et al., 2015).

Pain measures are important to gather patient feedback on their experience, as well as information with regards to a possible hypoalgesic effect from manual therapeutics (Chiradejnant et al., 2003; Krouwel et al., 2010; Lopez-Lopez et al., 2015; Millan et al., 2012; Sterling et al., 2001). The VAS worked well in the previous study in terms of feasibility and resulted in a significant decrease after the mobilisation intervention, albeit small. This study will therefore continue to utilise these measures and investigate further if there is abnormal distribution of results. The previous study collected the VAS with lumbar movements as this was generated in previous similar studies or with functional movements on the area treated (Appendix 15, Chiradejnant et al., 2003; Goodsell et al., 2000; Pecos-Martín et al., 2017; Yeo & Wright, 2011). However, previous studies have also recorded VAS without lumbar movements (Freddolini et al., 2014; Kobelt et al., 2017; Naraoka et al., 2017). To use time efficiently in the testing sessions and to reduce the risk of excessive fatigue, resting lower back VAS was deemed most appropriate.

Fatigue measures have shown to be useful indictor and integral to overall QoL given its reported as one of the most commonly experienced symptoms and can affect so many elements of movement and activity (Heine et al., 2015; McCullagh et al., 2008; Vucic et al., 2010). The fatigue measure Modified Fatigue Impact Scale (MFIS) is well known for work within the MS population (Farinotti et al., 2007; Garrett et al., 2013; Kehoe et al., 2015). However, this scale uses a total of 21 questions and categorises them for analysis. This could again make sessions very long for participants. While being an interesting element to assess, is not the focus of the study. Therefore, to incorporate this element without tiring out participants, a shortened version will be

used with 5 questions, also validated in previous studies (Backus et al., 2016; D'Souza, 2016).

5.0.5 Study Aims

The aim of this study was to investigate the effectiveness of the intervention with an MS population in a repeated session approach with both earlier studies informing methods and design.

The intervention treatment was compared to the same massage treatment used in study two; however, participants were randomly allocated to either an intervention or a massage treatment group. Time constraints on the project meant that all participants could not receive both treatments for repeated sessions and compare them to each other. Therefore, treatment groups were assessed as independent groups, and allowed for a randomised controlled trial analysis. The study tested objectively for muscle quality and stability measures, as well as self-reported measures for pain and fatigue, to investigate a well-rounded picture of the effects.

The researcher hypothesised that there would be a reduction in muscle stiffness, tone, body sway, pain, and fatigue measures because of the intervention compared to the massage treatment. The null hypothesis stated that the intervention would have no different effect on these measures compared to the massage treatment.

5.1 Methods

5.1.1 Participants

20 participants were recruited for this study in a mixed factor study design (between-subject, repeated measures). The recommended number of participants for repeated measures, between factors ANOVA is 36 (18 participants in each group). This was shown from a G-power calculation with a large effect size (0.4), a power of 0.8 and a significance level of 0.05. The previous study used the effect size from the pilot study results (0.25) and did not show significant results apart from VAS measures ($p = 0.008$, $n^2_{partial} = 0.333$). It was recommended by the Research Integrity Ethics Committee to estimate a larger effect size than the previous study since this did not reveal significant results. Due to time constraints, participant availability and feasibility, recruitment and data collection was completed after 20 participants. While this is

unfortunate and has an impact on the validity of the results, it was out with the researcher's control to continue recruitment beyond that time point.

Participants who took part in study two could take part in study three as long as they met the inclusion and exclusion criteria. As this study has a different protocol with the aim of looking at effects over the 4-session period, previous participation was deemed to have no effect on their response in the new intervention. Inclusion and exclusion criteria remained the same as study two (chapter 4, section 4.1.1), except both males and females were included in recruitment. A total of seven participants who took part in study two also took part in study three. Given these participants had already experienced both treatments, they would know which type of treatment they were receiving for their four sessions. This could add to their learned effect in the balance tests and could alter their bias depending on their treatment preference in the pain and fatigue measures.

Participants responding positively to absolute contraindications were unable to take part. Participants responding positively to any relative contraindications were excluded based on severity and GP recommendation. They were asked to request permission from their GP for their opinion as to whether it was safe for them to take part. The therapist was made aware of all relative contraindications before any treatment and all treatments were gentle and low grade. Participants were asked to inform the therapist or researcher if they felt in pain or discomfort at any point during the treatment.

5.1.2 Procedure

Recruitment strategy was the same as study two (chapter 4, section 4.1.2). Contacts already made from study two were re-contacted to inform them of the study without coercion.

Once participants had shown interest in taking part, they were sent a link to the same Novi Survey used for study two (Appendix 11) to gather information about their MS condition and contraindications. Only the researcher had access to this information on the Novi Survey. All participant information was pseudonymised according to their participant number. If the participant was eligible, they were randomly allocated to group A or group B by a random group generator on Microsoft Excel^{TM}, to organise

suitable times for their sessions. Group A received the massage for four sessions and group B received the mobilisation intervention for four sessions.

Participants were required to attend on four separate occasions, receiving the same treatment for each session. Though previous studies have recommended more sessions from their results, the remaining time on the project did not allow for more than four sessions per participant, given time for recruitment, testing and analysis for the study. Four sessions would still allow analysis for a cumulative effect, however previous research would indicate that 8-12 sessions is more likely to show benefit from a manual therapeutic intervention. This was a single-blind trial, so participants were blind as to which treatment they were receiving. All testing took place at the Edinburgh Napier University Sighthill campus Engage building in a physiotherapy room which was maintained at standard room temperature (20-25°). The participants were asked to attend sessions at the same time on four consecutive weeks, to have a consistent gap between sessions. This was possible for the majority of participant sessions apart from a small number of sessions.

Upon arrival, participants had the opportunity to read through the information sheet again and the researcher ran through the protocol with each participant. Participants were invited to ask any questions about the study before consent forms were given and encouraged to ask throughout the sessions if they wanted. They were also informed they could withdraw from the study at any point and it would not affect their treatment. Their data could be removed up until the point of dissemination of summarised results. Once written consent was given, anthropometric measures were taken for age, weight, and height. Information was also taken regarding their most prominent symptoms and location of symptoms. Results from their Novi Survey were reviewed to go through their MS condition and EDSS.

The licensed massage therapist worked under their own liability and performed both treatments on all participants for this study. The therapist received training from the physiotherapist who worked on studies one and two to perform the spinal mobilisation intervention. This training was monitored with force plate measurements (Kistler Instruments Ltd., Force Plate Type 2875A, Hampshire, UK) until the desired force was repeatedly applied. These forces were monitored during

the intervention treatment sessions to retain the same treatment as much as possible, however differences between therapists will still occur therefore this creates a limitation in the comparison between studies two and three.

For the spinal mobilisation intervention, the therapist performed the same 30-minute spinal mobilisation intervention as the other two studies (rate = 0.37Hz, 22 beats per minute, force = less than grade 1, threshold of 80N, location = L1-L5, further detail in chapter 3, section 3.1.2). This allowed analysis on the cumulative impact of the mobilisation intervention on an MS population group for MS-based symptoms. This has not been tested on an MS population group before and can therefore be assessed for MS based symptoms on this populations group. The force for both the intervention and the massage treatment were controlled using force plate data collection, using the same method as study two (chapter 4, section 4.1.2). The massage therapy involved a 30-minute general massage, with no specificities or consistencies. Manual contact was applied on mid-lower back; rate and force magnitude of touch was not constant. This treatment acted as an alternative therapy, allowing comparison of the specificities of the intervention, and blinding of treatment.

During the first session, the participant carried out all myometer, balance, pain, and fatigue tests pre their first session for both massage and intervention sessions. The myometer, balance and pain tests were then tested post the first session. During the subsequent three sessions, the participants completed the myometer, balance and pain tests post treatment and the final fatigue test following their last session. Participants therefore completed five sets of tests for the myometer, balance and pain, to test the cumulative effect rather than a pre and post analysis of each treatment session. The fatigue test was only completed pre and post all treatment sessions due to the set-up of the questionnaire. Once all testing sessions were complete, participants were thanked for their contribution and given a debrief sheet with further information and contact details to give to their GP or carer as appropriate.

5.1.3 Outcome Measures

Participants self-reported pain using a visual analogue scale (VAS). This was the same scale used in study two (chapter four, section 4.1.3), only without the lumbar movements to use time more efficiently. The VAS uses a pain rating scale from 0-10, 0 represented no pain and 10 represented worst pain felt. Participants were given a visual scale to rate their resting lower back pain in each of the testing sessions (Appendix 15).

Participants completed a shortened version of the Modified Fatigue Impact Scale (MFIS) consisting of five questions on the impact of fatigue in their lives over the past 4 weeks. There was a total possible score of 20 (Appendix 22). This was completed at the start of the first session and at the end of the fourth session.

Myometer tests were completed using the same method as study one (chapter three, section 3.1.3) collecting measurements for stiffness, tone, and elasticity. The measurement collection was the same protocol as studies one and two, collecting values on both sides of erector spinae muscle and using the higher mean value to determine the stiffer side of the spine for treatment

The participants then performed two balance tests positioned on the force plates. Test one involved a single leg stance test, the same protocol used in study two (chapter four, section 4.1.3) collecting measurements for body sway total path length AP path length, ML path length and velocity. The second test used was a sit-to-stand test. This required a calibration of force plates to the participant's body weight and used the same protocol as the forward lunge test calibration described in chapter four (section 4.1.3). Participants were seated on a chair directly in front of the force plate, with their feet resting on the force plate. They were asked to move from a sit to stand position, using only their leg strength (fig. 5.1). This was repeated five times. The researcher was available to help at any time if participants felt uncomfortable or unstable during the tests or therapy session. Participants were encouraged to rest between the balance tests or at any time they felt tired.

The software used to collect the force data (Kistler, MARS) gave an automatic output for the variables used in analysis (fig. 5.2-5.3). These were CoP body sway velocity,

rising index (the percentage of body weight applied to the force plates during the standing movement) and weight transfer (the time taken to stand).

Figure 5. 1 *The sit-to-stand test with participant moving from a seated to a standing position on the force plate (image from Kistler MARS Software v2.1 Manual).*
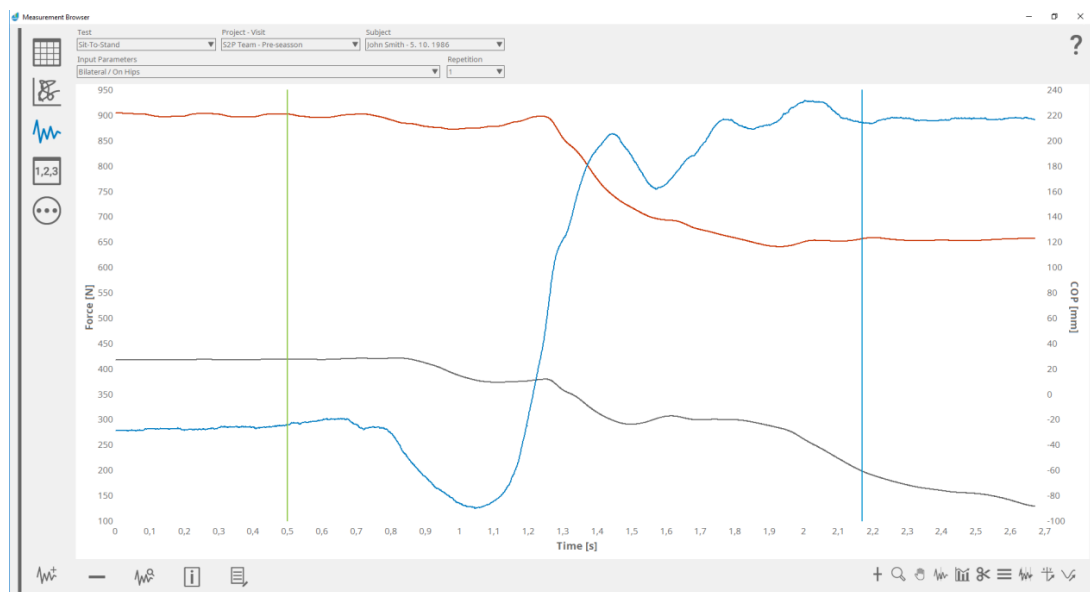
Figure 5. 2 *The force result measurement from which rising index and weight transfer were analysed from (image from Kistler MARS Software v2.1 Manual).*
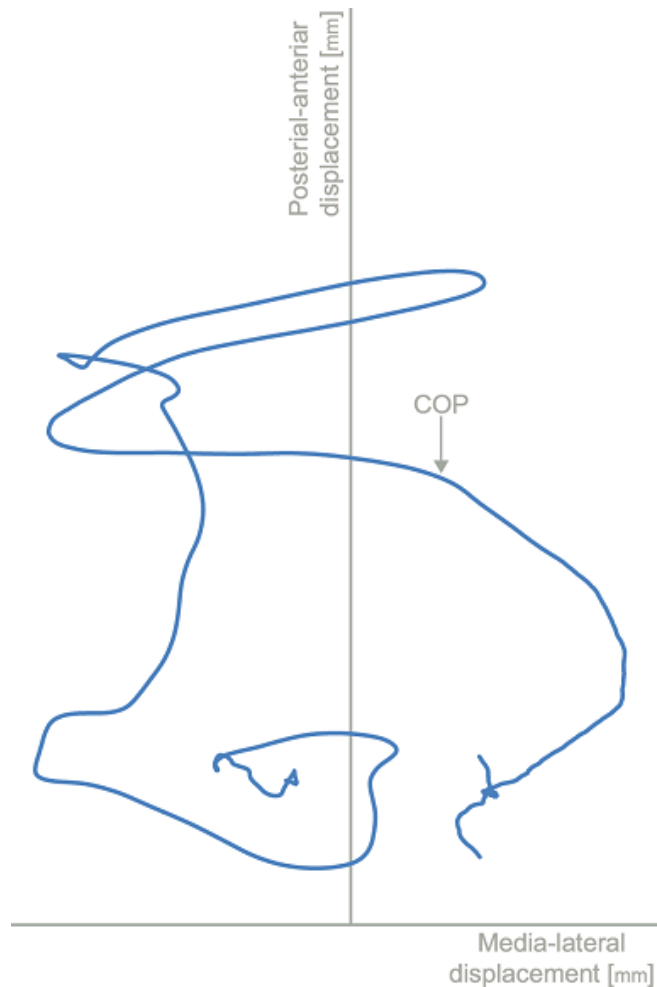
Figure 5. 3 *The CoP result from which CoP body sway velocity was analysed from (image from Kistler MARS Software v2.1 Manual).*

A total of five testing sessions were completed for each participant, pre and post session 1, and post sessions 2, 3 and 4.

5.1.4 Analysis

Data were collected and reduced in the same manner as study two (chapter 4, section 4.1.4). The sit-to-stand test results were collected using Kistler MARS Software (v2.1) and extracted onto Microsoft Excel spreadsheets. The mean value of the 5 trials for each variable in each testing session was calculated, resulting in 5 values for each variable (except fatigue) and each participant used for statistical analysis. The fatigue scores were a numerical value between 0-20 and only collected twice, pre and post all sessions, resulting in 2 values for each participant. Data collected from their Novi Survey and in their first session were collated and summarised into mean, range and dispersion values for their anthropometric and MS data. Analysis was carried out on

SPSS (version 23) using mean values with standard error dispersion values. All dependent variables for muscle response, single stance balance, sit-to-stand stability, pain, and fatigue scores were analysed each in a between-subjects repeated measures ANOVA. This was to determine differences between the two treatment groups and between the different time points. Pearson correlations were carried out on the myometer variables, comparing baseline measures to the level of change after the final session, since these have revealed significant correlations in the previous studies.

5.2 Results

Results in this chapter based on 20 participants with diagnosed MS.

Table 5. 1 Patient anthropometric data displayed with mean and SEM and range values. Data gathered in Novi survey and in their first session.

	Male Data Mean ± SEM (n = 8)	Female Data Mean ± SEM (n = 12)	All Data Mean ± SEM (n = 20)	All Data Range (n = 20)
Height (m)	1.8 ± 0	1.67 ± 0	1.72 ± 0	1.5 – 1.9
Mass (kg)	93.8 ± 11.4	71.8 ± 6.1	80.6 ± 6.2	56 – 158.5
BMI	29.3 ± 3.2	25.6 ± 1.8	27.1 ± 1.7	22.2 – 47.8
Age (years)	43 ± 1.9	41.5 ± 3.9	42.1 ± 2.4	24 - 71
EDSS	2.3 ± 0.2	2.3 ± 0.2	2.3 ± 0.2	1.5 - 4

Table 5. 2 Patient MS information with regards to their condition. Data gathered in Novi survey and in their first session.

MS Type	RRMS = 17
	PPMS = 2
	SPMS = 1
Most Symptomatic Functional System	Pyramidal = 8
	Sensory = 8
	Cerebral = 3
	Cerebellar = 1

Most Symptomatic Side	Right = 9
	Left = 5
	Both = 6
Dominant Side	Right = 17
	Left = 2
	Both = 1

All variables were assessed for normal distribution using the Shapiro-Wilk test, if abnormal distribution was found, group baseline data were tested for differences using a t-test for each group. This was only calculated on the baseline data to check if an abnormal distribution affected initial values between the two treatment groups since these were separate groups of people. If normality violations were found, these data were transposed into percentage change, relative to their baseline score, reducing the level of inter-participant variation and allow these data to be analysed on one scale. To transpose into percentage change values, the means for the variable in each testing session were still used. The mean values for each testing session were calculated relative to the baseline mean value for that variable.

5.2.1 Muscle Stiffness

Stiffness values were analysed as a percentage change, to normalise group variances. A between-subjects repeated measures ANOVA revealed no significant main effect for time ($F_{(1, 19)}$ = 1.132, p = 0.379), condition ($F_{(1, 19)}$ = 0.055, p = 0.817) or their interaction ($F_{(1, 19)}$ = 0.661, p = 0.628, (fig. 5.4). Correlations run between baseline stiffness and stiffness change after four sessions was non-significant for all data together, however the mobilisation intervention group correlation was significant (fig. 5.5, p=0.04, r = -0.65).
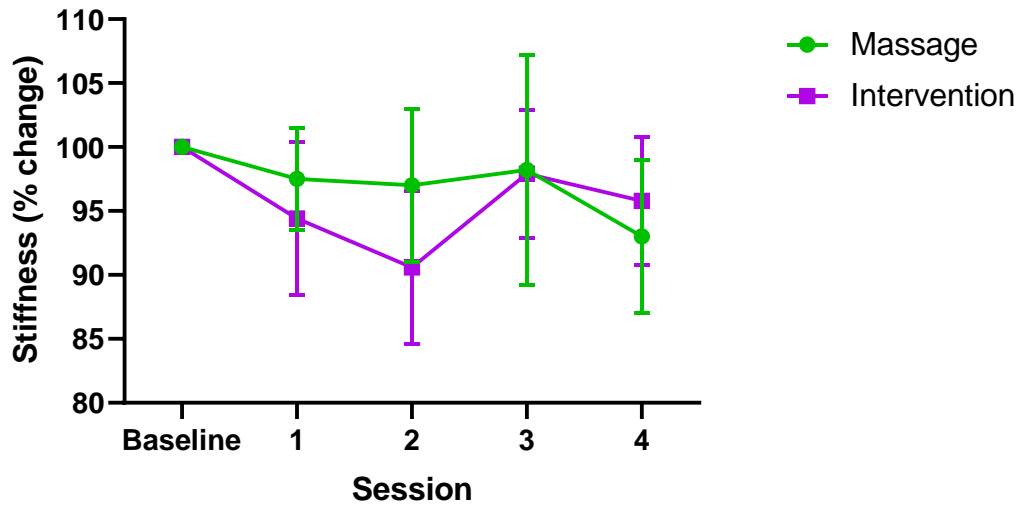
Figure 5. 4 Muscle stiffness change for intervention and massage treatments. Between-subjects repeated measures ANOVA data presented as percentage change with SEM error bars.
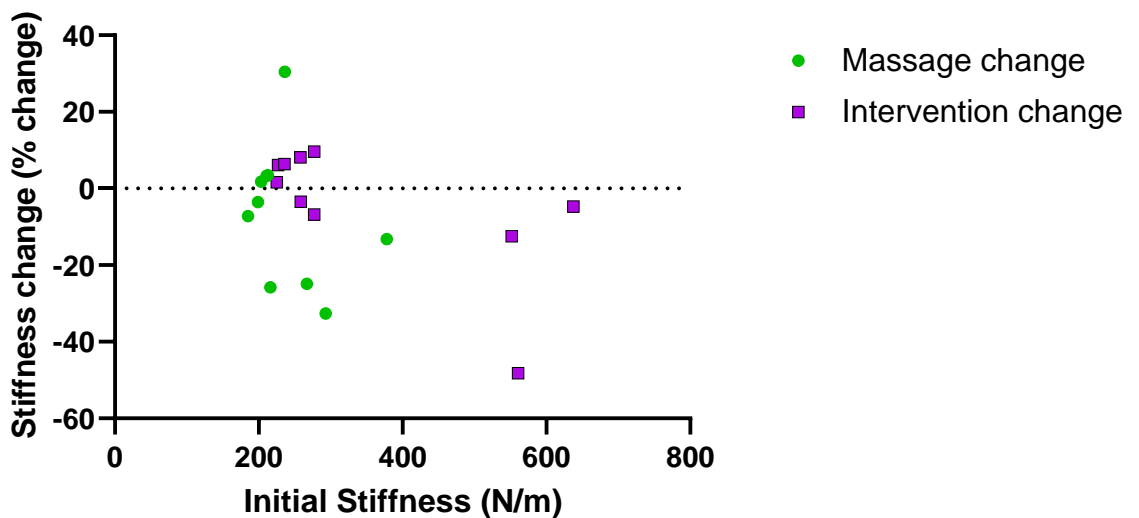
Figure 5. 5 Muscle stiffness significant bivariate correlation for mobilisation intervention between baseline stiffness and stiffness change after four sessions.

5.2.2 Muscle Tone

Tone values were also analysed as a percentage change, to normalise group variances. A between-subjects repeated measures ANOVA revealed no significant main effect for time ($F_{(1, 19)} = 2.345$, $p = 0.102$), condition ($F_{(1, 19)} = 0.001$, $p = 0.972$ or their interaction ($F_{(1, 19)} = 0.339$, $p = 0.847$, fig. 5.6). Correlations run between baseline tone and tone change after four sessions were non-significant for the two

treatment groups run separately, however when run with the data combined together this correlation is significant (fig. 5.7, p = 0.03, r = -0.48).

Figure 5. 6 *Muscle tone change for intervention and massage treatments. Between-subjects repeated measures ANOVA data presented as percentage change values with SEM error bars.*
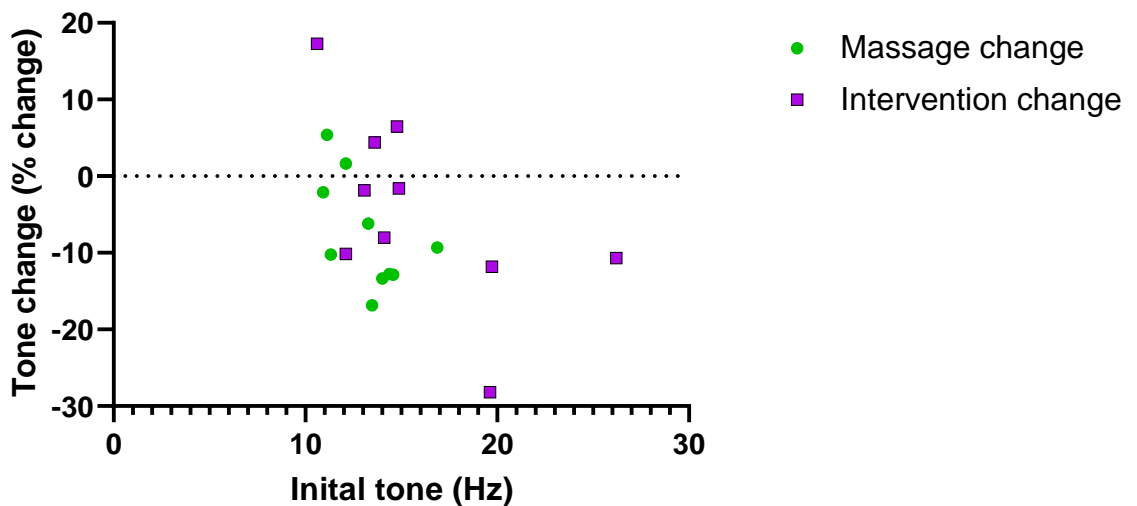
Figure 5. 7 *Muscle tone significant bivariate correlation between baseline tone and tone change after four sessions.*

5.2.3 Muscle Elasticity

No significant differences were found between the treatment groups for muscle elasticity and no normality violations, therefore the values given by the myometer (logarithmic decrement) were analysed. A between-subjects repeated measures

ANOVA revealed no significant main effect for time ($F_{(1, 19)} = 1.119$, $p = 0.384$), condition ($F_{(1, 19)} = 0.097$, $p = 0.759$) or their interaction ($F_{(1, 19)} = 0.846$, $p = 0.518$, fig. 5.8). All correlations run between baseline elasticity and elasticity change after four sessions were non-significant (fig. 5.9).
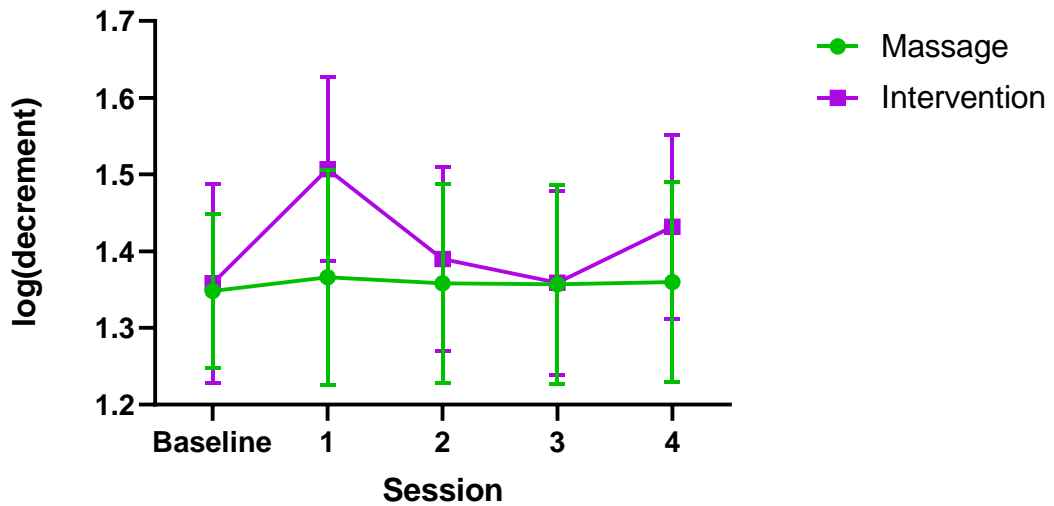
Figure 5. 8 Muscle elasticity change for intervention and massage treatments. Between-subjects repeated measures ANOVA data presented for log(decrement) values with SEM error bars.
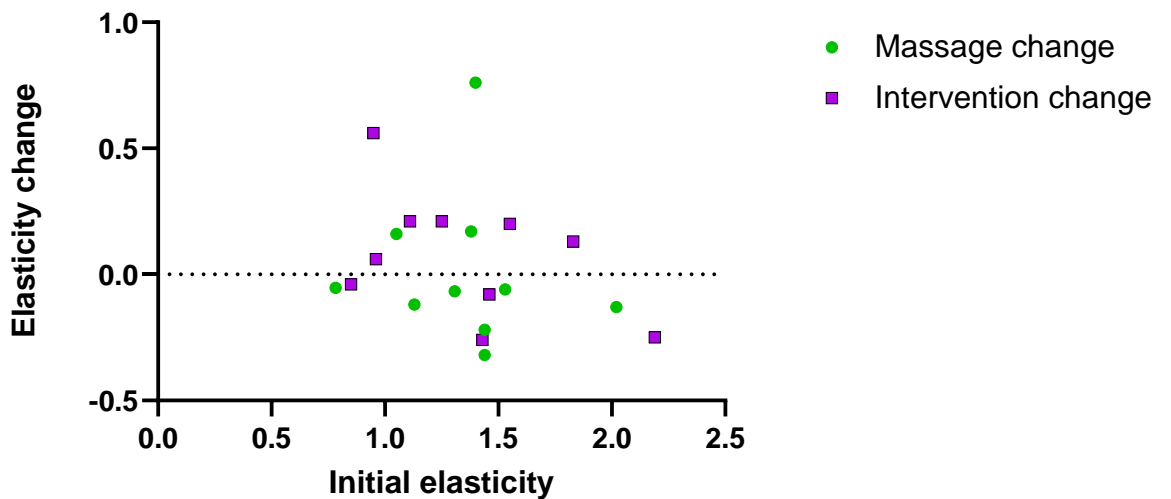
Figure 5. 9 Muscle elasticity non-significant bivariate correlation between baseline elasticity and elasticity change after four sessions.

5.2.4 Single Stance Results

A significant main effect for time was revealed for body sway total path length ($F_{(1, 19)} = 5.481$, $p = 0.006$, $n^2_{partial} = 0.594$), no significant main effect for condition ($F_{(1, }$

19) = 2.378, p = 0.14) and no significant interaction (F(1, 19) = 0.576, p = 0.685). Pairwise comparisons were then used with a Bonferroni adjustment to determine where specific differences lie, revealing significant reductions between time points for both intervention mobilisation and massage treatments with large effect sizes (massage: p = 0.002, $n^2_{partial}$ = 0.677, intervention: p = 0.034, $n^2_{partial}$ = 0.408, fig. 5.10). There were no significant differences revealed between treatment groups. Significance differences (p < 0.05) in the figures are denoted (*). Effect sizes are reported as partial eta squared values (0.01 = small, 0.09 = medium, 0.25 = large).

A significant main effect for time was revealed for body sway AP path length (F(1, 19) =4.265, p = 0.017, $n^2_{partial}$ = 0.532, fig. 5.11), no significant main effect for condition (F(1, 19) = 2.776, p = 0.113) and no significant interaction (F(1, 19) = 0.655, p = 0.633). However, pairwise comparisons with a Bonferroni adjustment revealed no differences between time points for either treatments. There were no significant differences between treatment groups.

A significant main effect for time was revealed for body sway ML path length (F(1, 19) =6.7, p = 0.003, $n^2_{partial}$ = 0.641, fig. 5.12), no significant main effect for condition (F(1, 19) = 1.053, p = 0.318) and no significant interaction (F(1, 19) = 0.461, p = 0.763). Pairwise comparisons with a Bonferroni adjustment revealed a significant difference in the intervention mobilisation treatment between time points with a large effect size (p = 0.016, $n^2_{partial}$ = 0.535) and no significant difference for the massage. There were no significant differences revealed between treatment groups.

The same analysis for body sway velocity changes revealed a significant main effect for time (F(1,19) = 5.531, p = 0.006, $n^2_{partial}$ = 0.596, fig. 5.13, no significant main effect for condition (F(1, 19) = 2.557, p = 0.127) and no significant interactions (F(1, 19) = 0.604, p = 0.665). Pairwise comparisons with a Bonferroni adjustment revealed a significant difference in the massage treatment between time points with a large effect size (p = 0.047, $n^2_{partial}$ = 0.453) and no significant difference in the intervention treatment. There were no significant differences revealed between treatment groups.
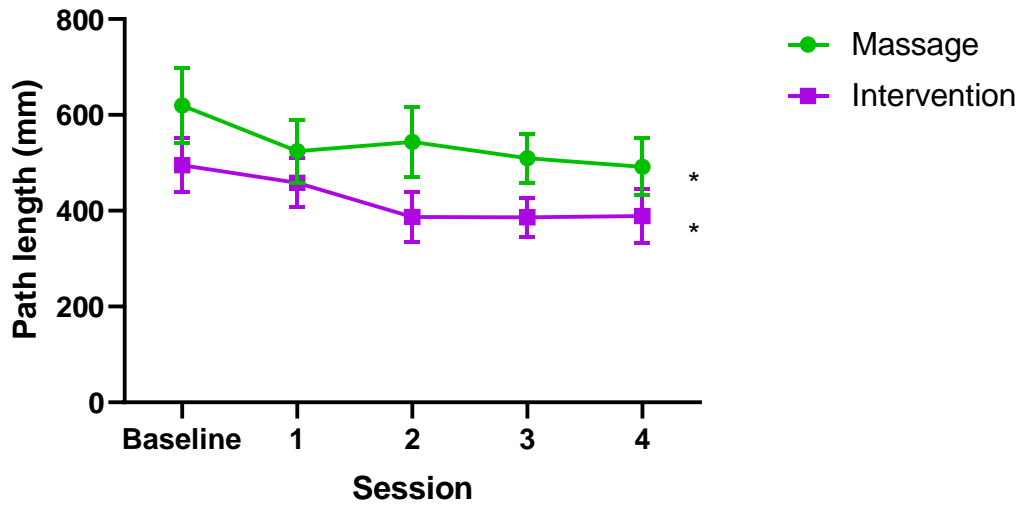
Figure 5. 10 *Body sway total path length change for mobilisation and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*
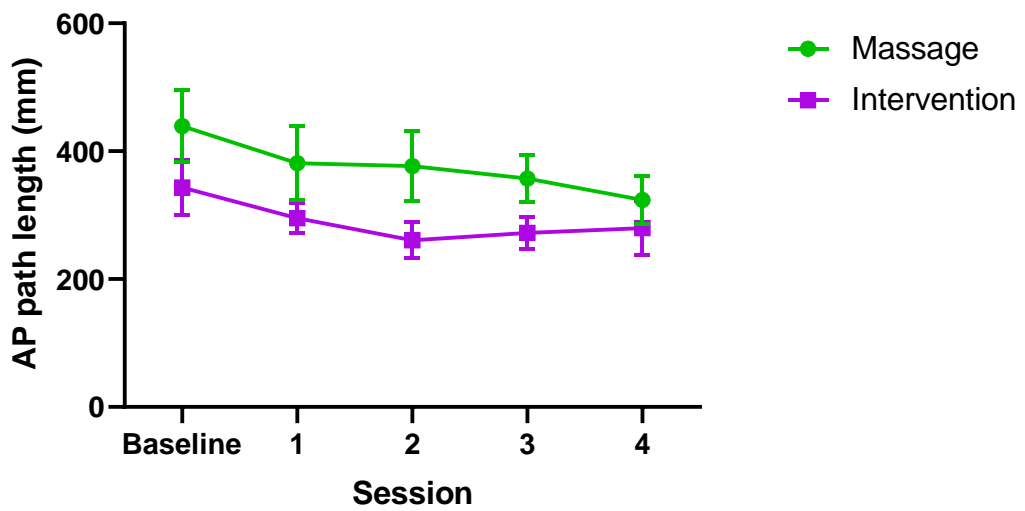
Figure 5. 11 *Body sway AP path length change for mobilisation and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*
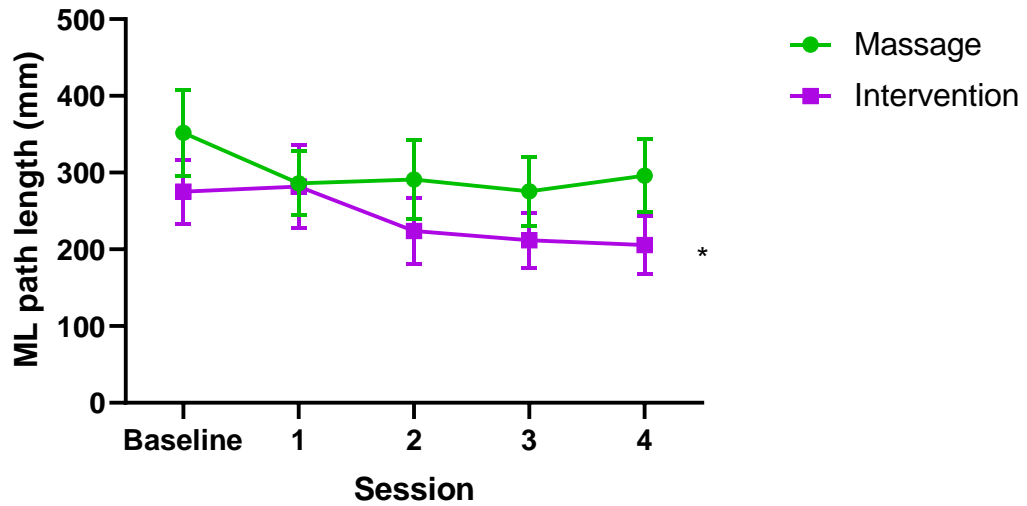
Figure 5. 12 *Body sway ML path length change for mobilisation and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*
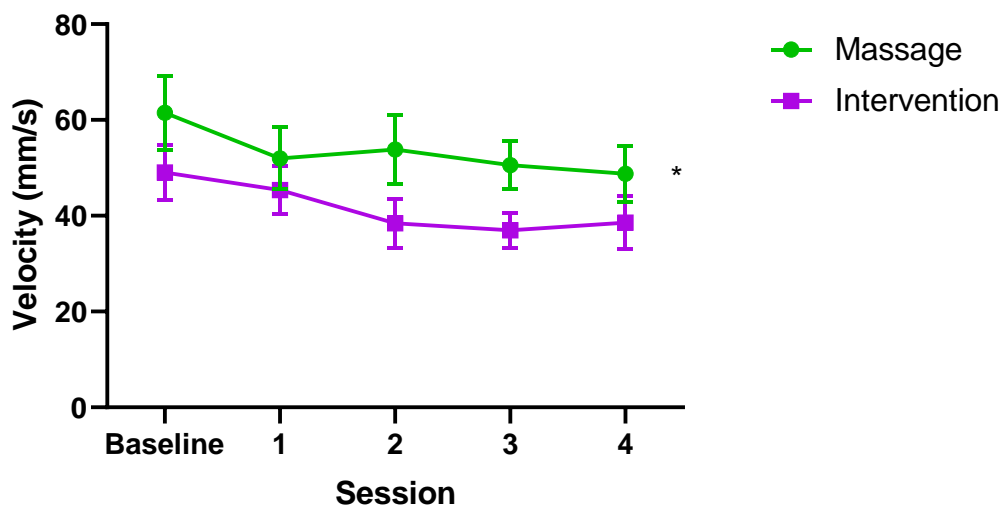
Figure 5. 13 *Body sway velocity changes for mobilisation and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*

5.2.5 Sit-to-Stand Results

The CoP body sway velocity was analysed as a percentage change to normalise group variances. A between-subjects repeated measures ANOVA revealed no significant main effect for time ($F_{(1, 19)} = 2.63$, $p = 0.12$), condition ($F_{(1, 19)} = 1.961$, $p = 0.178$) or their interaction ($F_{(1, 19)} = 0.634$, $p = 0.646$, fig. 5.14). There were no significant differences between treatment groups. A between-subjects repeated measures ANOVA for rising index revealed no significant main effect for time ($F_{(1, 19)} = 1.71$, p

= 0.2), condition (F(1, 19) = 0.323, p = 0.577) or their interaction (F(1, 19) = 0.04, p = 0.997, fig. 5.15).

The weight transfer variable was also analysed as a percentage change to normalise group variances. A between-subjects repeated measures ANOVA revealed a significant main effect for time (F(1, 19) = 9.829, $p < 0.001$, $n^2_{partial}$ = 0.724, fig. 5.16), no significant main effect for condition (F(1, 19) = 1.63, p = 0.218) and no significant interaction (F(1, 19) = 2.232, p = 0.104). Pairwise comparisons with a Bonferroni adjustment revealed both treatment groups to have significant differences between time points with large effect sizes (massage: p = 0.017, $n^2_{partial}$ = 0.532, intervention: p = 0.001, $n^2_{partial}$ = 0.678). No significant different between treatment groups were revealed.
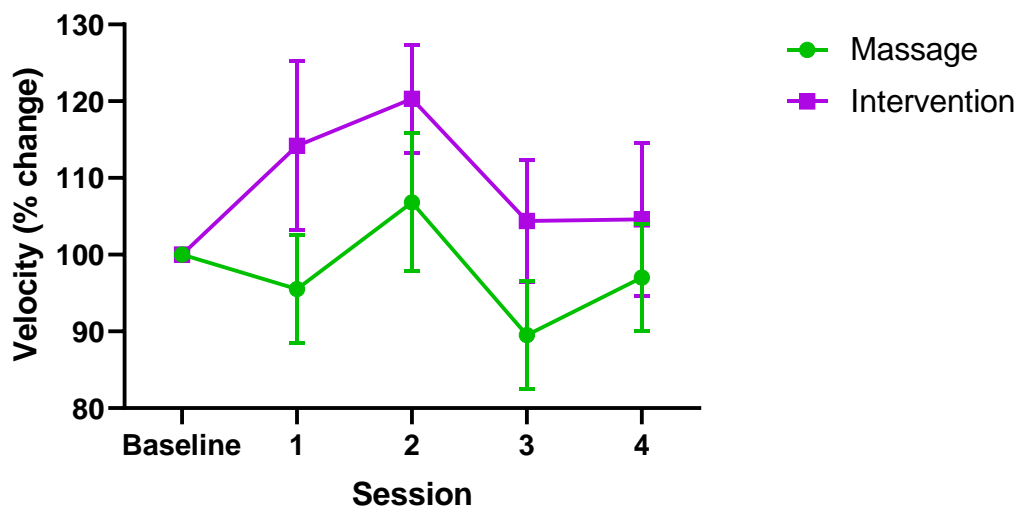
Figure 5. 14 *Body sway velocity changes for intervention and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*
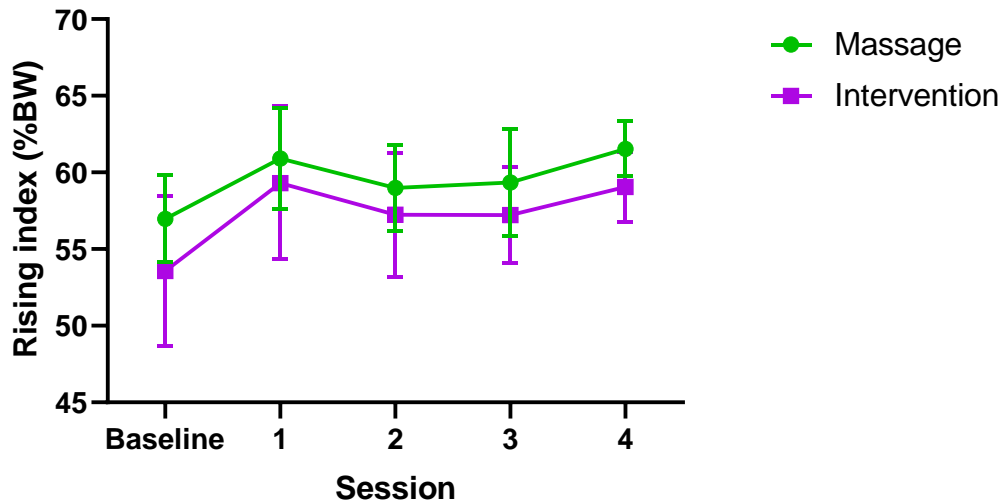
Figure 5. 15 *Rising index changes for intervention and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*
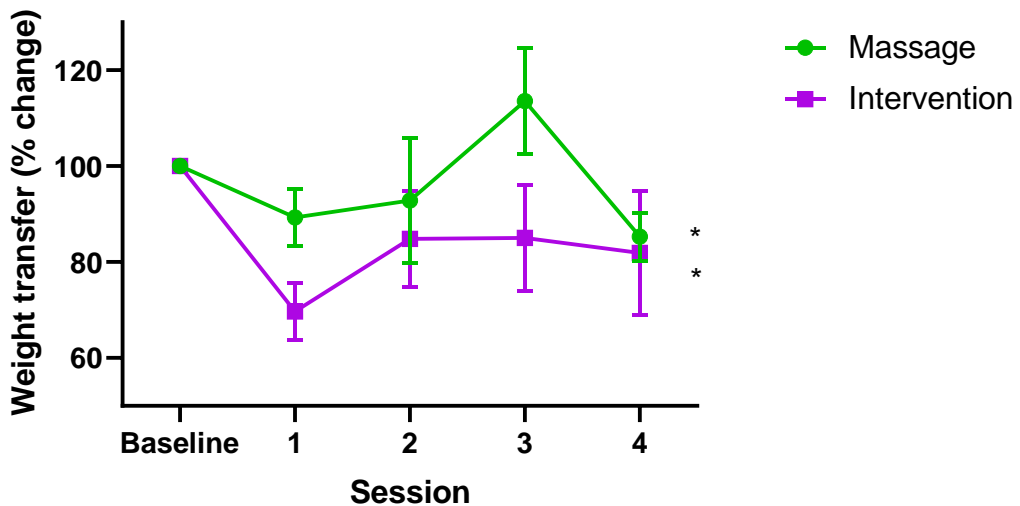
Figure 5. 16 *Weight transfer changes for intervention and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*

5.2.6 Visual Analogue Scale Results

VAS score resulted in normality violations with the Shapiro-Wilk test, however data could not be transposed to relative percentage changes as some participants scored 0 on their baseline levels. Therefore, the absolute values for these data have been presented. A between-subjects repeated measures ANOVA revealed no significant main effect for time ($F_{(1, 19)} = 0.655$, $p = 0.632$), condition ($F_{(1, 19)} = 0.193$, $p = 0.665$) or their interaction ($F_{(1, 19)} = 0.506$, $p = 0.732$, fig. 5.17).
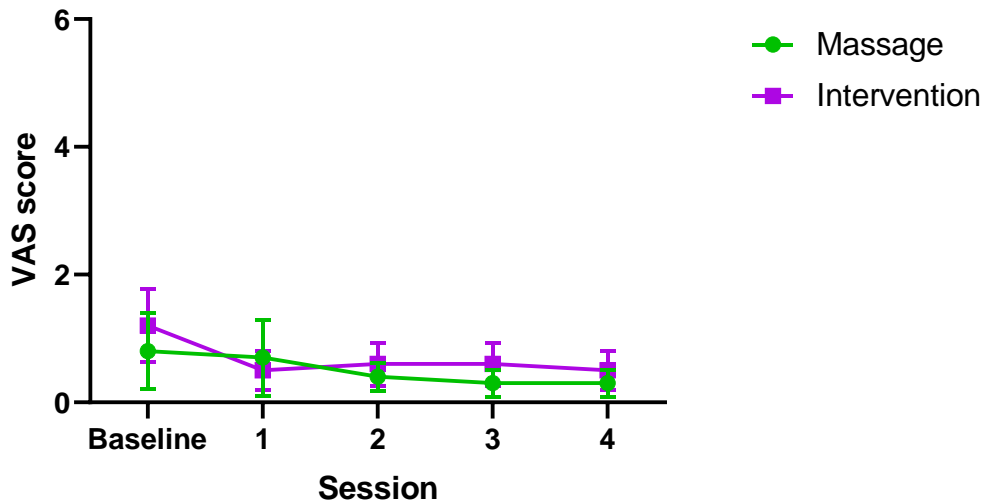
Figure 5. 17 *VAS change for intervention and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*

5.2.7 Fatigue Results

A between-subjects repeated measures ANOVA revealed a significant main effect for time ($F_{(1, 19)} = 7.416$, $p = 0.023$, $n^2_{partial} = 0.452$), no significant main effect for condition ($F_{(1, 19)} = 0.032$, $p = 0.862$) and no significant interaction ($F_{(1, 19)} = 1.691$, $p = 0.226$). Pairwise comparisons were then used with a Bonferroni adjustment to determine where specific differences lie, revealing a significant reduction for the intervention mobilisation treatment between time points with a large effect size ($p = 0.041$, $n^2_{partial} = 0.386$). A non-significant reduction was revealed for the massage treatment and no significant differences between the treatment groups (fig. 5. 18).
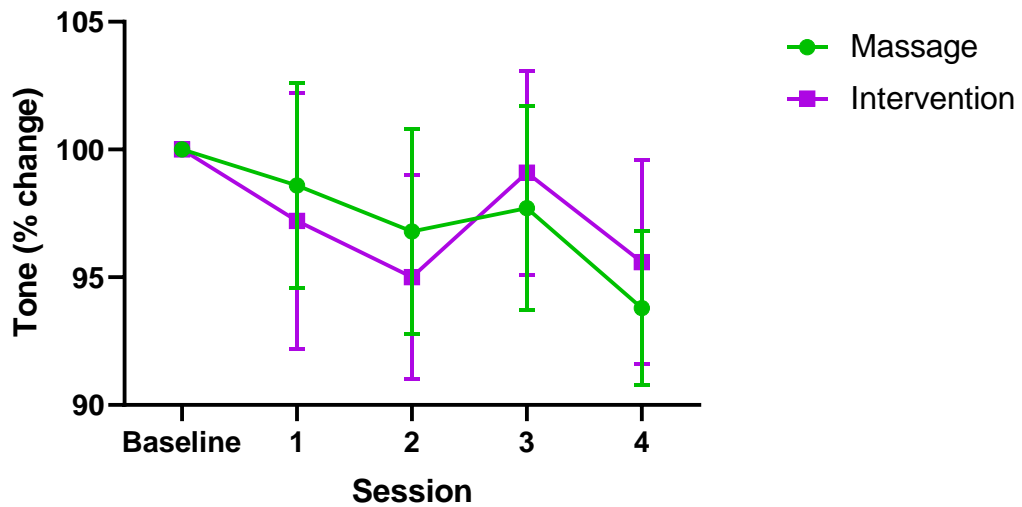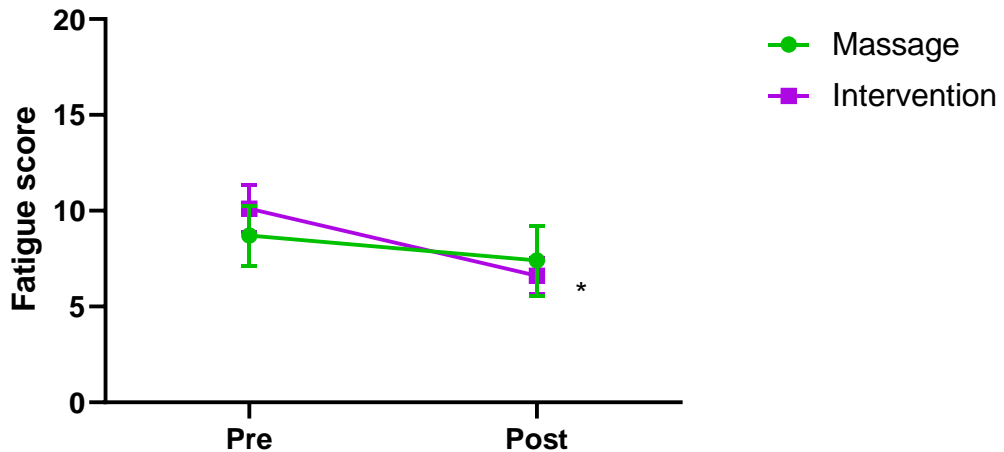
Figure 5. 18 *Fatigue score change for intervention and massage treatments. Between-subjects repeated measures ANOVA data presented with SEM error bars.*

5.3 Discussion

### 5.3.1 Myometer Results

High levels of stiffness in MS patients can reduce QoL due to the resulting effects of limited mobility. These can consequently lead to greater levels of fatigue, pain, anxiety, posture deficits, higher risk of falls and muscle spasticity (Freddolini et al., 2014; Little et al., 2014; Shum et al., 2013; Xia et al., 2014). Therefore, reductions in the level of para-spinal stiffness has potential to improve QoL, improve body awareness and efficiency of muscle and joint movement. If symptom management programmes were able to achieve a stiffness reduction effectively and consistently through therapeutics, there would likely be important positive associations for the QoL of people with MS (Etoom et al., 2018a; Stevens et al., 2013).

The results for muscle stiffness for both treatments in this study revealed a decrease over time within the four sessions (four weeks with a weekly session, fig. 5.4). However, these reductions were non-significant for both groups, and equivalent to approximately a 5% reduction. Statistical analysis did not reveal a cumulative effect of four sessions on stiffness and indeed these results reveal stiffness does not follow a linear increase or decrease, but rather fluctuations between sessions. The fluctuations seen for both treatment groups occur after the third session, and the

same result is mirrored in the results for tone (fig. 5.6). Though these could be random fluctuations appearing by chance, this could also be representative of part of a pattern that would emerge if treatment and testing continued for longer. For both tone and stiffness measures, a linear decreasing trend is displayed until the third session when an increased spike occurs and then decreases again after. This may give an indication as to the cumulative effect on these measures. There may be two or three treatment sessions that cause a decrease in stiffness and tone, and then occasional sessions where there is a spiked increase, and then start to decrease again with further sessions. This could be investigated further with a longer study for both stiffness and tone values in an MS population.

It is not possible to determine whether the stiffness levels measured at each session were maintained for the week between sessions however, there does appear to be a trend towards a decrease in stiffness over time in both treatment groups. With further opportunity to intervene and larger participant numbers, it is possible that a stiffness reduction pattern would have emerged. No significant differences were revealed between the two treatment groups. Therefore, if more sessions revealed a significant reduction, it would be important to determine whether the mobilisation intervention distinctively improves stiffness more than another form of manual touch, or whether this occurs with any form of manual therapy.

Manual therapy studies testing stiffness have revealed significant stiffness reductions with varying lengths of times and number of sessions. Lack of consistency within manual therapy methodology means that specific results associated with stiffness benefits are difficult to determine. A large population of people with MS suffer from spasticity as a main disabling symptom of their condition and has a severe and direct effect on QoL. The movement disorder caused by nerve disruption and characterised by sporadic increases in stiffness and tone, results in exaggerated and uncontrolled muscle spasms. This can be painful, can cause large disruptions to movement control, can directly relate to onset of fatigue, and often related to high levels of stiffness also. The treatments for reducing stiffness are often shared with treatments for reduced spasticity due to their interlinked consequences.

Negahban et al. (2013) reported significant spasticity improvements after 15 massage sessions over 3 months. Giovanelli et al. (2007) found significant spasticity improvements with MS patients after 15 manual therapy and stretch sessions in 15 days, however, with a vague description of the therapeutic protocol (Gafson et al., 2012; Negahban et al., 2018). These studies both measured spasticity using the Modified Ashworth Scale rather than an objective analysis, allowing more room for human error, and possible inter-rater discrepancies depending on training of the individual recording results from the scale. This can make comparisons between studies more difficult due to discrepancies in inter-rater reliability (Blackburn et al., 2002; Craven & Morris, 2010; Mutlu et al., 2008).

A range of results exist in the literature to determine the optimal number of sessions required to induce a significant stiffness reduction. Previous results from spinal manual therapy on stiffness reduction have shown significant stiffness reductions in as many as 12 and as little as 1 session. However, differences in assessment methods again create limitations in these comparisons (Ferreira et al., 2009; Fritz et al., 2011; Shum et al., 2013). The lack of significant results from this study and the lack of previous results in MS spinal therapy on stiffness to compare these results to would signify that 4 sessions was not enough to elicit a significant stiffness response if there is one. If the specifics of the required manual intervention dose and treatment type are defined, this can be harnessed to its most effective use to the people who require it most.

As already discussed, the results for tone (fig. 5.6) in this study mirror the results for stiffness (similar for study one, fig. 3.5 and study two, fig. 4.9), showing their similarities in functionality. The similarities of stiffness and tone mean that they often have a similar pattern of response, as seen previously also (Fröhlich-Zwahlen et al., 2014; Schneider et al., 2014). Hypertonality is associated with musculoskeletal disorders (Parkinson's, Stroke, MS) and its reduction has many similar implications to a reduction in stiffness. The reductions seen in figure 5.6 are likely to represent a possible pattern in reduction if treated for more than four sessions, like muscle stiffness.

In a study investigating the effect of an exercise therapy with progressive MS patients, reduced levels of tone were found to be associated with improved endurance and improved QoL score (Giesser et al., 2007). The participants in our investigation were mainly relapse-remitting and likely to be in a less severe stage of the disease, and therefore less likely to show these differences. The participants in this study also had average low EDSS scores with males and females in the study both showing an average of 2.25, and the highest EDSS only reaching 4, displaying minimal levels of disability (table 5.2). This is supported by the correlations found in all three studies, between baseline tone and stiffness and subsequent levels of change (fig 5.5 & 5.7). Progressive patients appear to be more likely to have higher levels of tone and stiffness and therefore more likely to show a reduction in these. However, investigations with progressive patients are limited due to the symptom difficulties experienced at this stage and the participant's ability to take part (Campbell et al., 2016). Therefore, developments in testing measures for the more disabled group within the MS population is both lacking and likely to have beneficial outcomes.

Muscle elasticity, based on the inverse of the log(decrement) presented, did not show any significant differences between time points for either treatment group (fig. 5.8). Similar to previous studies (Rätsep & Asser, 2011; Schneider et al., 2014), the values result in a different pattern of response compared to stiffness and tone. A decrease in the muscle decrement (the loss of mechanical energy) equates to an increase in elasticity, the pliability of the muscle (Rätsep & Asser, 2011). Since neither treatment resulted in a decrease of decrement, neither treatment showed to be beneficial for elasticity.

Limited literature exists on elasticity change in people with MS and could therefore warrant further investigation with larger numbers to try and decipher how this characteristic may respond during mobilisations. The lack of significant results for elasticity in all three studies in this investigation could imply this is a more variable measure to calculate, and a less consistent way of responding within the muscle. Other studies however have found associations between elasticity and stiffness and may therefore have a more vigorous testing method that warrants further investigation (Gavronski et al., 2007). Gavronski et al. (2007) found that as stiffness

increased, elasticity also increased, contrary to belief that elasticity should increase with stiffness decrease. This is however based on concepts stated in previous studies and not the findings of this study. Therefore, the nature of elasticity, its modifications, and the application of this in muscle control and movement requires further investigation.

Veldi et al. (2004) also found a decrease in muscle elasticity in Parkinson's patients who struggle with sleeping. This could be associated with subconscious tremors during sleep, affecting the muscle's ability to relax (Veldi et al., 2004). Therefore, these findings may indicate that an increase in elasticity could arise from subconscious activity or tremors in the muscle, and an increased level of variability in this recorded measure, which may be more apparent in an MS population compared to a general population.

5.3.2 Force Plate Results

Total path length body sway resulted in significant reductions with a large effect size after the four sessions, (fig. 5.10), a different result from the previous study, which showed a non-significant reduction after a single session (chapter four, fig 4.13). Body sway velocity had a similar pattern but with a significant reduction in the massage treatment (fig. 5.13). These reductions also have less fluctuation, and therefore may be more likely to continue decreasing. Where study two results revealed that a single session was not enough to significantly reduce total path body sway, four sessions does appear to have this significant effect. Body sway velocity can give added information than the path length depending on the stabilising strategy used by the participant. Postural control is based on a person's ability to return the body close to the equilibrium point when exposed to a perturbation (Karlsson & Frykberg, 2000). An increase in path length may then represent an increase in stabilising movements, where previously they may have stepped out to avoid falling and not necessarily represent a decrease in performance. However, a decrease in body sway velocity, would indicate an increased level of control in these stabilising movements (Ramdharry et al., 2006). Path length and velocity appear to have maintained the same pattern of reduction for both treatment groups with no significant differences

between them. Therefore, a reduction in path length was likely to have coincided with a reduction in velocity.

The results for directional path length, however, reveal differing significance for the treatment groups. Previous results from study two displayed AP direction significant improvements where ML direction did not (chapter four, section 4.2.4), and therefore relating to ankle stabilisation strategies that help to improve body sway in this direction (Karlsson & Frykberg, 2000). Study three results reveal improvements in both AP and ML directions with specific improvement in the ML direction for the intervention group (fig. 5.11, 5.12). The difference between these results is unlikely to be a central component, as similar reduction patterns are displayed and both treatments displayed significant reduction in total path length with no significant differences arising between treatment groups. These results therefore suggest that improvements in single leg balance can be because of stabilisation in either plane. This coincides with findings from Kanekar et al. (2013) who found improvements in both planes of motion in MS patients because of an increased proprioceptive stimulus. The previous findings from Rome et al. (2009) suggested that greater initial levels of AP sway led to greater levels of improvement, also coinciding with the findings from Karlsson and Frykberg (2000) suggesting this is due to an ankle stabilising strategy. This is an element of body sway balance that could be further investigated, with important implication on the lives of MS patients due to reduced risk of falls.

Neural re-organisation to enable motor learning is particularly important for people with MS due to the demyelination effects of their condition (Sumowski et al., 2018). Depending on what pathways within the CNS are affected by this may depend how well they are able to adjust to improve movements and balance. Certain individuals may require more practice and muscle relief compared to others affected in different pathways (Arya et al., 2011). However, a release of stiffness and tension in the muscles, particularly para-spinal muscles important for postural control, can improve the muscle quality and efficiency. Balance coordination is a complex combination of muscle quality as well as functional skill, therefore allowing both of these to improve will be the most efficient way of improving balance, and allowing this to then

incorporate into every-day activities and overall mobility (Stevens et al., 2013). Although significant balance improvements were found after both treatment groups, the lack of significance in muscle response data signify this improvement cannot be attributed to improved muscle efficiency.

As discussed in the previous chapter, these reductions may be attributed to a learned effect from having better practice over the different sessions. Similarly, the lack of significant reduction in stiffness and tone from this study means that the balance improvements cannot be explained by mechanical influence on muscles enabling better muscle efficiency. There is thus reason to suggest that practicing single leg balance, has a better outcome for improving balance than because of manual therapy, whether specific mobilisations or general massage.

Self-reported confidence interviews may have added a useful element in the results to decipher if the improvements in body sway could be attributed to improved confidence. This would suggest a learned effect and the creation of a positive environment for participants to feel they had space to practice and improve balance movements. However, this would have added an extra element to the testing sessions and could be subjected to bias from the participants and the researcher. Previous studies have however reported improved balance due to confidence (Büla et al., 2011; Mancini & Horak, 2010) and if it allows the participants to improve elements of the balance and take it into their every-day routine, their QoL should improve.

The sit-to-stand test was chosen rather than the forward lunge test due to its use in previous studies with informative results. It also encompasses a crucial part of daily movement that is critical for functional independence (Agrawal et al., 2011; Bernardi et al., 2004; Bowser et al., 2015; Fröhlich-Zwahlen et al., 2014; Reza et al., 2018). For people with MS particularly, weakness in the lower limbs may occur due to leg weakness because of pain, stiffness and disuse and can then result in a greater trunk flexion during this sit-to-stand movement. This was shown by Bowser et al. (2015) in their results with MS patients displaying significantly different aspects of the sit-to-stand movement compared to a general population. These aspects included decreased leg strength, greater trunk flexion, faster trunk flexion velocity, decreased

knee extensor power and slower rising time. Therefore, many elements can lead to a less efficient technique for rising to standing up position. These are said to be mainly derived from decreased leg extensor strength, which can be a common symptom for people with MS (Bernardi et al., 2004; Lambert et al., 2001; Van der heijden et al., 2009). This has then led to the trunk-flexion theory, which states that if leg weakness is shown, people take longer to stand up and use a greater trunk flexion to compensate for decreased leg strength requiring more energy.

This study did not examine kinematic measures and therefore cannot consider trunk flexion in its analysis. Although a reduction in body sway velocity would represent a more efficient movement, as this requires less energy to stand up (Bernardi et al., 2004). The results for both treatments in this study reveal no significant differences and no consistent pattern (fig. 5.14). They also showed a high level of variability and have been presented as a relative percentage change value to compensate for this.

Similarly, results for rising index has fluctuations and even displaying a gradual increase in both treatments over the four sessions (fig. 5.15). This measure describes the percentage of force used to stand up in relation to body weight. Therefore, an increase in this measure would signify a greater level of energy required. Faster movement will cause the percentage of body weight used in movement to increase (Agrawal et al., 2011; Bowser et al., 2015; Cheng et al., 1998), also demonstrated in the forward lunge results in study two (chapter four, section 4.2.5). In accordance with this, the results for weight transfer (representing the time taken to rise to standing) significantly decreased in both treatment groups (fig. 5.16). The cumulative increase in rising index and decrease in weight transfer both correspond with a faster movement from sitting to standing, but not a more controlled movement. Therefore, the stabilisation method of this movement could be investigated further whether by a learned or training effect or muscular therapeutic.

In a similar manner to single leg balance, improvement in stability for a sit-to-stand movement requires both elements of neuromuscular activity as well as concentration and proprioception. More perturbations are likely to occur in a single leg balance activity than a movement activity and may have more room for these to improve as seen with these body sway reductions (fig. 5.10-5.13). Muscular abnormalities

previously found in MS patients consisted of both early and late recruitment in leg muscles and suggested to be caused by impaired reflex system due to delayed transmission in certain pathways (Benedetti et al., 1999). This can be improved through neural re-organisation, however likely to be different for an MS population compared to a healthy population depending on demyelinated pathways in the CNS (Arya et al., 2011; Sumowski et al., 2018).

The sit-to-stand movement has been previously found to improve with improvement in leg extensor strength with MS participants (Bernardi et al., 2004; Bowser et al., 2015). Therefore, the neuromuscular recruitment of these leg extensor muscles may also influence the muscle's contraction ability. Given the leg strength deficits found in the MS population as well as other neurological disorders, this appears to be an important element to be aware of in relation to movement stability (Büla et al., 2011; Cruickshank et al., 2015). A leg strengthening protocol is likely to be beneficial for improvement in this measure. Again, interview data on self-reported improvement for this test may have been interesting to see if people reported any self-perceived improvements, or if this movement improved in their daily lifestyle and activities.

5.3.3 Visual Analogue Scale Results

Figure 5.17 displaying the pain results based on VAS indicates the low levels of pain reported by participants from baseline. Therefore, any reductions seen here are likely to be non-significant which was indeed the case. These results again revealed the same for both treatment groups and no distinction between the two treatments can be made based on these. A larger sample of participants with more variations in baseline pain may be a better representation of potential decreases in pain occurring during manual therapy.

Previous studies have indicated a relationship between stiffness and pain values and their levels of change (Shum et al., 2013). However, the lack of any findings regarding pain difference in this study means this association cannot be analysed. There was a greater likelihood of volunteers for the study from people who suffer less from pain. This was attempted to be managed in the methods with providing transport for participants and allowing a flexible as possible testing schedule. However, these

elements were still likely to influence the range of baseline pain scores and EDSS scores.

The study was designed around the concept of mobility and how to measure improvements in this. Pain is seen to interact to a high degree with mobility and factors into many symptoms experienced by MS patients and so was an important aspect to evaluate. Since the values collected for pain were insufficient for analysis, this association was not investigated, however future work could examine this further. Given the number of studies that report a hypoalgesic effect after manual therapy, investigations regarding pain pathway mechanisms and how they might be altered would be valuable for this research area (Millan et al., 2012; Moutzouri et al., 2012; Pecos-Martín et al., 2017; Perry & Green, 2008; Shum et al., 2013; Sterling et al., 2001).

5.3.4 Fatigue Results

Fatigue score was a new measurement assessed for this study to add a variable affecting QoL into the analysis. A short 5-question version of the MFIS was used asking participants to rate their fatigue from 1-4 in five different areas over the past four weeks. They were given this at the start of the first session and at the end of the last session and the highest possible score was 20. The limitations of the questionnaire are based around the possibility that the participants may remember their previous score form the start when completing at the end. They were however encouraged to complete the questions based on the effect of fatigue in the past four weeks rather than fatigue they felt before they started the study.

Results for these scores indicate a significant reduction in fatigue for the mobilisation intervention, and a non-significant reduction for the massage, though no significant differences between the groups were revealed and no significant interaction (5.18). Reduced fatigue has many implications for someone with MS given fatigue is one of the most commonly reported symptoms and one of the most debilitating (Backus et al., 2016; Yamout et al., 2013). It is also very difficult to explain and determine specific causes for. Therefore, an effective treatment to reduce these effects would be highly beneficial for MS research, since MS sufferers are known to deal with the effects of fatigue on a regular basis (McCullagh et al., 2008). These results support previous

findings with associations in stability and fatigue improvements due to the significant results in body sway and fatigue (Crenshaw et al., 2006). This is an area for potential research development in terms of how these measures may be associated with each other and the potential direct or indirect influence of mobilisation therapy.

The intervention group appears to have benefited more than the massage group for this measure. Therefore, an element of the specifics and consistent nature of the intervention, could have a greater effect than other manual therapies for this measure, like the VAS results reported in study two (chapter four, section 4.3.3). The specificities of the intervention compared to a generalised massage, may also have a placebo type effect where patients feel like are improving, because of the medicinal nature of this treatment. However, the results of a placebo effect cannot be negated due to the lack of placebo in the trial. The lack of a placebo comparator means that the reduction in self-reported fatigue could result due to the feeling of a beneficial experience, rather than as a direct result of the treatment. Further investigation in this area could do more in-depth analysis to focus on fatigue reductions and if certain types of manual therapeutics have a greater effect on this.

5.3.5 General Discussion

The only measure to display a significant improvement after the intervention compared to the massage was self-reported fatigue. Study two in a similar manner, revealed self-reported pain significantly reduced compared to the massage also. The objective measures (myometer and force plate tests) had more variability and fluctuations compared to the subjective measures, potentially due to less scope for variation in the scales used. This supports the rationale of using a full analysis, revealing objective and subjective measures as a true indication of effects taking place and would further support a mixed method design in future studies. The potential placebo effect occurring may still help to improve elements within QoL measures that are linked with chronic conditions by improving self-confidence and subsequently increasing levels of movement and participation in activity. Objective evidence for the specific benefits of the intervention is lacking in the results, however the significant improvements in stability and fatigue findings seem to suggest that both treatments are beneficial in some capacity. Given most participants reported

their most symptomatic category to be pyramidal and sensory, both relating to muscle recruitment, weakness and sensation, improvements in these areas of stability and fatigue is likely to benefit their functional daily activities.

The high variability found in the data resulted in abnormal distributions and could be an important aspect of how people with MS respond to manual therapeutics and therefore a larger sample size is required for a full representation of the data. The inadequate sample size and abnormal distribution of the data means that the results are less reliable and is therefore a limitation in the investigation. The full effects of this intervention would be beneficial to analyse with a higher number of participants. This effect is likely to require more treatment sessions, similar to previous studies who recommend benefits are seen after 12-15 sessions (Ferreira et al., 2009; Giovannelli et al., 2007; Negahban et al., 2013; Shum et al., 2013).

Other specific self-reported measures may have been an interesting added element to test whether perceived stiffness change was different to actual stiffness change, or whether balance confidence was different to actual balance differences in the objective data. This could be an element to incorporate into future study.

5.3.6 Study Limitations

The study did not recruit the full number of participants necessary from the sample size calculation. Given the level of variability that already exists in the population, a large sample size may be necessary for a normal data distribution and more reliable statistical results. Due to time restrictions on the study, the testing could not test for longer than 4 sessions per participant, however a longer-term study with further treatment sessions may show a more cumulative effect.

The lack of placebo in the trial means that the intervention is being compared to a different form of therapy and cannot negate a placebo effect taking place. Therefore, results may occur by chance. 7 participants from the previous study also participated in this study, and despite being blind to the treatment group they were in, would be aware of what treatment they were receiving based on their experience of the previous study.

The therapist performing the treatment was not the same as the previous studies in this investigation due to practicality reasons. Despite training for the intervention treatment, differences in inter-therapist techniques could have provided some differences making the comparison of study two and study three results challenging.

The participants recruited for the study had low levels of disability and low levels of pain and were therefore less likely to show a response in these measures. With an altered recruitment strategy, with better targeting for people with MS of a range of abilities, the more disabled category may be better represented in the study demographics. The study also could not recruit participants with an EDSS above 6 due to the balance tests required and therefore does not represent the more disabled population and the full range of disabilities with the MS population.

Improvements in the stability measures may occur due to practice and increased confidence in the exercises as oppose to either treatment having a direct effect on these. Questionnaires around improved confidence may have useful information for this aspect of the analysis.

5.4 Study Conclusions

In conclusion, the results from this study show both treatments to have a significant improvement on stability measures and fatigue, and non-significant reductions on muscle stiffness and tone. With lack of distinctions between the treatment group effects, there is likely to be a benefit from either type of manual therapeutic, without specific benefit from the mobilisation technique.

Though the study expected to find more trends within the data, there is potential for these measures to show more significant findings if continued to be collected for a longer period. Future studies with use of mixed methods to gain a full insight through interview data also would be beneficial to the development of this research.

Chapter Six

General Discussion and Conclusions

Analysis of the combined study results.

6.0 Introduction

The overall aim of this thesis was to report scientific findings on the investigation of a spinal mobilisation intervention already used in practice with MS patients with beneficial anecdotal reports. The lack of mobilisation intervention in MS literature provided a context for the investigation in MS rehabilitation and symptom management. As a unique form of mobilisations applied at a consistent low force, this was also an investigation to measure the forces, rate and timing that define the intervention and test it's efficacy with scientific methods.

The results from the pilot and two MS studies displayed some different findings in measures investigated around muscle response, stability, pain, and fatigue. These can be compared to each other to conclude results of the intervention for an immediate and cumulative response, with awareness of limitations. The differences between the studies created some limitations and their comparisons and were therefore less reliable. The key variable however in each study was muscle stiffness, as this was a variable repeatedly referred to in previous reports and has large associations with many aspects of daily life and functional independence.

6.1 Myometer Measures
6.1.1 Stiffness Changes and Correlations

The stiffness results from these studies have an interesting and beneficial value both to MS and general physiotherapy research. The significant correlations between baseline and level of stiffness change found in all three studies are clear indications of how muscles respond to both inactivity and manual therapy based on resistance to change (muscle stiffness). Since people with higher levels of baseline stiffness are more likely to show a change in stiffness, they are also more likely to build-up stiffness during inactivity. This was deciphered in the pilot study and these trends continued in both MS studies. Given the population recruited for both studies had

lower levels of disability with an average EDSS of 2.78 between them, this could be an important indicator in their level of activity since sedentary time could be an important factor in terms of their muscle composition and levels of stiffness. Activity and lifestyle questionnaires may have helped with this and could be implemented in future studies. This could help to determine if a certain level of sedentary lifestyle is damaging for muscle in terms of promoting high levels of stiffness, and in determining their level of response to manual therapy.

Since the myometer variables were the only ones tested in all 3 studies, these are the only variables that can be compared across all studies. Despite a hypothesis for a stiffness reduction in all three studies, the pilot study was the only one revealing a significant result. The lack of significance seen in this variable within the MS population is likely connected to the variability seen within the MS stiffness data and a larger range of values when compared to the pilot population. The study three results however show a 4% overall reduction in the massage group and 7% overall reduction in the intervention group, which is a similar level to the immediate reduction seen in the pilot study group. This would imply that people with MS are likely to require more than one session to see a reduction in stiffness, and more than four sessions to see a significant reduction. The similarity however in baseline stiffness and level of stiffness change between the studies, supports the notion that the mechanistic action between LBP and MS groups may be the same, however with greater variability levels in MS due to complications related to the condition.

The variability in MS results may also indicate a wider range of individual response to manual treatments, where some participants respond positively, and others do not. The proposed changes to muscle spindle activity due to signalling adaptations may be a delayed response in MS patients who suffer from CNS lesions affecting this (Pickar & Bolton, 2012; Reed et al., 2013), which could be contributing to the data variability. This could also be connected to levels of spasticity within MS patients as this can occur due to signal disruption within the CNS and result in abnormally high levels of stiffness and tone within muscle. Muscle recovery may also be hindered due to cell signal disruption.

The association between pain and stiffness has been investigated previously where significant correlations in change of stiffness and change in pain occur because of mobilisation therapy. Lower levels of spinal activity and higher levels of spinal stiffness have been shown in people suffering from back pain (Shum et al., 2013). The oscillatory force produced during mobilisation therapy as previously discussed may stimulate mechanoreceptors, altering the signalling events for both pain and stiffness. The mechanical mechanisms that alter pain as seen in previous hypoalgesic results (Chaitow, 2015; George et al., 2006; Lascurain-Aguirrebena et al., 2016b; Pentelka et al., 2012; Schmid et al., 2008) may also target the signalling events that monitor and alter the cell spindle activity, and subsequently the muscle stiffness. These characteristics can then also go on to perpetuate each other in the long-term due to the build-up of stiffness with inactivity (Ferreira et al., 2009; Fritz et al., 2011; Shum et al., 2013). A pain and stiffness correlation were not supported in these results and could again be due to variability within the data. There were low levels of pain reported in most participants. Therefore, with more baseline variation in this variable and higher initial levels of pain, a greater difference in pain may have been revealed and this may be correlated with differences in stiffness.

While significant differences between the intervention and a control arose in the pilot study, when compared to a general massage treatment, muscle stiffness displays similar trends in both treatment groups. Thus, the intervention was effective at reducing stiffness when compared to inactivity but did not appear to be different to another form of manual therapy. This implies that the mobilisation intervention could have the same or similar effect on muscle stiffness as any other type of manual therapy in the same area. Further studies could develop the investigation of different forces, rate, and timing of therapeutics, in terms of the effect they have on muscular response, either immediately or cumulatively. This has a large implication for MS symptom management as well as management of similar type conditions. An efficient and effective therapeutic for muscle stiffness should aid levels of daily activity and functional independence.

The MyotonPRO proved to be a reliable, easy to use, non-invasive form of objectively measuring muscle stiffness as shown previously (Bailey et al., 2013; Bizzini &

Mannion, 2003; Pruyn et al., 2015; Viir et al., 2006; Zinder & Padua, 2011) and could be used further to investigate other trends within stiffness data.

6.1.2 Tone and Elasticity

Both tone and elasticity were not commented on anecdotally, however investigated previously with stiffness in myometer studies (Aird et al., 2012; Bailey et al., 2013; Fröhlich-Zwahlen et al., 2014; Viir et al., 2006; Wang et al., 2016). Their purpose within muscle function remains important for movement health.

Tone results mimicked the same pattern as stiffness in all three studies, indicating their similarity in function and measurement, but with slightly different behaviours. The overall reduction in the third study showed tone reduced by 6% in the massage group and 4% in the intervention group. Again, despite not being a significant reduction, show a similar percentage level of reduction when compared to the immediate reduction in the pilot population. The effects of spasticity and other motor-based conditions associated with cell signalling disruption can lead to increased levels of muscle tone. Tone is responsible for the underlying electrical activity within the muscle, and abnormally high levels can lead to uncontrolled tendon jerks, a characteristic in several musculoskeletal conditions and associated with many movement difficulties (Dietz & Berger, 1983; Fröhlich-Zwahlen et al., 2014). Therefore, in a similar manner to stiffness reduction, the implication of this within MS symptom management could be very beneficial, if further investigation clarified the clinically significant level of reduction and the manual therapy dosage required for this effect. Tone also mimicked the similarity in correlations comparing baseline levels to levels of change, except for study two. Therefore, this may be stronger relationship for stiffness than it is for tone.

Elasticity results did not show a consistent pattern with different results in each study. Though study three results revealed many fluctuations within elasticity data, differences between the two treatments were apparent. Previous studies have also had inconsistent elasticity results (Bailey et al., 2013; Fröhlich-Zwahlen et al., 2014; Schneider et al., 2014) and therefore could be a variable worth investigating further in order to understand its role in muscle function and method of measurement.

Passive manual treatment may not be a successful way of improving elasticity and may require active movement or treatment to affect this positively.

6.2 Balance Measures
6.2.1 Body Sway Reductions

Body sway measures were only gathered in the MS studies, meaning their results can be compared between an immediate and cumulative effect difference. In both studies, all body sway measures for the single stance test resulted in reductions. Though in the immediate effect study there were no significant reductions except in the AP path length (fig. 4.14), many of these variables then became significant in the cumulative effect study. This implies that improvements in single stance can be made after one therapy session, as much as a 9% reduction in body sway as seen in fig. 4.13 after the intervention. This reduction can become significant after four treatment sessions, where both treatments revealed a 21% reduction in body sway. People with MS already show to have increased number of falls and increased level of body sway when compared to healthy controls. This could be because of many different types of symptoms that result in muscle weakness, visual difficulties, vestibular and balance difficulties, somatosensory loss, and spasticity. These can all be directly affected by nerve disruption and then collectively affect aspects of stability that lead to loss of muscular control and increased body sway (Kanekar et al., 2013; Ramdharry et al., 2006; Stevens et al., 2013).

Improvements in these measures, can have many implications for improved movement ability and reducing the risk of unexpected falls. With most participants in these studies displaying greater symptom level in pyramidal and sensory categories, this has a large implication on muscle control and recruitment. Both treatments revealed very similar trends and levels of significance in both MS studies for these measures. This either indicates that balance improvements occur regardless of manual therapy type, or that the learned effect has a greater effect on improvement than manual treatment. It is likely these result improvements are due to a combination of the treatment benefits and a learned effect. This would indicate that the benefit of these two effects, are greater than the specificities of the type of manual treatment.

However, the other balance tests (forward lunge and sit-to-stand) did not have the same consistent reductions in body sway. Several of these measures even revealed increases, even though they were performed the same number of times as the single stance test. This could be because they are more complicated movements and require more complicated levels of coordination. Maintaining stability during movement requires less re-centring work than single leg balance, particularly because both lower limbs are involved in maintaining stability. There may therefore be less room for improvement in body sway within the designated testing times.

The body sway measures used in this analysis were mainly derived from CoP using force plate analysis, which has been critical in the development of movement research (Adachi et al., 2012; Mancini & Horak, 2010; Raymakers et al., 2005; Rome et al., 2009; Wardoyo et al., 2016). A decrease in path length of body sway, should indicate less body sway and therefore improved balance. However, to improve balance, more recovery movements may be necessary, and a path length reduction would not necessarily represent this improvement. For these situations body sway velocity is a better indicator of this balance and control improvement (Ramdharry et al., 2006). Collecting both these variables is valuable and a reduction in both measures is ideal for balance improvement. Significant reductions in single stance path length together with velocity were only seen in the cumulative effect study with the massage treatment, despite having a similar reduction in path length to the mobilisation treatment. The difference in velocity and control of off-balance positions could therefore be an element in balance measures that helps to complete the story, where improvements can still be made.

6.2.2 Body Weight Usage

A reduction in percentage of body weight used in both movement tests for forward lunge and sit-to-stand would indicate an improved efficiency in these movements (Alkjær et al., 2009; Jonsson et al., 2004). Since all four outcome measures tested for these revealed an increase (fig 4.18 & fig. 5.15), it could be concluded that these movements did not improve in this respect, regardless of treatment or movement practice for one or for four sessions. This is supported by the increase in body sway measures for these movements also, indicating a decrease in the element of control

for these movements. For these movements to improve, decreases in body sway measures and percentage of force used should go hand in hand to improve the element of control for these activities highly associated with daily life activities. This is also seen in the faster movements revealed for these tests with decreased contact time, associated with less controlled movement.

People with MS and spinal lesions have even been clinically compared to people with a spinal cord injury based on their similarity of symptoms in muscle weakness and loss of sensation in lower extremities, spasticity and other symptoms affecting important aspects of gait (Giesser et al., 2007). This also coincides with the participants in this investigation and their most severe symptom categories within sensory and pyramidal types. Since improvements were seen in single stance tests but not the more dynamic movement tests, the margin for improvement may be smaller compared to the single stance, however also more likely to be mimicked in daily tasks and therefore an important area to focus on in terms of MS patient rehabilitation outcomes.

6.2.3 Time Reductions

The reduction in contact time measures for the forward lunge and sit-to-stand movements go hand in hand with the increases in body sway measures and relative force usage. Slower movement time of forward lunge and sit-to-stand have previously been used an indicator of movement deficiencies in disabled populations (Alkjær et al., 2009; Bowser et al., 2015). Although, within the context of these test situations, compared against their own previous movements and connected to the increase in body sway and force usage, this result appears to coincide with the faster less controlled movement. There may have been an element of this attributed to the testing situation and a desire to perform tests faster, leading to a loss of control. However, without testing session interviews or questionnaires to investigate this, the main conclusion derived must be that these movement tests did not improve. Further investigation into the relationship between these measures could be beneficial to target improvement for movement control.

Whether changes in these measures occur from a centralised neural location directly due to manual treatment or indirectly through practice and neural re-organisation,

there is potential for improvement in MS patient rehabilitation. Further targeted work to investigate more precisely how to improve these movements would be beneficial, as four sessions of manual treatment, regardless of the type of treatment, did not benefit this.

6.3 Pain and Fatigue Measures

6.3.1 Importance of Quality of Life Measures

The self-reported measures for pain and fatigue were in fact the only variables that revealed a significant change in the intervention treatment compared to the massage treatment in the MS studies. This implies the mobilisation treatment may be more effective at reducing pain and fatigue compared to a general manual therapeutic. This could be from a placebo type effect giving participants a feeling of greater effect due to medicinal properties of the intervention rather than general manual touch. However, due to the small sample size and variability within results in both studies, these results could also still be due to chance.

The pain results revealed a significant reduction in the intervention treatment compared to the massage treatment in study two with a 29% reduction between pre and post treatment, equivalent to approximately 0.5 reduction in VAS. This is in comparison to the massage treatment, revealing a non-significant reduction of 22%, and equivalent to 0.3 VAS reduction. However, when these reductions are compared to other spinal manual therapy studies investigating hypoalgesic effects, both are around a third of the clinically significant reduction in pain previously reported at approximately 1.5 VAS reduction, regardless of the severity of initial pain (Kelly, 2001; Shum et al., 2013). When compared to the study three results, neither treatments showed significant pain reductions, however both revealed reductions higher than 50% of the initial value, again equating to approximately 0.5 VAS. Therefore, a significant reduction or high percentage reduction, may not be enough to be a clinically significant reduction. The proposed mechanical influences on pain reduction through altering afferent signalling previously discussed may occur but may require either participants with greater levels of pain to see a clinically significant difference in this, or a more homogenous group with less variability in results.

The results for fatigue reduction were only investigated in study three and therefore cannot be compared to the other study results. However, in a similar manner to the results for pain in study two, the intervention treatment revealed a significant reduction with 35% decrease compared to the general treatment with a 15% decrease. As one of the symptoms that can be most disruptive for people in MS and can be affected by several other factors also linked to other symptoms, a clinically significant reduction in this area could have considerable impact for this population. If this reduction were also in synergy with pain and stiffness reductions, a centralised theory for mechanical modifications could be justified.

A decrease in fatigue has also been found to have a significant correlation with increase in QoL because of the connection with mobility and daily activities (Backus et al., 2016). There is an unclear pathophysiology for fatigue in MS patients and likely to be individual differences for each person, both directly in a CNS affected manner and indirectly through other symptom effects. Primary fatigue can result as a direct consequence of nerve demyelination and disturbed cell signalling, requiring more energy compared to someone with a healthy nervous system (Hebert et al., 2011; Vucic et al., 2010). Indirect influence of fatigue relates to fatigue caused on a secondary level by symptoms such as reduced mobility, depression, anxiety, and sleep disorders, resulting in overall effects of general lifestyle (Hebert et al., 2011b). The lack of clarity on what causes fatigue, means that therapeutics to treat it are difficult, therefore future investigations on correlations and associations would be beneficial. The improvements in this measure may have an association with improvements in stability and body sway reductions. The way in which these aspects affect each other and could be affected by manual therapy is a potential area for further investigation.

However as previously discussed, these self-perceived improvements were not supported by objective muscle measurements. Participants felt significantly better and this was an important aspect to measure as part of a full analysis. It has recognised an important area within this research to further investigate as the specificities of the intervention may induce a more meaningful result on QoL than generalised manual therapeutics. It also gives the participant a chance to reflect on

their experience from the treatment and testing, proving another beneficial element for them taking part. Nevertheless, further investigation is needed within this intervention and population group for these results to positively complement each other.

6.3.2 Other Objective Measures

Other means of objectively measuring pain have been assessed with the use of PPTs, which measures pain threshold by applying pressure. This has been proven an effective measure of pain improvement in previous studies (Krouwel et al., 2010; Pecos-Martín et al., 2017; Thomson et al., 2009; Willett et al., 2010). This resource was not available for this investigation and could perhaps provide further information about the physiological element of pain experienced, taking out the psychological element, which could be driving the significance in results within this investigation.

PPTs are often used to induce pain in participants who are not chronically ill or experiencing high levels of pain. Therefore, this measure could be used in MS studies with participants who do not experience a lot of pain, or in early/low disability levels of their condition. As this has generally been the case in this investigation, PPTs could be used for the investigation of analgesic effects of manual therapy. The investigation of mechanistic influence on central components connected to pain, stiffness, fatigue, and spasticity could be investigated in this manner with this population and within this context to explore these effects and help to provide evidence for this therapeutic benefit. This is beneficial for a condition and a population where health care and services may be limited because of the complexity of the condition.

6.4 PhD Overall Results Summary

The exploration in the pilot study revealed significant results that supported feasible use of the intervention for people with LBP when compared to a control and provided the intervention definitions. This included the significant finding of baseline stiffness as an influencing factor in level of stiffness change.

The variability seen in the MS patient data were prevalent in the muscle data for both an immediate and cumulative effect study. The lack of immediate effect seen in the MS population could be its lack of effectiveness when compared to another manual therapeutic. This is supported by very similar trends in data for the cumulative study.

Body sway measures improve significantly after four treatment sessions as well as self-perceived fatigue. People with MS without high levels of pain do not show a correlated reduction in stiffness and pain at a clinically significant level, though this relationship could be further investigated due to previous literature findings for this.

The optimal level, dose or type of manual treatment that is most beneficial for these measures is still to be determined for the MS population and the management of their symptoms. It likely that any form of manual treatment has some benefits without being significantly different to each other.

The development of MS physiotherapy research is growing but requires more investigation. Due to the heterogeneity of the MS condition and how it presents differently, an individual's needs can be very diverse. They can respond in different ways and at different rates, supported by the level of variability seen in these study investigations. Further research into the objective impact of these therapeutics, can save time, money, and resources, as well as benefitting the patient more directly and effectively.

6.5 Study Limitations

As previously mentioned, the main limiting factor for this investigation was the restriction of time. It would have been beneficial to do a longer-term study with MS patients over more than four sessions and with more participants involved. However, decisions were made based on information knowledge at the time and the MS feasibility study allowed the MS study design to be improved.

Both MS studies recruited 20 participants in each, however both required more from sample size calculations. Recruitment and testing were stopped at 20 participants in each study again due to timings, to enable analysis, new study design and writing to take place. MS patient recruitment was a slow process and if more successful within the designated time, a larger sample size may have produced improved results.

Though the myometer provides results based on objective findings, there is an element of human error possible with the measurements taken. The exact location for measurement was palpated, marked, and measured by the researcher to test the

same location each time. However, the potential for human error means that there could be mild inconsistencies in this element.

The lack of myometer data with MS participants meant that the pilot study data with LBP was used for sample size calculations and to inform the study design and feasibility. The lack of LBP within the MS population recruited then meant that these studies were comparing two different population groups. The variability within the MS population data meant that sample sizing was too small to elicit any significant results with a normal distribution within the data. This level of variability is likely to require a larger sample size to allow normal distribution and reliable results from this analysis.

The therapist used between the two MS studies was different due to practicality issues, often a factor within human testing. Despite training on the intervention treatment specifics, inter-therapist differences may have still occurred which would create a challenge for comparison of study two and study three results.

The general massage intervention was used as a comparable treatment, and ethically allowed participants to still receive treatment if they were attending the alternative treatment sessions. However, since this was not an actual placebo treatment, placebo effect on data results cannot be negated and some results may have occurred due to chance.

The recruitment for MS participants and for many chronic conditions can be challenging due to the debilitating nature of their condition and the activity required for taking part in a research study. The participants who volunteered for the study, by nature tended to be people who are early in their condition and have lower levels of disability as seen in the EDSS results. People with a higher level of disability are more likely to show changes in these symptoms.

6.6 Future Research Recommendations
Several elements of the investigation would benefit from further research. Further research into body sway measures, with lifestyle questionnaires and whether their daily movements have improved would be valuable. This would not only help to analyse whether these balance improvements have translated into daily life, but also

to analyse whether confidence plays a significant role in these improvements. Further investigation into the clinically significant level of change for body sway, force usage and contact time for balance measures would be beneficial to define for MS patients, and how this may impact their daily movement function. The potential association between stability measures and fatigue and how these influence each other would be beneficial for rehabilitation research of many musculoskeletal conditions.

Further investigation into the association between pain and stiffness could be done through objective forms of pain measurement. This could also be combined with analysis on baseline stiffness and help to determine predictors of response. Since this investigation did not find a significant difference between gender responses in MS data, this could be further investigated also to help determine whether physiological sex differences play a role in muscle response.

Since four sessions resulted in an improvement on some elements of pain, fatigue and body sway, an investigation into the number of sessions and when this is most beneficial to muscle response would be valuable. Further investigation into different level of mobilisation forces used and different timings of the treatment used could contribute to this also and could help to establish a dose response. This could be variable for the patient depending on their needs. This would also help to analyse the potential benefit from specific types of manual intervention and when a slower, consistent mobilisation therapy is specifically more beneficial than a standard manual therapy with no specificities.

The centre of any research involving physiotherapy and neurodegenerative disease should remain patient focussed, with a continual goal of improving experience of symptoms and improving QoL.

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Appendices

Appendix 1 Study One Approve Ethics Application

Project title: The impact of spinal mobilisation therapy on sufferers   **Version no: 3**
of lower back pain.

Full name & title: Miss Rebecca Isabel Hamilton   **School:** School of Life, Sport & Social
Sciences

E-mail address: ██████████████████   **Telephone:** ████████

Postal address: ████████████████████████████████████

Status: Staff (Edinburgh Napier University) ☐ **Student (Edinburgh Napier University** ☒

External Applicant ☐   *Please provide additional details below:*

Other researchers (name, role & affiliation): **Dr Susan Brown, Supervisor, School of Life, Sport and Social Sciences, Edinburgh Napier University, Dr Claire Garden, Supervisor, School of Life, Sport and Social Sciences, Edinburgh Napier University**	**Matriculation Number: 40100069** **Degree programme: Research Degree**

Independent advisor: Dr Anna Campbell   **Level of study: MRes/MPhil/PhD**

Financial support from outside Edinburgh Napier University (amount & source): Medical Research Scotland, Point One Clinic

Project start date: 27/06/2016   **Project duration: 18/08/2016**

Date application submitted: 07/04/2016   **Ref no. (LEAVE BLANK):** Click here to enter text.

	YOU MUST ANSWER ALL QUESTIONS	YES	NO	N/A
1	Will you describe the main procedures to participants in advance, so that they are informed about what to expect in your study?	☒	☐	☐
2	Will you tell participants that their participation is voluntary?	☒	☐	☐
3	Will your participants be able to read and understand the participant information sheet?	☒	☐	☐
4	Will you obtain written consent for participation?	☒	☐	☐
5	If the research is observational (including tape and video), will you ask participants for their consent to being observed?	☐	☐	☒
6	Will you tell participants that they may withdraw from the research without penalty and without reason?	☒	☐	☐

#	Question	Yes	(shaded)	No
7	With questionnaires and interviews, will you give participants the option of omitting questions they do not want to answer?	☒	☐	☐
8	Will you tell participants that their data will be treated with full confidentiality and that, if published, it will not be identifiable as theirs?	☒	☐	☐
9	Are the data to be stored anonymously (i.e. the identity of the person is NOT linked directly or indirectly with their data)?	☒	☐	☐
10	Will you debrief participants at the end of their participation (i.e. give them a brief explanation of the study and an opportunity to ask questions)?	☒	☐	☐
11	Will the research involve deliberately misleading participants (deception) in any way?	☐	☒	☐
12	Is there any realistic risk of any participants experiencing either physical or psychological distress or discomfort?	☒	☐	☐
13	Is the information gathered from participants of a sensitive, personal or contentious nature?	☒	☐	☐
14	Will any payment or reward be made to participants, beyond reimbursement or out-of-pocket expenses?	☐	☒	☐
15	Do participants fall into any of the following special groups? *If the answer is YES, indicate which group(s) by checking the appropriate box(es).*	☐	☒	☐

☐ Children (under 18 years)   ☐ People in custody

☐ Clinical population   ☐ People with learning or communication difficulties

☐ People with mental health issues   ☐ People engaged in illegal activities (e.g. drug-taking)

NOTE: You may also need to obtain clearance from Disclosure Scotland or an equivalent authority.

You must check **either Box A or Box B** below and provide **all** relevant information in support of your application in the Details of Project section. If you answered **NO** to any of **questions 1-10**, or **YES** to any of **questions 11-15** (with a shaded background), then you **must** check Box B.

DETAILS OF PROJECT

1. **Background information** *(300 words maximum; references should be cited and listed)*

Treatment of the spine can have significant impact on mobility of the whole body due to the mechanical, muscular and nerve influence (Bernitsas *et al.,* 2015; Palastanga *et al.,* 2006), particularly the lumbar spine showing a direct relationship between pain/stiffness and mobility (Shum *et al.,* 2013). The main limiting factor for mobility in the lumbar region is muscular tension. There has been a strong association shown between neuromuscular impairment and spinal deformities, showing the connection between spinal muscular function and spinal mobility (Palastanga *et al.,* 2006). Vertebral support from attaching muscles is also said to be important for prevention of spinal buckling during spinal loading, decreasing direct mechanical stress on the spine (Triano, 2001).

Spinal mobilisation therapy (SMT) has shown to have an immediate effect on pain, stiffness and mobility, however the mechanisms for these changes have not been fully established (Shum *et al.,* 2013; Triano, 2001). The therapy consists of low velocity movements and can vary in the force, direction and point of contact with the spine (Triano, 2001). It can improve range of motion (ROM) within vertebral segments as well as the whole spine (Chiradejnant *et al*., 2003; Chou and Huffman, 2007). To address this gap of knowledge in biomechanical explanation, the study will investigate the effects of tissue stiffness in the erector spinae and lumbar multifidus muscles, expected to give results relevant for lumbar back mobility (Little *et al.,* 2015). This will be tested on a general population who suffer with some level of lower back pain (LBP). LBP patients are commonly reported to have decreased spinal mobility due to pain and stiffness and previously shown to respond to SMT (Childs *et al*., 2001; Flynn *et al.,* 2002; Shirley and Lee, 1993; Shum *et al.,* 2013).

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2. Aims & research questions

- The proposed study has the intention of understanding better the biomechanical and physical effect of SMT by investigating the impact of SMT on spinal stiffness in LBP participants. The study will test the acute difference in spinal tissue stiffness.
- Specifically to examine the acute difference in the muscular tone, dynamic stiffness and elasticity characteristics of erector spinae and lumbar multifidus muscle groups.
- Investigation into category of pre-existing pain levels and anthropometric measures if any patterns arise in tissue stiffness differences.
- Validation of the therapy will determine the potential use for further *clinical* populations such as Multiple Sclerosis (MS) patients.

3. Participants

- ***Number & nature of sample:*** Recommended number of participants for a repeated measures ANOVA is 44 participants. This shown by G-power with a large effect size (0.25) and power of 0.95. Based on an alpha level of 0.05 to compare 2 dependent group means. Therefore 44 participants with LBP will be recruited.

- ***Inclusion/exclusion criteria:*** Inclusion criteria - participants suffering from lower back pain. This is defined as pain in the region between the 12th rib and the gluteal folds and can be present with or without leg pain. The study will include participants with either acute or chronic pain and can be pathological or non-specific. Participants will be within the working age of 18 – 65. Exclusion criteria - participants on medication other than paracetamol. Participants responding positive to any absolute contraindications for spinal therapy. These include, fractures, dislocations, bone tumours, infectious diseases, osteomyelitis, segmental instability, cervical arterial dysfunctions, multilevel nerve root pathology, progressive neurological deficit, upper motor neuron lesions, spinal cord damage, or any skeletal condition. Participants responding positive to any relative contraindications will be excluded based on severity. These include the following conditions: osteoporosis, herniated disc, spinal instability, rheumatoid arthritis, pregnancy, local infection, inflammatory disease, active or history of cancer, hypermobility syndrome, connective disease, cervical anomalies, previous spinal surgery, respiratory problems, cardiovascular disease, open wounds, thrombosis, blood clot, segment hypermobility.

- ***Recruitment of participants:*** Participants will be recruited via poster, social media and word of mouth. The poster and information sheet will be used electronically and in person when interest is shown to participate as a response from advertisement. When participants show interest in person the researcher will only cite information from the poster and explain the information sheet. No coercion will be added when speaking face to face and information will only be given after interest is shown. Questions regarding the study will be encouraged and participants will be encouraged to read through the information sheet before

volunteering for the study. An invitation email has been attached to this application as an example email in response to participants who have shown interest in advertisement, or as recruitment within the University if approved to be sent to the staff population.

4. Outline of methods & measurements *(approx. 500 words)*

44 participants will be recruited and will be tested in both a control and manual therapy session over 2 different dates. The order of these sessions will be randomly assigned. Participants will be recruited from Edinburgh Napier University general population. All testing will take place in the afternoon to retain consistency in testing, at Edinburgh Napier University and temperature will be kept at room temperature (20°). A contraindications questionnaire will be completed by each participant to ensure participant safety in taking part. Anthropometric measures will be taken by the researcher for age, sex, weight, height and waist measurements. The Oswestry Low Back Pain Disability Questionnaire will be used to classify level of pain and disability for categorisation before testing (Fairbank, 2000; Krismer and Van Tulder, 2007). This will take approximately 20 minutes and allow for acclimatisation of the participant to the room temperature. The equipment will be set up by the researcher. The therapy session will consist of the therapy treatment and muscle stiffness testing before and after the treatment.

All participants will be tested for spinal tissue stiffness before and after the treatment. Participants will lie in a prone position on a plinth and muscle stiffness measurements will be taken using a myometer digital palpation device (MyotonPRO, Myoton Ltd., London, UK). This is a handheld device held perpendicular to the muscle and collects measurements by calculating the response from small oscillations sent through the muscle (Andonian *et al*., 2015; Little *et al*., 2015; Viir *et al.,* 2006). Measurements will be taken on both sides of the spine on erector spinae muscles (longissimus) and lumbar multifidus, testing the lumbar extensor muscles. Measurements for oscillation frequency (Hz), dynamic stiffness (N/m) and the logarithmic detriment (elasticity) will be taken on muscles of either side of spine. This will take approximately 10 minutes pre and post treatment.

The manual therapy will be conducted by a trained physiotherapist; Mr Chongsu Lee who is a chartered physiotherapist at Point One Clinic Ltd and will be working under his own liability policy. The physiotherapist will go through the contraindications questionnaire previously answered by the participant to ensure their safety. The physiotherapist will use palpation to determine an area of the spine where stiffness and tension is apparent. The treatment will then involve the mobilisation of 2 or 3 spinal joints for 30 minutes. The control experiment will involve no physical touch during the treatment. The participant will lie in a prone position and encouraged to relax for 30 minutes. Participants will be in the treatment room no longer than 2 hours for each session.

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5. Risks to participants

Screening interview and Oswestry questionnaire - Emotional risk due to questions regarding conditions, pain levels and disabilities. Interview and questionnaire will be conducted in sensitive manner and not rushed. If the participant becomes emotional at any point during the session, the researcher and the physiotherapist will manage the situation sensitively. The participant will be encouraged to take their time when answering questions and are not required to answer questions felt too uncomfortable to answer. Participants will be made aware they are able to withdraw from the study at any point with no need for a reason. If the participant choses to withdraw from the study they will be encouraged to rest before leaving the study.

Anthropometric measures - emotional risk due to measurements of a sensitive nature such as age and weight. Measurements will be taken in confidentiality.

Lower back muscle stiffness testing - risk of discomfort in prone position. Participants can use a bolster under ankles for comfort and will be asked regarding comfort regularly.

Spinal mobilisation therapy - risk of pain or discomfort during therapy. Physiotherapist use of patient feedback if any pain or discomfort felt during manual therapy. The physiotherapist is not present during the control treatment. The researcher will be available for assistance if discomfort felt during measurement collecting or treatment. Relaxation will be encouraged and Edinburgh Napier security staff who are first aid trained are reachable if required.

6. Consent and participant information arrangements, debriefing

Participants will be sent an information sheet in advance via email to read before attending investigation session. The protocol will be explained again in person and consent form given for participant to complete at their will. Once experiment is complete, a debrief sheet will be given to participant with further information and contact details regarding the project, as well as stating thanks for taking part.

7. Ethical considerations raised by the project and how you intend to deal with them.

Participants do not need to answer questions they are not comfortable with answering. Answers for Oswestry Low Back Pain Disability Questionnaire will be answered in written form and not spoken in person. If uncomfortable during the therapy researcher will be present to make any necessary adjustments.

Participants recruited will be suffering from acute or chronic LBP, however will be recruited from a general population that continue with their typical routine and not severely affected. Participants will also adhere to the inclusion/exclusion criteria to eliminate any pathological danger from the spinal therapy.

DECLARATION

There is an obligation on the researcher to bring to the attention of the Faculty Research Ethics Approval Sub-Group any issues with ethical implications not clearly covered by this application form.

I request ethical and governance approval for the research described in this application. I have read Edinburgh Napier University's policies and guidelines relating to ethics and governance in

research, and those of relevant professional bodies (e.g. BPS, BSA, IFPA, SIR, NMC) and agree to abide by these.

A ☐   **I consider that this project has no significant ethical implications to be brought to the attention of the Faculty Research Ethics Approval Sub-Group**

B ☒   **I consider that this project <u>may</u> have significant ethical implications to be brought to the attention of the Faculty Research Ethics Approval Sub-Group**

Signature   **Date**

I am the Director of Studies or supervisor for this research. I have read this application and approve it. I do not consider that any part of the research process will cause physical and/or psychological harm to participants, or be detrimental to the reputation of Edinburgh Napier University.

Signature   **Date**

- **You must also attach Participant Information Sheet(s), Consent Form(s), as well as copies of any questionnaires, details of interview questions you plan to use, debrief sheets and notices advertising the study. You may need to create different versions of these materials (e.g. parental Participant Information Sheet and Consent Form if research involves children); if so, all the different versions should be attached. Materials should be printed on paper headed with the University logo.**
- **If you will be recruiting participants via an outside organisation and/or will be conducting research on the premises of an outside organisation, you must provide a copy of written permission from the appropriate organisation(s).**
- **Submit the completed and signed form (with supporting materials) to** ███████ ██ **an electronic copy should also be sent to: ethics.fhlss@napier.ac.uk.**

PhD Study requires volunteers for:

Impact of Spinal Mobilisation Therapy on Lower Back Pain

Participants must be:

- Aged within 18-80
- Suffering from acute or chronic lower back pain
- Taking no anti-inflammatory medication

Participants will be required to take part in two testing sessions consisting of spinal mobilisation therapy and spinal muscular stiffness testing. This will take place at the Edinburgh Napier University Sighthill Campus.

For more information regarding this study please contact Rebecca Hamilton at ███████████████████████████████

Appendix 3 Study One Exclusion Criteria Questionnaire

Have you had a previous injury?   Yes/No

If so what Injury? _____

Do you have a current injury?   Yes/No

If so what injury? _____

Is your back pain related to a pathological condition?   Yes/No

If so what condition? _____

Are you on any medication?   Yes/No

If so what medication? _____

Are you currently pregnant?   Yes/No

If so how long? _____

Have you ever had any of the following? (Relative contraindications)

  Osteoporosis

  Herniated disc/spinal instability

  Rheumatoid arthritis

  Inflammatory disease

  Active or history of cancer

  Hypermobile syndrome/segment hypermobility

  Cardiovascular disease

  Connective tissue disease

  Cervical anomalies/Nerve root disorder

  Spinal surgery

  Respiratory problems

  Thrombosis

  Open wounds/local infection

  Fractures/dislocations

If so please give details.

_____

Have you ever had any of the following? (Absolute contraindications)

  Segment instability

  Infectious disease

Osteomyelitis

Bone tumour

Neurological deficit

Upper motor neuron lesion

Spinal cord damage

Cervical arterial dysfunction

If so please give details.

Participant Information Sheet

My name is Rebecca Hamilton and I am a research student from the School of Life, Sport and Social Sciences at Edinburgh Napier University. As part of my degree course, I am undertaking a study for my PhD project. The title of this study is: "The impact of spinal mobilisation therapy on sufferers of lower back pain".

This study will investigate the effect of spinal mobilisation therapy on lower back muscle stiffness. The difference in muscle stiffness will be tested before and after therapy session. I am looking for volunteers to take participate in the project. To be eligible you must be between the ages of 18 and 70 and a sufferer of lower back pain. You must not be on any anti-inflammatory pain medication. You must not respond positively to any of the absolute contraindications listed in Appendix A and any relative contraindications must be discussed.

If you chose to take part you will attend 2 sessions lasting 45 minutes, one spinal therapy session and the other a control session. Anthropometric measures for age, weight, sex, height, and waist measurements will be taken. You will work through a lower back pain questionnaire to categorise your level of pain. Muscle stiffness measurements will be taken before receiving a 30-minute spinal therapy session, or a 30-minute control session. After which muscle stiffness measurements will be taken again. There is a risk that you will feel uncomfortable during the therapy. However you will be able to feedback to myself and the physiotherapist to modify anything uncomfortable. You will be free to withdraw from the study at any stage. You will not have to give a reason, and it will not affect your treatment.

All data will be anonymised. Names will be replaced with a participant number or a pseudonym, and it will not be possible for your personal data to be identified in any reporting's of the study. Any data collected will be kept in a secure place to which only the researcher has access. Personal data will be kept until the end of this study in October 2016 and will then be deleted. Summary data will then be used in the study and may be published in relevant journals.

The findings of this project will be useful to a population with lower back pain in their pursuit of a therapeutic. The intention is to investigate the difference in spinal tissue stiffness and relate to improved quality of life and whole body mobility.

If you would like to contact an academic supervisor of this project, you are welcome to contact Dr Susan Brown or Dr Claire Garden, whose contact details are below. If you would like to contact an independent person, who knows about this project but is not involved in it, you are welcome to contact Dr Anna Campbell. Her contact details are also given below.

If you have read and understood this information sheet, asked any questions, and would like to be a participant in the study, please now see the consent form.

Contact details of researcher

Name of researcher: Rebecca Hamilton

Address: ████████████████████████████████████
████████████████

Email / Telephone: ████████████████████████████

Contact details of supervisors

Name of supervisor: Dr Susan Brown

Address: ████████████████████████████████████
███████████████

Email/Telephone: ████████████████████████

Name of supervisor: Dr Claire Garden

Address: ████████████████████████████████████
███████████████

Email/Telephone: ████████████████████████

Contact details of the independent adviser

Name of adviser: Dr Geraldine Jones

Address: ████████████████████████████████████
███████████████

Email/Telephone: ████████████████████

Contraindications

Relative Contraindications	Absolute Contraindications
Osteoporosis	Bone tumour
Herniated disc	Infectious disease
Signs of spinal instability	Osteomyelitis
Rheumatoid arthritis	Segmental instability
Pregnancy	Healing fractures/dislocations
Local infection	Cervical arterial dysfunction
Inflammatory disease	Multilevel nerve root pathology
Active or history of cancer	Progressive neurological deficit
Hypermobility syndrome	Upper motor neuron lesions
Connective disease	Spinal cord damage
Cervical anomalies	
Previous spinal surgery	

Respiratory problems	
Cardiovascular disease	
Open wounds	
Thrombosis	
Blood clot	
Segment hypermobility	

Appendix 5 Study One Consent Form

<div align="center">

Participant Consent Form

</div>

"The impact of spinal mobilisation therapy on sufferers of lower back pain"

I have read and understood the information sheet and this consent form. I have had an opportunity to ask questions about my participation.

I understand that I am under no obligation to take part in this study.

I understand that I have the right to withdraw from this study at any stage without giving any reason.

I agree to participate in this study.

Name of participant: _____

Signature of participant: _____

Signature of researcher: _____

Date: _____

Contact details of the researcher

Name of researcher: Rebecca Hamilton

Address: ███████████████████████████████████████
                  ███████████████

Email / Telephone: ██████████████████████████████████

Appendix 6 Study One Oswestry Low Back Pain Disability Questionnaire

Scoring instructions

For each section the total possible score is 5: if the first statement is marked the section score = 0; if the last statement is marked, it = 5. If all 10 sections are completed the score is calculated as follows:

Example: 16 (total scored)

                 50 (total possible score) x 100 = 32%

If one section is missed or not applicable the score is calculated:

               16 (total scored)

               45 (total possible score) x 100 = 35.5%

Minimum detectable change (90% confidence): 10% points (change of less than this may be attributable to error in the measurement).

Interpretation of scores

0% to 20%: minimal disability:	The patient can cope with most living activities. Usually no treatment is indicated apart from advice on lifting sitting
21%-40%: moderate disability:	The patient experiences more pain and difficulty with sitting, lifting and standing. Travel and social life are more difficult and they may be disabled from work. Personal care, sexual activity and sleeping are not grossly affected and the patient can usually be managed by conservative
41%-60%: severe disability:	Pain remains the main problem in this group but activities of daily living are affected. These patients
61%-80%: crippled:	Back pain impinges on all aspects of the patient's life. Positive intervention is required.
81%-100%:	These patients are either bed-bound or exaggerating their

Instructions

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. Please answer by checking ONE box in each section for the statement which best applies to you. We realise you may consider that two or more statements in any one section apply but please just shade out the spot that indicates the statement which most clearly describes your problem.

Section 1 – Pain intensity

☐ I have no pain at the moment

☐ The pain is very mild at the moment

☐ The pain is moderate at the moment

☐ The pain is fairly severe at the moment

☐ The pain is very severe at the moment

☐ The pain is the worst imaginable at the moment

Section 2 – Personal care (washing, dressing etc)

☐ I can look after myself normally without causing extra pain

☐ I can look after myself normally but it causes extra pain

☐ It is painful to look after myself and I am slow and careful

☐ I need some help but manage most of my personal care

☐ I need help every day in most aspects of self-care

☐ I do not get dressed, I wash with difficulty and stay in bed

Section 3 – Lifting

☐ I can lift heavy weights without extra pain

☐ I can lift heavy weights but it gives extra pain

☐ Pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently placed eg. on a table

☐ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned

☐ I can lift very light weights

☐ I cannot lift or carry anything at all

Section 4 – Walking*

☐ Pain does not prevent me walking any distance

☐ Pain prevents me from walking more than 1 mile

☐ Pain prevents me from walking more than 1/2 mile

☐ Pain prevents me from walking more than 100 yards

☐ I can only walk using a stick or crutches

☐ I am in bed most of the time

Section 5 – Sitting

☐ I can sit in any chair as long as I like

☐ I can only sit in my favourite chair as long as I like

☐ Pain prevents me sitting more than one hour

☐ Pain prevents me from sitting more than 30 minutes

☐ Pain prevents me from sitting more than 10 minutes

☐ Pain prevents me from sitting at all

Section 6 – Standing

☐ I can stand as long as I want without extra pain

☐ I can stand as long as I want but it gives me extra pain

☐ Pain prevents me from standing for more than 1 hour

☐ Pain prevents me from standing for more than 30 minutes

☐ Pain prevents me from standing for more than 10 minutes

☐ Pain prevents me from standing at all

Section 8 – Sex life (if applicable)

☐ My sex life is normal and causes no extra pain

☐ My sex life is normal but causes some extra pain

☐ My sex life is nearly normal but is very painful

☐ My sex life is severely restricted by pain

☐ My sex life is nearly absent because of pain

☐ Pain prevents any sex life at all

Section 9 – Social life

☐ My social life is normal and gives me no extra pain

☐ My social life is normal but increases the degree of pain

☐ Pain has no significant effect on my social life apart from limiting my more energetic interests eg, sport

☐ Pain has restricted my social life and I do not go out as often

☐ Pain has restricted my social life to my home

☐ I have no social life because of pain

Section 7 – Sleeping

☐ My sleep is never disturbed by pain

☐ My sleep is occasionally disturbed by pain

☐ Because of pain I have less than 6 hours sleep

☐ Because of pain I have less than 4 hours sleep

☐ Because of pain I have less than 2 hours sleep

☐ Pain prevents me from sleeping at all

Section 10 – Travelling

☐ I can travel anywhere without pain

☐ I can travel anywhere but it gives me extra pain

☐ Pain is bad but I manage journeys over two hours

☐ Pain restricts me to journeys of less than one hour

☐ Pain restricts me to short necessary journeys under 30 minutes

☐ Pain prevents me from travelling except to receive treatment

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Appendix 7 Study One Anthropometric and ODI Sheet

Anthropometric Measures

Participant Number: _____Date of birth:_____

Sex: Male/Female   Height (cm):   _____

Weight (Kg):   _____Waist (cm):   _____

ODI Scoring Results

Total Score   =

Total Possible Score   =

Final Percentage   = total score/total possible score *(100)

Final percentage   =   %

Debrief Sheet

Many thanks for your participation in the project. The aim of this project is to provide useful information with regards to spinal therapy and lower back pain.

If you have any initial feedback from the therapy please feel free to pass it onto to the researcher. If you wish to know more about the project please feel free to ask any questions. The contact details of the researcher are provided below if you should wish to give feedback or ask any questions.

Contact details of the researcher

Name of researcher: Rebecca Hamilton

Address: ██████████████████████████████
                               █████████████████████

Email / Telephone: ███████████████████████

Appendix 9 Study Two Approved Ethics Application

Project title: The immediate effect of spinal therapy in multiple sclerosis.

Version no: 2

Full name & title: Miss Rebecca Isabel Hamilton   **School:** School of Applied Sciences

E-mail address: ███████████████████   **Telephone:** ███████████

Postal address: ██
██

Status:Staff (Edinburgh Napier University)☐**Student (Edinburgh Napier University)**☐

External Applicant ☐   *Please provide additional details below:*

Other researchers (name, role & affiliation):	**Matriculation Number: 40100069**
Dr Susan Brown, Director of Studies, School of Applied Sciences, Edinburgh Napier University, Dr Claire Garden, Supervisor, School of Applied Sciences, Edinburgh Napier University	**Degree programme: Research Degree** **Level of study: MRes/MPhil/PhD**

Financial support from outside Edinburgh Napier University (amount & source): Medical Research Scotland, Point One Clinic

Project start date: 20/03/17   **Project duration: 07/08/17**

Date application submitted: 02/12/16   **Ref no. (LEAVE BLANK):** Click here to enter text.

	YOU MUST ANSWER ALL QUESTIONS	YES	NO	N/A
1	Will you describe the main procedures to participants in advance, so that they are informed about what to expect in your study?	☒	☐	☐
2	Will you tell participants that their participation is voluntary?	☒	☐	☐
3	Will your participants be able to read and understand the participant information sheet?	☒	☐	☐
4	Will you obtain written consent for participation?	☒	☐	☐
5	If the research is observational (including tape and video), will you ask participants for their consent to being observed?	☐	☐	☒
6	Will you tell participants that they may withdraw from the research without penalty and without reason?	☒	☐	☐
7	With questionnaires and interviews, will you give participants the option of omitting questions they do not want to answer?	☒	☐	☐

8	Will you tell participants that their data will be treated with full confidentiality and that, if published, it will not be identifiable as theirs?	☒	☐	☐
9	Are the data to be stored anonymously (i.e. the identity of the person is NOT linked directly or indirectly with their data)?	☒	☐	☐
10	Will you debrief participants at the end of their participation (i.e. give them a brief explanation of the study and an opportunity to ask questions)?	☒	☐	☐
11	Will the research involve deliberately misleading participants (deception) in any way?	☐	☒	☐
12	Is there any realistic risk of any participants experiencing either physical or psychological distress or discomfort?	☒	☐	☐
13	Is the information gathered from participants of a sensitive or contentious nature?	☒	☐	☐
14	Will any payment or reward be made to participants, beyond reimbursement or out-of-pocket expenses?	☐	☒	☐
15	Do participants fall into any of the following special groups? *If the answer is YES, indicate which group(s) by checking the appropriate box(es).*	☒	☐	☐

☐ Children (under 18 years)   ☐ People in custody

☒ Clinical population   ☐ People with learning or communication difficulties

☐ People with mental health issues   ☐ People engaged in illegal activities (e.g. drug-taking)

NOTE: You may also need to obtain clearance from Disclosure Scotland or an equivalent authority.

You must check **either Box A or Box B** below and provide **all** relevant information in support of your application in the Details of Project section. If you answered **NO** to any of **questions 1-10**, or **YES** to any of **questions 11-15** (with a shaded background), then you **must** check Box B.

DETAILS OF PROJECT

8. **Background information** *(references should be cited and listed)*

The management of individualised symptoms occurring within multiple sclerosis (MS) is a key element for management of the condition (Khan *et al.,* 2007). Nerve signal disruption results in a wide variation of potential symptoms, mobility often being a main issue (Vollmer *et al.,* 2002). It can be difficult for patients and health professionals to identify the most efficient rehabilitation programme to help manage their symptoms. Rehabilitation programmes often need regular re-evaluation, and longer time to have an effect (Demaree *et al.,* 1999; Dimitrov and Turner, 2014). Bernistas *et al.* (2015) showed a correlation between the atrophy of the spine and disability with the Expanded Disability Status Scale (EDSS), which is historically used as a predictor for disease

symptomatic status (Kurtzke, 1983). The effects of MS on the lower extremities and core strength/balance are often related to spinal cord atrophy and could therefore also be affected by spinal treatment.

Manual therapy (MT) over the spine has previously shown to have a positive effect on pain, stiffness and mobility without full understanding as to why (Chiradejnant *et al.,* 2003; George *et al.,* 2006). Measuring the effects of a therapeutic programme is often done with clinical outcomes using disability scales and pain scales, most of which are either subjective or secondary measurements. The interpretation of these results are then often dependent on many factors out of control of the researcher (Langdon and Thompson, 1999). Para-spinal muscles are said to contribute to spinal stability, functionality and prevention of buckling of the spine (Triano, 2001). By alleviating pain and stiffness in spinal tissue over time, improved para-spinal muscle usage can enhance neuromuscular associations in the long-term.

Spinal mobilisations is an MT technique introduced into physiotherapy in the 1960s by Geoffery Maitland. This method, still used today, is particularly common for the treatment of back pain (Piekarz and Perry, 2016; Maitland *et al.,* 2014). Often tested in sessions for under 7 minutes, at a rate of 2-3 Hz, it describes a low velocity and high amplitude therapy with oscillatory manual contact (Perry and Green, 2008; Shum *et al.,* 2013). Whereas manipulation therapy applies thrusts with high velocity, mobilisations work by separating facet joints, and stretching the para-spinal muscles (Maigne and Vautravers, 2003; Lee and Evans, 2000). The spine experiences movement by rotation of pelvis and thoracic cage, compression of skin and tissues, and movement of spinal joints (Chansirinukor *et al.,* 2003; Shum *et al.,* 2013).

Spinal mobilisation therapy has been used within Point One Clinic at a slower rate for a longer period of time with positive feedback from MS patients. This provided a rationale for a biomechanical analysis on the intervention to scientifically investigate its effect on this people group. Specifically, the study will provide information on para-spinal stiffness with the use of a myometer, Myoton Pro. This has not been investigated with an MS population before, however has been tested with similar chronic conditions such as Parkinson's disease and stroke (Marusiak *et al.,* 2012; Chuang *et al.,* 2012). The information for para-spinal stiffness, elasticity and tone data will contribute to bridging the gap between neurophysiological response and mobility outcome measures. These are said to be key elements of the biomechanical make-up and functionality of muscles (Schneider *et al.,* 2015). The Myoton Pro is a handheld, non-invasive device and has previously been validated and given reliable results for investigation into stiffness, elasticity and tone of soft tissue (Pruyn *et al.,* 2015; Schneider *et al.,* 2015). The biomechanical information based on para-spinal soft tissue and walking gait that can be gathered in this study will provide an objective contribution to understand spinal therapy and rehabilitation. This will then facilitate improved therapeutics for the MS sufferer.

The study will also test functional stability in single leg stance and lunge using measurements for centre of pressure and body sway. This analysis is often used in clinical testing and will help analyse the potential effect on lower extremity stability (Ramdharry *et al.,* 2006). Tests for pain in basic lumbar movements will be used, which is common practice in lower back therapy (Goodsell *et al.,* 2000; Shum *et al.,* 2013). Though this is not an objective measurement it is often referred to as a useful measure for effect in lower back therapy and produced many results in promoting an analgesic effect. The mobilisation intervention has been previously tested with a positive immediate effect on para-spinal stiffness with lower back pain participants and therefore has potential to show similar results with an MS population.

This study proposes an investigation as a feasibility study, to assess the protocol of testing manual therapy over the spine with MS patients, and gather data to analyse the results as an immediate effect. The information gathered in this study will be used to design a study for a long-term intervention aiming to provide information that has clinical impact for MS rehabilitation. The MRC

definition for a clinical trial describes an investigation looking to enable health care decisions about the safety and efficacy of a new treatment, and adding to medical knowledge. Since a feasibility study is not providing knowledge for the final outcome, but rather information to assess the protocol, it will not be tested as a clinical trial. This is said to be crucial for efficient study design management of a clinical randomised controlled trial (Rajadhyaksha, 2010; Tickel-Degnen, 2013) It is therefore clinical research but not governed by the same regulations as medical trials.

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9. Aims & research questions

The aim of this study is to investigate the immediate effect of a particular model of a spinal mobilisation intervention, with an MS population group. The effect will be tested on para-spinal stiffness, levels of lumbar pain and ground reaction forces in stability. The intervention will be tested against a placebo therapy to test the differences that are occurring are due to specific techniques within mobilisation therapy. The intention of this study is to act as a feasibility study for an investigation with MS patients and a long term spinal mobilisation intervention.

Does the intervention have an immediate effect on para-spinal stiffness?

Does the intervention have an immediate effect on pain during lumbar movements?

Does the intervention have an immediate effect on functional stability?

10. Participants
- ***Number & nature of sample:*** Recommended number of participants for repeated measures, within factors ANOVA is 24. This is shown in G-power with a large effect size (0.25), a power of 0.95 and significance level of 0.05. This is an appropriate number of participants for a feasibility study (Julious, 2005) and therefore the study will aim to recruit 24 participants with MS.

- *Inclusion/exclusion criteria:* Inclusion criteria; must be female, must have an MS diagnosis, must be diagnosed within the range of 2 and 6 in the Expanded Disability Status Scale (EDSS) which ranges from minimal disability within the disease up until requiring a simple walking aid for mobility (Kurtzke, 1983), must be within the ages of 18-70, must be able to stand on one leg for approximately 3 seconds. Exclusion criteria; must not be connected with Point One Clinic, must not respond positive to spinal therapy absolute contraindications which include bone tumour, inflammatory/infectious/metabolic disease affecting the spine, dysplasia, healing fractures/dislocations, spinal cord damage, cauda equine syndrome, aortic dysfunction and severe haemophilia. Participants responding positive to any relative contraindications will be excluded based on severity, these include spinal disc prolapse, spondylosis, spondylolisthesis, inflammatory arthritides, osteoporosis, hypermobile syndrome, pregnancy, cancer, cardiovascular disease, respiratory disease, healing injury and adverse reaction to previous spinal treatment (Maitland *et al.,* 2014). The physiotherapist will not be able to comment on safety of participant's involvement due to the conflict of interest. Therefore, participants responding positive to any relative contraindications will be asked to request permission from their GP whether it is safe for them to take part. The physiotherapist will be made aware of any relative contraindications before treatment. All treatments will be gentle and low grade.
- *Recruitment of participants, including details of formal permissions from another organisation (where appropriate):* Participants will be recruited via poster, social media (Facebook, Twitter and Instagram) and word of mouth. Physiotherapy and health centres will be contacted by email or in person to ask if there is interest in the study to put up a poster advertisement. Requests have been made to advertise within charities for MS. Once ethical approval has been acquired, further enquiries into charity and private based health and therapy centres will be made, either over the phone, email or in person. The poster and information sheet will be used electronically and in person when interest is shown to participate as a response from advertisement. When interest is shown in person the researcher will only cite information from the poster and explain the information sheet. No coercion will be added when speaking face to face. Questions regarding the study will be encouraged and participants will be encouraged to read through the information sheet before volunteering for the study.
- *Details of any relationship with participants which may affect the research:* If the participant is known by the researcher the results for VAS pain scale could be biased due to pressure of success in the study. However honest answers for VAS scale will be encouraged and data for ground reaction forces (GRF) and para-spinal stiffness cannot be biased as they will be generated by mechanical equipment.

11. Outline of methods & measurements

24 female participants will be recruited to take part in this study. Due to the results from a previous study showing significant male and female differences (Owens *et al.,* 2007) and previous research showing the need for gender specific interventions (Kehoe *et al.,* 2015). The male to female ratio of MS prevalence is approximately 1:2.4 in the UK (Mackenzie *et al.,* 2013); therefore female participants were chosen so that the study is gender specific and relevant to current MS prevalence.

After a participant has shown interest in the study and agreed to take part, a link to the Novi Survey created will be sent to collect information about their MS condition and any contra-indications they may positively respond to. They will be given a participant number in order to maintain security on their personal medical information. Only the researcher will have access to

this information. If the participant does not meet the inclusion criteria they will be informed they are unable to participate. If the participant responds positively to one of the relative contra-indications, they will be informed that they require written permission from their GP and sent the GP information sheet for this. If all inclusion criteria are met, the researcher will then randomly allocate the participant to a group and organise suitable times for their sessions.

Participants will be tested on two separate occasions, once during a placebo therapy and once during spinal mobilisation intervention. Participants will be blind as to which therapy they are receiving. The participants will be randomly allocated to group A or group B by a random group generator on excel. Group A will take part in the placebo therapy first and then the intervention therapy and vice versa. Taxi arrangements will be made by the researcher to pick up and drop off the participant for the testing. All testing will take place at the Edinburgh Napier University Sighthill campus and temperature will be kept at room temperature (20-25°C).

Participants will have the opportunity to read through the information sheet again and the researcher will run through the order of events. Participants will be invited to ask any questions about the study before consent forms are given. Once the participant has given written consent, anthropometric measures will be taken by the researcher for age, weight and height. The results from their Novi questionnaire will be reviewed in person to go through their MS information and any contraindications. Participants will complete a visual analogue scale (VAS) for lumbar movements for flexion, extension, lateral flexion and rotation rating their pain during these movements on a scale of 0 – 10. Force plates will be used in single leg stance tests and single leg lunge tests for each side. Para-spinal stiffness testing will be done with participants lying in a prone position on a plinth using a myometer digital palpation device (MyotonPRO, Myoton Ltd., London, UK). This is a handheld device held perpendicular to the muscle and collects measurements by calculating the response from small oscillations sent through the muscle (Andonian *et al*., 2015; Viir *et al.,* 2006). Measurements will be taken on both sides of the spine on erector spinae muscles (longissimus). Measurements for oscillation frequency (Hz), dynamic stiffness (N/m) and the logarithmic detriment (elasticity) will be taken both sides of the spine. The side that results in a higher stiffness value will be the side receiving therapy.

The chartered physiotherapist working under their own liability will then perform a 30 minute therapy session of either spinal mobilisations or a placebo therapy. Mobilisation therapy will consist of oscillatory movement over L1-L5 region of the spine, at a rate less than 1Hz and grade less than 1. During this therapy the physiotherapist's manual contact is constant and is not lifted from the participant's spine. This is a very gentle therapy with less force being felt than sitting on a massage chair. The placebo therapy will consist of a light massage over the L1-L5 region, where manual contact, rate and force is not constant. This is similar to placebo therapy from previous studies also testing mobilisations (Perry and Green, 2008; Haas *et al.,* 2014). The plinth will be mounted over the force plates to quantify and compare the forces applied in both therapies.

Once therapy is complete participants will then be tested again for para-spinal stiffness, balance tests on the force plates and VAS scale for lumbar movements. Once both testing sessions have been completed, participants will be thanked for their contribution and given a debrief sheet with contact details and information regarding the study to give to their GP or carer if they wish.

References

Andonian, B., Masi, A., Aldag, J., Barry, A, Coates, B., Emrich, K., Henderson, J., Kelly, J. and Nair, K. (2015). Greater resting lumbar extensor myofascial stiffness in younger ankylosing spondylitis patients than age-comparable healthy volunteers quantified by MyotonPRO. *Archives of Physical Medicine and Rehabilitation,* 96(11), 2041 – 2047.

Haas, M., Vavrek, D., Peterson, D., Polissar, N. and Neradilek, M. (2014). Dose-response and efficacy of spinal manipulation for care of chronic low back pain: a randomised controlled trial. *The Spine Journal,* 14(7), 1106 – 1116.

Julious, S. (2005). Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics,* 4, 287 – 291.

Mackenzie, I., Morant, S., Bloomfield, G., MacDonald, T. and O'Riordan, J. (2014). Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. *Journal of Neurology, Neurosurgery and Psychiatry,* 85(1), 76 – 84.

Owens, E., DeVocht, J., Gudavalli, R., Wilder, D. and Meeker, W. (2007). Comparison of posteroanterior spinal stiffness measures to clinical and demographic findings at baseline in patients enrolled in a clinical study of spinal manipulation for low back pain. *Journal of Manipulative and Physiological Therapeutics,* 30(7), 493 – 500.

Perry, J and Green, A. (2008). An investigation into the effects of a unilaterally applied lumbar mobilisation technique on peripheral sympathetic nervous system activity in the lower limbs. *Manual Therapy,* 13(6), 492 – 499.

Viir, R., Laiho, K., Kramarenko, J. and Mikkelsson, M. (2006). Repeatability of trapezius muscle tone assessment by a myometric method. *Journal of Mechanics in Medicine and Biology,* 6(2).

12. Risks to participants' and researcher's safety & wellbeing

Anthropometric measures – emotional risk to participant regarding condition, disabilities, age and weight. The MS questions and measurements will be conducted in a sensitive manner and not rushed. If the participant becomes emotional at any point during the session, the researcher will manage the situation sensitively. The participant will be encouraged to take their time when answering questions and are not required to answer questions they do not feel comfortable to answer.

VAS pain scale testing – physical risk from lumbar movements and emotional risk in description of pain. Participant will be encouraged to only move within their capabilities and the researcher will be present to assist them if needed. Participant will be encouraged to rest when they feel is necessary or when feeling tired.

GRF testing – physical risk from single leg balance tests. Participant will be encouraged to only move within their capabilities and the researcher will be present to assist them if needed. Participant will be encouraged to rest when they feel is necessary or when feeling tired.

Para-spinal stiffness testing - risk of discomfort in prone position. Participants can use a bolster under ankles for comfort and will be asked regarding comfort regularly.

Spinal mobilisation/placebo therapy - risk of pain or discomfort during therapy. Physiotherapist use of patient feedback if any pain or discomfort felt during manual therapy. The researcher will be available for assistance if discomfort felt during measurement collecting or treatment. Relaxation will be encouraged and Edinburgh Napier security staff who are first aid trained are reachable if required.

13. Consent and participant information arrangements, debriefing, withdrawal from the study

Participants will be sent an information sheet and contraindications questionnaire in advance via email to read before attending the session. The protocol will be explained again in person and

consent form given for participant to complete at their will. Once experiment is complete, a debrief sheet will be given to participant with further information and contact details regarding the project, as well as stating thanks for taking part.

Participants will be made aware that they are able to withdraw from the study at any time with no need for a reason. If the participant choses to withdraw from the study they will be encouraged to rest before leaving the study. Their data will be deleted and an extra participant will be attempted to be recruited.

14. Anonymity and confidentiality

All data collected and information given will be done so in confidentiality with the researcher, which will be made clear to the participant. The physiotherapist will only be present during the therapy session and not present in the collection of any data. Participant names will be replaced with number in collective data and not identifiable to them personally.

15. Data protection arrangements

All data collected during testing will be inputted to an excel spread-sheet with the participant's name replaced by a random number and will therefore be unidentifiable. The contact details and code for participant numbers will be stored on separate file. This will be kept on the V:drive of a University password protected computer which only the researcher has access and anti-virus software will be kept up to date. This will be backed up regularly to an external hard drive that is stored in a locker with a lock and key, which only the researcher has access to. The medical data collected will be kept in the Novi software which is also password protected and unidentifiable. The computer will be locked when the researcher is away from the desk and anti-virus software will be kept up to date. Any reports or publication for the study will not disclose identifiable information of the participants and will only use summary data.

16. Ethical considerations raised by the project and how you intend to deal with them

Participants do not need to answer questions they are not comfortable with answering and do not need to continue with any form of testing they are not comfortable with. The will be encouraged to take their time in the testing and made aware they can withdraw from the study without any need to give a reason. Participants will adhere to the inclusion/exclusion criteria to eliminate any pathological danger from either spinal therapies. If they do not respond to positively to any contraindications, GP permission is not required as MS patients will often self-refer to therapeutics beneficial for symptomatic based treatment. Participants will be allowed a friend/family/carer to accompany them for ease and to make them more comfortable.

DECLARATION

There is an obligation on the researcher to bring to the attention of the School Research Integrity Committee any issues with ethical implications not clearly covered by this application form.

I request ethical and governance approval for the research described in this application. I have read Edinburgh Napier University's policies and guidelines relating to ethics and governance in research, and those of relevant professional bodies (e.g. BPS, BSA, IFPA, SIR, NMC) and agree to abide by these.

A ☐	I consider that this project has minor/no significant ethical implications to be brought to the attention of the School Research Integrity Committee
B ☒	I consider that this project may have significant ethical implications to be brought to the attention of the School Research Integrity Committee

Signature   **Date**

I am the Director of Studies or supervisor for this research. I have read this application and approve it. I do not consider that any part of the research process will cause physical and/or psychological harm to participants, or be detrimental to the reputation of Edinburgh Napier University.

Signature   **Date**

- **You must also attach the following documentation, where appropriate (please tick to confirm or provide information as to why the materials are not available):**
  Research materials (questionnaire, interview schedule, experimental stimuli, etc.)
  Recruitment materials (poster, leaflet, social media message, covering letter, etc.)
  Participant information sheet

  Consent form

  Debrief sheet

  Evidence of permission from outside organisation

- **You may need to create different versions of these materials (e.g. parental Participant Information Sheet and Consent Form if research involves children); if so, all the different versions should be attached. Materials should be printed on paper headed with the University logo.**
- **Submit the completed and signed form (with supporting materials) to** ▮▮▮▮▮ ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮**; an electronic copy should also be sent to: ethics.fhlss@napier.ac.uk.**

PhD Study requires volunteers for:

The Immediate effect of Spinal Therapy with Multiple Sclerosis Patients
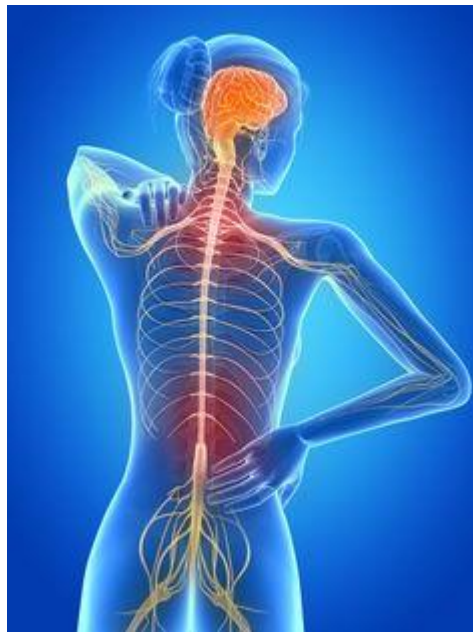
Participants must be:

- Female
- Diagnosed with MS
- Aged within 18-80
- Ability to walk independently

Participants will be required to take part in two testing sessions consisting of spinal manual therapy and lower back muscle quality, stability and movement tests. This will take place at the Edinburgh Napier University Sighthill Campus.

For more information regarding this study please contact Rebecca Hamilton at

Appendix 11 Study Two and Three Novi Survey Questionnaire

MS study questionnaire

Thank you for showing interest in taking part in this study. Please complete the set of questions in this questionnaire to confirm that you are eligible.

1. **What is the participant number you were allocated?**

   This is to assure that there is complete confidentiality in the information that you give.

   Participant number ☐

2. **Are you currently receiving any manual therapy for your spine?**

   [_____] 0 / 2000

3. **Have you ever had an appointment or a connection with Point One Physiotherpay Clinic?**

   [_____] 0 / 2000

▶

This is to check for any absolute contraindications and make sure that it is safe for you to receive spinal therapy.

1. Have you been diagnosed with any serious bone related condition?

	Please answer yes or no	
	Yes	No
Tumour (benign or malignant)	☐	☐
Infectious disease (e.g. tuberculosis)	☐	☐
Metabolic (e.g. osteomalacia, softening of bones)	☐	☐
Birth defect (dysplasia)	☐	☐
Inflammatory (e.g. severe rheumatoid arthritis)	☐	☐
Traumatic (current healing fractures/dislocations)	☐	☐

If you answered 'yes' or have been diagnosed with a condition not listed, please give details.

0 / 2000

2. Have you been diagnosed with any serious neurological condition (excluding MS)?

	Please answer yes or no	
	Yes	No
Spinal cord/spinal nerve compression	☐	☐
Spinal cord damage	☐	☐
Cauda Equina syndrome (spinal cord nerve swelling)	☐	☐

If you answered 'yes' or have been diagnosed with a condition not listed, please give details.

0 / 2000

3. Have you been diagnosed with any serious vascular condition (relating to blood vessels)?

	Please answer yes or no	
	Yes	No
Aortic dysfunction (e.g. aneurism/blood clot)	☐	☐
Severe haemophilia (causing bleeding into joints)	☐	☐

If you answered 'yes' or have been diagnosed with a condition not listed, please give details.

0 / 2000

◀ ▶

This is to check for any relative contraindications so we are aware of anything that could respond adversly to spinal therapy.

1. Have you been diagnosed with any of the following?

	Please answer yes or no	
	Yes	No
Spinal disc prolapse (spinal disc herniations, tear in disc cartilage causing nerve to bulge out pressing on the nerve)	☐	☐
Spondylosis (degeneration of spinal discs)	☐	☐
Spondylolisthesis (spinal instability/displacement of discs)	☐	☐
Inflammatory arthritides (rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis, osteoarthritis)	☐	☐
Osteoporosis (decreased bone strength low level bone mass)	☐	☐
Hypermobile syndrome (segment or joint hypermobility)	☐	☐
Abnormal cell growth (active or history of cancer)	☐	☐
Cardiovascular disease (history of thrombosis or using blood clot prevention medication)	☐	☐
Respiratory disease (pneumonia, bronchitis, asthma)	☐	☐

Please give further details if necessary.

0 / 2000

2. Are you currently pregnant or had previous pregnancy complications?

0 / 2000

3. Do you currently have an injury that is healing?

This includes local infection, open wounds, fractures and dislocations.

0 / 2000

4. Have you ever had any adverse reaction to a spinal treatment?

This could be a reaction to previous spinal surgery or previous spinal manual therapy.

0 / 2000

This is to gather some basic information about your MS condition.

1. What type of MS have you been diagnosed with (Relapse-Remitting, Secondary Progressive etc.)?

0 / 2000

2. How many years ago was your diagnosis?

0 / 2000

3. What is your rating on the Expanded Disability Status Scale (EDSS)?

This is a number between 1 and 10 and can be determined by either yourself or your GP. If you are unsure of this rating please see website link here https://www.mstrust.org.uk/a-z/expanded-disability-status-scale-edss

Please give further details if necessary.

0 / 2000

4. Which functional system is most symptomatic for you?

These are the different disability categories the EDSS scale is based on. If you are not aware of these please see link to website here https://www.mstrust.org.uk/a-z/expanded-disability-status-scale-edss

Please give further information if necessary.

0 / 2000

Participant Information Sheet

Study Title: The immediate effect of spinal therapy in multiple sclerosis.

Study Summary

My name is Rebecca Hamilton and I am a PhD researcher from Edinburgh Napier University. I am carrying out a study that will test the immediate effect of manual therapy over the spine on multiple sclerosis patients. This is to collect information that will enable us to develop a study to investigate what happens in a long-term spinal therapy intervention. This study is funded by Medical Research Scotland and Point One Clinic; both interested in finding out more scientific information on spinal therapy in multiple sclerosis.

Who can take part in the study?

I am looking for 24 volunteers to take part. To be suitable you must be between the ages of 18 and 70, be female, you must have an MS diagnosis, you must have an EDSS rating less than 6, and you must be able to stand on one leg for approximately 3 seconds. If you are interested you should read through the contra-indications listed in table A and B. If you have had any of the conditions listed in table A, you will not be able to take part in the study. If you have had any conditions listed in table B, you should ask permission from your GP in order to take part. I can provide you with a GP information sheet and you can use this information sheet, to answer any questions your GP has regarding your involvement in the study. Contact details are also provided below to answer any further questions. If you have a connection with Point One Clinic you will not be able to take part either due to a conflict of interest.

What will the study involve?

The study will look at the effects of two different spinal manual therapy techniques. I will test you in 3 areas before and after each of these therapies in order to investigate their immediate effect. These will be stiffness levels in your lower back muscles, pain during lower back movements and stability in single leg standing and lunging.

If you chose to take part you will attend 2 sessions that suit your availability, lasting a maximum of 2 hours. In your first session I will gather basic information about your MS condition, and measurements for your weight, height and age. You will perform a single leg lunge on each side which will test stability, basic movements using your lower back muscles to test your levels of pain and the stiffness in your lower back muscles will be measured. You will then receive a 30-minute, low grade, spinal manual therapy. You will not know which technique you are receiving. This will be revealed to you at the end of both sessions. Once therapy is complete you will be tested in the same measurements again. There is a risk that you will feel uncomfortable during the therapy or testing. However, you will not be required to answer or perform any tests which you are not comfortable with and can give feedback to myself to modify anything uncomfortable. You will be free to withdraw from the study at any stage. You will not have to give a reason, and it will not affect your treatment.

Possible benefits

By taking part in the study I cannot guarantee that it will help with the rehabilitation in your MS condition, however it will give you the opportunity to try 2 different types of spinal manual therapy and see if there is any immediate effect in your stiffness, pain and stability. Your contribution will also help with gathering knowledge about physiotherapy within MS and could benefit others in the wider MS community. Although I cannot provide you with any financial gift for participating, there will be taxi arrangements made to pick you up and drop you off in order to attend, unless you prefer your own method of transport.

Possible Disadvantages

There is always a possibility that you will be uncomfortable during the therapy, or during the testing. However, you do not need to continue with any part of these which you are not comfortable with and you can withdraw from the study at any time. The information collected from your testing will not be kept if you chose to withdraw from the study.

Further Information

All the information about yourself will not be identifiable to you as your name will be replaced with number. It will not be possible for anyone other than myself to identify your personal information during the study. This information will be kept in a safe place to which only I have access. Personal information will be kept until the end of this study in September 2017 and will then be destroyed. The combined information from all participants will then be used in the study report and may be published in relevant journals. The findings of this study will contribute to the research in rehabilitation within MS sufferers in finding a therapy that makes a difference in pain, stiffness and mobility.

If you would like to contact an academic supervisor for this project, you are welcome to contact Dr Susan Brown or Dr Claire Garden, whose contact details are provided. If you would like to contact an independent person, who knows about this project but is not involved in it, you are welcome to contact Dr Geraldine Jones.

If you have any other questions, please do not hesitate to contact me using the details for Rebecca Hamilton provided.

Contact details of researcher

Name of researcher: Rebecca Hamilton

Address: ███████████████████████████████████
███████████████

Email / Telephone: ████████████████████████████████

Contact details of supervisors

Name of supervisor: Dr Susan Brown

Address: ███████████████████████████████████
███████████████

Email/Telephone: ██████████████████████████

Name of supervisor: Dr Claire Garden

Address: ████████████████████████████████████
████████████████

Email/Telephone: ████████████████████████

Contact details of the independent adviser

Name of adviser: Dr Geraldine Jones

Address: ████████████████████ ████████████████████
████████████████

Email/Telephone: ████████████████████████

Table A. Absolute Contraindications

Condition category	Further details, these include:
Serious bone related condition	Tumour (benign or malignant)
	Infectious disease (e.g. tuberculosis)
	Metabolic (e.g. osteomalacia, softening of bones)
	Birth defect (dysplasia)
	Inflammatory (e.g. severe rheumatoid arthritis)
	Traumatic (healing fractures/dislocations)
Serious neurological condition (excluding MS)	Spinal cord/spinal nerve compression
	Spinal cord damage
	Cauda Equina syndrome (spinal cord nerve swelling)
Serious vascular condition (relating to blood vessels)	Aortic dysfunction (e.g. aneurism/blood clot)
	Severe haemophilia (causing bleeding into joints)

Table B. Relative Contraindications

Condition	Further details
Spinal disc prolapse	Spinal disc herniation, tear in disc cartilage causes it to bulge out pressing on nerve
Spondylosis	Degeneration of spinal discs
Spondylolisthesis	Spinal instability/displacement of discs
Inflammatory arthritides	Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis, osteoarthirtis

Osteoporosis	Decreased bone strength, low level bone mass
Hypermobile syndrome	Segment or joint hypermobility
Pregnancy	Current pregnancy, previous problematic pregnancy
Abnormal cell growth	Active or history of cancer
Cardiovascular disease	History of thrombosis or using blood clot prevention medication
Respiratory disease	Pneumonia, bronchitis, asthma
Current healing injury	Local infection, open wounds, fractures, dislocations
Adverse reaction to spinal treatment	Previous spinal surgery, previous reaction to spinal manual therapy

Appendix 13 Study Two Consent Form

Participant Consent Form

Study Title: The immediate effect of spinal therapy in multiple sclerosis.

Participant Identification number:

Please initial box

1. I confirm that I have read and understood the information sheet for the study titled above. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without needing to give any reason. I understand that the way in which I am treated throughout the study will not be affected if I chose to withdraw.

3. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

4. I agree to take part in the above study.

_____   _____   _____

Name of participant   Date   Signature

_____   _____   _____

Name of researcher   Date   Signature

Contact details of the researcher

Name of researcher: Rebecca Hamilton

Address: ███████████████████████████████ ██████

████████████████████

Email / Telephone: ███████████████████████████

240

Appendix 14 Study Two Testing Sheet

Participant number: Participant Group:

Anthropometrics

Height (m)	Weight (N)	Weight (Kg)	BMI	DOB	Dominant side

Erector spinae mark length (cm)	Erector spinae mark width (cm)

Session 1 date:

Testing side:

VAS scoring

VAS score: initial	VAS score: post lumbar movements pre massage	VAS score: post lumbar movements post massage	ROM in lumbar movements post massage

Myoton Pro

Pre massage	Stiffness (N/m)	Stiffness (N/m)	Post massage	Stiffness (N/m)	Stiffness (N/m)
	left side	right side		left side	right side
1			1		
2			2		
3			3		
Mean			Mean		

Session 2 date:

Testing side:

VAS scoring

VAS score: initial	VAS score: post lumbar movements pre massage	VAS score: post lumbar movements post massage	ROM in lumbar movements post massage

Myoton Pro

Pre massage	Stiffness (N/m)	Stiffness (N/m)	Post massage	Stiffness (N/m)	Stiffness (N/m)
	left side	right side		left side	right side
1			1		
2			2		
3			3		
Mean			Mean		

Extension/Flexion   Left/Right Side Bending   Left/Right Rotation

| No Pain | | | | | Moderate Pain | | | | | Worst Pain |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |

0   2   4   6   8   10

Figure 16. 1 Intervention force data recorded equates to mobilisations at threshold of 80N and 0.37Hz (22 beats per min on the metronome).
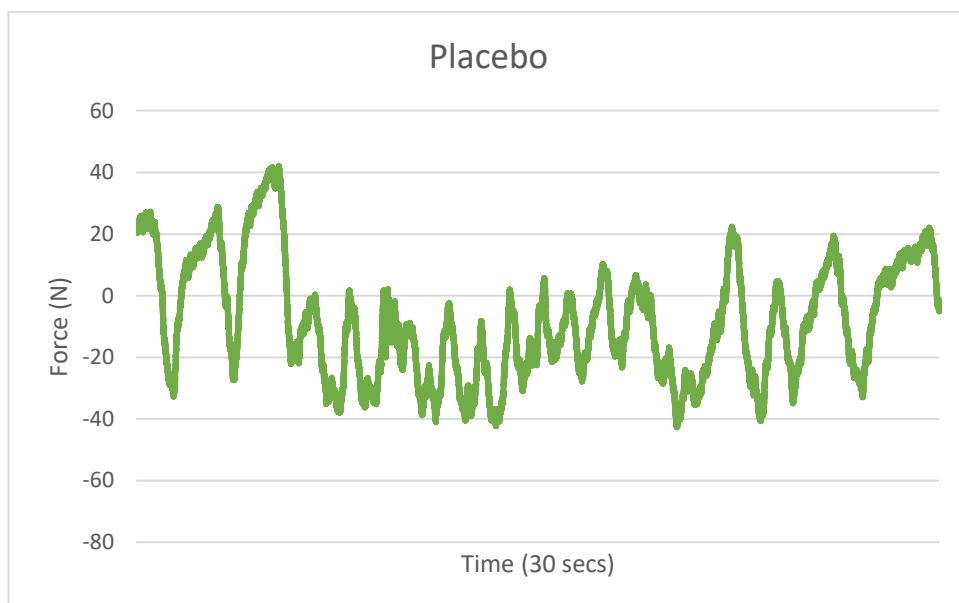
Figure 16. 2 General massage force data recorded with no force, rate or location specificities.

Debrief Sheet

I would like to thank you for your participation in this study. The aim of this study is to provide useful information with regards to spinal manual therapy and rehabilitation within MS. The different techniques of therapy you received were a mobilisation therapy which uses light passive oscillatory movements around the spine in a consistent motion, and a placebo which was a light grade massage with no consistent movements. The reasons for these 2 techniques is to scientifically investigate mobilisations over in the spine which requires testing against a placebo in similar condition but without the consistent movement.

Your contribution in this study is greatly appreciated and assists in the further investigation of spinal therapy with multiple sclerosis patients. If you experience any adverse side effects or have any initial feedback please get back in touch or contact your GP. If you have any more questions regarding the study feel free to ask. Contact details for myself, academic supervisors and the independent advisor are provided below.

Contact details of researcher

Researcher: Rebecca Hamilton

Address: ████████████████████████████████████
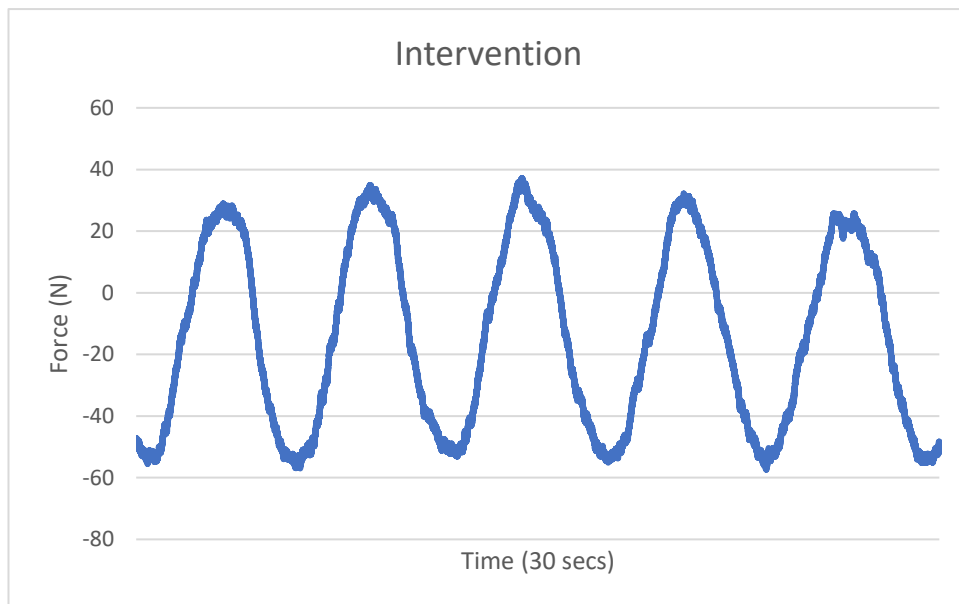   ████████████████

Email/Telephone: ████████████████████████████████

Contact details of supervisors

Supervisor: Dr Susan Brown

Address: ████████████████████████████████
                     ████████████████

Email/Telephone: ████████████████████████

Supervisor: Dr Claire Garden

Address: ████████████████████████████████
                     ████████████████

Email/Telephone: ████████████████████████

Contact details of the independent adviser

Adviser: Dr Geraldine Jones

Address: ████████████████████████████████████
                     ████████████████

Email/Telephone: ████████████████████

Appendix 18 Study Three Approved Ethics Application

Project title: Investigating the effect of spinal therapy in people with Multiple Sclerosis.   **Version no: 2**

Full name & title: Miss Rebecca Isabel Hamilton   **School:** School of Applied Sciences

E-mail address: ████████████████████   **Telephone:** ████████

Postal address: ████████████████████████████████████
████

Status:Staff (Edinburgh Napier University)☐**Student (Edinburgh Napier University)**☐

External Applicant ☐   *Please provide additional details below:*

Other researchers (name, role & affiliation):   **Matriculation Number: 40100069**

Dr Susan Brown, Director of Studies, School of Applied Sciences, Edinburgh Napier University, Dr Claire Garden, Supervisor, School of Applied Sciences, Edinburgh Napier University   **Degree programme: Research Degree**

Level of study: MRes/MPhil/PhD

Financial support from outside Edinburgh Napier University (amount & source): Medical Research Scotland, Point One Clinic

Project start date: 24/09/2018   **Project duration:** 6 months

Date application submitted: 07/09/2018   **Ref no. (LEAVE BLANK):** Click here to enter text.

	YOU MUST ANSWER ALL QUESTIONS	YES	NO	N/A
1	Will you describe the main procedures to participants in advance, so that they are informed about what to expect in your study?	☒	☐	☐
2	Will you tell participants that their participation is voluntary?	☒	☐	☐
3	Will your participants be able to read and understand the participant information sheet?	☒	☐	☐
4	Will you obtain written consent for participation?	☒	☐	☐
5	If the research is observational (including tape and video), will you ask participants for their consent to being observed?	☐	☐	☒
6	Will you tell participants that they may withdraw from the research without penalty and without reason?	☒	☐	☐
7	With questionnaires and interviews, will you give participants the option of omitting questions they do not want to answer?	☒	☐	☐

8	Will you tell participants that their data will be treated with full confidentiality and that, if published, it will not be identifiable as theirs?	☒	☐	☐
9	Are the data to be stored anonymously (i.e. the identity of the person is NOT linked directly or indirectly with their data)?	☒	☐	☐
10	Will you debrief participants at the end of their participation (i.e. give them a brief explanation of the study and an opportunity to ask questions)?	☒	☐	☐
11	Will the research involve deliberately misleading participants (deception) in any way?	☐	☒	☐
12	Is there any realistic risk of any participants experiencing either physical or psychological distress or discomfort?	☒	☐	☐
13	Is the information gathered from participants of a sensitive or contentious nature?	☒	☐	☐
14	Will any payment or reward be made to participants, beyond reimbursement or out-of-pocket expenses?	☐	☒	☐
15	Do participants fall into any of the following special groups? *If the answer is YES, indicate which group(s) by checking the appropriate box(es).*	☒	☐	☐

☐ Children (under 18 years)   ☐ People in custody

☒ Clinical population   ☐ People with learning or communication difficulties

☐ People with mental health issues   ☐ People engaged in illegal activities (e.g. drug-taking)

NOTE: You may also need to obtain clearance from Disclosure Scotland or an equivalent authority.

You must check **either Box A or Box B** below and provide **all** relevant information in support of your application in the Details of Project section. If you answered **NO** to any of **questions 1-10**, or **YES** to any of **questions 11-15** (with a shaded background), then you **must** check Box B.

DETAILS OF PROJECT

17. Background information *(references should be cited and listed)*

The management of individualised symptoms occurring within multiple sclerosis (MS) is a key element for management of the condition (Khan *et al.,* 2007). Nerve signal disruption results in a wide variation of symptoms, with mobility often a main issue (Vollmer *et al.,* 2002). It can be difficult for patients and health professionals to identify the most efficient rehabilitation programme to help manage their symptoms. Rehabilitation programmes often need regular re-evaluation, and longer time to have an effect (Demaree *et al.,* 1999; Dimitrov and Turner, 2014). Effects of therapeutics are often measured using clinical outcomes and disability scales, mostly subjective or secondary measurements. The interpretation of these results also often dependent

on many factors out of control of the researcher (Langdon and Thompson, 1999). Therefore an objective form of analysis for manual therapeutics can help to determine the specifics of their effects and when they are most useful.

Manual therapy (MT) over the spine has previously shown to have a positive effect on pain, stiffness and mobility without full understanding as to why (Chiradejnant *et al.,* 2003; George *et al.,* 2006). Spinal mobilisations is an MT technique used within physiotherapy practice for many years and still common today (Piekarz and Perry, 2016; Maitland *et al.,* 2014). Often tested in sessions for under 7 minutes, at a rate of 2-3 Hz, it describes a low velocity and high amplitude therapy with oscillatory manual contact (Perry and Green, 2008; Shum *et al.,* 2013). The spine experiences movement by rotation of pelvis and thoracic cage, compression of skin and tissues, and movement of spinal joints (Chansirinukor *et al.,* 2003; Shum *et al.,* 2013). Spinal mobilisation therapy has been used within Point One Clinic at a slower rate (0.4 Hz) for a longer time (30 mins) with positive anecdotal feedback from MS patients.

Para-spinal muscles are said to contribute to spinal stability, functionality and prevention of buckling of the spine (Triano, 2001). By alleviating pain and stiffness in spinal tissue over time, improved para-spinal muscle usage can enhance neuromuscular associations in the long-term. Para-spinal muscles can be a main limiting factor for movement of the whole body when highly tense and stiff, contributing to clinical disability status (Bernistas *et al*.,2015). The information for para-spinal muscle quality data will contribute to bridging the gap between neurophysiological response and mobility outcome measures (Schneider *et al.,* 2015). Specifically, the study will provide this with use of a myometer, Myoton Pro. This has not been investigated with an MS population before this project, however has been tested with similar chronic conditions such as Parkinson's disease and stroke, where it has been previously validated with reliable results (Marusiak *et al.,* 2012; Chuang *et al.,* 2012).

Information on body sway and balance will also be gathered to help analyse the potential effect of this intervention on lower extremity stability. The study will test functional stability in single leg stance and lunge using measurements for centre of pressure and body sway, often used for clinical testing (Ramdharry *et al.,* 2006). Tests for pain in basic lumbar movements will be used, which is common practice in lower back therapy (Goodsell *et al.,* 2000; Shum *et al.,* 2013). Though this is not an objective measurement it is often referred to as a useful measure for effect in lower back therapy and can be used for comparison across the objective measures.

The biomechanical information based on para-spinal soft tissue and walking gait that can be gathered in this study will provide an objective contribution to understand spinal therapy and rehabilitation, facilitating improved therapeutics for patients. This is a key element for symptom management, aiding in improved physical mobility and subsequently improving quality of life.

This spinal mobilisation technique has been tested as an intervention firstly in a lower back pain (LBP) population and then with an MS population, both testing for immediate effects. The MS population did not show any significant findings in contrast to the LBP population who did, providing rationale for testing a longer-term effect as MS patients may take longer to show a response. This study proposes an investigation into the effects of the spinal mobilisation intervention after repeated sessions, as a contribution to research in MS rehabilitation and therapeutics.

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18. Aims & research questions

The aim of this study is to investigate the effect of a particular spinal mobilisation intervention after 4 weekly sessions, with an MS population group. The effect will be tested on para-spinal muscle response (stiffness, tone, elasticity), body sway, stability and levels of lumbar pain. The intervention has not had effect previously after a single session, therefore the study is analysing the effect after repeated sessions to investigate if a longer response time is required. The

intervention will be tested against a placebo therapy to test the differences that are occurring are due to specific techniques within mobilisation therapy.

Does the intervention have an effect on para-spinal muscle characteristics after 4 sessions?

Does the intervention have an effect on functional stability after 4 sessions?

Does the intervention have an effect on lower back pain after 4 sessions?

19. **Participants**
   - ***Number & nature of sample:*** Recommended number of participants for repeated measures, between factors ANOVA is 36, with 18 people in each group. This is shown in G-power with a large effect size of 0.4 (using partial eta squared), a power of 0.8 and significance level of 0.05. The study will aim to recruit as close to this number as possible, however with the time restrictions on the study this may not be possible.
   - ***Inclusion/exclusion criteria:*** Inclusion criteria; must have an MS diagnosis, must be diagnosed less than 6 in the Expanded Disability Status Scale (EDSS) which ranges from minimal disability within the disease up until requiring a simple walking aid for mobility (Kurtzke, 1983), must be within the ages of 18-80. Exclusion criteria; must not be connected with Point One Clinic, must not respond positive to spinal therapy absolute contraindications which include bone tumour, inflammatory/infectious/metabolic disease affecting the spine, dysplasia, healing fractures/dislocations, spinal cord damage, cauda equine syndrome, aortic dysfunction and severe haemophilia. Participants responding positive to any relative contraindications will be excluded based on severity, these include spinal disc prolapse, spondylosis, spondylolisthesis, inflammatory arthritides, osteoporosis, hypermobile syndrome, pregnancy, cancer, cardiovascular disease, respiratory disease, healing injury and adverse reaction to previous spinal treatment (Maitland *et al.,* 2014). Participants responding positive to any relative contraindications will be asked to request permission from their GP whether it is safe for them to take part. The therapist will be made aware of any relative contraindications before treatment. All treatments will be gentle and low grade.
   - ***Recruitment of participants, including details of formal permissions from another organisation (where appropriate):*** Participants will be recruited via poster, social media (Facebook, Twitter and Instagram) and word of mouth. Physiotherapy and health centres will be contacted by email or in person to ask if there is interest in the study to put up a poster advertisement. Contacts were made to MS charities and health centres in recruitment of last study which will be used again. Once ethical approval has been acquired, further enquiries into charity and private based health and therapy centres will be made, either over the phone, email or in person. The poster and information sheet will be used electronically and in person when interest is shown to participate as a response from advertisement. When interest is shown in person the researcher will only cite information from the poster and explain the information sheet. No coercion will be added when speaking face to face. Questions regarding the study will be encouraged and participants will be encouraged to read through the information sheet before volunteering for the study.
   Details of any relationship with participants which may affect the research: If the participant is known by the researcher they may feel pressured to participate in the research even if they don't feel comfortable. However honesty and questions will be encouraged by the researcher and they will be informed they can withdraw from the study at any point. Data gathered from participants is all

objective gathered from biomechanical devices and therefore cannot be affected by any relationship with the participant and researcher.

20. Outline of methods & measurements

36 participants will be recruited to take part in this study. After a participant has shown interest in the study and agreed to take part, a link to the Novi Survey (https://survey.napier.ac.uk/n/zz35j.aspx) created will be sent to collect information about their MS condition and any contra-indications they may positively respond to. They will be randomly placed in a placebo or intervention group by an excel random group generator and given a participant number in order to maintain security on their personal medical information. Only the researcher will have access to this information. If the participant does not meet the inclusion criteria they will be informed they are unable to participate. If the participant responds positively to one of the relative contra-indications, they will be advised to request permission from their GP and sent the GP information sheet for this. If all inclusion criteria are met, the researcher will then organise suitable times for their sessions.

Participants will be tested on 4 separate occasions. The first session will consist of a spinal treatment session and measurement testing pre and post the intervention. The following 3 sessions will then have measurement testing only post the spinal treatment. Travel arrangements will be offered and arranged by the researcher to enable participants to come into the campus facilities for the sessions. All testing will take place at the Edinburgh Napier University Sighthill campus and temperature will be kept at room temperature (21°).

Participants will have the opportunity to read through the information sheet again and the researcher will run through the order of events. Participants will be invited to ask any questions about the study before consent forms are given. Once the participant has given written consent, anthropometric measures will be taken by the researcher for age, weight and height. The results from their Novi questionnaire will be reviewed in person to go through their MS information and any contraindications. Measurements for lower back pain will be taken using a visual analogue scale (VAS) scale. This a subjective measure of pain, however shown to be common practice in the gathering of data for lower back therapeutics and can therefore be compared to the objective measures. Force plates will be used in single leg stance tests and a sit-to-stand test. Para-spinal stiffness testing will be done with participants lying in a prone position on a plinth using a myometer digital palpation device (MyotonPRO, Myoton Ltd., London, UK). This is a handheld device held perpendicular to the muscle and collects measurements by calculating the response from small oscillations sent through the muscle (Andonian *et al*., 2015; Viir *et al.,* 2006). Measurements will be taken on both sides of the spine on erector spinae muscles (longissimus). Measurements for oscillation frequency (Hz), dynamic stiffness (N/m) and the logarithmic detriment (elasticity) will be taken both sides of the spine. The side that results in a higher stiffness value will be the side receiving therapy.

The massage therapist working under their own liability will then perform a 30 minute therapy session of either a spinal mobilisation intervention, or a placebo general massage. The intervention consists of oscillatory movement over L1-L5 region of the spine, at a rate less than 0.37 Hz and grade less than 1. During this therapy the therapist's manual contact is constant and is not lifted from the participant's spine. This is a very gentle therapy with less force being felt than sitting on a massage chair. The general massage will consist of only effleurage movements at grade 1 and will have no consistent region or pressure rate.

Once all testing sessions have been completed, participants will be thanked for their contribution and given a debrief sheet with contact details and information regarding the study to give to their GP or carer if they wish.

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21. Risks to participants' and researcher's safety & wellbeing

Anthropometric measures – emotional risk to participant regarding condition, disabilities, age and weight. The MS questions and measurements will be conducted in a sensitive manner and not rushed. If the participant becomes emotional at any point during the session, the researcher will manage the situation sensitively. The participant will be encouraged to take their time when answering questions and are not required to answer questions they do not feel comfortable to answer.

GRF testing – physical risk from single leg balance tests. Participant will be encouraged to only move within their capabilities and the researcher will be present to assist them if needed. Participant will be encouraged to rest when they feel is necessary or when feeling tired.

Para-spinal stiffness testing - risk of discomfort in prone position. Participants can use a bolster under ankles for comfort and will be asked regarding comfort regularly.

Spinal treatment - risk of pain or discomfort during therapy. Physiotherapist use of patient feedback if any pain or discomfort felt during manual therapy. The researcher will be available for assistance if discomfort felt during measurement collecting or treatment. Relaxation will be encouraged and Edinburgh Napier security staff who are first aid trained are reachable if required.

22. Consent and participant information arrangements, debriefing, withdrawal from the study

Participants will be sent an information sheet including information on contraindications in advance via email to read before attending the session. The protocol will be explained again in person and consent form given for participant to complete at their will. Once experiment is

complete, a debrief sheet will be given to participant with further information and contact details regarding the project, as well as stating thanks for taking part.

Participants will be made aware that they are able to withdraw from the study up until the point when their data is anonymised and analysed. If the participant choses to withdraw from the study, they will not need to give a reason for their withdrawal and will be encouraged to rest before leaving the study. Their data will be deleted and an extra participant will be attempted to be recruited.

23. Anonymity and confidentiality

All data collected and information given will be done so in confidentiality with the researcher, which will be made clear to the participant. The therapist will only be present during the therapy session and not be involved in the collection or analysis of data. Participant names will be replaced with number in collective data and not identifiable to them personally.

24. Data protection arrangements

All data collected during testing will be pseudonymised on an excel spread-sheet with the participant's name replaced by a random number and will therefore be unidentifiable. The contact details and code for participant numbers will be stored on separate file. This will be kept on the V:drive of a University password protected computer which only the researcher has access and anti-virus software will be kept up to date. This will be backed up regularly to an external hard drive that is stored in a drawer with a lock and key, which only the researcher has access to. The medical data collected will be kept in the Novi software which is also password protected and unidentifiable. The computer will be locked when the researcher is away from the desk and anti-virus software will be kept up to date. Any reports or publication for the study will not disclose identifiable information of the participants and will only use summary data.

25. Ethical considerations raised by the project and how you intend to deal with them

Participants do not need to answer questions they are not comfortable with answering and do not need to continue with any form of testing they are not comfortable with. The will be encouraged to take their time in the testing and made aware they can withdraw from the study without any need to give a reason. Participants will adhere to the inclusion/exclusion criteria to eliminate any pathological danger from either spinal therapies. If they do not respond to positively to any contraindications, GP permission is not required as MS patients will often self-refer to therapeutics beneficial for symptomatic based treatment. Participants will be allowed a friend/family/carer to accompany them for ease and to make them more comfortable.

DECLARATION

There is an obligation on the researcher to bring to the attention of the School Research Integrity Committee any issues with ethical implications not clearly covered by this application form.

I request ethical and governance approval for the research described in this application. I have read Edinburgh Napier University's policies and guidelines relating to ethics and governance in research, and those of relevant professional bodies (e.g. BPS, BSA, IFPA, SIR, NMC) and agree to abide by these.

A ☐	I consider that this project has minor/no significant ethical implications to be brought to the attention of the School Research Integrity Committee
B ☒	I consider that this project may have significant ethical implications to be brought to the attention of the School Research Integrity Committee

Signature   **Date**

I am the Director of Studies or supervisor for this research. I have read this application and approve it. I do not consider that any part of the research process will cause physical and/or psychological harm to participants, or be detrimental to the reputation of Edinburgh Napier University.

Signature   **Date**

- **You must also attach the following documentation, where appropriate (please tick to confirm or provide information as to why the materials are not available):**
  Research materials (questionnaire, interview schedule, experimental stimuli, etc.)
  Recruitment materials (poster, leaflet, social media message, covering letter, etc.)
  Participant information sheet

  Consent form

  Debrief sheet

  Evidence of permission from outside organisation

- **You may need to create different versions of these materials (e.g. parental Participant Information Sheet and Consent Form if research involves children); if so, all the different versions should be attached. Materials should be printed on paper headed with the University logo.**
- **Submit the completed and signed form (with supporting materials) to** ██████ **██; an electronic copy should also be sent to: ethics.fhlss@napier.ac.uk.**

PhD Study requires volunteers for:

The effect of a spinal therapy in people with Multiple Sclerosis
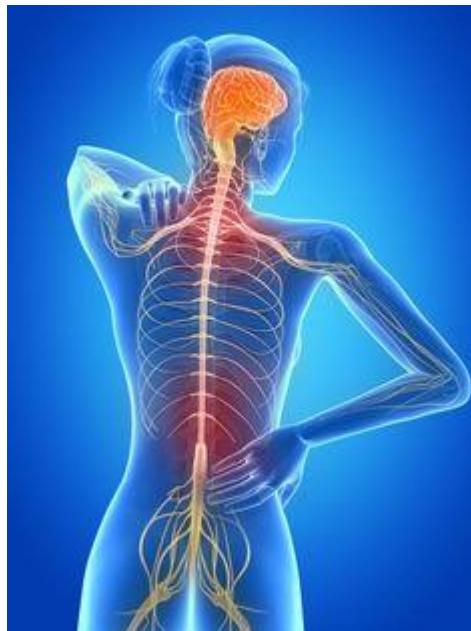
Participants must be:

- **Diagnosed with MS**
- **Aged within 18-80**
- **Ability to walk independently**

Participants will be required to take part in four testing sessions consisting of spinal therapy and lower back muscle quality, stability and movement tests. This will take place at the Edinburgh Napier University Sighthill Campus. Transport can be provided for people to come to the facilities.

For more information regarding this study please contact Rebecca Hamilton at ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮

Participant Information Sheet

Study Title: Investigating the effect of spinal therapy in people with multiple sclerosis.

Study Summary

My name is Rebecca Hamilton and I am a PhD researcher from Edinburgh Napier University. I am carrying out a study that will test the effect of a spinal therapy on people with multiple sclerosis (MS). This is to collect information that will contribute to knowledge in MS therapeutics. We are testing 2 different types of spinal therapy, one a general, low grade massage, and the other a mobilisation therapy working at a specific rate and specific pressure. This study is funded by Medical Research Scotland and Pacla Medical; both interested in finding out more scientific information on spinal therapy in MS.

Who can take part in the study?

I am looking for 38 volunteers to take part. To be suitable you must be between the ages of 18 and 80, you must have an MS diagnosis, you must have an EDSS rating less than 6, and you must be able to walk independently. If you are interested you should read through the contra-indications listed in table A and B. If you have had any of the conditions listed in table A, you will not be able to take part in the study. If you have had any conditions listed in table B, you are advised to ask permission from your GP in order to take part. I can provide you with a GP information sheet and you can use this information sheet, to answer any questions your GP has regarding your involvement in the study. Contact details are also provided below to answer any further questions. If you have a connection with Point One Clinic you will not be able to take part either due to a conflict of interest.

What will the study involve?

The study will look at the effects of 2 different spinal therapy techniques. You will be randomly allocated to a group to receive 4 sessions with one of these therapy types. I will test you in 3 different aspects to investigate whether the therapy has an effect on these areas. These will be lower back muscle stiffness, lower back pain and lower limb stability.

If you chose to take part you will attend 4 sessions that suit your availability. We will aim to have these sessions once a week and they will each last a maximum of 2 hours. In your first session I will gather basic information about your MS condition, and measurements for your weight, height and age. You will perform a single leg stance and sit-to-stand tests to test stability, you will rate your lower back pain on a VAS scale, your fatigue, and your lower back stiffness will be tested. You will then receive a 30-minute, low grade, spinal manual therapy. Once therapy is complete you will be tested in the same measurements again. For the following 3 sessions you will only be tested after receiving therapy and not before. There is a risk that you will feel uncomfortable during the therapy or testing. However, you will not be required to answer or perform any tests which you are not comfortable with and can give feedback to myself to modify anything uncomfortable. You will be free to withdraw from the study up until the point when your information has been anonymised and analysed. If you chose to withdraw you will not need to give a

reason and it will not affect your treatment. You can tell me you wish to withdraw verbally or by email and all information associated with you will be destroyed.

Possible benefits

By taking part in the study I cannot guarantee that it will help with the rehabilitation in your MS condition, however it will give you the opportunity to try a type of spinal therapy and see if there is any effect in your stiffness, pain and stability. Your contribution will also help with gathering knowledge about physiotherapy within MS and could benefit others in the wider MS community. Although I cannot provide you with any financial gift for participating, travel arrangements will be made for you, unless you prefer your own method of transport.

Possible Disadvantages

There is always a possibility that you will be uncomfortable during the therapy, or during the testing. However, you do not need to continue with any part of these which you are not comfortable with and you can withdraw from taking part in the study when you like. The information collected from your testing will not be kept if you chose to withdraw from the study before it has been anonymised and analysed.

Further Information

All the information about yourself will not be identifiable to you as your name will be replaced with number. It will not be possible for anyone other than myself to identify your personal information during the study. This information will be kept on a password protected file on a university server, to which only I have access. Personal information will be kept until the end of this project on October 2019 and will then be destroyed. The anonymised information from all participants will then be used in the report of the study in my PhD thesis and may be published in relevant journals. This information will be retained in the University for 10 years after which it will be destroyed. The findings of this study will contribute to the research in rehabilitation within MS sufferers in finding a therapy that makes a difference in pain, stiffness and mobility.

If you would like to contact an academic supervisor for this project, you are welcome to contact Dr Susan Brown or Dr Claire Garden, whose contact details are provided. If you would like to contact an independent person, who knows about this project but is not involved in it, you are welcome to contact Dr Geraldine Jones.

If you have any other questions, please do not hesitate to contact me using the details for Rebecca Hamilton provided.

Contact details of researcher

Name of researcher: Rebecca Hamilton

Address:

Email / Telephone:

Contact details of supervisors

Name of supervisor: Dr Susan Brown

Address:

Email/Telephone: ██████████████████████████

Name of supervisor: Dr Claire Garden

Address: ████████████████████████████████████
████████████████████

Email/Telephone: ██████████████████████████

Contact details of the independent adviser

Name of adviser: Dr Geraldine Jones

Address: ████████████████████████████████████
████████████████████

Email/Telephone: ██████████████████████████

Table A. Absolute Contraindications

Condition category	Further details, these include:
Serious bone related condition	Tumour (benign or malignant)
	Infectious disease (e.g. tuberculosis)
	Metabolic (e.g. osteomalacia, softening of bones)
	Birth defect (dysplasia)
	Inflammatory (e.g. severe rheumatoid arthritis)
	Traumatic (healing fractures/dislocations)
Serious neurological condition (excluding MS)	Spinal cord/spinal nerve compression
	Spinal cord damage
	Cauda equina syndrome (spinal cord nerve swelling)
Serious vascular condition (relating to blood vessels)	Aortic dysfunction (e.g. aneurism/blood clot)
	Severe haemophilia (causing bleeding into joints)

Table B. Relative Contraindications

Condition	Further details
Spinal disc prolapse	Spinal disc herniation, tear in disc cartilage causes it to bulge out pressing on nerve
Spondylosis	Degeneration of spinal discs

Spondylolisthesis	Spinal instability/displacement of discs
Inflammatory arthritis	Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis, osteoarthritis
Osteoporosis	Decreased bone strength, low level bone mass
Hypermobile syndrome	Segment or joint hypermobility
Pregnancy	Current pregnancy, previous problematic pregnancy
Abnormal cell growth	Active or history of cancer
Cardiovascular disease	History of thrombosis or using blood clot prevention medication
Respiratory disease	Pneumonia, bronchitis, asthma
Current healing injury	Local infection, open wounds, fractures, dislocations
Adverse reaction to spinal treatment	Previous spinal surgery, previous reaction to spinal manual therapy

Participant Consent Form

Study Title: The immediate effect of spinal therapy in multiple sclerosis.

Participant Identification number:

Please initial box

1. I confirm that I have read and understood the information sheet for the study titled above. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw without needing to give any reason. I understand that the way in which I am treated throughout the study will not be affected and my information will be destroyed if I chose to withdraw.

3. I understand that the information collected about me will be anonymised, used to support other research in the future, and retained for at least 10 years at the University.

4. I agree to take part in the above study.

_____   _____   _____
Name of participant   Date   Signature

_____   _____   _____
Name of researcher   Date   Signature

Contact details of the researcher

Name of researcher: Rebecca Hamilton

Address:

Email / Telephone:

Modified fatigue impact scale – 5 item

Because of my fatigue during the past 4 weeks

	Never (0)	Rarely (1)	Sometimes (2)	Often (3)	Almost Always (4)
1. I have been less alert.					
2. I have been limited in my ability to do things away from home.					
3. I have trouble maintaining physical effort for long periods.					
4. I have been less able to complete tasks that require physical effort.					
5. I have had trouble concentrating.					

Appendix 23 Study Three Testing Sheet

Testing document

Participant number:

Anthropometrics

Height (m)	Weight (N)	Weight (Kg)	BMI	DOB	EDSS	Most symptomatic FS

Dominant side	Symptomatic side	Erector spinae measurements (cm)	Pre fatigue score	Post fatigue score

Session 1 date: Testing side: Testing group:

Pre massage	Stiffness (N/m)	Stiffness (N/m)	Post massage	Stiffness (N/m)	Stiffness (N/m)
	left side	right side		left side	right side
1			1		
2			2		
3			3		
Mean			Mean		
Pre VAS			Post VAS		

Session 2 date:

Post massage	Stiffness (N/m)	Stiffness (N/m)
	left side	right side
1		
2		
3		
Mean		
Post VAS		

Session 3 date:

Post massage	Stiffness (N/m)	Stiffness (N/m)
	left side	right side
1		
2		
3		
Mean		
Post VAS		

Session 4 date:

Post massage	Stiffness (N/m)	Stiffness (N/m)
	left side	right side
1		
2		
3		
Mean		
Post VAS		

Debrief Sheet

I would like to thank you for your participation in this study. The aim of this study is to provide useful information with regards to spinal manual therapy and rehabilitation within MS. You received 4 sessions of either a mobilisation therapy, which uses light passive oscillatory movements around the spine in a consistent motion, or a general low grade massage without consistent pressure and movements.

The study is based around positive reports from the mobilisation therapy claiming to have improvements in lower back pain and stiffness. Gentle lower back massage has also shown to be beneficial in these areas. You may therefore find benefits in your lower back muscle stiffness, stability and function after these 4 treatments. The purpose of exploring these techniques was to test whether the consistency of the mobilisation technique shows a better effect than a general massage.

Your contribution in this study is greatly appreciated and assists in the further investigation of spinal therapy with MS patients. If you experience any adverse side effects or have any initial feedback please get back in touch or contact your GP. If you have any more questions regarding the study feel free to ask. Contact details for myself, academic supervisors and the independent advisor are provided below.

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