# CAN A STRESS MANAGEMENT PROGRAMME REDUCE STRESS AND IMPROVE QUALITY OF LIFE IN PEOPLE DIAGNOSED WITH MULTIPLE SCLEROSIS?

**by**

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## DECLARATION

**I declare that this thesis is my own account of my research and contains as its main content work which has not previously been submitted for a degree at any tertiary education institution.**

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## ABSTRACT

The National Institute for Health and Care Excellence clinical guidelines, together with the global consensus document 'Brain Health', acknowledge that modification of lifestyle factors contribute to the holistic care of people with Multiple Sclerosis (MS). While people with MS often report stressful life events as a precursor to developing MS, and despite increasing evidence of perceived stress as a risk factor for disease activity, the evidence for effectively managing stress in this population is limited. This study examined the effect of an educational program that incorporates progressive muscle relaxation (PMR), meditation and mindfulness exercises (ME) on people with MS over a six-month period.

100 people with relapsing remitting MS were randomly assigned to receive either stress management education (SME) or wait list (WL). The SME group received four one-on-one sessions during which they learned PMR, meditation and ME and were asked to perform these 5-7 days of the week for six months. The primary outcome measure was change in perceived stress as measured by: the stress Visual Acuity Scale (sVAS), the stress component of the Depression, Anxiety and Stress Score (DASS21), and salivary cortisol levels. The secondary outcome measure was change in quality of life as measured by the Multiple Sclerosis International Quality of Life Questionnaire (MusiQoL).

None of the parameters evaluated changed between pre-and post SME ($p \leq 0.05$). These results indicate that SME does not significantly improve levels of stress or quality of life in people with MS. In contrast to previous research this study suggests there is no association with the study intervention in reducing perceived levels of stress. Future studies could include barriers to adherence.

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# CHAPTER ONE

# SETTING THE SCENE: THE RESEARCH IN CONTEXT

## 1.0 Introduction to the Study

Multiple Sclerosis (MS) is a complex neurological disorder that is not yet entirely understood. In Australia there are around 23,000 people with MS and it is considered the most common neurological disorder in young Australians (MSAustralia, 2005). Incidence and prevalence of MS are rapidly increasing, and the gender ratio is increasing for women, at 3:1 female to male being diagnosed (Ribbons, Lea, Tiedeman, Mackenzie, & Lechner-Scott, 2017). There is evidence to support that MS is an immune cell mediated disease leading to destruction of myelin and axons within the central nervous system (Haines, Inglese, & Casaccia, 2011). It is likely that people with a genetic predisposition for MS encounter environmental exposure/s that trigger immune attack on myelin, the fatty protein that protects nerve fibres, reducing conduction of nerve impulses along the neurones. The result is acute, localised inflammation, scarred myelin and damaged or destroyed axons. This presents as clinical attacks and transient or permanent clinical dysfunction depending on location resulting in sensory, motor, autonomic, mood or cognitive difficulties. Over time people with MS often experience fewer acute inflammatory attacks and accumulate increasing disability.

Comprehensive care practices that maximise positive outcomes for people with MS have been steered by evidenced based practice, which includes the recently updated National Institute for Health and Care Excellence (NICE) clinical guidelines and the international consensus document, Brain Health: Time Matters in Multiple Sclerosis (Giovannoni et al., 2016) . Both these documents promote early access to treatment and comprehensive review

by MS specialists, focusing on chronic disease modifiable lifestyle factors (Giovannoni et al., 2016). Well established modifiable lifestyle factors include low levels of Vitamin D3, and childhood obesity. These factors are known to contribute to disease onset and progression (Ascherio, Munger, & Simon, 2010; Langer-Gould, Brara, Beaber, & Koebnick, 2013). The role of stress in disease onset and the ongoing effect of perceived stress on the course of MS has only recently been studied in more detail (Mohr, Hart, Julian, Cox, & Pelletier, 2004). There are varied approaches on how to manage perceived stress, and its impact on disease activity is under investigation. This project attempts to add to current knowledge of the management of perceived stress by using objective and subjective data measures.

### 1.1 Background to the Study

The scope of what is now known about MS has evolved from those early writings to encompass disease pathophysiology and heritability. It is generally agreed to be a disorder of the immune system, and likely to be influenced by environmental factors. In 2013 the International Multiple Sclerosis Genetics Consortium identified over 150 genetic variants that are associated with MS (International Multiple Sclerosis Genetics et al., 2011).

Various external and internal factors have also been identified as influential to the disease course: for example, the ability to emotionally adapt to receiving a diagnosis of MS and the ability to cope with the chronicity of MS. External factors include access to health care providers, supportive carers and family members, and remaining actively engaged in employment (Dennison, Moss-Morris, & Chalder, 2009). There is evidence to support the view that increased stress can lead to depression, anxiety, poor coping skills, reduced quality of life, lack of social connectedness and poor self-efficacy for people with MS (Hughes, Robinson-Whelen, Taylor, & Hall, 2006).

Exposure to major negative stressful life events may increase the risk of new or enlarging transverse relaxation time T2 lesions which can be viewed on MRI up to 2 months after exposure to the event (Burns, Nawacki, Kwasny, Pelletier, & Mohr, 2014). The Burns' study hypothesised that perceived stressful life events occurring in the period leading up to MRI predicted acute new lesion accumulation, as measured by Gadolinium enhancement and number of new T2 lesions on MRI. Participants were followed up for 48 weeks and assigned to either an intervention group of stress management or wait list group. 121 people with MS completed regular MRI assessments, documentation and assignation of potential stressful life events using The Life Events List (LEL) every 4 weeks. Study participants also completed the Brief Inventory of Perceived Stress (BIPS), the Hospital anxiety and Depression Scale (HADS-A) and the Centre for Epidemiological Studies Depression Scale (CES-D). Negative stressful events were aggregated from responses that were "slightly bad" to "very bad" and positive stressful events were aggregated from responses that were "slightly good" to "very good". Events were considered major if there was a perceived physical threat to the person with MS (PwMS) or someone close to them. The randomly assigned stress management group were treated by a clinical psychologist or social worker using a specific therapist manual for managing stress in MS; this programme addressed five core skills of problem solving, relaxation, engagement in positive activities, cognitive restructuring and increasing social support in addition to optional comorbidity treatment of depression or MS symptomatology. This 16-session intervention took place over 20-24 weeks. The control group were provided with usual treatment for 40 weeks and then offered the option of attending a stress management workshop. Results of the Burns' et al. study showed that moderate to major negative stressful events did not influence Gadolinium enhanced lesions. Major negative stressful events did increase risk for Gadolinium enhanced on MRI, with an odds ratio of 1.77 for each additional major negative stressful event. Positive stressful events

reduced new or enlarging T2 lesions on MRI overall, diminishing with the number of positive stressful events (OR 0.53). The stress management intervention used resulted in a reduced risk for new or enhancing lesions but also fewer participants reported negative stressful events, reducing the chance of a causal relationship. Despite this, one of the conclusions drawn by Burns' et al. that the stress management intervention may have improved the participants' ability to cope with stressful events, and perhaps to a larger degree, helped PwMS to avoid stressful events altogether. The study was robustly designed and bias was well considered, leading from a previous, related study (Mohr et al., 2012). The intervention programme was delivered by qualified clinicians and data collection was maximised by regular data collection and objective in nature (regular MRI and assessed by blinded neurologists). The favourable outcome is enhanced by these characteristics. However, in clinical environments these resources are frequently unavailable to PwMS; either due to high cost, health service limitations or geographical location. From a translational perspective, this study intervention needs to be tested under the more likely scenario of treatment delivered by non-psychologists and in fewer sessions.

Managing stress might positively affect MS progression; is the conclusion made by several investigators of studies examining the role of stress management small populations of people with MS and the summary of the literature reviewed for this project. Relaxation breathing and PMR twice daily over 8 weeks (Artemiadis et al., 2012), PMR daily for 2 months (Ghafari et al., 2009), a 16 session MS specific stress management programme over 2 months (Mohr et al., 2012), 8 sessions of mindfulness-based stress reduction (MBSR) strategies (Kolahkaj & Zargar, 2015), a 6 session stress self-management workshop (Hughes et al., 2006) and cognitive behavioural therapy (CBT) combined with progressive deep-muscle relaxation (F. W. Foley, Bedell, LaRocca, Scheinberg, & Reznikoff, 1987) have all been shown to reduce perceived stress in people with MS. Each of these studies used small

cohorts of PwMS, short lasting face to face interventions and relied on subjective assessments to measure levels of stress. Each of these studies will be critically reviewed in the following chapter.

In the Hunter New England Local Health District, the model of care for PwMS is a health promotion model of routine outpatient follow-up after diagnosis, and outpatient management of relapses and disease progression, with the aim of avoiding inpatient stays as much as possible. PwMS are encouraged to participate in their care as key stakeholders, for example by choosing and managing prophylactic treatment. This approach to disease management is not unique to MS but does promote adjustment to a diagnosis of a chronic illness. Taking control reduces hospitalisations and improves adherence to treatment (Beach, Keruly, & Moore, 2006; Lorig et al., 1999). Furthermore, health promotion activities, for example wellness programmes and clinical intervention programmes in MS, have been shown to have long term benefits in self-efficacy and health related quality of life (HRQoL) (Kuspinar, Rodriguez, & Mayo, 2012; Minden et al., 2013).

The Hunter New England Local Health District employs a holistic health care model, and in addition to the patient, the team consists of MS nursing and medical specialists, with streamlined referral networks that include rehabilitation, allied health, psychiatry, psychology and pain management. The MS nurse specialist is often the first resource to contact considering new symptoms, difficulty managing existing symptoms, educational and employment advocacy and prophylactic therapy management. The role of this specialist nurse is to educate and counsel people with MS, triage new or worsening symptoms and work collaboratively with other health professionals who work with this population of people. The MS nurse specialist is

therefore well placed to deliver health promotion activities and assess, educate and evaluate basic stress management strategies.

This current research will evaluate the effectiveness of a nurse-led interventional programme of stress management in a cohort of people diagnosed with MS from the Hunter New England Local Health District of NSW. The interventional programme will consist of education and counselling in stress management techniques.

### 1.2 Significance of the Study

Despite considerable literature describing stress in MS there are few studies that have evaluated stress management programmes (Artemiadis et al., 2012; F. W. Foley et al., 1987; Ghafari et al., 2009; Kolahkaj & Zargar, 2015; Mohr et al., 2012). Each of these stress management studies have used psychology or psychiatry clinicians to assess and counsel on stress and stress management; none utilise the MS specialist nurse (MSSN) in engaging or counselling PwMS. The studies have largely used self-rating assessments of the interventions, lacking objective examination of the intervention effect. This project aims to use and enhance the existing nurse-patient relationship to educate PwMS about the role of stress in MS, teach basic stress management strategies, and assess intervention effect in both objective and subjective assessments, all in the ambulatory, self-management model of care familiar in the Australian setting.

A recent systematic review of stress management interventions in MS highlighted the need for larger (multicentre) prospectively designed studies, using biological and clinical measures of disease (Reynard, Sullivan, & Rae-Grant, 2014). The review sought to identify and evaluate the efficacy of stress management interventions in the MS population. Of the 117 studies that were identified, only 8 were considered of robust study methodology, design and analysis. Closer review of the 8 studies showed likely efficacy of stress management

interventions but variable study design with limitations. The main limitations included lack of biological and clinical markers of efficacy, and small, single centre studies. As a result, this current single centre study sought to redress the issue of biological markers of intervention efficacy by introducing salivary cortisol examination. This current study employed a robust prospective randomised, case control design and used both objective and self-rating tools assessing outcome to contribute meaningful evidence to the stress management in MS discussion.

Access to care for people with MS can be difficult owing to the cost of private care, long waiting lists for public service provision and geographical obstacles of distance to care providers. However, collaborative care, incorporating both medical and psychological care of individuals presenting with psychological issues, has increased, with improved access and reduced waiting time for people to receive care. A study that surveyed over 3000 PwMS found that 60% of this group had experienced mental health issues and of this group those who had better mental health outcomes had received mental health care delivered by mental health specialists in the same facility as their MS care providers (Minden et al., 2013). Additionally, enhanced care is being achieved by utilising other health professionals (including nurses) in providing front line care in a collaborative model of care to people experiencing chronic illness, including mental health issues (Knowles, Chew-Graham, Adeyemi, Coupe, & Coventry, 2015).

MS nurses have regular and routine contact with people with MS, especially at the beginning of the disease, when a diagnosis is being made, when new symptoms occur or when a patient is struggling to cope with MS-related issues. The nurse and patient can quickly develop a strong rapport as the nurse becomes a positive avenue of information and support (Forbes & While, 2009) that encompasses education, counselling and advocacy.

Experienced MS specialist nurses have considerable post-graduate knowledge about MS; often navigating the sometimes subtle and subjective nature of disease relapses and transient symptomatology. MS nurse specialists often informally educate about and promote stress management to people with MS. This project will provide more insight in the MS nurse specialist role and will promote MS nurse-led interventions and research.

The previous studies examining this phenomenon have been limited in methodological design (Reynard et al., 2014). This study adds objective evidence to the complement of measurements in assessing the effect of stress management strategies on perceived stress in MS. Salivary cortisol is a measure of stress response, collected at baseline and at follow up one month after intervention commencement. None of the other studies have attempted to include this objective bio marker of stress levels.

### 1.3 Theoretical Framework

The terms stress and stressor were arguably first introduced by Hans Selye in 1936 (Jackson, 2014). Although he wasn't the first researcher of the time to investigate responses to external stimuli, Selye contributed significantly to the knowledge of physiological changes in people when experiencing a stressful event. Selye defined stress as 'the non-specific result of any demand upon the body, be the effect mental or somatic'(Selye, 1956) and describes a stressor as a biological response of the body rather than a stimuli initiating response. Selye conceived the phrase 'general adaptation syndrome' (GAS), which he used to characterise the pattern of biological response to stressors: initial alarm phase, resistance or adaptation, followed by exhaustion or death (Selye, 1950). This theoretical framework reflected his contemplations as a medical student interacting with people experiencing chronic conditions; that these people had a commonality in that they "looked and felt sick" (Jackson, 2014). Human studies followed animal studies, initially focusing on the adrenal system in mediating

response to external stimuli. Selye and colleagues further outlined the adaptive (or maladaptive) physiological response to stress using the GAS. As hormonal changes play a pivotal role as products and by products of the GAS, Selye resolved that a maladaptive response to stressors can lead to disease states (Jackson, 2014).

Influential to the concept of GAS was the work of Walter Cannon. In 1915 Cannon described the biological regulatory balance between the autonomic nervous system and the endocrine system (Dusek & Benson, 2009). He employed the terms 'homeostasis' and 'fight or flight' as parts of the acute stress response to describe the constant adjustment to environmental change, and the body's acute reaction to severe or sudden threat (Dusek & Benson, 2009). The theories of acute stress response and the GAS support each other as foundations of the biological response to stressors.

Criticisms of this GAS theory argue that this model ignores the impact of psychological and environmental factors. It postulates that response is automatic, irrespective of the individual's cognitive appraisal of the stressor (Tennes & Kreye, 1985). It also does not account for variability in personality. For example, some people relish the opportunity to speak publicly, others loath it. Despite the criticisms of the GAS, Selye's conceptualisation of the humoral adaptive response to stress it remains the foundation for modern models of stress response and stress management in chronic disease.

In addressing the lack of cognitive appraisal of stress Lazarus and Folkman in which year? shifted the emphasis of the biological to the cognitive domain and proposed a theoretical model of stress, appraisal and coping that has been empirically tested in chronic disease, including MS (Pakenham, 1999). Lazarus and Folkman conceptualised that responses to stress induce a subjective appraisal of the stress event, which would then influence coping. This appraisal response model is further characterised as primary appraisal

and secondary appraisal; primary appraisal refers to the assessment of the stressor significance (‘is this important to me?’); secondary appraisal refers to the assessment of one’s ability to control the stressor and /or resources available to manage the stressor (Folkman, Lazarus, Gruen, & DeLongis, 1986). In situations where a person feels the stressor is not important it is less likely to cause distress. Equally, if the person feels the stressor is important to them but they have the ability to manage or control the stressor (or their response to the stressor) they are also likely to experience less distress. In this way, positive appraisal of a stress event can drive effective coping and well-being. Lazarus (1966) also proposed that stress and coping are reciprocals of each other, in that effective coping equalled controlled stress and ineffective coping leads to increased stress. The model of stress and coping is used to guide this study of stress management in MS.

### 1.4 Research Questions

This study will address the following three research questions:

1. Can a stress management intervention reduce perceived stress in people with MS?
2. Can a stress management programme improve quality of life with people with MS?
3. Can the effect of stress management intervention be maintained beyond the intervention programme?

### 1.5 Aims of the Study

This MindS study was designed as a true or classic experimental, randomised control trial, prospectively planned for a pre-test, post-test method. This study design using objective (salivary cortisol evaluation) and subjective measures (Depression, Anxiety and Stress Scale or DASS21 and the Multiple Sclerosis International Quality of Life Scale or MusiQoL) was employed in order to understand the intervention's effect in the context of complex human phenomenon being studied, and to address the lack of objective examination of intervention

effect identified in the literature (Reynard et al., 2014). A further objective of this study was to explore the effectiveness of this intervention in the context of self-managed strategies for a known risk factor for increased MS disease and barriers to effective implementation of these strategies. Electronic databases PubMed, Ovid, CINAHL, Proquest, Medline/Medline Plus and psychINFO were searched for the key terms multiple sclerosis and stress, stress management in multiple sclerosis, mindfulness, relaxation technique and relaxation breathing and quality of life.

# CHAPTER 2

# LITERATURE REVIEW

## 2.0 Introduction

Articles examining stress management interventions in populations of people with MS and using a randomised control trial design were included in this review. All studies included were prospective in design and all required informed consent from both case and control participants. Participants included in these studies had confirmed diagnosis of MS, were frequently described as stable on disease modifying therapy (DMT) and Expanded Disability Severity Score (EDSS) was often described as part of the demographics of the study cohorts but not used as an outcome measure.

## 2.1 Multiple Sclerosis

Symptoms of MS were first described in the 14$^{th}$ century when Lidwina (the Virgin) of Schiedam in the Netherlands, fell while ice skating and went on to develop visual disturbance, weakness and pain (Murray, 2004). It is reported that Lidwina experienced relapses and remissions of her illness over the course of her life and went on to become the patron saint of figure skating and sickness (Orrell, 2005). Despite the work of Robert Carswell, who associated the presence of MS lesions with the disease, and Jean Cruveilhier, who described clinical symptoms in a person who subsequently went on to develop MS, it was not until 1868 that the disease was given a name,' la sclerose en plaques' or Multiple Sclerosis, by Jean-Martin Charcot. Charcot is closely associated with MS because he was the first to correlate symptomatology with the anatomical pathophysiology. He also described the differences between MS and other nervous disorders such as Parkinson's Disease (Kumar, Aslinia, Yale, & Mazza, 2011).

The disease mechanism of MS is understood to be a breakdown of the blood brain barrier, allowing activated immune cells to cross into the central nervous system and attack myelin tissue, an insulating barrier around the axons. This damage slows or interrupts neuronal conduction clinically inducing area-specific dysfunction. Examples of this dysfunction are optic neuritis, limb weakness (motor system) and paraesthesia (sensory system) but also bladder dysfunction or difficulties with concentration. Factors influencing MS prognosis include age at onset, disease course, lesion load on magnetic resonance image (MRI), and time to second and subsequent relapses (Moreau & Confavreux, 2000).

MS can be divided into relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS) subtypes. RRMS is the most commonly diagnosed form (80-85%) (Ebers, 2004) and features periods of remission between acute attacks of inflammation. This inflammation is the focus of available therapy and best response is seen where treatment is commenced early (Mahurkar, Suppiah, & O'Doherty, 2013). Patients with RRMS can progress to SPMS which is characterised by fewer acute relapses and a gradual progression in disability. The time of onset of SPMS is influenced by age at onset of disease (Koch, Uyttenboogaart, van Harten, & De Keyser, 2008). Lastly PPMS features a continual increase in disability from onset without acute relapses (Ebers, 2004). No treatment has shown efficacy in this disease course.

Despite there being currently ten therapies available for MS, no therapy cures MS. Treatments are taken life long and adherence to therapies in this population of people is variable (Locklear, 2015; Wong, Gomes, Mamdani, Manno, & O'Connor, 2011) Treatments for MS can be categorised into first, second and third line therapies. The first line therapies include beta interferon (Avonex, Betaferon, Plegridy and Rebif) and glatiramer acetate (Copaxone). These therapies modulate the immune system, have moderate efficacy but a long standing, relatively safe profile (Wingerchuk & Carter, 2014). All are administered by self-

injection. Common side effects include localised injection site reactions and cold and flu-like symptoms (Wingerchuk & Carter, 2014). More recently a pegylated version of interferon (Plegridy) has been introduced to the market, reducing the frequency of injections but carrying similar side effects. Second line therapies are orally administered and frequently well tolerated. They include teriflunamide (Aubagio), fingolimod (Gilenya) and dimethyl fumarate (Tecfidera). While there are limited head to head studies comparing these newer therapies to the injectables it is likely they have similar or better effect. (Cohen et al., 2010; Fox & Rhoades, 2012) For more moderate to aggressive disease natalizumab (Tysabri) and alemtuzumab (Lemtrada) are frequently used. These more effective therapies are considered immunosuppressive and bring related side effects that need to be regimentally monitored. The goal for treating MS is to reduce future risk for relapse and minimise future disability. This treatment goal is referred to as NEDA or No Evidence of Disease Activity. NEDA can be demonstrated by no new lesions on magnetic resonance imaging (MRI), no clinical attacks of MS and no progression of neurological disability as measured by the EDSS (Giovannoni et al., 2015). Whilst mainstream medicine focusses on reducing future MS disease by starting one of these therapies at the time of diagnosis and actively monitoring PwMS for new disease, most clinicians recognise that prophylactic therapy is only one aspect of managing MS. The other factors that can be managed, often called modifiable lifestyle factors, actively involve the PwMS and have been shown to affect the MS disease course and experience of MS, either directly or indirectly. These factors include getting regular exercise, eating a well-balanced diet, avoiding smoking and managing stress (D'hooghe, Nagels, Bissay, & De Keyser, 2010).

MS is diagnosed according to the revised McDonald criteria (Polman et al., 2011). Evidence of demyelination over time and space is required to make a diagnosis of MS. A clinician examining a patient for MS will use clinical history, neurological examination and

MRI as primary tools for disease diagnosis and disease progression or stability. Lesion load, location and clinical symptomatology can to some extent predict disease progression (Fernández, 2013). For example, disability progression can be predicted by a greater number of lesions, poor recovery from relapses and spinal cord and brainstem relapses (Jokubaitis et al., 2016)

The generally-held consensus about the pathogenesis is that MS is autoimmune in nature. MS likely occurs in people who are genetically predisposed and who are exposed to various environmental factors which trigger an immunological change (Comabella & Khoury, 2012). Among the identified environmental risk factors are low vitamin D levels, exposure to Epstein - Barr virus (EBV) (Zivadinov et al., 2009) and nicotine smoking (Salzer et al., 2013).

### 2.2 Stress in Multiple Sclerosis

Another environmental factor for consideration is stress. The role of stress in MS has been studied at length. Stressful life events at or around the time of relapse is reported to bring a five-fold increased risk of relapse (Mitsonis et al., 2008; Saul et al., 2016). Stress is succinctly described by Jose Sa (2008) as the presence of a change in life, where the readjustment to change surpasses the ability to cope. This definition is all the more complex considering that stress is for each person tolerated and responded to differently (Goretti, Portaccio, Zipoli, Razzolini, & Amato, 2010). Hans Selye was one of the first to investigate the pathophysiology of stress, studying the response to stress since the 1930's (Selye, 2013). His General Adaptation Syndrome (GAS), originally published in 1950, proposed that stressors produce complex physical, chemical and/or psychological changes, and are subcharacterised in three stages: alarm reaction, resistance and exhaustion (Selye, 1956). He postulated that response to stress is affected by genetics and is highly adaptive. Furthermore,

Selye coined the term ‘stressor’ to mean the perceived threat that triggers the response to stress (Szabo, Tache, & Somogyi, 2012).

Before examining the role that stress plays in MS, it is important to review the usual biological response to stress in more detail. Responding to a perceived stressful event involves a highly complex biological series of steps. In a normally functioning body response to perceived stress is managed by the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (Gold et al., 2005). This complex system is managed by the immune, endocrine and nervous system and is acutely responsive and adaptive (Deckx, Lee, Berneman, & Cools, 2013). It has been suggested that neuro-endocrine-immunological homeostasis interruption may lead to a higher risk for autoimmune disease (Deckx et al., 2013). Smith & Vale (2006) describe the physiological response to a perceived emotional or physical threat: the hypothalamus releases corticotropic releasing factor (CRF), in turn stimulating the pituitary gland to release adrenocorticotropic hormone (ACTH), which then leads to the adrenal gland releasing epinephrine, norepinephrine, catecholamine and glucocorticoid. The resultant hormonal surge allows for an acute response by the person to the stressor or stressful event and maintenance of an activated alert state until the perceived threat diminishes. Additionally, the HPA axis has an effect on a wide range of physiological processes other than the immune response. These include digestion, emotional response, energy metabolism and sexual function (Du & Pang, 2015).

The animal model of MS, experimental autoimmune encephalitis (EAE) has been used for 80 years to hypothesise a raft of neuro-immunological disease features including histopathology, neurobiology and effect of therapeutic agents (Gold, Linington, & Lassman, 2006). It has been proposed that an under responsive HPA axis increases susceptibility for EAE (Gold et al., 2005).

One of the more recently proposed mechanisms for HPA axis dysregulation relates to hyperactivity of the HPA axis, leading to increasing MS severity (Gold et al., 2005). In MS HPA axis dysregulation has been shown to negatively affect cognition, disease course and mood (Heesen, Gold, Raji, Wiedemann, & Schulz, 2002), this correlation is less clear for the role of HPA axis dysregulation has in MS fatigue; the Heesen (2002) study of 40 PwMS found no correlation of altered HPA axis effect on fatigue. Whereas in contrast, a similar-sized but prospective study of 31 people with MS found a significant correlation of HPA axis dysfunction, evidenced by high ACTH levels in their study population (Gottschalk et al., 2005). Obvious discrepancies between the studies and acknowledged by Gottschalk is the difference in MS type (RRMS versus mostly progressive MS) and treatment (mostly treatment naïve versus current therapy-exposed). From a neuroimmunological position both factors are likely to affect normal HPA axis function.

HPA dysregulation may be correlated with the MS clinical course. Kümpfel et al. (2014) found elevated cortisol levels in plasma samples in a group of 60 MS patients with active disease and in 29 healthy controls. These levels were mildly elevated in RRMS patients and significantly elevated in PPMS patients. Longer term accumulated HPA dysregulation was confirmed in their follow up study. Additionally, but not significantly, higher levels of HPA axis hyperactivity was associated with untreated RRMS patients when compared to the DMT treated population. A limitation of that study is that while those treated with corticosteroids for relapse were excluded, eight of the 40 in the treatment group received monthly corticosteroids as prophylactic therapy. Despite this the authors have proposed a novel mechanism of HPA axis longitudinal dysregulation, which should be evaluated in a larger study with stricter inclusion criteria.

One’s ability to cope with stressful events can be influenced by one’s perception of the ability to control the stressor or stress event. This is referred to as locus of control and can

be either internally or externally-driven (José Sá, 2008). An external locus of control occurs when one perceives that external influences like luck or fortune determine life events. In contrast, an internal locus of control occurs when one believes they are in control of life events and can alter outcomes (Vuger-Kovacić, Gregurek, Kovacić, Vuger, & Kalenić, 2007). These opposing positions are further influenced by one's approach in coping with stress. It is generally understood that a problem-focused approach is more likely to reduce stress than an emotion-focused approach (Barlow, Turner, Edwards, & Gilchrist, 2009; Dennison, Yardley, Devereux, & Moss-Morris, 2011).

The overall incidence of stress occurring in MS has been reported as being as high as 96% (Buljevac et al., 2003). Examples of stress in MS can be adjusting to the diagnosis of MS, to an acute relapse or change in social support. All of this can bring on chronic stress and lead to anxiety and/or depression (MSTrust, 2012). Stress is, of course, not limited to disease but includes other life stressors. Family and relationship stress, and financial stress are but two examples.

Despite the lack of robust evidence, people with MS and their carers link stressful life events with MS disease activity (Brown, Tennant, Dunn, & Pollard, 2005). Conducting studies examining the effect of stress in MS are notoriously difficult because of the complex nature of stress, study trial design and the lack of objective measurement of stress (Heesen, Mohr, et al., 2007). In Brown et al.'s (2005) review of literature of stress-relapse interactions both prospective and retrospective studies have found positive and negative outcomes for the effect of stress on MS disease. Additionally, Brown et al. suggest that because people with MS believe there is a strong link between stress and disease activity there may be a bias in reporting MS symptomatology.

Studies showing stress as a factor to increased disease activity are frequently based on subjective measures of stress. On the other hand, Mohr and team (2000) have combined

subjective (self-rating) and objective (MRI) outcome measures in a cohort of people with MS. The study found that relationship conflict increased the risk for new radiological disease activity at eight weeks' past stressor event. In 2010 Yamout and colleagues (Yamout, Itani, Hourany, Sibaii, & Yaghi, 2010) conducted a small retrospective study to examine the effect of stress on MS. The study compared new enhancing lesions on MRI for the period before, during and post war and found an increasing likelihood of clinical relapses and radiological disease activity during the Israeli-Lebanese war in July 2006. Both studies were conducted with small cohorts and had different study designs but they do provide some of the first objective evidence of the effect of stress on MS disease activity.

Types of stressor events have been postulated as a factor in perceived stress. Severe stress induces high levels of cortisol release, known to have anti-inflammatory effects. A number of studies in MS have examined stress frequency, severity and type of stress and found that moderate, chronic stress is a factor for increased risk of MS relapse, as is the timing of the stress event (Ackerman et al., 2002; Brown et al., 2009; Mitsonis et al., 2008; Mohr et al., 2000; Potagas et al., 2008; Yamout et al., 2010).

The study by Potagas et al. (2008) found that an increasing number of stressful life events contributed to MS disease. This one-year prospectively designed study followed 37 women with MS. The group consisted of women over the age of 18 years, had a mean EDSS of 0.5 (range 0-3) and a confirmed diagnosis of RRMS. Participants recruited to this study were also required to have had at least one relapse in the previous year. The mean number of relapses for this cohort was 1.5 (range 1-4). During the study, none of the participants were treated with prophylactic therapy, as per local investigator-institution protocol, although they were treated with corticosteroids for acute relapses. Stressful events were self-reported in a questionnaire format collected every 4 weeks. In this group of people stressful events were explored by the study team to further describe episodes and define as mild or serious events

of stress. Categories of stressful life events included family problems, sentimental/sexual problems, professional/financial problems, social problems, everyday problems and health problems or a family member or friend. 291 events were reported, predominantly mild events, 268:23 (mild: serious). Eighty per cent of the group experienced MS relapse during the one-year observation period. Of the relapsing participants, half had a single MS relapse and the remainder had 2-3 relapses in the course of the study. A bias of this study is not treating the study group with DMT. Clinical relapse is, in practice, the time to review the MS disease severity and consideration of therapy efficacy or if not on therapy, time to commence DMT. Ongoing clinical attacks are very likely to be stressful to PwMS, potentially leading to over reporting of events or at the least, more frequent medical review of the PwMS, interruption to the PwMS' life, and a reduced ability to carry out their personal and professional responsibilities. The investigators found factors for greater risk for MS relapse included disease duration equal to or greater than three years (hazard ratio 2.3), between two and four mild stressful events before the study commencement (hazard ratio 2.0), three, four or five stressful events during the study ($p$ = <0.0001, hazard ratio 6.7), Hamilton rating scale for anxiety (HAM –A) score of 14-17 and 18-33 (hazard ratio 2.1 and 4.4 respectively) and episode of infection ($p$ = <0.0001, hazard ration 5.5). Furthermore, the number of stressful life events correlated with anxiety scores, as measured by the HAM –A. No stressful life events were associated with a lower HAM –A. Participants with increasing number of stress life events had associated increased anxiety (HAM-A) scores. This outcome was not true for severe stressful life events, with no association found with increased risk for relapse.

The Brown et al. (2009) group set out in their study to determine if it's possible to identify predictors to psychological distress and fatigue in 2009. The researchers aimed to longitudinally evaluate anxiety, depression and fatigue temporally. They prospectively studied MS stress events every 3 months for 2 years in a population of people with MS (n=

101). Disease factors were evaluated for relationship with demographic, psychosocial and lifestyle factors. Stressors were classified as acute (less than six months in duration) or chronic (longer than 6 months in duration), MS relatedness (whether the stressful event is related to the person's MS or not), and positive or negative stress using the Bedford college life events and difficulties schedule (LEDS). The stressors were further categorised into chronicity, frequency, severity, cumulative effect, MS-relatedness, valence and positive versus negative stress. Using univariate categorical and continuous measures for data analysis, this study found that the presence of life event stressors predicted increased fatigue, depression predicted anxiety and fatigue and psychological distress also predicted unhealthy behaviours (e.g. smoking, recreational drug use, no exercise and reduced relaxation).

The role of stress event frequency can be seen in a small prospective study by Mitsonis et al. (2008). Limited to female participants this project followed 26 women with MS for 56 weeks. The participants were seen every 4 weeks and additionally completed self-report diaries. Stressful events were categorised as short term or long term and were determined for severity using the Recent Life Change Questionnaire. This study found the number and duration of stressful events were associated with an increased risk of relapse, with just one long-lasting stress event increasing the risk of relapse 3-fold. The type and severity of stressor were found to have no influence on relapse risk. The timing of stressors plays a role in the relationship between stress and MS relapse risk. Observational studies have shown that the period immediately following stressful life events (independent of stressor severity) can hold an increased risk for clinical relapse (Ackerman et al., 2002; Yamout et al., 2010).

There are conflicting views on the effect of severe stress on relapse. Nisipeanu and Korczyn (1993) and Yamout et al. (2010) chose the well-defined stress event of living in a war zone to investigate risk of relapse likelihood. The earlier study prospectively followed 32

patients with definite MS through their experience of living in Tel Aviv during the Persian Gulf War of 1991. The demographics of this small group were reasonably representative of the MS population: 18 women and 14 men with an EDSS range of 1.0-6.0, an average age of 38 years and an average disease length of 4.7 years (range 2 to 15 years). The number of relapses in the previous 2 years for each person with MS was 2-5. The only treatment received by that group was steroids for acute relapse. During the 3-month follow up only 3 confirmed relapses occurred in the group, which was a significant reduction compared to the pre-war relapse rate. As well as having a small cohort size, a fundamental issue with this study is bias for reporting new neurological symptoms in the context of difficulty seeking medical attention during active bombing and subsequent difficulty mobilising around the city. It is possible that relapses were less often reported for minor relapses.

More recently, however, a larger study of people with MS during war time (Yamout et al., 2010) found a significant increase in MS disease activity, both in clinical relapses and by radiological measurement. This study of 216 people, who were directly affected by the Israeli-Lebanese war in 2006, compared relapse rate and number of new lesions before, during and after the war to a control group examined outside of war. This more detailed study reported both an increased risk for clinical relapse and new lesions on MRI during war time. This study has greater validity to the previous study as it had a larger study cohort, used objective MRI data assessments and included a control group. A likely criticism of this study is that there is no measurement or discussion of the relationship between timing of the stressor and the relapse. Exposure to stress (emotional and physical) is a usual consequence of the human condition, as are relapses of MS. Adding in acute stress of living in a war zone it is reasonable to cogitate where correlation ends and concurrence intersect.

Few studies have examined the relationship between stress and MS disease onset. Riise et al. (2011) carried out a population based study that enrolled nurses in the US

National Health System in 2 groups: the first in 1976 (NHS l) and the second group (NHS ll) in 1989. This large study identified 369 (NHS l: 77 participants and NHS ll: 292 participants) people diagnosed with probable or definite MS. The study asked participants every 2 years about their level of stress at work and home (as a generalised statement of minimal, light, moderate or severe) and about severe childhood and adolescent stress (sexual and physical abuse). This study found no relationship between stress and disease onset. Limitations of this study include not including stress event information beyond physical and/or sexual childhood and/or adolescent abuse. The every-other-year survey did not capture any detail about stressors beyond their type, perhaps missing information including stress frequency, event type and timing. Lastly, the cohort is limited to include female nurses only, which is not wholly representative of the MS population.

While the evidence above could clinically support stress as a risk factor for MS disease this contrasts with the known HPS axis model of immune mediated cortisol release. Under stress the immune system will release cortisol, an anti-inflammatory hormone. Animal models of neurological inflammation, experimental autoimmune encephalitis (EAE), have shown that stress can reduce inflammation (Heesen, Gold, Huitinga, & Reul, 2007). In humans it is proposed that severe stress triggers cortisol release and is thereby protecting against inflammation while moderate or mild stress does not (Heesen, Gold, et al., 2007). In relation to the above studies this concept does not hold true, as both studies used populations under severe stress and yet came to different conclusions. Furthermore, neither study incorporated analysis of cortisol levels, and so confluence of hypothesis and outcome is merely speculative.

The studies described indicate an evolving assemblage of literature for the role that stress plays in MS; specifically, the number, timing, type and severity of stressful events. The sparsity of literature outlined above demands further research to better understand the

relationship between stress and MS activity, especially including objective study measurements.

### 2.3 Stress Management in Multiple Sclerosis

There is a substantial economic burden associated with MS. In Australia this burden is frequently a result of loss of productivity with estimates of annual costs identified ranging from AUD $36,369 (for mild disability) to AUD $ 65,305 (for severe disability) (Palmer, Colman, O'Leary, Taylor, & Simmons, 2013). Of the literature about stress management strategies searched, six papers met the criteria for inclusion in this review. The most compelling evidence of benefit in managing stress in MS is by Mohr et al. (2012). This 48-week study conducted in the United States was case-controlled (n = 121) with participants using a routine clinical questionnaire to assess stress reduction benefit. The case group (n = 60) received stress management therapy for 24 weeks and comparisons were made with a wait list control group (n =61). The stress management therapy programme involved 16 sessions with licensed psychologists. The programme comprised CBT with additional individualised sessions for specific psychological and MS-specific issues. The wait list group participated in a workshop some 10 months or more after enrolment. MRI, a commonly-used tool for assessing MS disease activity and progression was then conducted on participants during the therapy and at 24 weeks. A significant reduction ($p$=0.04, absolute risk reduction = 22.2%) in the number of brain lesions was ascertained compared to the control group at the first-time point of analysis. Unfortunately, this benefit was not sustained beyond the 24 weeks of stress management treatment programme. While this was a labour-intensive intervention it tailored the intervention to meet the needs of the individual participants and there was a very high intervention adherence rate and low dropout rate. The authors acknowledge limitations of the study, one of which being limited clinical outcome measures. This study has not been replicated and differs from the other studies in intervention type,

assessment measures used and delivery type. It's value for comparison to the current study is limited.

A prospectively-designed, randomised control trial conducted by Artemiadis et al. (2012) in Greece found that implementing stress management of relaxation breathing and PMR twice a day for 8 weeks produced a small reduction in perceived stress ($p$= 0.2). This trial of 61 participants used a range of self-rating measures (Perceived Stress Scale, Health Locus of Control, State-Trait Anxiety Inventory Scale, Beck Depression Inventory and Symptoms of MS survey) to evaluate the intervention against a waitlist group. This study recruited from a pool of PwMS and excluded people who were under consenting age (i.e. 18 years), those treated with corticosteroids for acute relapse, those living in rural areas, and people taking psychotropic medications (e.g. antidepressants). They also excluded people with progressive MS. Some of the exclusion criteria are reasonable (over the age of 18 years is an ethical consideration, participants from rural areas is practical exclusion and excluding those treated with corticosteroids will reduce the risk of mood and psychiatric side effect on stud outcome). Excluding those treated with psychotropic therapies and progressive MS introduces effect bias and reduces the study generalisability. The small cohort size and lack of objective measurements are also criticisms of this study.

PMR as a stress management strategy was also used by Ghafari et al. (2009) in a small quasi experimental design study trial of 66 people (33 case participants and 33 control participants) with MS. Similar to the study conducted by Artemiadis, the participant demographics excluded those who had used relaxation techniques in the 6 months prior to study enrolment. This group were further narrowed by excluding potential participants with 'other acute or chronic physical disorders, severe cognitive deficits, hearing loss, vocal disorder or having signs of psychiatric disease' (Ghafari, 2009). Case participants were asked to perform this stress management strategy daily over 8 weeks while the control group had no

intervention during the course of the project. A small selection of self-rating questionnaires (Individual Information Questionnaire, SF-8 Health survey and a self-reported check-list) were used to assess benefit. The SF-8 was repeated at 4 weeks and at 8 weeks after baseline; test-retest reliability was 0.89. The results of this study showed similar scores for health-related quality of life before the study but the case and control group were significantly different (in favour of the intervention group) at 1-month ($p$=0.0001) and 2 months ($p$=0.0001) post intervention. An obvious criticism of this study is the shortage of intervention measurements, including objective appraisal of the intervention. Supplementing the SF-8 with more comprehensive mood assessment would have provided a comprehensive examination of the intervention's effect. PPMS was not represented in the study cohort. The small cohort and absence of perceived stress measures reduce this study's comparability with the primary outcome of the current study.

Stress Inoculation Training (SIT) was conducted by Foley et al. in an outpatient setting with MS patients (F. W. Foley et al., 1987). Forty-one participants were assigned to either the SIT or usual care. Analysis was completed on 36 participants as five failed to complete the pre-post-test self-reports. The participants had clinically definite MS; 85% females (n= 30), had an average age of 39 years, were separated or divorced (55%), and were unemployed (58%). This particular project differs to the other studies in that the cohort being studied had greater disability and active disease (as evidenced by a mean EDSS of 6, range 1.0-8.0, and clinical relapse confirmed at all-time points of the study – entry: 60%, post-test: 58%, 6-month follow up: 60%). There is no clarification of MS type but the cohort description suggests that people with both early and late disease were included. The SIT was a 6-session programme based on CBT and utilised more complex psychological therapy. Additionally, PMR was employed in some sessions of the programme. This intervention was facilitated by an advanced practice psychology student, supervised by licensed clinical

psychologists. Intervention evaluation was measured using the Beck Depression Inventory, the State-Trait Anxiety Inventory, the Hassles Scale and Rotter's Internal -External Locus of Control Scale. At analysis, the SIT group (n =20) had significant reductions in depression, state anxiety, hassles and improved problem-based coping compared to the control wait list group. Unfortunately, longitudinal evaluation was only able to be performed on half (n= 10) of the SIT group. However, the investigators report sustained benefit for the SIT intervention at follow up. This outcome may represent a type 1 statistical error because of the small followed cohort, which might have also selected only highly motivated participants.

Another prospectively designed case-control trial by Hughes et al. (2006) found sustained benefit from a stress management programme that was group-based, moving away from one-on-one sessions described in the previous interventions. This project evaluated a health promotion-focused support group for women with a range of chronic, largely physically-affecting illnesses.

This self-management health promotion workshop was held weekly for 6 weeks. The group of 63 participants were randomly assigned to either small group workshop sessions (n=25) or wait-list (n= 38). The six sessions addressed theory-driven topics of understanding stress and stress triggers, learning stress management techniques and practising and promoting the techniques for ongoing use, independent of the group. Multiple measures of outcome held that the programme showed benefit in reducing stress. Pre-test/post-test and 3-month evaluation of multiple self-rating measures, including the SF 36, Perceived Stress Scale (PSS), General Mental Health and Role Limitations. Medical Outcomes Study Short Form -36 (SF36), Generalised Self-Efficacy Scale, Stress Management Self Efficacy Scale, Social Connectedness Scale-Revised, Health Promoting Lifestyle Profile. PSS were significantly reduced ($p$=0.0001) over time in the intervention group whereas the waitlist group did not show significant perceived stress reduction ($p$=0.486). Of the SF36

subcategories, only mental health showed a significant difference between the intervention and wait list cohorts (at 3 months' post study commencement, $p$=<0.01). Of the remaining measures, social connectedness (p=<0.5) represented a measure that improved beyond the intervention, i.e. 3 months after the workshop. As a study whose main goal was to ameliorate stress and promote health it showed lasting positive improvements in social connectedness and self-efficacy through group workshops. Limitations of this study are the small sample size (of which the subpopulation of MS was small), further amplified by attrition at the final follow up, the use of multiple self-rating study measures (no adjustment for multiple testing) and lack of objective outcome measures.

Kolahkaj & Zargar (2015) administered an 8-week mindfulness based stress reduction programme to 40 women with MS in Ahvaz, Iran. The mean age for this cohort was 25 years in both the intervention and the wait list group. The only study measure for this study was the DASS21, which was measured at baseline, at the end of the 8-week programme and repeated 8 weeks later again. The outcome was improvement of stress, anxiety and depression scores ($p$=<0.01). The limitations of this study include small cohort, lack of male participants and lack of objective measures. Bias is introduced in this study as potential participants were completed a study briefing session prior to being randomised, reducing natural attrition. The effect of this method of recruiting will be including only highly motivated participants, thus reducing the generalisability of the outcome.

A recent small feasibility study explored the role of mindfulness based stress management (MBSM) in PwMS with considerable disability (Simpson, Mair, & Mercer, 2017). The study included participants of any type of MS and with an EDSS of equal to or less than 7.0. The aim was to determine if recruitment, programme delivery, retention, outcome measurements and likely effect of the MBSM intervention were feasible. Of these objectives, all were met with varying effect size. MBSM was delivered in up to eight group

sessions, delivered by trained clinicians. Attendance to the sessions was considered good if participants attended four or more sessions; 60% of intervention participants attended this number of times. Content for the intervention included home practice materials on top of skills learned at the face to face sessions. Outcome measures were all self-rating questionnaires. This type of assessment is not costly and easy to administer but reduced the robustness of the results. The primary outcome of the study was met with a significant reduction in perceived levels of stress ($p<0.01$), measured at the completion of the face to face sessions but diminished to a small effect size ($p=0.13$) at 3 months' post face to face sessions. Secondary endpoint measure of quality of life measures scored a small effect size at intervention end and negligible at 3 months 'post intervention. As a feasibility study this project demonstrates promise for the role of MBSM to reduce stress and improve quality of life. However, significant difficulties including short lasting effects and intervention attendance need to be addressed for the results to be demonstrated in larger studies. Again, the study cohort is small, the intervention type is different to the current study (group sessions) and assessment measures all are self-rated. Recruitment bias for moderate or high disability excludes a significant portion of the MS community and further reduces eligibility for comparison with the current study.

Table 1. Summary, studies of stress management in MS

| Publication | Study design | n= | Intervention type | Primary Outcome and Measurement | P -value |
|---|---|---|---|---|---|
| Simpson et al. 2017 | RCT[1] | 25:25 | MBSR[2], group sessions for up to 8 weeks | Perceived Stress (PSS[8]) | < 0.01 |
| Kolahkaj et al. 2015 | RCT | 20:20 | MBSR, group sessions for up to 8 weeks | Perceived Stress Depression, Anxiety (DASS21) | < 0.001 |
| Artemiadis et al. 2012 | RCT | 31:30 | Relaxation breathing and PMR, up to 8 weeks duration | Perceived Stress (and Dep/Anx.[3] and health locus of control) (PSS) | < 0.2 |
| Mohr et al. 2012 | RCT | 60:61 | CBT[4] based stress management, up to 16 sessions | MRI[5] (new Gad lesions) | < 0.02 |
| Ghafari et al. 2009 | RCT | 33:33 | PMR[7] over 8 weeks | QoL[6] (SF-8) | < 0.05 |
| Hughes et al. 2006 | RCT | 39:39 | Stress management workshops | Perceived Stress (PSS) | < 0.0001 |
| Foley et al. 1987 | RCT | 20:16 | CBT +PMR, up to 6 sessions | Distress (and Depression, Anxiety) (Hassles Scale) | < 0.01 |

[1]RCT = randomized controlled trial [2]MBSR = mindfulness-based stress reduction [3]Dep/Anx. = depression/anxiety

[4]CBT = cognitive behavioural therapy [5]MRI = magnetic resonance imaging [6]QoL = quality of life

[7]PMR = progressive muscle relaxation [8]PSS = perceived stress scale

## 2.4 Mindfulness

Mindfulness is a practice based on Buddhist philosophy of non-judgemental, moment to moment awareness of being that is increasingly being used as a therapy in a range of chronic conditions, for example cancer (Bauer-Wu, 2010) and chronic pain (McCracken & Vowles, 2014). Mindfulness is a practice that can be used by an individual or in group settings. When applied to stress management mindfulness encourages an intentional awareness of thought to develop a plenteous understanding of the lived experience to reduce intense and instantaneous reactivity to stressful events (Grossman, Niemann, Schmidt, & Walach, 2004).

Mindfulness has been much studied in well populations (Duncan & Bardacke, 2010; Sharma & Rush, 2014), chronically ill populations (Carlson, Speca, Patel, & Goodey, 2003;

Teasdale et al., 2000) and stressed populations (Grossman et al., 2004). MBSR programmes have evolved in the 21st century (Bauer-Wu, 2010) as wholistic approaches to health care. Bauer-wu (2010) suggests interventions based on MBSR continue to be implemented and studied as the health benefits for mindfulness are increasingly evidenced over a large range of illnesses and populations. MBSR and mindfulness based cognitive therapy (MBCT) studies have shown to change brain connectivity by functional MRI (fMRI) and functional connectivity MRI (fcMRI). In 2011 Kilpatrick found that after an 8-week programme of mindfulness meditation training, a population of healthy women had increased connectivity over auditory and visual pathways on fMRI. More recently, Gotink, Meijboom, Vernooij, Smits, and Hunink (2016) reviewed the available evidence for functional and structural changes in the brain after an MBSR programme of 8 weeks duration. Changes to the prefrontal cortex, cingulate cortex, the insula and hippocampus were reported.

In MS mindfulness has been scantly studied. A mindfulness of movement (Tai Chi/Qi Gong) programme was assessed in a small pilot study of 16 people with MS (Mills & Allen, 2000) in the United Kingdom. This controlled study (cases n=8, control n=8) was undertaken on people with SPMS and assessments on balance and MS Symptom Rating Questionnaire. It was demonstrated that mindfulness of movement was beneficial in coping with MS at the end of the intervention and 3 months after the intervention.

Grossman et al. (2010) performed a randomised control trial of mindfulness training in people with MS to assess the effect on health-related quality of life, depression and fatigue. One hundred and fifty people with MS were randomised into case (n=76) and control groups (n= 74). The intervention was group based and consisted of 8 weekly sessions, a full day retreat and home work. The study population were either RRMS (with no more than 2 relapses in the previous year) or SPMS and had an EDSS of $\leq$6.0 and $\leq$1 step increase of EDSS in the previous year. The cohort has similar demographic makeup between case and

control groups and also reflected the general MS population. Outcome was assessed with largely patient-reported measures, including the Profile of Health-Related Quality of Life in Chronic Disorders, Hamburg Quality of Life Questionnaire in Multiple Sclerosis, Centre for Epidemiologic Studies Depression Scale, Modified Fatigue Impact Scale, Speilberger Trait Anxiety Inventory, neuropsychological assessment and a post intervention questionnaire. Intention to treat analysis showed that mindfulness training in this cohort improved quality of life for at least 8 months among mild to moderately impaired patients independent of depression, fatigue of other psychosocial problem. While this study has shown improvement in depression, anxiety, fatigue and overall quality of life in MS it does not specifically address perceived levels of stress and so cannot be used to draw conclusions about mindfulness as a tool for stress management.

More recently an Iranian study evaluated an 8-week MBSR group course on women with MS (Kolahkaj & Zargar, 2015). The study used the DASS21 tool to examine depression, anxiety and stress before, immediately after and two months after completing the course. Participant numbers were low (20 in each intervention and usual care groups) and only included women, but were able to demonstrate a decrease in depression, anxiety and stress, not only between the intervention and usual care groups, but also pre-test compared to post-test (immediately following and 8 weeks after conclusion of the course). The course employed mindful breathing, watching, hearing, eating, meditation, behavioural awareness and body scanning over 8 weekly sessions. The usual care group were assessed at the same time as the intervention group and offered the course at the conclusion of the study.

The available literature has demonstrated that simple, self-management techniques of stress management can have short and long-term benefits in the MS population, on reducing perceived stress, quality of life and other psychological measures of wellness. Mindfulness interventions are well-established as an effective tool to reduce stress in non-MS populations.

Prospective, controlled and randomised studies of mindfulness interventions in the MS population are limited.

# CHAPTER 3

# METHODOLOGY

## 3.0 Introduction

This chapter describes the methodological approach and procedures used to conduct the study. The design, sample and data collection procedures are described. The instruments used are presented and the reliability and validity of the instruments are discussed. This chapter also includes details of data analysis and the ethical considerations concerned with undertaking this study.

## 3.1 Research Design

This controlled, prospecting study combined quantitative and qualitative research approaches to examine the research questions. Over the course of the project participants were asked to evaluate their levels of stress, their assessment of how they managed their stress and their assessment of how the intervention affected their levels of stress. Quantitative data was collected using repeated measures, at baseline and at 1 month, 3 months and 6 months intervals, and included salivary cortisol levels and levels of perceived stress. Perceived stress was assessed using the DASS21, stress Visual Analogue Scale (sVAS) and MusiQoL. All three questionnaires contain a subjective rating of perceived stress levels. Thematic content was performed on responses derived from participants' diary completion. The diary was primarily used to gather information on intervention adherence; diary completion beyond adherence was optional to study participants (see Appendix 1). This integrative approach seeks to examine the human, lived experience; enabling an exploration of the complex human physiological and emotional response to stress by asking participants to describe their feelings and responses to stress and stress management as well as using a

standardised evaluation of their perceived levels of stress. Using mixed method in research can answer research questions from a number of perspectives, reduce the gaps in data collected and reduce the likelihood of assumptions being made by the researcher during data interpretation (Bulsara, 2015). A mixed method approach is therefore relevant for this study. This approach, also known as triangulation research, has gained popularity over traditional single approach models in social sciences research. In early social sciences research this approach was frequently cited by Campbell and Fiske in the 1950s (Jick, 1979) and continues to be a popular approach to social science and nursing research. In this study, the data was derived concurrently.

### 3.2 Setting

Participants were recruited for the study from the MS clinic within a tertiary hospital in Newcastle, Australia. This MS service provides care to over 800 people with MS. The service includes undertaking neurological assessment for suspected MS as well as providing advice and care for people with newly diagnosed and long-standing MS.

The setting is a large outpatient department that houses multiple medical clinics every day of the working week. The consulting rooms have a mostly clinical aesthetic, with an examination bed and chairs, wall oxygen and suctioning equipment and strong lighting. Each consulting room is set up with a computer and a phone. Outside the cluster of consulting rooms is the focal hub of administrative and nursing support – the noise from this area is rarely heard from inside the nearby consulting rooms. The study participants were seen in various consulting rooms within this area. There was very little variation between the rooms. Occasionally participants were seen in the Neurology Clinical Support Unit or their home due to lack of space in the outpatient department or convenience for the study participant and/or study investigator (i.e. participant limitation of time to be seen and unable to secure a room

the outpatient department). During the course of the study it was identified that some participants were unable to be recruited due to living a considerable distance from the hospital and not being able or motivated to attend for the weekly intervention sessions. These study participants were offered home sessions, which were duly coordinated and conducted by the study investigator.

During the study visits the participants were seen one on one. Occasionally a participant was accompanied by a friend or relative. Support people were encouraged to wait in the waiting area for the duration of the visit. Participants attending the hospital for the study were offered car parking vouchers. This was done to avoid penalising participants for the extra time or making participation in research prohibitive.

### 3.3 Sample Population

The participants recruited to this study were people with MS (PwMS) between the ages of 18 and 65 residing in the Hunter New England region of New South Wales and utilising the MS clinic at the John Hunter Hospital for their care. The sample group was made up of both male and female participants, although female participants made up the greater proportion of study participants, reflecting of the MS female: male ratio of 3 females to each male (Kalincik et al., 2013). The study included a wide range of social backgrounds: people employed, not employed, on home duties, retired or on disability pensions. Participants were in relationships (married, de facto or not living together), single or divorces. Potential participants identified and offered information about the study in the clinic over the recruitment period of 18 months.

#### 3.3.1 Inclusion/ Exclusion Criteria

The age of the participants was limited to being between 18 and 65 years of age (to reduce risk of age-related cognition issues) and all participants had a diagnosis of MS. Length

of disease since diagnosis was noted but not used for exclusion to participation. Previous exposure to or use of meditation and/or PMR was not considered an exclusion recruitment. Exclusion criteria included: -

1. People with significant medical and/or psychological illness,
2. MS relapse with or without steroid treatment within one month of enrolment in the study,
3. Cognitive dysfunction (determined by inability to complete the Audio Recorded Cognitive Screen),
4. Inability to read or write English,
5. Severe muscular spasms, and
6. Participants with recent treated relapse.

Recent treated relapse was excluded because the standard treatment for relapses consists of intravenous high dose steroid; apart from affecting the objective outcome measure, a side effect of this therapy is altered mental state. The rationale for excluding untreated relapse was to avoid the significant emotional distress or adjustment as a direct result of the relapse. In addition, clinical stability during the assessment period is required to exclude potential bias from improvement after relapse. Cognitive dysfunction and inability to write or read in English would compromise the person's ability to complete the screening and follow up assessments, and follow the instructions while performing meditation and PMR exercises. People with severe muscular spasms were excluded from the study because this would prevent participants from performing the PMR; an intervention that required participants to methodically tense and relax muscle groups.

### 3.3.2 Recruitment

Participants were recruited through the neurology outpatient department during the period January 2015 to July 2016 and were approached to consider the study by one of the clinic neurologists, neuro-immunology fellow or the clinical trial coordinator. The clinic appointment list was examined by the study investigator for potential participants and the clinician involved was provided with a study participant information and consent form (PICF) to give to the potential participant. One of the team members introduced the study to potential participants during routine consultations. (see Appendix 2). Any questions from potential participants were answered by one of the team or the study investigator. If potential study participants were happy to proceed to consent they gave written consent in the presence of the neurologist. Their contact details were then forwarded to the study investigator. At this point the study participant was randomised to intervention (case) or wait list (control) group and initial assessments were either collected or scheduled for collection.

## 3.4 Informed Consent Process

Ethical approval for this study was obtained from Hunter New England Local Health District Human Research Ethics Committee (approval number 14/06/18/4.02) and the Murdoch University Human Research Ethics committee (approval number 2014/118) Informed consent was obtained by either the neurologist or MS clinical trial coordinator. Potential participants were identified prior to or during routine outpatient clinics and offered verbal and written information about the study. Once the neurologist or clinical trial coordinator were confident that all questions regarding the study were answered and the participant had agreed to participate, both the neurologist and the participant would sign and date the consent form. The participant's details were then forwarded to the researcher to enrol in the study.

### 3.5 Randomisation

To maximise study robustness a free online randomisation tool, Research Randomizer, was used to assign consented participants to either the intervention (case) group or the wait list (control) group. This tool was developed by the Social Psychology Network (Urbaniak & Plous, 2013) and uses a pseudo-random number generator. The programme provided a series of number '1's and '2's for 100 participants. Each '1' indicated a case participant and a '2' indicated a waitlist participant. An assignation of case or wait list was allocated upon receiving written consent completion.

### 3.6 Intervention (Case Information Package)

Intervention or case participants were provided an informational package at baseline. This contained an educational brochure on stress in MS entitled Taming Stress in MS: Staying Well (F. Foley, 2012), a meditation compact disc (CD) with a twenty minutes guided meditation and a ten-minutes guided PMR. The meditation was designed and recorded by a local psychologist with design input from the study investigator. The pretext and text for the guided meditation was designed by the psychologist and the study investigator to provide a general introduction to meditation, with an emphasis on mindfulness. This was done to assist those participants who have never had or have only had little experience with guided (or otherwise) meditation. The PMR text was taken from Taming Stress in Multiple Sclerosis: Staying Well (Foley, 2012), recorded and used with permission from the author, Fred Foley, for this project (see Appendix 3, ffoley1@oal.com).

Mindfulness exercises included diaphragmatic breathing and body scanning, key meditation skill development of focussing on being present in the now, and finally reflecting on individual stressful scenarios and applying mindfulness principles for future exposure to said stressor exposure. This reflection consisted of recognising the emotion attached to the

stressor (e.g. fear or sadness), exploration of the feeling - assignation and description of how that feels in the body (e.g. headache or tight muscles, hot or jelly-like, rating out of 10), acceptance or allowing of the emotion, practising non-identification or acceptance of those feelings. In this way, the participant learned to respond differently and feel differently about situations that have previously caused increased stress. These mindfulness skills were practised weekly with the PI and the participants took home the study kit, which included the MindS meditation and PMR CD, diary and Taming Stress in Multiple Sclerosis: Staying Well. Participants were encouraged to perform meditation and PMR on a daily basis for 20 minutes per session.

### 3.7 Screening

Screening assessments were applied once the consent form was signed and the participant randomised. The Audio Recorded Cognition Screen (ARCS) was used to determine if the participant had a significant level of cognitive impairment, which would preclude her/him from inclusion. If at the time of consent or enrolment an ARCS had recently been performed (within 12 months), for example, as part of routine clinic care, then that assessment would be used for the study screening measure. The EDSS was used to describe the population, in order to define the level of physical disability in the study population.

#### 3.7.1 Audio Recorded Cognition Screen (ARCS)

For screening potential participant's routine cognitive assessment was used to identify people with limitations in cognition. Severe cognitive dysfunction was exclusion for participation in the study. Cognitive screening is performed routinely in clinical practice and if performed within 12 months of study entry the score was sourced from the participant's health records to minimise the burden on patients of repetitive screening and to reduce learned effect of this assessment. The Audio Recorded Cognition Screen (ARCS) is a short

screening tool to assess cognition domains including executive function, memory, visual spatial construction and language. The ARCS is administered by audio disc. Validation of the ARCS tool in MS was undertaken in 2010 and it was found to have better sensitivity (86%) compared to an equivalent tool, the Paced Auditory Serial Addition Test (PASAT) (68%) at an equal specificity (71%) (Lechner-Scott et al., 2010).

### 3.7.2 Expanded Disability Severity Score (EDSS)

The EDSS was used to describe the sample population and to describe disease stability or progression over the course of the study. The EDSS is an ordinal clinical rating scale that is rated according to seven neurological functions (visual, cerebral, pyramidal, cerebellar, brainstem, sensory, bowel and bladder, and ambulation) affected in MS (Kurtzke, 1983). It is used as a quantitative method of assessing disability. An EDSS of 0.0 indicates a normal neurological examination, 1.0 indicates signs but no disability, after 4.0 indicates walking distance is limited to 500m, at 5.5 a walking aid is likely to be necessary from some to most of the time, and from 7.5 a wheelchair is required. Disease stability in the EDSS is an improvement or no change in score over 6 months whereas commonly progression is considered a sustained increase of 1.0 points or more over 6 months (Healy, Engler, Glanz, Musallam, & Chitnis, 2013). EDSS is an examination routinely undertaken with MS patients and has previously been reported in the literature as being a reliable and valid measure of impairment and disability (Sharrack, Hughes, Soudain, & Dunn, 1999). For the purposes of this study the EDSS was undertaken at baseline by a qualified assessor (all assessors were certified with Neurostatus certification (Kappos, 2016).

### 3.8 Data Collection

Demographic information including date of birth, sex, MS classification (RRMS, SPMS or PPMS), date of diagnosis, date and score of most recent neurological assessment (EDSS), current employment status, current relationship status, current medical comorbidities, currently prescribed medications, historical or current diagnosis or depression, anxiety or stress by doctor, psychologist or psychiatrist, historical or current prescription to treat depression, anxiety or stress was collected. The baseline survey also collected information about at-the-time methods of managing stress.

Follow up visits were performed at one month (F1) and six months (F2). Follow up assessments included relapse details: if a relapse or worsening of MS occurred since baseline or last study visit, diagnosis of new or change in medical comorbidities, including depression, anxiety or stress, since baseline or last study visit, new prescribed medications, including antidepressants, anti-anxiety agents or anti-stress agents since baseline or last study visit, any medication adverse effects since baseline or last study visit. Additional information collected included change in relationship status since baseline or last study visit, change in employment status since baseline or last study visit, number of days meditation was performed out of last 7 days (for intervention or case participants), number of days per week on average meditation was performed since baseline or last study visit (for intervention or case participants), number of days PMR was performed out of last 7 days (for intervention or case participants) and number of days per week on average PMR was performed since baseline or last study visit (for intervention or case participants). A review of frequency of performing meditation and/or PMR the required five out of seven days (on average) per week since baseline or last study visit for intervention or case participants. At-the-time methods of managing stress were performed, as was a comparison of baseline and follow up stress component of DASS21,

including participant's perceived reason/s for change or non-change of result (for intervention or case participant).

### 3.9 Diary

Intervention or case participants were provided with a weekly diary to indicate when they performed meditation and/or PMR. The purpose of the diary was to measure adherence to the intervention and dose effect of performing meditation and/or PMR. Participants were also offered space on the diary to complete a reflection of their experience of performing the stress management strategies and their perceived stress exposures. This last purpose of the diary was not compulsory for participants to complete but rather contributed to the mindfulness exercises undertaken in weeks one to four. The stress visual analogue scale (VAS) was included on the diary documentation. This was to capture in real time overall level of perceived stress, week to week.

### 3.10 Instruments

There were four main assessment tools used in the MindS study. They were salivary cortisol level, Depression, Anxiety and Stress Severity short scale (DASS21), Multiple Sclerosis International Quality of Life questionnaire (MusiQoL) and sVAS. The salivary cortisol level, DASS21 and MusiQoL were performed at baseline and one month after baseline. The DASS21 and MusiQoL were repeated additionally at six months post baseline. VAS was completed weekly by participants and formed part of the diary.

#### 3.10.1 The Depression, Anxiety and Stress Severity Scale (DASS21)

The DASS21 is a quantitative self-report measure of distress which includes items on depression, anxiety and stress. The scale is a Likert scale. While the DASS is available in a 42-item scale, the short form was used in this study as the two scales are comparative

(Antony, Bieling, Cox, Enns, & Swinson, 1998) and the shorter version is less burden to complete by participants. The DASS 21 is a set of 21 questions asking the participant to rate their level of stress, anxiety and depression as they have experienced it over the previous 7 days.

The DASS21 has reported good psychometric properties in several patient populations including those with neurological conditions. Consistency and reliability of the scale ranged from 0.93-0.94 (Henry & Crawford, 2005) as measured by Cronbach's alpha coefficient. In addition, the instrument is considered an appropriate instrument regarding its brevity, reliability and previously reported sound structure linear self-rating scale where 0 is the lowest level of perceived stress and 10 is the worse stress perceivable (Henry & Crawford, 2005). The DASS21 was performed at baseline and at F1 and F2.

### 3.10.2 Visual Analogue Scale (VAS)

The Visual Analogue Scale (VAS) is a self-rating, validated stress measurement scale (Lesage, Berjot, & Deschamps, 2012). This tool was used to assess the participant's perceived level of stress, week to week, over the course of the project. This scale is a linear self-rating scale where 0 is the lowest level of perceived stress and 10 is the worse stress perceivable.

### 3.10.3 Multiple Sclerosis International Quality of Life (MusiQoL)

The MusiQoL is multidimensional tool asking respondents to rate 31 items related to their ability to complete and participate in activities of daily living, psychological wellbeing, MS symptoms, relationships with friends and family, sentimental and sexual life, coping, rejection and relationship with the health care system. This scale is also a Likert psychometric scale that required respondents to rate their responses on an agree-disagree scale for a series of statements (Schneider, 2013). Responses are scored *'never/not at all',*

*'rarely/a little', 'sometimes/somewhat', 'often/a lot',* and *'always/very much'.* The questionnaire takes about 10 minutes to complete. Results of the MusiQoL are linear and rate from 0-100; the higher the score the better the quality of life of the respondent completing the questionnaire.

The MusiQoL is a validated tool to measure quality of life specific to people with MS and has previously been reported to have sound psychometric properties (Simeoni, 2008). This international study, including a large number of PwMS patients (n=1992) conducted by the Simeoni group (2008) found internal consistency was satisfactory for all dimensions with Cronbach's alpha coefficients ranging from 0.68 to 0.92 MusiQoL was assessed for this study at baseline and at F1 and F2.

### 3.11 Salivary Cortisol

Salivary cortisol is a useful tool to objectively measure a physiological response to stress and stress changes (Matousek, Dobkin, & Pruessner, 2010). Using salivary cortisol was chosen as a straightforward and reasonably inexpensive method of collecting the expected 1200 samples required. The Salivette kit contained a 'bullet' shaped cotton gauze in a plastic collection tube. Due to their robust stability, the 3 samples for each collection point could be stored in the refrigerator after collection and delivered to the pathology agent within a week of collection. Cortisol levels can be affected by circadian rhythm, diet (especially caffeine and acidic products), stress and exercise. Salivary cortisol testing by Salivette kit occurred at baseline and again at week four for both interventional (or case) group and usual care (or waitlist) group. To incorporate the circadian effect three samples were collected at each assessment: 0800hrs, 1400hrs and 2000hrs. Participants were asked to refrain from eating, drinking or taking medication for up to 45 minutes before collecting the sample, as well as avoiding extreme exercise for up to 30 minutes before collecting the sample. Immediately prior to sample collection participant were asked to rinse their mouth out with water and

gently chew the cotton bullet for one minute. Finally, they would return the cotton bullet to the Salivette tube and store in the refrigerator before delivering to a Pathology North Laboratory within a few days. Normal reference ranges for each test are as follows: 0600 to 0800hrs- 5.5 to 28.9 nm/L, 1800 to 2000hrs – 1.1 to11.6 nm/L and midnight - <7.0 nm/L.

### 3.12 Data Analysis

This study relied largely on quantitative analysis but also included rudimentary qualitative examination of the research questions, using thematic content analysis. Some observational outcomes are also documented. Salivary cortisol levels were compared on both groups at weeks one and four. Comparison of DASS21, MusiQoL and VAS provided subjective analysis. The DASS21 responses stratified low to high stress for pre-and post-test analysis and the data analysed using multifactorial logistic regression to measure the effectiveness of the intervention.

The demographic information was analysed using descriptive analysis. In addition, analysis of the written responses to the survey data collected between case and wait list groups about their reflection on their management of stress were compared qualitatively. Qualitative data from the open-ended question item was grouped by thematic coding (Gibbs, 2007). Comparison was drawn between perceived levels of stress, ability to recognise increased stress levels, current methods of stress management and perceived effectiveness of these employed techniques for both wait lists and cases at baseline and at each of the follow up time points. This was correlated with stress scores of the DASS21.

Disease and demographic information were collected at baseline and at the follow up visits. Changes in disease or social/occupational status might influence levels of stress. Participants who scored high on the DASS21 were referred for further assessment and management but remained in the study if they so wished.

### 3.13 Ethical Considerations

A number of ethical considerations arose during the study design and implementation. The study gained approval through the Hunter New England Local Health District Human Research Ethics and Governance Committee and the Murdoch University Ethics Committee. Both committees had standard, but conflicting, positions about recruitment for studies where the primary investigator was the only clinician for usual care. As a result, recruitment and consent was completed by the neurologist or clinical trials coordinator.

Another ethical consideration was identifying participants with significant depression, anxiety and/or stress issues in the context of duty of care. More specifically being able to identify when participants should be referred for further assessment and management. The DASS21 has the ability to screen for depression, anxiety and stress but is not recommended for making a diagnosis independent of clinical assessment by psychologist/psychiatrist or mental health nurse specialist (Lovibond & Lovibond, 1995).

Referrals for further assessment and management were made on the basis of DASS21 scores and purposeful engagement of the participant, both by direct discussion about altered mood and non-direct observation. This assessment encompassed information historically learned or observed about the participant, derived from the existing relationship (and history) between the nurse and participant, previous therapeutic engagement, information from the treating neurologist and eliciting the participant's psychosocial wellbeing throughout the course of the study. Participants with higher DASS21 scores with or without other evidence for altered mood or coping were offered referral for more specialised support. These participants were eligible to remain in the study.

### 3.14 Summary

This chapter has outlined the MindS study design and defined methods used for study recruitment, consent, randomisation, data collection and analysis. It demonstrated the reasons for using the tools chosen, those being salivary cortisol level as objective measure as well as a trio of participant subjective assessments. Finally, ethical implications of research involving people in dependent relationships and duty of care were defined and explored. The following chapter will present the findings of this approach.

# CHAPTER 4

# FINDINGS

## 4.1 Introduction

This chapter describes the demographics of the participant group, provides quantitative results and explores the qualitative subject matter. This evaluation of results will focus on baseline responses comparative to F1 and F2. At F1 82% of surveys (questionnaire, diary, sVAS, DASS21 and MusiQoL) were available for analysis and 49% of complete cortisol samples (n=6 samples) were available for analysis. At F2 42% of surveys (questionnaire, diary, sVAS, DASS21 and MusiQoL) were completed. As a result of intervention adherence and significant outlier results the data was re-analysed using the median scores instead of mean scores.

This chapter will describe participant group demographics (total number, total number female participants, total number male participants, MS type (RRMS, SPMS or PPMS), MS duration average and most recent EDSS. Employment and relationship state at baseline and follow up is provided. History of depression, anxiety and/or stress and medication treatment for these states at baseline and one month follow up are provided.

Means of the intervention groups were compared across timepoints using the general linear model repeated measures analysis of variance. An alpha-level of 0.05 was used as the significance threshold. Post hoc (observed) power indicated that this sample size had less than 50% to detect the mean differences observed in this study.

## 4.2 Demographics

116 PwMS were offered written and verbal information and one person failed the screening process due to current severe psychological illness. From the group of PwMS offered study participation 103 people were recruited. Of this group, two participants

withdrew consent before randomisation (both due to change in their employment and were not able to attend the hospital for the one on one sessions) and one was excluded due to significant, psychological illness. This participant was referred to his general practitioner for management. The remaining recruits were randomly placed into either the intervention group (n=50) or the wait list group (n=50).

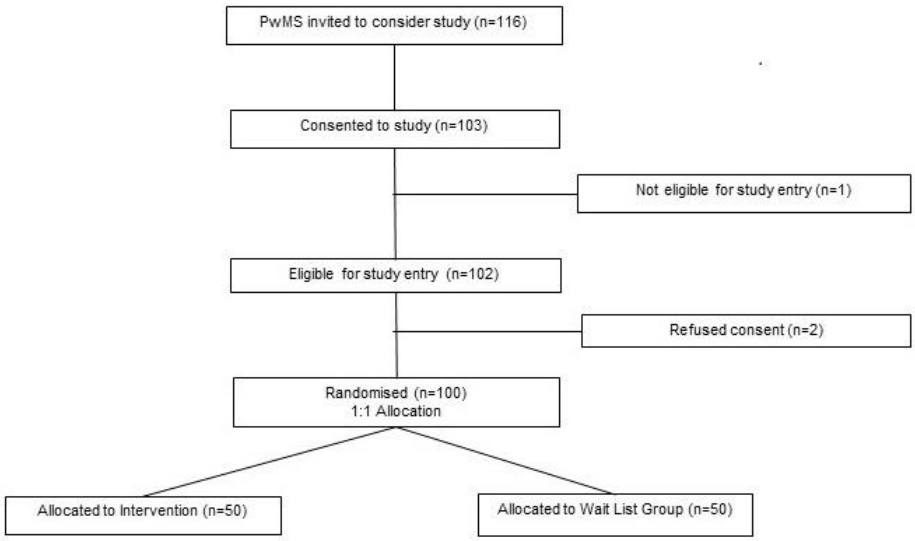



Figure 1 Flowchart of participants

Eighty-six per cent of participants were female and 14% male. At baseline 69% were married (n=50) or in de facto (n=19) relationships. 31% reported their relationship status as single. At completion of the study 68% remained in married or de facto relationships and 32% were single. The majority of participants experienced not change in their relationship status over the course of the study.

Eighty percent of participants were on MS therapy (see table 3). 78% of cases and 72% of waitlist group were diagnosed with and treated for comorbidities, including disorders affecting psychological and other neurological health (e.g. migraine). 22% of the study cohort

was also diagnosed with other autoimmune disorders (5 cases and 6 controls; Crohn's disease, diabetes mellitus, Graves' disease, Sjogren's disease). This cohort is representative of the wider population. In particular, age and EDSS are a good representation of the clinical group affected by MS.

Table 2. Gender and MS disease demographics of study cohort.

| Cohort demographics | Intervention group | Waitlist group |
|---|---|---|
| Number, n (%) | 50 (50) | 50 (50) |
| Female, n (%) | 44 (88) | 42 (84) |
| Male, n (%) | 6 (12) | 8 (16) |
| Median age in years (range) | 44 years (22 to 67 years) | 43 (19 to 72 years) |
| MS type- RRMS, n (%) | 46 (92) | 44 |
| MS type- SPMS, n (%) | 4 (8) | 4 |
| MS type – PPMS, n (%) | 0 (0) | 2 |
| MS duration average in years (range) | 9.8 years (1 to 35 years) | 9.0 years (1 to 37 years) |
| EDSS median (range) | 2.6 (0.0 to 6.5) | 2.7 (0.0 to 6.5) |

Table 3. MS therapy use in study cohort at baseline

| MS therapy | n (%) | | n (%) |
|---|---|---|---|
| Case total not on Tx. | 12 (24) | Wait list total not on Tx. | 8 (16) |
| Case total on Tx. | 38 (76) | Wait list total on Tx. | 42 (84) |
| Avonex | 2 (4) | Avonex | 0 (0) |
| Copaxone | 3 (6) | Copaxone | 2 (4) |
| Gilenya | 19 (38) | Gilenya | 14 (28) |
| Lemtrada | 0 (0) | Lemtrada | 5 (10) |
| Plegridy | 1 (2) | Plegridy | 3 (6) |
| Rebif | 0 (0) | Rebif | 1 (2) |
| Tecfidera | 6 (12) | Tecfidera | 8 (16) |
| Tysabri | 7 (14) | Tysabri | 9 (18) |

Tx. = Treatment

### 4.2.1 Employment

Of the 100 participants 64% were engaged in casual, part-time or full-time employment. 26% were drawing a pension (2 aged pension and 24 disability support

pension). 10% of the cohort were either unemployed or looking for work (n=2), unemployed and not actively looking for work (n=1), on home duties (n=4) or retired (n=3). At follow up 8% of participants reported a change in their employment; 3 participants previously employed became unemployed (1 of these participants ceased employment and commenced a disability pension), 3 participants remained working but in different roles and 2 participants reduced hours due to MS.

Table 4. Employment at baseline

| Employment | Intervention group, n (%) | Waitlist group^, n (%) |
|---|---|---|
| Full time employment | 17 (34) | 14 (28) |
| Part time employment | 17 (34) | 13 (26) |
| Casual employment | 2 (4) | 1 (2) |
| Disability pension | 10 (20) | 14 (28) |
| Aged pension | 2 (4) | 2 (4) |
| Unemployed | 1 (2) | 2 (4) |
| Not working, not actively looking for work | 1 (2) | 3 (6) |

^ 1 participant did not report employment status

### 4.2.2 MS Relapse during the Study and Referral for Management of Significant Anxiety, Depression and/or Stress

During the intervention period 9% (n=9) of people experienced relapse of their MS**.** 8 of these relapses were confirmed by neurological assessment and 7 people were treated with a course of intravenous methylprednisolone (1gram daily for 3 days). The remainder of the study participants remained relapse free. As demonstrated in table 5, 54% (n=54) of overall participants were being treated for anxiety, depression and/or stress with pharmacological agents. At follow up 62% (n=62) were taking pharmacological agents for treating anxiety, depression and/or anxiety; one participants had ceased an antidepressant, two participants had increased their dose of antidepressant and one participant changed antidepressant type. Information about participation in formal psychological treatment, e.g. CBT, was not collected. One study participant was entered into the study but at the baseline visit reported

significant depressive and anxiety symptoms. This person was referred back to their general practitioner and psychologist for ongoing management and excluded from participating in the study. Consideration was given to continuing the participant in the study as per the study protocol for managing participants with existing or newly presenting depression, anxiety or severe stress but after discussion with the participant he was withdrawn from the study.

### 4.2.3 Depression, Anxiety or Stress History, including pharmacological management

Of the total 100 participants 52% (n=52) had a history of depression, anxiety or stress. 20% (n=10) and 16% (n=8) of intervention and wait list groups respectively had a diagnosis of depression, anxiety of stress prior to the onset of MS. 40% (n=20) and 28% (n=14) of intervention and waitlist groups respectively were diagnosed with depression, anxiety and/or stress after MS onset. Of this group 9% (n=6) had anxiety only, 77% (n=47) had depression only, 12% (n=7) had anxiety and depression and 2% (n=1) had depression and high levels of stress (diagnosed by the participant's general practitioner). 42 of the 52 participants (i.e. 81%) had either recently taken or were currently taking prescribed medication for management of anxiety, depression and/or stress. Table 5 outlines the current prophylactic medication used in this cohort to manage depression, anxiety and stress.

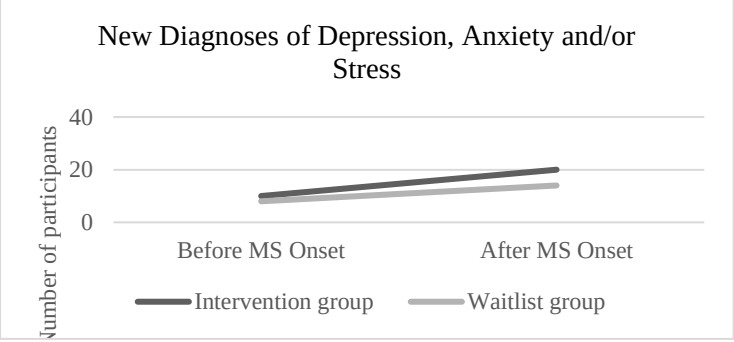



Figure 2. Number of new depression, anxiety and/ or stress diagnoses, by group.

Table 5. Antidepressant and anti-anxiety therapy use in study cohort at baseline

| Medication | Intervention group treated, n= | Waitlist group treated, n= |
|---|---|---|
| *Selective serotonin reuptake inhibitors* | | |
| Sertraline (Zoloft) | 3 | 2 |
| Citalopram (Cipramil) | 0 | 2 |
| Escitalopram (Lexapro) | 9 | 4 |
| Fluoxetine (Lovan, Prozac) | 3 | 4 |
| Desvenlafaxine (Pristiq) | 2 | 3 |
| *Serotonin and noradrenaline reuptake inhibitors* | | |
| Duloxetine (Cymbalta) | 2 | 1 |
| Venlafaxine (Effexor) | 1 | 1 |
| *Benzodiazepines* | | |
| Diazepam (Valium) | 1* | 1 |
| *Tricyclic antidepressants* | | |
| Amitriptyline (Endep) | 3# | 0 |
| Total n PwMS on DAS treatment | 24 | 18 |

* diazepam used in combination with duloxetine in 1 participant

# amitriptyline used in combination with escitalopram in 2 participants

### 4.2.4 Methods of Coping with Increased Perceived Stress

Participants were asked to list the activities they engaged in to manage or alleviate their stress. This information was collected using a 17-item list or activities, including an open item for them to list activities they participant in that weren't included in the provided list. Participants were able to tick as many items as they wanted but not asked to rate these activities for stress management success. This information was collected at baseline, 1 month and 6 months. Table 6,7 and 8 outline the strategies employed by participants to manage perceived stress at baseline and follow up.

Table 6. Baseline strategies employed to manage stress

| Activity to manage stress at baseline | Number of PwMS who used this strategy (cases) | Number of PwMS who used this strategy (wait lists) |
|---|---|---|
| Exercise | 28 | 24 |
| Medication | 13 | 10 |
| Drinking alcohol | 11 | 12 |
| Smoking tobacco | 7 | 7 |
| Using illegal drugs | 3 | 2 |
| Regular meditation | 8 | 7 |
| Using mindfulness | 4 | 9 |
| Cognitive Behavioural Therapy (CBT) | 2 | 3 |
| Talking to a psychologist | 7 | 8 |
| Talking to their family | 30 | 26 |
| Talking to their general practitioner (GP) | 14 | 9 |
| Talking to their MS team | 10 | 4 |
| Shopping | 12 | 9 |
| Spending time with family and/or friends | 28 | 20 |
| Deliberately avoiding the stressor | 21 | 25 |
| Doing nothing at all | 7 | 7 |
| Other (detail) | 19 | 14 |
| Crying | 1 | 1 |
| Eating | 2 | 2 |
| Getting angry with people | 1 | - |
| Avoid social events | - | 1 |
| Self-harm | - | 1 |
| Gambling | - | 1 |
| Yell | 1 | - |
| Internalise | 1 | - |
| Try to stay busy | - | 1 |
| Lying down or sleeping | 3 | 1 |
| Walking the dog | 1 | 1 |
| Playing with cat | 1 | - |
| Doing puzzles | 2 | - |
| Gardening | 3 | 4 |
| Clean house | - | 1 |
| Fishing | 2 | - |
| Going to the beach | 1 | - |
| Reading | 2 | 1 |
| Watching movies or television | 4 | 1 |
| Drinking tea/ coffee | 1 | 1 |
| Cooking/ Baking | 1 | 1 |
| Listening to music | 1 | - |
| Using the computer/iPad games/video games | 2 | 1 |
| Making candles | 1 | - |
| Scrapbooking | 1 | - |
| Colouring in | 1 | - |
| Knitting/Crocheting | 2 | 2 |
| Journaling | 1 | - |
| Genealogy | - | 1 |
| Prayer/bible study | 1 | 1 |
| Driving | 1 | - |
| Remedial massage | - | 1 |
| **Total strategies: total no. respondents** | **224:47** | **196:47** |

Table 7. F1: strategies employed to manage stress

| Activity to manage stress at F1 | Number of PwMS who used this strategy (cases) | Number of PwMS who used this strategy (wait lists) |
|---|---|---|
| Exercise | 21 | 23 |
| Medication | 15 | 8 |
| Drinking alcohol | 5 | 4 |
| Smoking tobacco | 2 | 6 |
| Using illegal drugs | 11 | 1 |
| Regular meditation | 16 | 9 |
| Using mindfulness | 12 | 9 |
| Cognitive Behavioural Therapy (CBT) | 1 | 2 |
| Talking to a psychologist | 4 | 6 |
| Talking to their family | 20 | 19 |
| Talking to their general practitioner (GP) | 6 | 6 |
| Talking to their MS team | 8 | 6 |
| Shopping | 6 | 14 |
| Spending time with family and/or friends | 23 | 18 |
| Deliberately avoiding the stressor | 16 | 15 |
| Doing nothing at all | 1 | 7 |
| Other (detail) | 8 | 4 |
| Try to stay busy | - | 1 |
| Lying down or sleeping | 2 | 1 |
| Walking the dog | 1 | 1 |
| Bee keeping | - | 1 |
| Doing puzzles | 1 | - |
| Gardening | - | 2 |
| Reading | 1 | 1 |
| Watching movies or television | 1 | - |
| Cooking/ Baking | 1 | 1 |
| Listening to music | 1 | - |
| Using essential oils | 1 | - |
| Colouring in | 1 | - |
| Knitting Crocheting | 1 | - |
| Remedial massage | - | 1 |
| Renovating caravan | 1 | - |
| Watching sport | - | 1 |
| **Total strategies: total no. respondents** | **165:37** | **157:40** |

Table 8. F2: strategies employed to manage stress

| Activity to manage stress at 6 months | Number of PwMS who used this strategy (cases) | Number of PwMS who used this strategy (wait lists) |
|---|---|---|
| Exercise | 21 | 23 |
| Medication | 7 | 4 |
| Drinking alcohol | 6 | 5 |
| Smoking tobacco | 1 | 6 |
| Using illegal drugs | 2 | 1 |
| Regular meditation | 15 | 8 |
| Using mindfulness | 12 | 6 |
| Cognitive Behavioural Therapy (CBT) | - | 3 |
| Talking to a psychologist | 1 | 1 |
| Talking to their family | 23 | 22 |
| Talking to their general practitioner (GP) | 7 | 6 |
| Talking to their MS team | 3 | 2 |
| Shopping | 5 | 5 |
| Spending time with family and/or friends | 16 | 18 |
| Deliberately avoiding the stressor | 13 | 13 |
| Doing nothing at all | 2 | 6 |
| Other (detail) | - | - |
| Try to stay busy | - | 1 |
| Lying down or sleeping | 1 | - |
| Walking the dog | - | 1 |
| Bee keeping | - | - |
| Doing puzzles | 1 | - |
| Gardening | 1 | - |
| Reading | 2 | - |
| Watching movies or television | 1 | - |
| Cooking/ Baking | - | 1 |
| Listening to music | 1 | - |
| Prayer | - | 1 |
| **Total strategies: total no. respondents** | **141:42** | **133:38** |

### 4.2.5 Level of perceived stress as measured by stress visual acuity scale

Perceived stress was measured by the sVAS, which is a linear self-rating scale where 0 is the lowest level of perceived stress and 10 is the worse stress perceivable. The baseline mean level of stress for the case cohort is 4.4 out of 10 (medium level of stress) and dropped to 3.8 out of 10 at follow up. The mean sVAS for wait list cohort was 3.7 out of 10 at baseline and 4.2 out of 10 at follow up. The result between groups, from baseline to F1 is $p$=0.8. AS demonstrated by the p value in table 10 F2 change is not significant.

Table 9. Perceived Stress (sVAS) between subjects mean, baseline to F1.

| Intervention | Timepoint | Mean | Std. Error | 95% Confidence Interval | | F Statistic | P-Value |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| Intervention | 1 | 4.4 | 0.6 | 3.3 | 5.6 | 0.044 | *p*=0.8 |
| | 2 | 3.8 | 0.6 | 2.6 | 4.9 | | |
| No Intervention | 1 | 3.7 | 0.5 | 2.8 | 4.6 | | |
| | 2 | 4.2 | 0.5 | 3.2 | 5.1 | | |

Table 10. Perceived Stress (sVAS) between subjects mean, baseline to F2.

| Intervention | Timepoint | Mean | Std. Error | 95% Confidence Interval | | F Statistic | P-Value |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| Intervention | 1 | 4.9 | 0.9 | 3.1 | 6.7 | 0.003 | *p*=0.3 |
| | 2 | 2.9 | 0.7 | 1.5 | 4.3 | | |
| No Intervention | 1 | 4.2 | 0.6 | 2.9 | 5.5 | | |
| | 2 | 3.7 | 0.5 | 2.7 | 4.7 | | |

### 4.2.6 Level of perceived stress as measured by stress component of DASS21

The DASS21 is a validated 21-item self-rating tool for measuring depression, anxiety and stress. Participants are asked to convey the presence of depression, anxiety and stress symptoms over the past week. Each item is scored from 0 (*did not apply to me at all over the past week*) to 3 (*applied to me very much or most of the time over the past week*). Of the aggregated score 0-14 indicates a normal level of stress, 16-18 is mild stress, 20-24 is moderate stress, 26-32 is severe stress and 34-40 is extremely severe stress. The mean score for the case cohort at baseline was 14.2 ($p$ = 0.9, 95% CI [10.3, 18.1] and 12.9 at F1 follow up, ($p$ = 0.9, 95% CI [9.1, 16.7], and 11.9 at 6-month follow up ($p$=0.3, 95% CI [7.4, 16.2] (see table 11). The mean score for the wait list cohort was 14.3 (95% CI [11.1, 17.5] at baseline and 13.1 (95% CI [10.0, 16.2] at F1 (see table 11) and 10.3 at the F2 (95% CI [7.5,

13.1] (see table 12). Again, there was no significant difference between groups, from baseline F1.

In stratifying the responses from normal to extremely severe stress, 50% of the overall study cohort scored ‘normal’ stress at baseline and 53% at follow up; 16% of the overall study cohort scored ‘mild’ stress at baseline and 4% at follow up; 9% of the overall study cohort scored ‘moderate’ stress at baseline and 18% at follow up; 14% of the overall study cohort scored ‘severe’ stress at baseline and 7% at follow up; and 4% of the overall study cohort scored ‘extremely severe’ stress at baseline and 4% at follow up. Responses were incomplete for 7% of the overall cohort at baseline and 14% at follow up.

Table 11. Perceived Stress (stress component of DASS21) between subjects, baseline to F1.

| **Intervention** | **Timepoint** | **Mean** | **Std. Error** | **95% Confidence Interval** | | **F Statistic** | **P-Value** |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| Intervention | 1 | 14.2 | 2.0 | 10.3 | 18.1 | 0.007 | *p*=0.9 |
| | 2 | 12.9 | 1.9 | 9.1 | 16.7 | | |
| No intervention | 1 | 14.3 | 1.6 | 11.1 | 17.5 | | |
| | 2 | 13.1 | 1.5 | 10.0 | 16.2 | | |

Table 12. Perceived Stress (stress component of DASS21) between subjects, baseline to F2.

| **Intervention** | **Timepoint** | **Mean** | **Std. Error** | **95% Confidence Interval** | | **F Statistic** | **P-Value** |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| Intervention | 1 | 16.3 | 2.4 | 11.5 | 21.1 | 1.19 | *p*=0.3 |
| | 2 | 11.9 | 2.2 | 7.4 | 16.2 | | |
| No Intervention | 1 | 12.8 | 1.5 | 9.8 | 15.8 | | |
| | 2 | 10.3 | 1.4 | 7.5 | 13.1 | | |

### 4.2.7 Cortisol

Cortisol was measured at 0800hrs, 1400hrs and 2000hrs at baseline and follow up, one month later. These three readings were averaged to give a single result. Normal reference ranges for each test are as follows: 0600 to 0800hrs- 5.5 to 28.9 nm/L, 1800 to 2000hrs – 1.1 to11.6 nm/L and midnight - <7.0 nm/L. For most participants, this was an unpleasant process, as described in another study using salivary cortisol kits (Kalman & Grahn, 2004). 26 case participants and 26 wait list participants returned all samples required for comparison. 11 case participants and 9 wait list participants completed only baseline samples, despite phone and message reminders. Two participants (one case and one waitlist participant) completed only the follow up cortisol samples. Feedback about performing the cortisol included it was difficult to collect and it was extremely unpleasant to chew on the cotton bullet for the length of time required to produce a sample. One participant had difficulty generating enough saliva, which resulted in one of the three samples being insufficient to measure. One participant had significantly abnormal levels of cortisol and this participant's measures were excluded from analysis. The cortisol assessment was a significant addition to the data collected, as it represented the only objective analysis of stress levels. The number of incomplete cortisol results does not affect validity of the result.

Cortisol levels for the intervention group were 7.3 nm/L (95% CI, [5.5 nm/L,9.0 nm/L]) at baseline and 7.6 nm/L (95% CI, [4.2 nm/L,11.0 nm/L]) at F1. Wait list cortisol levels were 5.1 nm/L (95% CI, [3.2nm/L, 6.9 nm/L]) at baseline and 7.6 nm/L (95% CI, 4.0 nm/L, 11.1 nm/L) at F1. The result between groups, from baseline to one month follow up is $p$=0.5.

Table 13. Mean cortisol of intervention and waitlist group, baseline to F1.

| Intervention | Timepoint | Mean | Std. Error | 95% Confidence Interval | | P-Value |
|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | |
| Intervention | Baseline | 7.3 | 0.9 | 5.5 | 9.0 | *p*=0.5 |
| | F1 | 7.6 | 1.7 | 4.2 | 11.0 | |
| No intervention | Baseline | 5.1 | 0.9 | 3.2 | 6.9 | |
| | F1 | 7.6 | 1.8 | 4.0 | 11.1 | |

Normal cortisol reference ranges: 0600 to 0800hrs- 5.5 to 28.9 nm/L, 1800 to 2000hrs – 1.1 to11.6 nm/L and midnight - <7.0 nm/L.

### 4.2.8 Quality of life as measured by the MusiQoL

The MusiQoL self-rating questionnaire is a quality of life tool, developed for and validated in the MS population (Simeoni et al., 2008). Participants were asked to complete MusiQoL at baseline, at one-month post face to face session follow up and 6 months post face to face session. Interventional participants scored a mean of 63.9 (95% CI, [58.1, 69.8]) at baseline, 67.2 (*p*=0.3, 95% CI, [61.8, 72.5]) at F1 and 73.3 (*p*=0.3, CI 95% [66.3, 80.4]) at F2. Wait list participants scored 67.3 (95% CI, [62.6, 72,0]) at baseline, 70.8 (95% CI, [66.6, 75.3]) at F1 and 69.2 (95% CI, [64.7, 73.8]) at F2. At both F1 and F2 the waitlist group had a slight improvement of quality of life. Completion rate of this measurement was 84% (n=84). The result between groups, from baseline to F1 is *p*=0.3 and baseline to F2, *p*=0.3.

Table 14. Mean quality of life (MusiQoL), baseline to F1.

| Intervention | Timepoint | Mean | Std. Error | 95% Confidence Interval | | F Statistic | P-Value |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| Intervention | 1 | 63.9 | 2.9 | 58.1 | 69.8 | 1.11 | *p*=0.3 |
| | 2 | 67.2 | 2.7 | 61.8 | 72.5 | | |
| No Intervention | 1 | 67.3 | 2.4 | 62.6 | 72.0 | | |
| | 2 | 70.9 | 2.2 | 66.6 | 75.3 | | |

Table 15. Mean quality of life (MusiQoL), baseline to F2.

| Intervention | Timepoint | Mean | Std. Error | 95% Confidence Interval | | F Statistic | P-Value |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| Intervention | 1 | 65.8 | 3.6 | 58.5 | 73.1 | 0.036 | p=0.3 |
| | 2 | 73.3 | 3.5 | 66.3 | 80.4 | | |
| No Intervention | 1 | 68.5 | 2.3 | 63.8 | 73.2 | | |
| | 2 | 69.2 | 2.3 | 64.7 | 73.8 | | |

**4.3 Secondary Data Analysis**

Given the presence of several outliers a non-parametric statistical analysis was applied to the data, which is more robust to deviations of central tendency due to outliers. Specifically, the difference between the 6-month follow-up and baseline values was calculated for each test variable. A Mann-Whitney-U test was performed to compare medians between the intervention and non-intervention groups. As with the parametric analysis an alpha-level of 0.05 was used as the statistical significance threshold.

In this analysis, median score comparison does reflect a significant effect of intervention on the case group for QoL, as demonstrated in figure 5. However, there is no significant effect of intervention in perceived stress using the SVAS and DASS21.

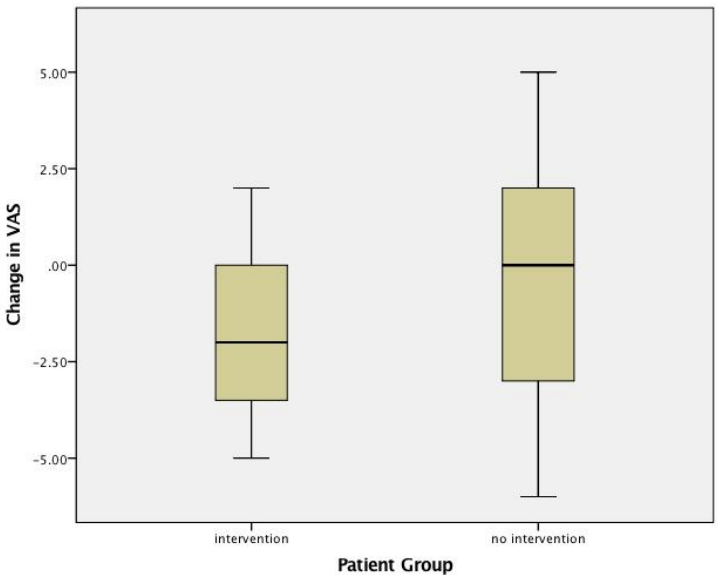
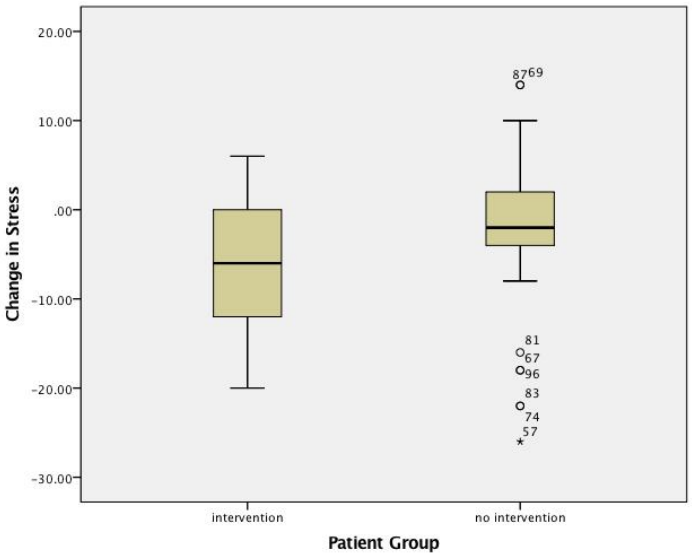


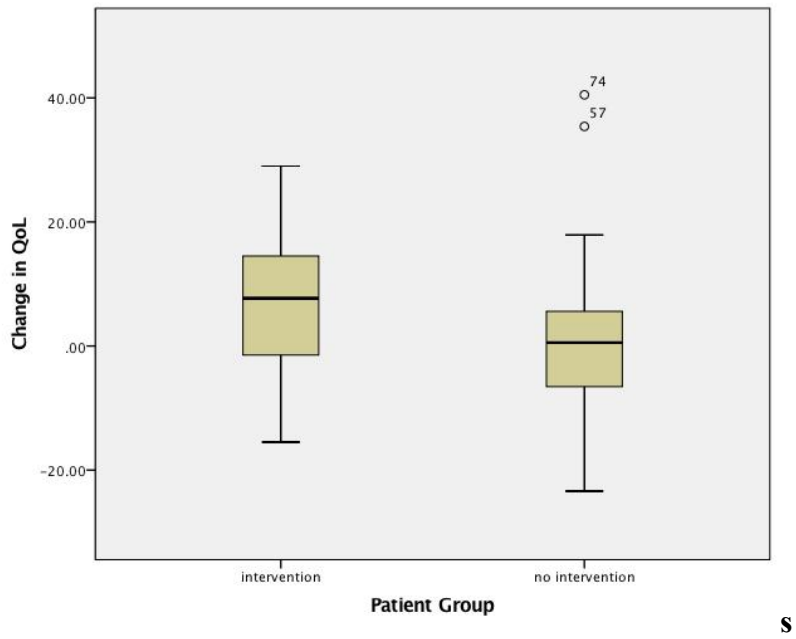

Figure 3. Median change in perceived stress (sVAS) between subjects.




o= outlier, participant 81, 67, 69, 83 and 74

*****= extreme outlier, participant 57

Figure 4. Median change in perceived stress (DASS21) between subjects.




s

o = outlier, participants 74 and 57  QoL=quality of life

Figure 5. Median change in quality of life (MusiQoL) between subjects.

### 4.4 Intervention adherence

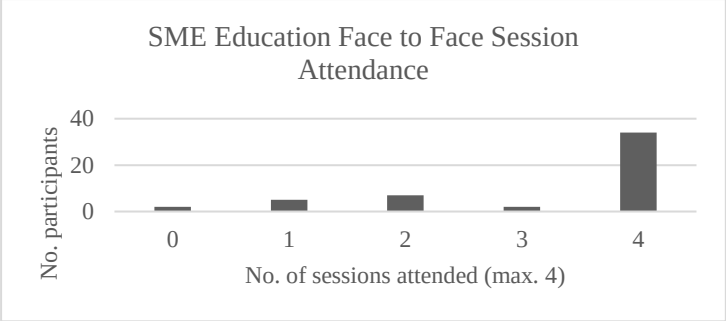
Participants were enrolled into this study irrespective of presenting stress levels, and half of the participants had normal levels of perceived stress over the course of the study. Reducing the cohort to those interventional participants whose levels of stress at baseline were moderate, severe or extremely severe, 12% (n=6) participants fell into this category. All six participants had improved levels of stress at F1. From an observation perspective of this small group two of the six participants had good adherence to performing PMR, i.e. performed PMR 5-7 days on average per week. The remaining 4 participants had poor adherence to performing PMR, i.e. 0-2 days per week on average. The interventional effect for meditation was less related: one of the 6 participants had reasonable adherence to performing meditation, i.e. 3-4 days per week on average; and five participants had poor adherence to performing meditation, i.e. 0-2 days per week on average.

In reverse, the next observation is of those who were adherent to the programme. Of the 12 interventional participants (24% of cases) who performed PMR 5-7 days per week on average (i.e. good adherence) there was a perceived stress levels remained largely static. Of the 14 interventional participants (28% of cases) who performed meditation 5-7 days per week on average (i.e. good adherence) 12 stayed the same or improved their level of stress, while 2 participants experienced a worsening of their perceived stress. Making the same observation using the SVAS, of the adherent participants just over half had improved levels of stress. MusiQoL scores for adherent participants were better in 12 participants and worse in five.

Although compromised by adherence analysis of the cortisol levels of both groups shows that intervention participants began with higher levels of cortisol than the wait list group. By the follow up measurement both groups had increased cortisol levels: although the intervention group's level rose minimally and the wait list group rose by more. All cortisol means remained in the normal reference range at baseline and follow up.

MusiQoL was completed by 84% of overall study participants. The means of both groups improved from baseline to F1 and F2 and both groups mean scores were at the higher (i.e. a good quality of life) end of the scale at all time points.

Adherence with the study intervention was recorded by the attendance to one on one sessions with the study investigator and study diary entries to reflect daily practice of SME. 68% of intervention participants attended 4 of 4 one on one sessions, 4% attended 3 sessions, 14% attended 2 sessions, 10% attended 1 session and 4% attended no sessions.

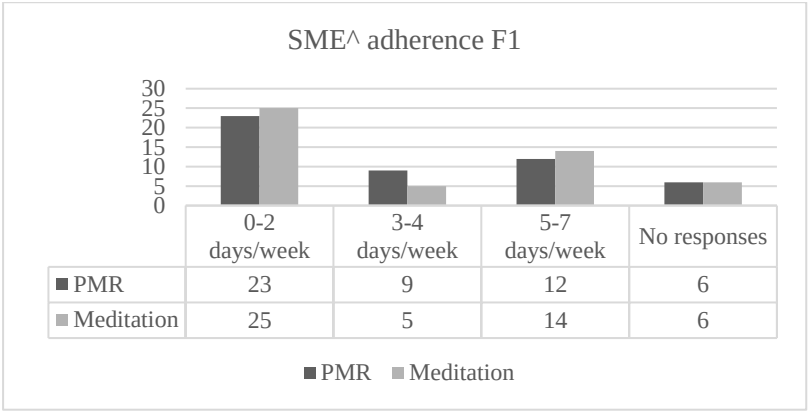



^SME = stress management exercise

Figure 6. Stress management exercise attendance to education sessions, max. 4 sessions.

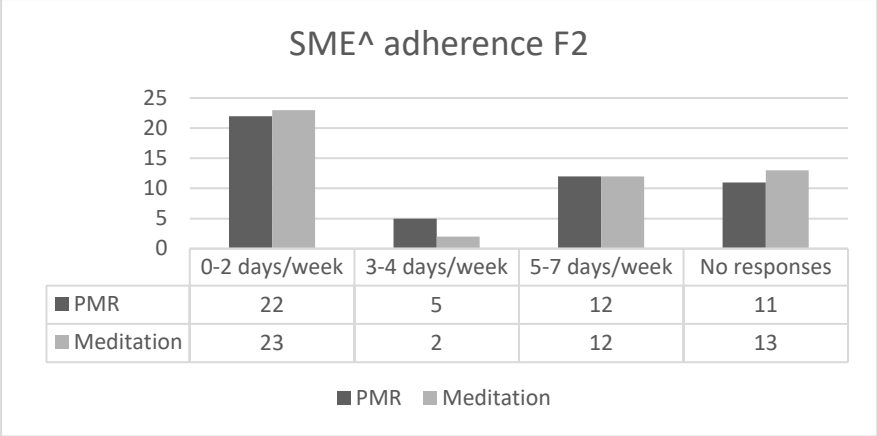
Good adherence to home practice of SME was considered as performing either the meditation or PMR five to seven days per week, for 20 minutes per session using the provided study CD. Reasonable adherence was recorded as performing PMR and/or meditation two to four times per week and poor adherence was considered non-participation to one day of PMR and /or meditation per week.

For F1, 26% and 24% of intervention group had good adherence to the programme of performing meditation and/or PMR respectively; i.e. five to seven days per week. For F2, 24% of the intervention group had good adherence to meditation and PMR.




^SME = stress management exercises

Figure 7. Adherence to stress management exercises at F1.




^SME = stress management exercise

Figure 8. Adherence to stress management exercises at F2.

Reasons for poor adherence were explored by thematic coding. Common themes given for not performing the stress management strategies as per protocol were 1) strategy dissatisfaction, 2) prioritisation issues, 3) personal stress or distress, and 4) MS or bodily symptoms. Strategy dissatisfaction included using one of the strategies as per protocol but not the other due to preference for one or dislike for one of the strategies, denied benefit from strategy, not feeling stressed enough to perform SME, or SME too hard to perform. Prioritisation issues included participants 'not having time', 'too busy', 'forgot', and 'too lazy'. Personal stress or distress included feeling too stressed or too upset to perform SME. MS or bodily symptoms included fatigue and pain (in this instance pain was related to experiencing spasms during PMR). Although some participants did not respond to this question, prioritisation issues represented the most common reason for non-adherence.

### 4.5 Qualitative evaluation

The majority of data analysis undertaken in this study was quantitative. A smaller analysis evaluated feedback from participants, collected from baseline and follow up

questionnaires and from the intervention participant diaries. The areas for thematic analysis included ways that study participants self-managed their perceived stress.

### 4.5.1 SME Themes and Change in Practice of Managing Stress over Time

Participants were asked to define their current stress management strategies from a 16-item list of common stress management strategies. These strategies included exercise, prescription medication, drinking alcohol, smoking tobacco, using illegal drugs, regular meditation, using mindfulness, CBT, talking to a psychologist, talking to family, talking to a general practitioner, talking to the MS team, shopping, spending time with family and/or friends, deliberately avoiding the stressor, and doing nothing at all (see tables 6,7 and 8). As there was no standardised or validated comprehensive list of stress management strategies used in MS, this list was generated by listing the SME under examination in this study, standard evidenced-based interventions and referrals for people experiencing psychological issues. Additionally, they were asked to add to that list if their usual method of managing stress was missing from the choices. The use of these strategies was then described in terms of frequency using numbers of study participant utilising that strategy. The purpose for this examination was to see if there was differentiation from within and across the whole study population and between baseline and follow up.

Firstly, the distribution of the 16 strategies was similar between and across the study population. The strategy occurring with least frequency was once (‘doing nothing’, case group, 1 month follow up) and highest occurring strategy was 28 times (‘exercise’, case group, baseline). This thematic grouping was developed further from by delineating the uses of strategies into low frequency (less than 10 participants using a strategy at any single time point), moderate frequency (10-20 participants using a strategy at any single time point) and high frequency (20+ participants using a strategy at any single time point). Throughout the

study participants employed the strategies of regular exercise, talking about their stress to family members, spending time with family and/or friends and avoiding the stressor with high frequency. Of the medium frequently used strategies included prescription medication use, using alcohol, counselling with a general practitioner and shopping. Less frequently smoking tobacco or marijuana, using other illegal drugs, meditation, mindfulness, CBT, talking or counselling with a professional psychologist, talking or counselling with their MS team and doing nothing were employed.

At follow up some changes in other SME strategies were noted: alcohol was used infrequently, meditation, and mindfulness were used at a medium frequency, avoiding the stressor reduced frequency to medium use and for the case group only shopping was reduced to low frequency use. All other strategies were employed at a similar frequency to baseline. Relating to the case participants only, over the course of the study meditation and prescription medication were utilised more and 'doing nothing' used less by the time of follow up.

For further SME thematic exploration, the original 16 strategies employed were thematically divided into either healthy (or somewhat better ways to manage stress; e.g. exercise), not healthy (or somewhat not a better way to manage stress; e.g. using illegal drugs) or neither healthy nor unhealthy groups. Each of the identified strategies were independently grouped by the principle investigator, the psychologist advising the study and the neurologist involved with the MS clinic. More empirical than scientific, the purpose for this type of thematic exploration was to determine if other SME types commonly used by the study population were in line with what MS specialists were using as part of routine health promotion. Full agreement between the three clinicians (MS nurse specialist, MS specialist neurologist and MS specialist psychologist) was found with exercise, mindfulness/meditation, CBT, psychology counselling, GP counselling, MS team counselling and spending time/talking with family and /or friends for positive health promoting activities

for managing stress. Of these, health promoted strategies exercise and spending time with and talking to family/friends was employed with high frequency by the study participants. GP counselling was utilised with moderate frequency. Mindfulness, meditation, CBT, psychology counselling and MS team counselling were used with only a low frequency. Equally, using alcohol, smoking tobacco and using illegal drugs were unanimously agreed upon by the clinician group as unhealthy stress management strategies and contraindicated in health promotion and used with low to moderate frequency by study participants.

Less well defined and somewhat difficult to achieve consensus on without the benefit of context, some stress management strategies were not clearly healthy or unhealthy. These strategies in moderation might be perceived as healthy but no frequency or amount was recorded. Additionally, the reasons or scenarios around these strategies are unclear. For example, if drinking alcohol in moderation happens in the context of meeting friends to talk about increased levels of stress, this might be considered a healthy strategy. Alternatively drinking to excess on a frequent basis to numb unpleasant sensations or thoughts associated with stress is then not considered a healthy strategy for managing stress. The strategies in which full agreement was not reached were: using prescription medication, shopping, avoiding the stressor and doing nothing. Using prescription medication and doing nothing was used in low frequency by the study population; shopping in moderate frequency and avoiding the stressor were used with high frequency.

### 4.5.2 Participant's Perception of Change over Time

59% of participants responded to the more detailed questions of 'do you think your level of stress has improved?' and 'why do you think your level of stress has changed?' The chart below shows that at F1 around one quarter of participants felt their levels of stress had improved since learning SME. One third of participants felt no change at F1, and 2 participants felt unsure and reported worsening stress levels respectively.

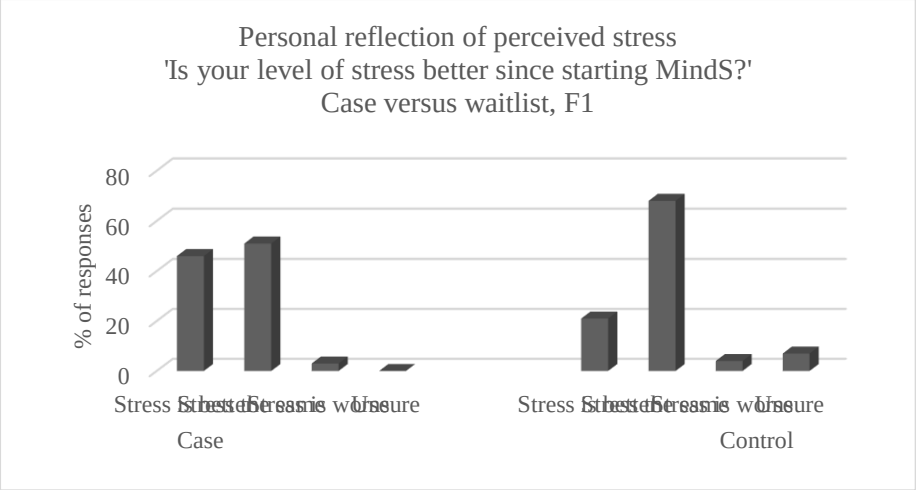



Figure 9. Personal reflection of perceived stress change, baseline to F1.

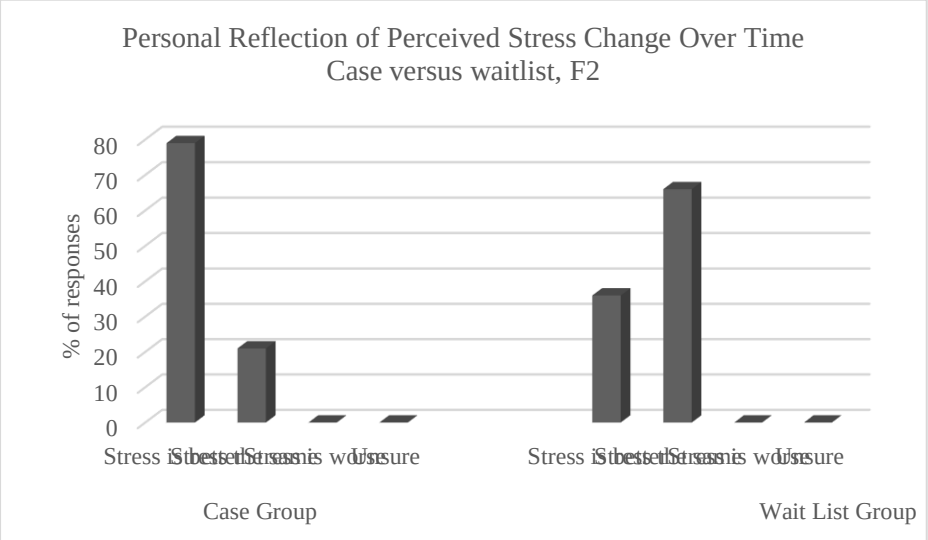



Figure 10. Personal reflection of perceived stress change, baseline to F2.

### 4.3.3 Participant Feedback

Direct feedback for case participants who felt an improvement and those who didn't were shared. Some of the feedback includes: -

Participant 1-34 at F1 said 'yes' to improved levels of stress: "We have had a very stressful month (moved to a new house, kids changed day-care, husband going for new job, son is currently sick, poor sleep). I am tired and symptomatic but definitely coping. I believe I would normally be very agitated, upset and unreasonable".

Participant 1-01 at F1 said ‘yes’ to improved levels of stress: “I think I'm accepting that sometimes 'shit happens' and I know that it eventually has an end”.

Participant1-23 at F2 said ‘yes’ to improved levels of stress: “For the most part I believe I am handling it better; now I take the time to go through the exercises and also break down the stressor and put it aside”.

Participant 1-20 at F1 said ‘no’ to improved levels of stress: “I still let stress get to me”.

Participant 1-13 at F1 said ‘no’ to improved levels of stress: “I'm not coping very well, everything is stressing me out and upsetting me. I'm losing the plot at everything”.

# CHAPTER 5.

# DISCUSSION

## 5.1 Executive summary

PMR, meditation and mindfulness did not significantly reduce stress or improve quality of life in the MS cohort. Comparison of mean in each participant group did not show evidence of a change between baseline and follow-up. Hence, these data provide no evidence of an intervention effect. This was a consistent result across all measures: sVAS, DASS21, MusiQoL and salivary cortisol. Comparison of median in each participant group was undertaken due to the presence of outliers and as a result, potential confounding of results. In this secondary analysis, there was no significant intervention effect on perceived stress as measured by the DASS21, sVAS and cortisol, but there was a significant effect by the intervention on quality of life in the case group.

## 5.2 Outcomes

The primary outcome of the intervention in reducing perceived stress in PwMS was not met. When median scores were analysed there was a significant effect of the intervention from baseline to F1 and F2 on quality of life, although not for perceived stress or cortisol. For perceived stress, this contrasts with the positive outcome of the majority of studies listed in the literature review. Quality of life is comparable to the studies using QoL as a measure of effect. Cortisol has not been used in previous studies, so this particular result is unique. Direct comparison of this study with the literature is difficult because no two studies used the same SME technique, were conducted in the same setting or used the same measurement assessments. Further augmenting this discussion point is the fact that predominantly positive studies reach publication. All but the Mohr (2012) study were small cohorts, not large enough to avoid type 1 error. These smaller studies should be replicated in a larger cohort to confirm

the intervention effect, which, with the heterogeneity of the study interventions and assessments, has not been achieved. Moreover, all of these studies relied on self-rating measurements for outcome, reducing reliability of intervention effect further (Artemiadis et al., 2012; F. W. Foley et al., 1987; Ghafari et al., 2009; Hughes et al., 2006; Kolahkaj & Zargar, 2015; Simpson et al., 2017). This might explain why the intervention effect has not been reported to last (Hughes et al., 2006; Mohr et al., 2012; Simpson et al., 2017). The only study that showed persistence of effect (of quality of life) was at three months post intervention (Ghafari et al., 2009). No study was able to show persistent benefit from intervention in reducing perceived stress beyond the face to face sessions.

### 5.3 Adherence

Adherence is a key point for discussion. The current study found adherence to home practice of SME difficult. It is interesting that a very recently published study of similar nature by Simpson (et al., 2017) also found adherence to be problematic. 60% of study participants completed what was considered acceptable number (i.e. 4-8) of group MBSR session and further 60% of participants returned adherence data, showing an average of 32.5 minutes of MBSR practice per day (Simpson et al., 2017) . Reasons given for not attending the sessions included bodily pain, work commitments, holidays and ‘slept-in’. Despite this they were able to show at the conclusion of the sessions a significant improvement in perceived stress, anxiety, depression and self-compassions measures, all evaluated by self-rating scales. Unfortunately, the study outcome measures were less robust for quality of life. Negligible differences were seen for quality of life and perceived stress at 3 months post intervention. In comparison to the current study barriers to adherence were similar and included bodily symptoms and prioritisation issues. The current study also found strategy dissatisfaction and personal distress barriers to adherence.

This study and the current study both did not use screening scores of perceived levels of stress as inclusion/exclusion criteria.

### 5.4 Level of Perceived Stress Versus Measured Level of Stress

Another observation made for the current study was that many participants considered themselves more stressed than their own assessments allowed for. 'Very' and 'really' stressed were descriptions frequently made by study participants at the consent and baseline interview. However, baseline levels of stress as measured by the sVAS, DASS21 and salivary cortisol indicated that most participant's levels of stress fell into the normal or only slightly higher than normal level of stress. This represents an interesting discord, worthy of further analysis. The scope of this study did not prospectively include exploration of this phenomenon but possible reasons for this could include cultural and social attitudes to stress, as well as personality traits for exaggeration or over reporting. Once again, future studies and clinical application of stress management strategies would benefit from prospective consideration of this phenomenon.

The phenomenon of reported (anecdotal and, to a lesser extent, self-rated questionnaire) perceived stress being different to biological evidence of stress (cortisol levels) is interesting as it raises for discussion the phenomenon of what people perceive as stress, the individual response to stress and how stress is reported. The current study did not ask participants to define stress but, rather, asked participants to report their current methods of managing stress and to perform specific SME. The studies outlined in the literature review also did not engage in a closer examination of participants' understanding of stress.

Basic emotions: happiness, surprise, fear, disgust anger, and sadness are said to be hardwired, largely determined by genetics and evolution (Ekman, 1992). While basic emotions are present at birth more complex emotions and feelings, like stress, continue to

develop over a person's lifetime, affected by experience, cultural and social factors. Recent research in the area of emotion development suggests that experiencing emotions to specific situations can be a learned outcome (Barrett, 2017). The next step in this theory suggests emotions are attributed to the bodily feelings with reference to experience, culture, gender and other factors, but not always to the same emotion for every person. For example, two people bungy jumping from the same bungy location on the same day are likely to experience similar bodily feelings e.g. sweating, racing heart but one may attribute that experience to fear and the other to exhilaration. The same concept may be applicable to perceived stress. For example, a looming work deadline for some people will inspire creativity and productivity and in others an inability to meet the deadline. This discord between feeling overwhelmed by stressors and being objectively stressed might be somewhat explained by this theory of complex emotion development. The learned emotional concepts and learned responses to stressors can be manipulated to influence behaviour, for better or worse. Using this approach to change health behaviour is the basis of CBT, mindfulness and chronic disease management programmes.

In MS, evidence for achieving health behaviour changes are varied. MS Brain Health (Giovannoni et al., 2016) robustly supported health behaviours include keeping physically active, keeping weight in normal range, keep one's mind active, avoiding tobacco smoking and limit alcohol to a moderate intake. Developing interventions that address making health behaviour change is influenced by intervention characteristics (e.g. complexity of and manner of delivery), individual factors (e.g. existing mental health issues), demographic characteristics (e.g. gender, age and socioeconomic status), social and interpersonal factors. Barriers to one being able to make changes include poor health literacy, poor general literacy, self-efficacy, coping style and personality. On top of these psychosocial and literacy barriers, cultural differences also influence a person chance of engaging with positive lifestyle

changes. The relationship between the person receiving the education/counselling and the person providing the education is also important to its success. Finally, to sustain change the effort must persist beyond inevitable difficulties that come over time. Personal motivation important to health behaviour change. The current study did not recruit particularly motivated participants, in order to reduce selection bias. This recruitment strategy enhanced the realistic effect of the intervention and lent an understanding to some of the barriers to this type of intervention. The current study protocol addressed some of the issues described above; i.e. literacy and practical barriers to participating in the study. Coping style and previous response to stressful stimuli were explored for the participant to make changes to future exposures to the stressors. Cultural and social barriers were identified with individuals but no detailed exploration of this theme was undertaken.

A recent qualitative study of health behaviour in MS observed there were 5 themes contributing to barriers for people with MS to make health behaviour change (Plow & Golding, 2016). These themes are 1) roles, priorities and preferences; 2) sense of duty; 3) problem of fatigue and mobility; 4) taking control; and 5) resilience. Of the 17 PwMS interviewed in focus groups or one-on-one, the experience of having MS, in the context of their rest of their lives was usually a motivator for multiple health behaviour change. People were more likely to make multiple health behaviour change if they felt they had control over the disease, even in the context of persistent symptoms, e.g. fatigue and mobility issues. Unfortunately, barriers to making change also stemmed from persistent MS symptoms, like fatigue and mobility problems. While some participants used this knowledge to plan their day, allowing for breaks and expecting fatigue, others found this aspect of MS was demotivating and they were less likely to participate in activities that in the longer term might make their symptoms less debilitating. For the health care professionals delivering health care packages that are largely self- monitored and self-administered, this complexity will affect

adherence to programmes. In the setting of the MindS study this observation may go some way to explain poor adherence to the performing mediation and PMR.

Following on from, and somewhat related to, the previous discussion point is that poor adherence may reflect response to the homogenous nature of the protocol. This was evidenced by the fact that the participant who had previous experience with or were at least familiar with the concept of meditation and PMR were more likely to adhere to the protocol and were using participation in the study as a motivator to return to or enhance their routine practice. On the flip side, some participants voiced discomfort performing meditation and/or PMR. For example, when the skills were introduced or participant diaries were reviewed for compliance some participants said they weren't comfortable with or hadn't performed either meditation and/or PMR as 'it really isn't their thing'.

Ironically the reason given for some participant's less than expected intervention adherence was they found they were too stressed to perform the stress management strategies on a regular basis. On further (but unfortunately brief) discussion and examination of coping style these participants were more likely to respond to stressors by ignoring them and pushing on with their daily activities. This coping style could represent a group of people that should be flagged for additional support in making a health behaviour change.

### 5.5 Study strong points

In prospectively planning this study, consideration was given to the level of robust assessment required to add to the existing literature. The two robust features of this study are a larger study cohort and using salivary cortisol for objective measure of intervention effect. In design, this study reflected the day to day realities of a largely self-managed intervention, and barriers to routinely and regularly performing SME were identified. For successful

integration of SME as part of managing modifiable lifestyle factors these barriers should be addressed.

### 5.6 Study weak points

This study recruited PwMS, without regard for baseline levels of perceived stress. Half of the overall group entered and finished the study with a normal level of stress, measured both objectively and subjectively. Recruiting this way eliminated selection bias but it is likely that this influenced the outcome. Salivary cortisol testing was completed by half of study participants, equally in both groups, although it is not likely to significantly affect the study results. The survey was returned by half of the participants at F2, which will affect the results.

### 5.7 Conclusions to be drawn

The literature review has shown that increased stress can impact MS, and managing stress can improve living with MS. In contrast, the current study has shown that in a random cohort PwMS (with a large range of age and disability) performing mindfulness, meditation and PMR had no significant effect on perceived levels of stress but may have an effect on quality of life. Barriers to performing SME could be thematically categorised into four themes of strategy dissatisfaction, prioritisation issues, personal stress or distress and MS or bodily symptoms. Non-SME strategies employed by participants included exercise, formal and/or non-formal counselling, avoidance tactics and medicating/blocking strategies. Emotional behaviour responses, distraction tactics and other relaxation techniques were also employed. Future studies should focus on populations of PwMS who have at baseline increased stress levels, and barriers to adherence should be considered.

# APPENDICES

## Appendix A

## Recruitment Script

*Hi. I am the clinical trials coordinator for the MS clinic. Since you attend the clinic I would like to introduce the Mindfully Managing Stress in MS (MindS) study to you. Do you have a couple of minutes to talk about the study?*

*This study is a local observational study to investigate a stress management intervention in MS. The investigator is Susan Agland who is also the clinical nurse specialist for the clinic.*

*Would you be interested to learn more about this study? (Offer the PICF to the potential participant)*

*(If yes) To give you some background on the study: there is growing evidence that stress may be associated with increased risk for MS relapse. This study plans to examine people with MS' perceived levels of stress over 6 months once they have participated in a stress management intervention.*

*Participants will be randomly assigned to be in either the interventional group or the wait list wait list group. This means that some will participate in a stress management programme and some will be in the wait list group for which the intervention is tested against. Participants in the wait list wait list group will be offered the programme if it shows benefit in reducing perceived stress and/ or an improvement in quality of life.*

*Perhaps you would like some time to consider the patient information and consent form? Is it OK for me to forward your name to the investigator to follow up with you?*

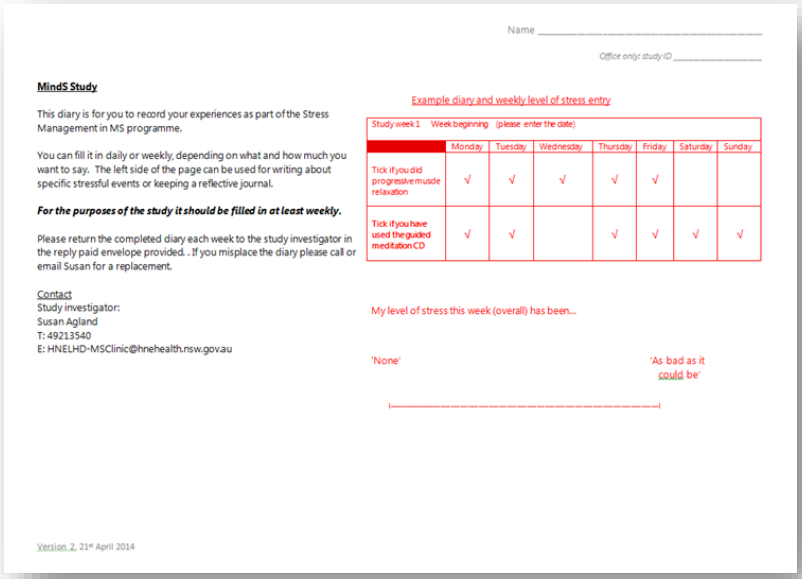
*If you have any questions please feel free to call Susan on 40420331 or email*

*hnelhd-msclinic@hnehealth.nsw.gov.au*

*Thank you.*

# Appendix B.

# Diary



Name _____

*Office only: study ID* _____

**MindS Study**

This diary is for you to record your experiences as part of the Stress Management in MS programme.

You can fill it in daily or weekly, depending on what and how much you want to say. The left side of the page can be used for writing about specific stressful events or keeping a reflective journal.

***For the purposes of the study it should be filled in at least weekly.***

Please return the completed diary each week to the study investigator in the reply paid envelope provided. . If you misplace the diary please call or email Susan for a replacement.

Contact
Study investigator:
Susan Agland
T: 49213540
E: HNELHD-MSClinic@hnehealth.nsw.gov.au

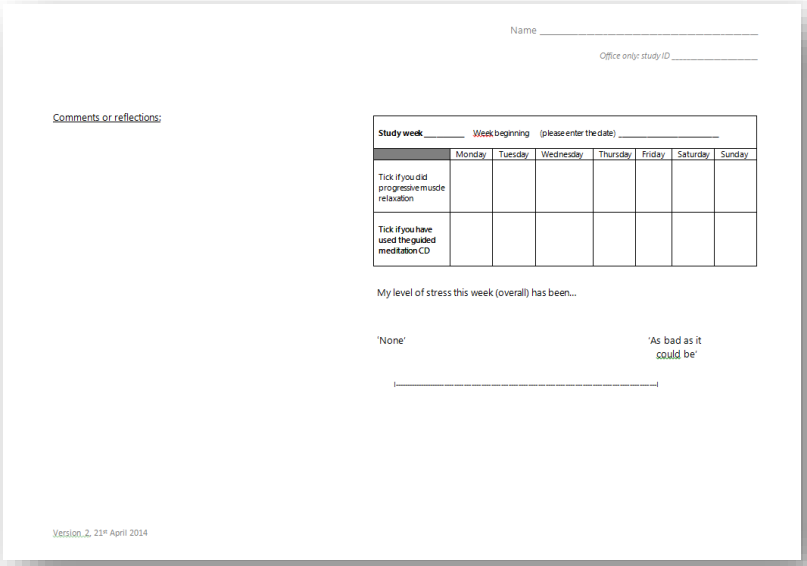
Example diary and weekly level of stress entry

| Study week 1 Week beginning (please enter the date) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday | Sunday |
| Tick if you did progressive muscle relaxation | √ | √ | √ | √ | √ | | |
| Tick if you have used the guided meditation CD | √ | √ | | √ | √ | √ | √ |

My level of stress this week (overall) has been...

'None' 'As bad as it could be'

Version 2, 21st April 2014



Name _____

*Office only: study ID* _____

Comments or reflections:

**Study week** _____ Week beginning (please enter the date) _____

| | Monday | Tuesday | Wednesday | Thursday | Friday | Saturday | Sunday |
|---|---|---|---|---|---|---|---|
| Tick if you did progressive muscle relaxation | | | | | | | |
| Tick if you have used the guided meditation CD | | | | | | | |

My level of stress this week (overall) has been...

'None' 'As bad as it could be'

Version 2, 21st April 2014

## Appendix C

**Progressive muscle relaxation from TAMING STRESS IN MULTIPLE SCLEROSIS**
www.mssociety.ca

*Progressive muscle relaxation is often used as an aid to stress management. And, done in bed before you go to sleep, it can be an aid to a sound night's sleep.*

*Going through your body's entire group of muscles – tensing, relaxing, and focusing on the changes – will take about 12 to 15 minutes. If it takes less than that, you are moving at a non-relaxing speed. These exercises will provide the most benefit if you do them twice a day. If there are some muscle groups that you cannot work with comfortably, skip them. If you have significant spasticity in some muscles, strongly tensing those muscle groups could trigger a spasm. You may want to speak with a physiotherapist or other MS health professional about ways to work in a more comfortable way. Many people, especially those with cognitive problems, find that the exercises are easier to do along with a pre-recorded tape. You can prepare the tape yourself or ask someone with a relaxing voice to do it for you. You will work with each of 17 muscle groups in a specific order. Tense, but don't strain each muscle group. Hold the tense position for the slow count of five, paying attention to the way those muscles feel. Relax the muscles – letting them go totally limp. Focus for a count of five on how the muscles feel when relaxed.*

*To prepare for the exercise, wear comfortable, loose-fitting clothing, remove glasses or contact lenses, and sit up in a chair without crossing your legs or arms. You may also do this lying down in bed.*

*1 Clench both hands. Focus on how your hands feel and how the tension moves into the forearms. Relax. Notice what the muscles in your hands and forearms feel like now.*

*2 Touch your fingers to your shoulders. Raise your arms level with your shoulders. Focus on the tension in your biceps and upper arms. Relax and focus on the change in feeling.*

*3 Shrug your shoulders, raising them as high as possible. Focus on the tension in your shoulders. Relax and focus on the change.*

*4 Wrinkle your forehead. Notice where tension occurs – around your eyes and forehead. Relax and focus on the change.*

*5 Close your eyes tightly. Focus on the tension. Relax and focus on the change.*

*6 Clench your teeth. Focus on the tension in your jaw, mouth, and chin. Relax and focus on the change.*

*7 Press as much of your tongue as possible onto the roof of your mouth. Focus on the tension in your mouth and throat. Relax and focus on the change.*

*8 Move your head slowly backwards as far as you comfortably can, keeping your shoulders level. Focus on the tension in your neck and upper back. Relax and focus on the change.*

*Note: If you experience Lhermitte's sign – an electrical-like shock in your spine when you tip your neck forward – skip step 9.*

*9 Pull your head forward, down onto your chest. Focus on the tension in your neck, shoulders, and upper back. Relax and focus on the change.*

*10 Move away from the back of your chair, arch your back and push your arms upward. Focus on the tension in your back and shoulders. Relax and focus on the change.*

*11 Fill your lungs with air and hold the breath. Focus on the tension in your chest and back. Exhale all the way, relax and focus on the change.*

*12 Pull your stomach as far back toward your spine as you can. Focus on the tension in your stomach muscles and changes in your breathing. Relax and focus on the change.*

*13 Without pulling your stomach in, tense your stomach muscles. Focus on the tension. Relax and focus on the change.*

*14 Tense the muscles in your buttocks. Focus on the tension. Relax and focus on the change.*

*15 Flex your thigh muscles by straightening your legs or tensing the muscles. Focus on the tension. Relax and focus on the change.*

*16 Lift your feet off the ground. Point your toes up, your heels down. Focus on the tension in your feet, ankles, and calves. Lower your feet, relax, and focus on the change.*

*17 Lift your feet slightly and curl your toes all the way down. Focus on the tension on the top of your feet and in your arches. Lower your feet, relax, and focus on the change.*

*18 After you have learned to be aware of tension in all 17 muscle groups, you may want to focus only on those groups that give you the most trouble. Tense and relax those groups – often the jaw, neck, and stomach –several times during the day. Check your "high tension" muscle groups from time to time to judge how relaxed you are.*

## Appendix D

# DASS21

*Name:* *Date:*

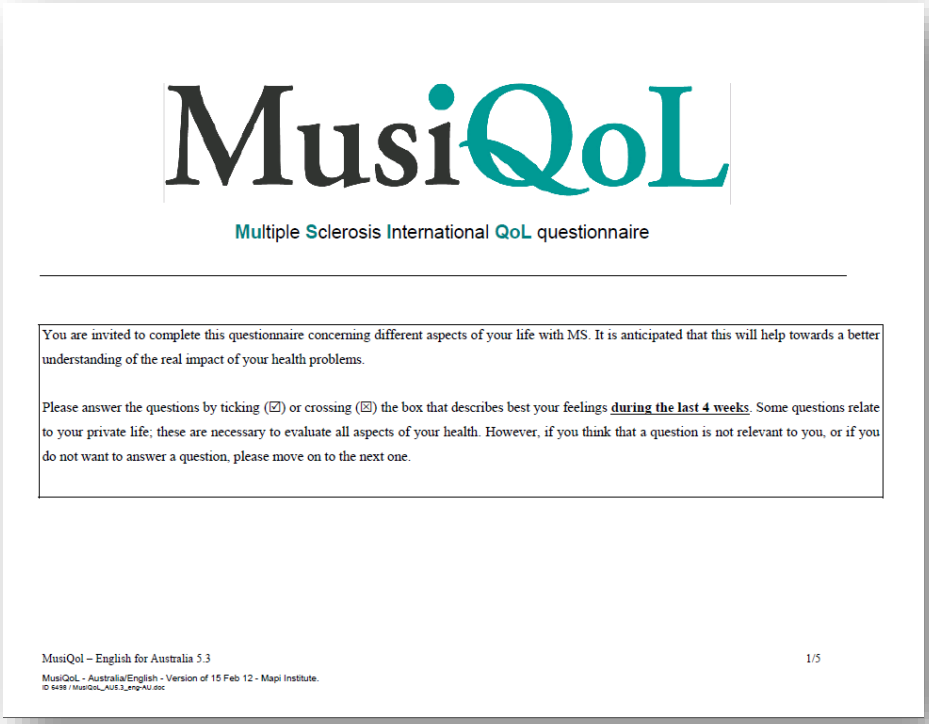
Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

*The rating scale is as follows:*

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

| | | | | | |
|---|---|---|---|---|---|
| 1 | I found it hard to wind down | 0 | 1 | 2 | 3 |
| 2 | I was aware of dryness of my mouth | 0 | 1 | 2 | 3 |
| 3 | I couldn't seem to experience any positive feeling at all | 0 | 1 | 2 | 3 |
| 4 | I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion) | 0 | 1 | 2 | 3 |
| 5 | I found it difficult to work up the initiative to do things | 0 | 1 | 2 | 3 |
| 6 | I tended to over-react to situations | 0 | 1 | 2 | 3 |
| 7 | I experienced trembling (eg, in the hands) | 0 | 1 | 2 | 3 |
| 8 | I felt that I was using a lot of nervous energy | 0 | 1 | 2 | 3 |
| 9 | I was worried about situations in which I might panic and make a fool of myself | 0 | 1 | 2 | 3 |
| 10 | I felt that I had nothing to look forward to | 0 | 1 | 2 | 3 |
| 11 | I found myself getting agitated | 0 | 1 | 2 | 3 |
| 12 | I found it difficult to relax | 0 | 1 | 2 | 3 |
| 13 | I felt down-hearted and blue | 0 | 1 | 2 | 3 |
| 14 | I was intolerant of anything that kept me from getting on with what I was doing | 0 | 1 | 2 | 3 |
| 15 | I felt I was close to panic | 0 | 1 | 2 | 3 |
| 16 | I was unable to become enthusiastic about anything | 0 | 1 | 2 | 3 |
| 17 | I felt I wasn't worth much as a person | 0 | 1 | 2 | 3 |
| 18 | I felt that I was rather touchy | 0 | 1 | 2 | 3 |
| 19 | I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat) | 0 | 1 | 2 | 3 |
| 20 | I felt scared without any good reason | 0 | 1 | 2 | 3 |
| 21 | I felt that life was meaningless | 0 | 1 | 2 | 3 |

## Appendix E



MusiQoL

Multiple Sclerosis International QoL questionnaire

You are invited to complete this questionnaire concerning different aspects of your life with MS. It is anticipated that this will help towards a better understanding of the real impact of your health problems.

Please answer the questions by ticking (☑) or crossing (☒) the box that describes best your feelings **during the last 4 weeks**. Some questions relate to your private life; these are necessary to evaluate all aspects of your health. However, if you think that a question is not relevant to you, or if you do not want to answer a question, please move on to the next one.

MusiQol – English for Australia 5.3 1/5

MusiQoL - Australia/English - Version of 15 Feb 12 - Mapi Institute.
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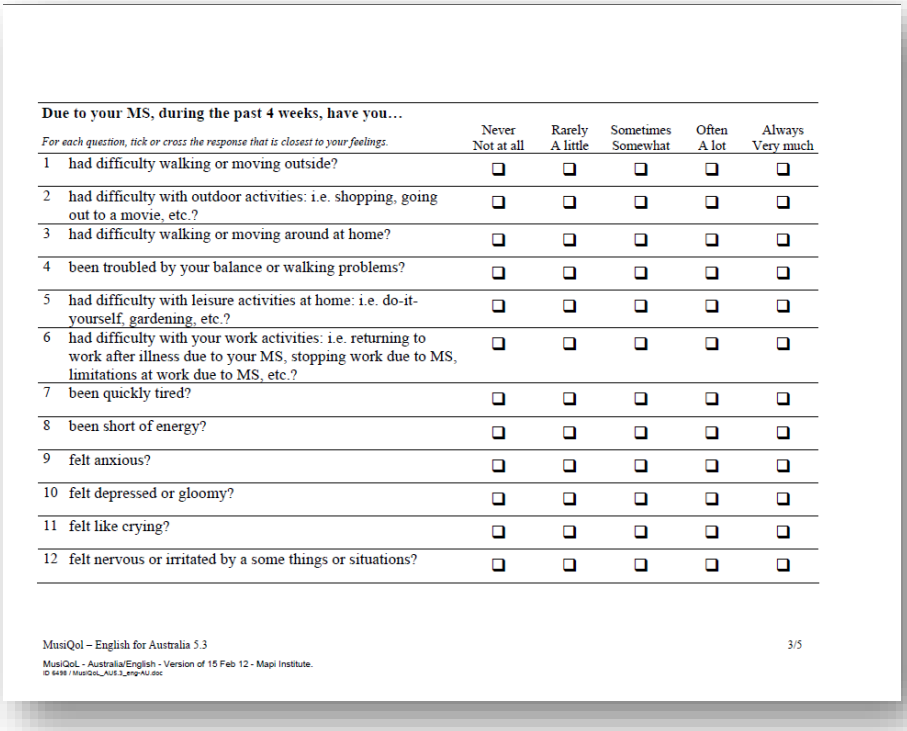


| **Due to your MS, during the past 4 weeks, have you…** *For each question, tick or cross the response that is closest to your feelings.* | Never Not at all | Rarely A little | Sometimes Somewhat | Often A lot | Always Very much |
|---|---|---|---|---|---|
| 1 had difficulty walking or moving outside? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 2 had difficulty with outdoor activities: i.e. shopping, going out to a movie, etc.? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 3 had difficulty walking or moving around at home? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 4 been troubled by your balance or walking problems? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 5 had difficulty with leisure activities at home: i.e. do-it-yourself, gardening, etc.? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 6 had difficulty with your work activities: i.e. returning to work after illness due to your MS, stopping work due to MS, limitations at work due to MS, etc.? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 7 been quickly tired? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 8 been short of energy? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 9 felt anxious? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 10 felt depressed or gloomy? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 11 felt like crying? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 12 felt nervous or irritated by a some things or situations? | ❑ | ❑ | ❑ | ❑ | ❑ |

MusiQol – English for Australia 5.3 3/5

MusiQoL - Australia/English - Version of 15 Feb 12 - Mapi Institute.
ID 6498 / MusiQoL_AUS 3_eng-AU.doc

| **Due to your MS, during the past 4 weeks, have you…**<br>*For each question, tick or cross the response that is closest to your feelings.* | Never<br>Not at all | Rarely<br>A little | Sometimes<br>Somewhat | Often<br>A lot | Always<br>Very much |
|---|---|---|---|---|---|
| 13 been troubled by loss of memory? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 14 had difficulty concentrating: i.e. when reading, watching a film, following a discussion, etc.? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 15 been troubled by your vision: worsened or uncomfortable? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 16 experienced unpleasant feelings: i.e. hot, cold, etc.? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 17 talked with your friends? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 18 felt understood by your friends? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 19 felt encouraged by your friends? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 20 talked with your spouse/partner or your family? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 21 felt understood by your spouse/partner or your family? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 22 felt encouraged by your spouse/partner or your family? | ❑ | ❑ | ❑ | ❑ | ❑ |

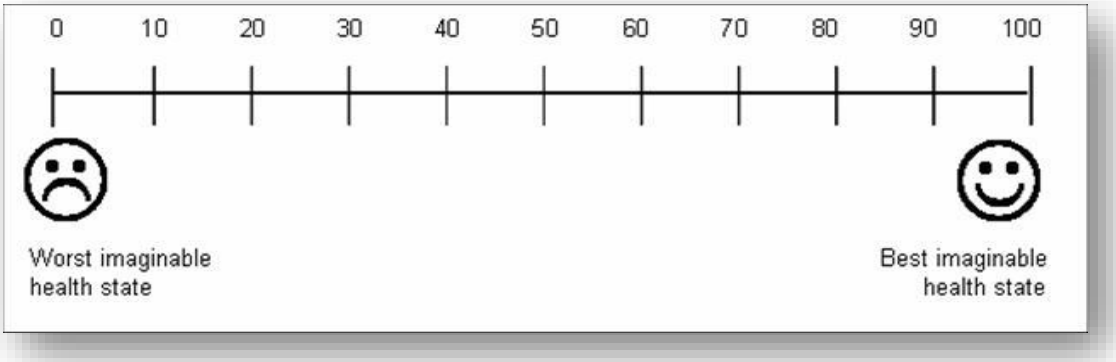


| **Due to your MS, during the past 4 weeks, have you…**<br>*For each question, tick or cross the response that is closest to your feelings.* | Never<br>Not at all | Rarely<br>A little | Sometimes<br>Somewhat | Often<br>A lot | Always<br>Very much |
|---|---|---|---|---|---|
| 23 felt satisfied with your love life? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 24 felt satisfied with your sex life? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 25 felt that your situation is unfair? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 26 felt bitter? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 27 been upset by the stares of other people? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 28 been embarrassed when in public? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 29 been satisfied with the information on your disease or the treatment given by the doctors, nurses, psychologists, etc. taking care of your MS? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 30 felt understood by the doctors, nurses, psychologists, etc. taking care of your MS? | ❑ | ❑ | ❑ | ❑ | ❑ |
| 31 been satisfied with your treatments? | ❑ | ❑ | ❑ | ❑ | ❑ |

**Thank you very much for your participation.**

## Appendix F

Stress VAS



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