Therapeutic Exercise for those moderately affected with Multiple Sclerosis

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"Keeping on inhaling that knowledge and wisdom" Queenie McCulloch, 2009

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The sun is still shining; I'm going to enjoy it.

Authors declaration

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

Signature 

Printed name Yvonne C Learmonth .

Publications arising from this work

Learmonth, Y. C., Marshall-McKenna, R., Paul, L., Mattison, P., Miller,L. (2012). A qualitative exploration of the impact of a 12-week group exercise class for those moderately affected with Multiple Sclerosis. Disability and Rehabilitation (in press).

Learmonth, Y.C., Paul, L., McFadyen, A.K., Mattison, P., & Miller, L. (2012). Reliability and clinical significance of mobility and balance assessments in Multiple Sclerosis. International Journal of Rehabilitation Research, 35, (1) 69.

Learmonth, Y. C., Paul, L., Miller, L., Mattison, P.,McFadyen, A. K. (2011). The effects of a 12-week leisure centre-based, group exercise intervention for people moderately affected with Multiple Sclerosis: a randomised controlled pilot study. Clinical Rehabilitation, 26, (7) 579-593.

Abstract

Multiple Sclerosis (MS) is a chronic progressive disease which presents with a variety of cognitive, motor and sensory deficits. Rehabilitation strategies to help manage some of these deficits include increasing physical activity and undertaking therapeutic exercise. A literature review begins this thesis and where relevant gaps are highlighted. These include; minimal literature on the long-term effects of therapeutic exercise, the views of those with MS taking part in therapeutic exercise and the characteristics of outcome measures used to assess those with MS. To address these areas three studies are presented related to therapeutic exercise for those moderately affected with MS (defined as an Expanded Disability Status Score of 5 to 6.5).

In the first study, a 12-week therapeutic exercise programme was delivered to twenty people with MS, whilst 12 people acted as controls who received usual care. Clinical outcomes were assessed at five time points over the intervention and 12-month follow-up period of the study. No statistically significant results emerged to suggest the intervention was effective, however calculated effect sizes indicated the intervention had a positive effect on areas related to the physiological (strength, mobility, fatigue and body composition), functional (mobility, balance and activity participation) and psychological (mood and quality of life) status of participants.

The second study sought to establish the views and opinions of participants, who had attended the exercise intervention. Three inter-related themes emerged. These were (1) the Exercise Class, which developed as a bridge to allow participants to realise (2) the Benefits of the Class, helping them to overcome (3) Barriers to Exercise. Results suggested the benefits to participating in exercise and the exercise intervention included social support and symptom improvement. Barriers to exercise included perceived psychosocial factors, symptoms and lack of service.

A third study investigated the test re-test reliability of four outcome measures used in the first study, calculations were done to establish the clinically significant change and precision of the outcome measures. The test re-test reliability of the outcome measures was good, with the calculated clinical change and precision of the outcome measures in those moderately affected with MS highlighting the problems of assessing those with MS.

The overall investigation suggests that therapeutic exercise and monitoring its effect in MS is good. Clinical and research recommendations emerged from this work, these include that the heterogeneity of symptoms presented in MS should be considered in future research designs and that group therapeutic exercise may improve physiological, functional and psychological status of those with MS, with the social benefits important to participants.

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1 Introduction

Multiple Sclerosis (MS) is a chronic progressive disease which presents with a variety of cognitive, motor and sensory deficits (Compston and Coles 2008). Rehabilitation strategies to help manage some of these deficits include increasing physical activity and undertaking therapeutic exercise. A thorough review of the current literature surrounding therapeutic exercise in MS is provided in this thesis as is information on three studies undertaken regarding therapeutic exercise in MS. These studies were designed to gather information on the impact of a therapeutic exercise programme and to gather information on the reliability of outcome measures commonly used to assess motor deficits in MS.

1.1 Therapeutic exercise in Multiple Sclerosis

Therapeutic exercise, is described as the "prescription of a physical activity program that involves the client undertaking voluntary muscle contraction and/or body movement with the aim of relieving symptoms, improving function or improving, retaining or slowing deterioration of health" (Taylor et al 2007). Therapeutic exercise is therefore an important treatment modality in MS and is the major topic of this thesis.

1.2 The investigations central to this thesis

This thesis included studies regarding therapeutic exercise for people moderately affected with MS, i.e. people who had an Expanded Disability Status Score (EDSS) of 5 (ambulatory without aid or rest for about 200 m) to 6.5 (constant bilateral assistance required to walk about 20m without resting (Kurtzke 1983).

The main investigation (Study 1) involved a randomised control trial (RCT) to assess the impact of a 12-week therapeutic exercise intervention in people moderately affected with MS. This exercise intervention took a combined approach (i.e. included aerobic, resistance and balance exercises), was undertaken in groups, it was held in community leisure facilities and was led by a physiotherapist and an exercise professional. Two smaller studies were undertaken, to complement this main investigation;

Study 2 was a qualitative analysis of participants' views on the exercise class whilst Study 3 was an assessment of the reliability of the mobility and balance outcome measures which were used in Study 1.

The overall investigation was a collaboration between The University of Glasgow and National Health Service (NHS) Ayrshire and Arran with assistance from KA Leisure and East Ayrshire Leisure Services. The majority of funding was provided by NHS Ayrshire and Arran (Bevan Endowment) and the University of Glasgow. Additional financial support was provided by KA Leisure, East Ayrshire Leisure Services and the Ayrshire and Arran Branch of the Multiple Sclerosis Society.

1.3 Contribution to knowledge

In undertaking this thesis, additional knowledge has been added to the growing body of literature surrounding therapeutic exercise in MS. The impact of a group exercise programme for people moderately affected with MS is established using quantitative analysis, as are the views and opinions on therapeutic exercise of those taking part in the exercise intervention. In addition, the reliability, clinical significance and precision of clinically relevant outcome measures used in the assessment of people moderately affected with MS are established. These are important areas for the healthcare management of people with MS, and offer insight into therapeutic exercise and assessment of outcome measures in this population.

1.4 Aims of this investigation

The overall aim of this investigation was to explore the impact of therapeutic exercise on those moderately affected with MS.

1.5 Research questions

Primary research question:

What is the effect of a group therapeutic exercise class on the physiological, functional or psychological status of people with MS who have moderate disability?

Research questions of individual projects:

- What are the short and longer term effects of a 12-week community based group exercise class in people moderately affected with MS, against controls with MS of a similar age, gender and disability level who received usual care?

- Is a 12-week community based group exercise class effective in improving the physiological, functional or psychological status of people moderately affected by MS?

- What are the participants' views on exercise and the therapeutic exercise intervention

- What are the reliability, clinically significant minimal detectable change and standard error of measurement scores of outcome measures used in people with moderate MS?

To answer these questions three studies were undertaken:

1. The quantitative analysis of the impact of a 12-week leisure centre-based, group exercise intervention for people moderately affected with Multiple Sclerosis.

2. A qualitative analysis of a 12-week group exercise intervention for people with Multiple Sclerosis.

3. The quantitative analysis of the reliability, clinical significance and precision of mobility and balance assessments in Multiple Sclerosis.

The studies, their individual aims and results are discussed within Chapters 4, 5 and 6 of this thesis.

1.6 Dissertation Guidance

It is the intention of the author that the information contained within this dissertation be accessible and interesting to a broad range of readers; health professionals, exercise professionals, academics, researchers and those who are interested in finding out about management strategies for MS. As such, sections of this thesis are published as individual projects within their own right.

The dissertation provides a great depth of information and to guide the reader Figure 1.1 provides possible paths through. Chapter 4, 5 and 7 assume knowledge of strategies used to manage and assess patients with neurological problems, and are written to be understood by healthcare professionals. Those interested in establishing strategies to manage MS sufferers may be most interested in the methods and results described in Chapters 4 and 5. Academics and researchers may find value in the findings of Chapter 4-6, dependant on their research interests. Although Chapters 4-6 can be read in any order, Chapters 4 and 5 and Chapters 4 and 6 complement one another. Clinical and research recommendations from the overall investigation are provided in Chapter 7.

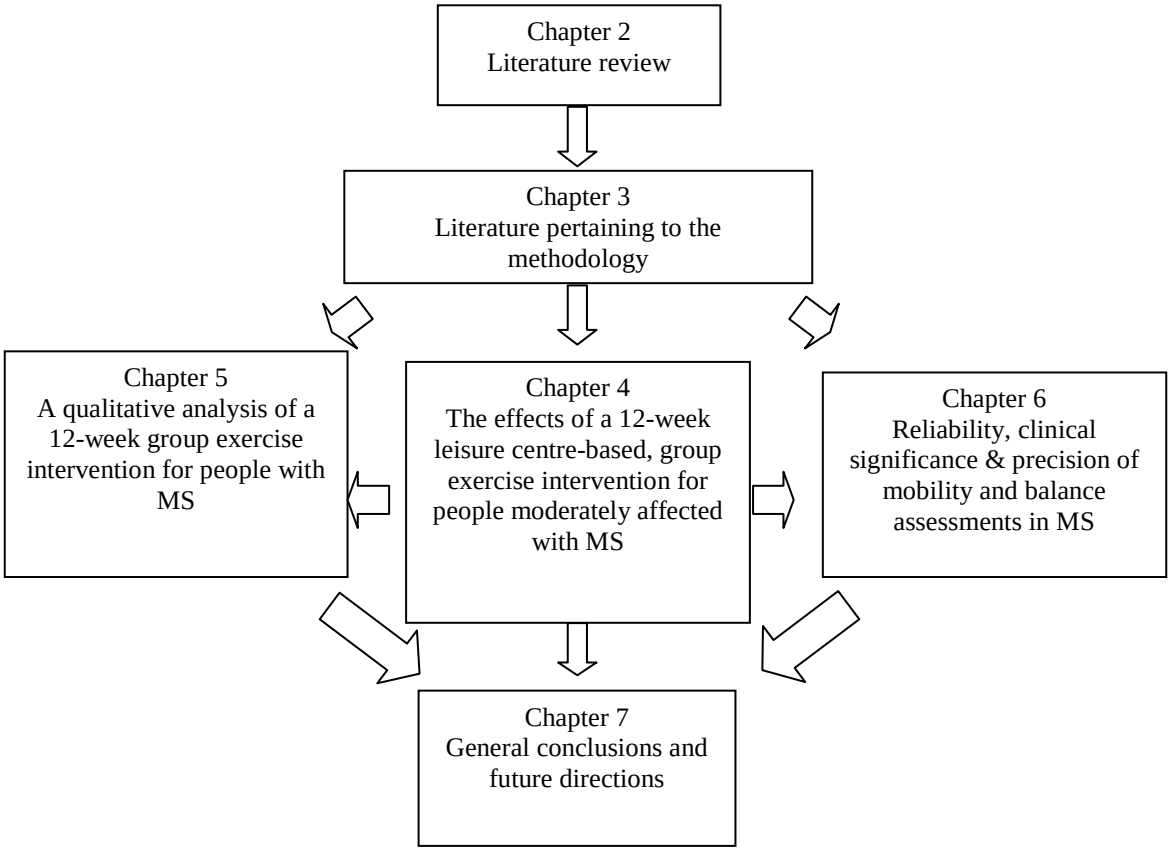

Figure 1.1 Paths through the dissertation

2 Literature review

Multiple Sclerosis (MS) is a chronic progressive autoimmune disease which impacts the neurological system. The condition involves intermittent immune mediated inflammatory changes within the myelin sheath, the protective coating around nerve fibres. These changes are often associated with new symptoms and are recognised as a relapse in the disease. This damage is cumulative and will result in the loss of integrity within the underlying nerve axon with subsequent axonal degeneration, this damage is the main determinant of disability progression (Compston and Coles 2002). Different patterns of MS (Section 2.2.1) follow a slightly different pathological process; one which is characterised by progressive primary axonal loss, and manifests in progressive deterioration, without relapse (Compston and Coles 2002).

Symptoms commonly involve deficits in motor function leading to major disability (Compston and Coles 2008). Rehabilitation therapy and in particular therapeutic exercise can help manage some symptoms related to motor function (Rietberg et al 2004). The main aim of this thesis was to explore the impact of therapeutic exercise on the physiological (strength, mobility, fatigue and body composition), functional (mobility, balance and activity participation) and psychological (mood and quality of life) status of people moderately affected with MS.

This chapter describes the current literature related to MS and therapeutic exercise providing the background for the thesis.

2.1 Introduction

The literature review provides the background and justification for the research (Bruce 1994), allowing a comparison of the past research in therapeutic exercise for those with MS. Establishing the *status quo* within the current MS exercise literature allowed the investigation to develop from the work of others. By obtaining a detailed knowledge of the topic, it was possible to design relevant studies to fill the literature gap.

This section will begin with a description of the key features of, and therapies for, MS, before expanding on the therapeutic exercise literature in MS, providing a background to therapeutic exercise interventions and qualitative data related to therapeutic exercise in MS. In Chapter 3 a literature review of the outcome measures used in this study will be presented, where further explanation of the reliability of outcome measures will be given.

2.2 Multiple Sclerosis

2.2.1 Pathophysiology, Classification and Diagnosis

Multiple Sclerosis (MS) has been described for many years as an inflammatory disorder resulting in widespread demyelination and axonal degeneration within the central nervous system (CNS). This manifests clinically as increased neurological deficit. Inflammation occurs in various regions of the brain and CNS, most commonly adjacent to the lateral ventricles within the corpus callossum of the cortex, subcortical white matter, optic nerves, brainstem and throughout the CNS. It can result in blockages to action potentials travelling through the axons of the CNS and axon transection or damage to the axon's myelin sheath (demyelination), as illustrated in Figure 2.1 (Compston and Coles 2008). Remyelination and repair can occur, resulting in lesions, visible under magnetic resonance imaging (MRI Figure 2.2), however this tissue repair may be limited, and results in the clinical features associated with MS. Diagnostic criteria are shown in Table 2.1.

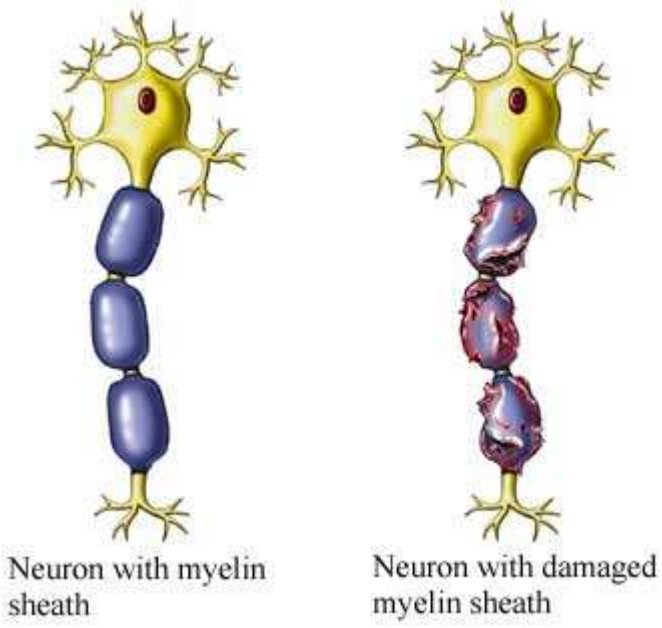

Figure 2.1 Nerve fibre (neuron) from a healthy individual and person with MS

(Nucleus Medical Media 2011).

In the majority of cases clinical symptoms indicate the involvement of motor, sensory and autonomic systems which can be used for diagnosis. Empirical evidence of more widespread cerebral involvement can be found through MRI, where lesions indicate areas of damage; either T1 Gadolinium-enhanced brain lesions, showing currently active areas of MS, or T2 lesions which may, in addition, show older or inactive lesions (van Waesberghe et al 1998). With evidence of elevated immunoglobulin G in the cerebrospinal fluid also a notable indicator (Polman et al 2011) of the disease.

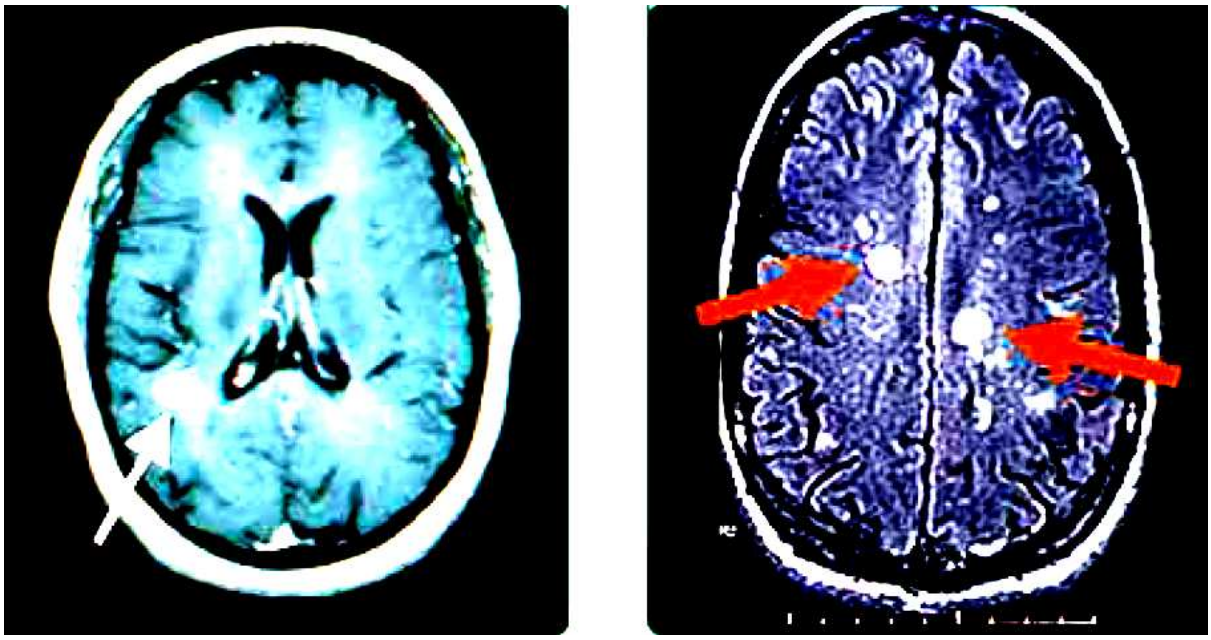

Figure 2.2 Magnetic Resonance Imaging of damaged MS brains.

Arrows indicating Gadolinium enhancing; T1 (left) T2 (right) lesions (EMD Serono 2012)

Table 2.1 Diagnostic criteria for MS

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

Adapted from McDonald et al(2001) and Polman et al (2011).
MRI – Magnetic Resonance Imaging, CSF – Cerebrospinal Fluid, T2 – Lesion indicating evidence of MS, VEP - Visual Evoked Potentials (evidence on brain activity)

MS is commonly described as one of several clinically defined types, which describe the course of the disease. However, it is not necessarily a natural progression from one to the next, and often a clear classification of type of MS cannot be made. Relapsing-remitting MS, is the most common (80% of people at onset, National Institute for Health and Clinical Excellence; NICE (2003)), manifesting in a relapse of symptoms followed by periods of remission. Secondary progressive MS describes cases where fewer periods of remission occur and neurological deficits progressively worsen. NICE (2003) indicates that about 50% of people diagnosed with relapsing remitting MS develop the secondary progressive form within 10 years. Primary progressive MS is the least common (10-15% of people at onset, NICE (2003)), in this form neurological deficits progressively worsen from the onset (Talbot 2010). Primary progressive MS may differ to other types of MS in the underlying damage within the immune system. Whereby milder inflammatory damage occurs overtime, with the accumulation of disability being ultimately more progressive, rather than the clear relapsing pattern more commonly seen (Compston and Coles 2002). However some people with more progressive MS may also experience occasional relapses, and thus a subsidiary form of Primary progressive MS, which has no clear definition, is Progressive relapsing MS, whereby relapse occurs alongside progression of the disease, and subsequent disability (Lublin and Reingold 1996). Another form of MS, when there has been no change in any neurological systems for 15 years or more is known as benign MS (Lublin and Reingold 1996). The pattern of clinical symptoms and descriptors is complex, variable and unpredictable; however, the types are displayed in Figure 2.3.

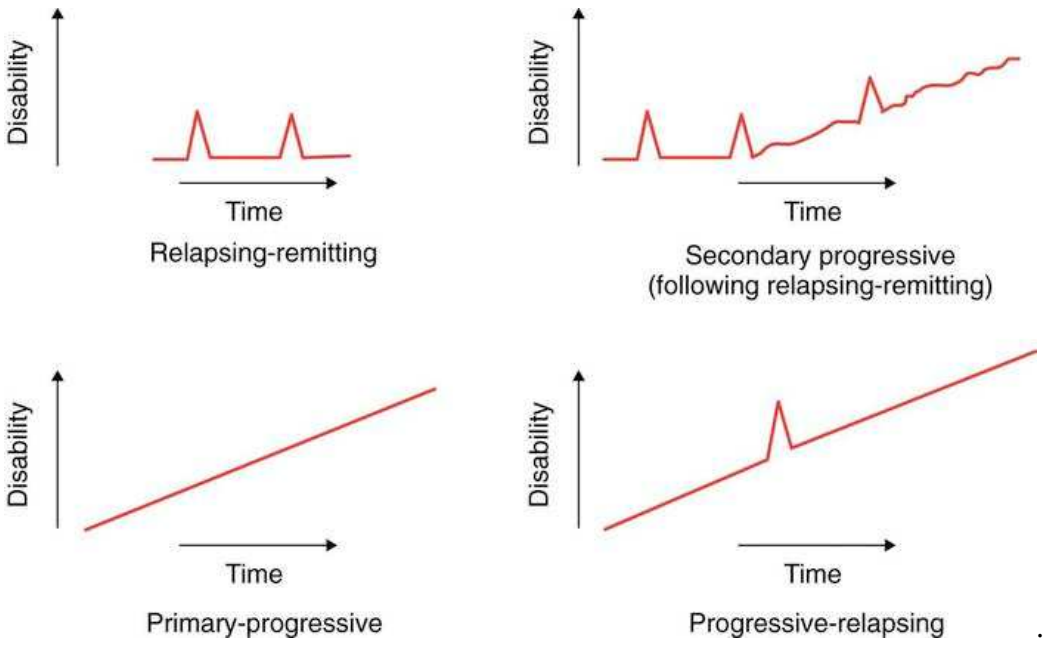

Figure 2.3 Clinical types of MS

(adapted from Lublin and Reingold (1996))

2.2.2 Epidemiology and prevalence

MS is the most common progressive neurological disease affecting young people, it is more than twice as common in women than men, with disease onset usually in the third or fourth decade of life (Compston and Coles 2002). Life-expectancy is around 25 years following diagnosis, but is nearing that of the general population (Confaxreux & Compston, 2004), with most people dying of unrelated causes (Compston and Coles 2002).

The cause of the disease is unknown, despite a genetic predisposition (Compston and Coles 2002). Environmental factors such as infections, diet, country of birth and country of residence are also amongst the most common risk factors and are discussed in detail by Ascherio and Munger (2007a; 2007b) and Handel et al (2010a; 2010b). Linked with both the genetic and environmental risk factors, the prevalence of MS varies around the world, found most commonly in countries populated by those of primarily European ancestry, such as Ireland, the United Kingdom, South East Australia, New Zealand, Sweden, Finland and Southern Canada/Northern United States (Compston and Coles 2008). In Europe the UK is estimated to have the highest prevalence , with up to 250 cases per 100, 000 people having been reported in a past Scottish study (Poskanzer et al 1980). This is high since the prevalence of MS is deemed to be high if there are more than 60 cases of MS in a population of 100,000 people (Olek 2008).

It was first observed by Dr Bramwell in 1903, that there was an unusually high rate of MS within his Edinburgh practice in comparison with America (McDonald 1986). Since then many studies have looked at this interesting observation. Scotland, in particular, has reportedly high prevalence rates. With reports of 127-250 cases per 100,000, in different studies around the country (cited in Rothwell and Charlton (1998)), compared to studies in England and Wales where prevalence rates are lower, ranging from 99 cases per 100,000 (Roberts et al 1991) to 146 cases per 100,000 (Hirst et al 2009). The primary study by Rothwell and Charlton (1998) found a prevalence rate in the Scottish region of Lothian to be 203 cases per 100,000. Researchers have had difficulty explaining the higher rates of MS found in Scotland, however there has been an increased interest in this area in recent years, with tentative explanations surrounding Vitamin D deficiency, lower levels of sunlight and diet (Ebers 2008; Handel et al 2010b) in addition to genetics.

2.2.3 Clinical features

Clinical features and symptoms vary amongst those who have MS. Clinical features may include; fatigue, mobility impairments, weakness, balance impairments, stiffness and spasms, memory and other cognitive problems, bladder and bowel problems, pain and unpleasant sensations, emotional problems, visual changes, and dizziness (Motl et al 2008b). Symptoms can be heterogenic, for

example mobility impairments may range from slight leg weakness to being fully wheelchair dependant.

A study of 301 people with MS living in Wales provided information on the frequency of symptoms (Matthews 1998) displayed in Table 2.2. This table not only highlights the most common symptoms (weakness, sensory symptoms, ataxia, bladder symptoms, and fatigue), amongst those with MS whilst indicating that not all symptoms may be present throughout the course of the disease.

Table 2.2 Frequency of symptoms

Symptom	Ever (n (%))	At onset (n (%))
Weakness	268 (89)	66 (22)
Sensory Symptoms	263 (87)	103 (34)
Ataxia	248 (82)	32 (11)
Bladder Symptoms	213 (71)	5 (2)
Fatigue	171 (57)	5 (2)
Cramps	156 (52)	2 (0.6)
Diplopia	155 (51)	25 (8)
Visual symptoms	148 (49)	38 (13)
Bowel Symptoms	126 (44)	0
Dysarthria	110 (37)	2 (0.6)
Vertigo	107 (36)	13 (4.3)
Facial pain	106 (35)	5 (2)
Poor memory	96 (32)	1 (0.3)
Headache	90 (30)	6 (2)
Mental symptoms	68 (23)	1 (0.3)
Deafness	51 (17)	2 (0.6)
Facial weakness	48 (16)	4 (1)
Dysphagia	40 (13)	1 (0.3)

Data from Matthews (1998)

2.2.4 Predicting prognosis

The Expanded Disability Status Scale (EDSS) (Kurtzke 1983) is the most widely used measure of disability for MS. It describes both neurological and functional aspects of the disease. The scale quantifies neurological impairments, in each of eight neurological functional systems (FS); pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. These are combined with ambulation ability/mobility and give a measure of disability on a scale from 0 (normal) to 10 (death due to MS) (See Appendix 9.1). In general, as the number of symptoms increases so will the EDSS level.

The EDSS has, for many years attracted criticism (Section 3.7.2), despite this it is still a commonly used tool clinically and in research allowing for comparison between study populations. Authors have noted a poor response to change (Sharrack et al 1999) and that scores are clustered around 3/4 and 5/6 (Whitaker et al 1995; Jacobs et al 1999). Grades above three are heavily reliant on mobility, thus at the higher end of the scale a newly acquired FS problem may not necessarily modify the EDSS score.

The definitions of mild, moderate and severe MS are often linked with the EDSS, however the original author (Kurtzke 1983) did not use these definitions. Moderate MS, defined in the present study as 5 (ambulatory without aid or rest for about 200 m) to 6.5 (constant bilateral assistance required to walk about 20m and without resting) was the description used by Freeman et al (1997) and Hammond et al (2000). However there is a discrepancy in the literature as moderate MS has been described by others as an EDSS score of 5-7 (Filipi et al 2011), 4-6 (Craig et al 2003) or 3-4 (Goldman et al 2008).

Higher levels of disability have been associated with a poorer prognosis, and faster disease progression (Cottrell et al 1999). A prevalence study showed that persons with milder MS (EDSS 0-3) at initial disease diagnosis, have a much better prognosis than those with moderate or severe MS (EDSS 4-9) (Hammond et al 2000). These authors also found that an increased number of multiple symptoms at disease onset had a negative effect on prognosis.

Brain imaging (MRI) is also increasingly used to predict prognosis. It has been shown in a 20 year follow-up study that more damage to the brain at baseline (number of T2 lesions) is associated with a higher disability score after 20 years (Fisniku et al 2008). However brain imaging is not utilised within this thesis and thus will not be explored in any depth.

2.2.5 Treatments for Multiple Sclerosis symptoms

As has been discussed MS symptoms and prognoses vary widely, and thus there is no one specific treatment, although many options are available. These will be discussed in brief and taken from the National Institute for Health Clinical Excellence (2003) guidelines of acute exacerbations and long-term management in MS, with updates to these guidelines acknowledged as appropriate.

Management of acute exacerbations

When a severe exacerbation or attack of symptoms occurs medical treatment such as corticosteroids are often administered, and hospitalisation may be necessary dependent on the severity of the exacerbation. Corticosteroids will often be administered (intravenous or high dose oral methylprednisolone) for 3-5 days. Rehabilitation will target the sudden increase in disability, with referral to the appropriate specialist within the rehabilitation service.

Long-term management

Where relapses are the predominant feature of the disease, as in Relapsing-remitting MS, National Institute for Health and Clinical Excellence (2003) guidelines suggest that patients are offered disease modifying therapy (DMT), either interferon beta or glatiramer acetate under the guidance of their neurologist. Other medical treatments which include azathioprine, mitoxantrone, intravenous immunoglobulin, plasma exchange and intermittent methyprednisolone should be prescribed judiciously if appropriate. Updates to these guidelines suggest that natalizumab be prescribed to rapidly evolving cases of severe relapsing remitting MS (National Institute for Health and Clinical Excellance 2007) . Whilst fingolimod has recently been recommended for those with highly active relapse-remitting MS (National Institute for Health and Clinical Excellence 2012).

Maintaining functional activities and social participation is important and can be managed through rehabilitation. Assessment and access to a multidisciplinary neurological rehabilitation service is important. This will offer early intervention of any change in symptoms, whilst offering disease management to minimise the impact of disease progression.

It is advised by National Institute for Health and Clinical Excellence (2003) that as a minimum the following specialists are involved in a multidisciplinary neurological rehabilitation service:

- Doctors
- Nurses
- Physiotherapists
- Occupational Therapists
- Clinical Psychologists
- Social workers

These services will aim to maintain the person with MS in their chosen vocational activity, encourage leisure and social interaction, maintain mobility, maintain activities of daily living and help manage symptoms (such as those referred to in Table 2.2).

2.2.6 Symptom management in Multiple Sclerosis

Within this thesis, the role of therapeutic exercise will be the primary focus related to symptom management. The medical and pharmacological treatments for managing MS symptoms will therefore not be discussed in great depth, however the interested reader is referred to the following texts.

Khan et al (2008b) provides a comprehensive review of the common multidisciplinary therapy approaches to management in MS, finding that multidisciplinary approaches are effective in managing MS, although no recommendations on optimum dose or type of therapy to guide best practice emerged.

Thompson et al (2010) provides a good source of reference for multidisciplinary therapy approaches (including occupational therapy and physiotherapy), pharmacological and surgical treatments in MS to address symptoms such as; spasticity, ataxia, impaired mobility, bladder/bowel and sexual dysfunction, fatigue, cognitive problems, mood disturbance, visual and brainstem symptoms. The authors conclude that a diverse range of management options are available and should be utilised when appropriate. They acknowledge that although there are promising treatments on the horizon, improvement in study design is required before recommendations in clinical practice can be made.

Freedman et al (2002) provide a consensus statement on the use of DMTs in MS, with other authors updating these guidelines (Wiendl et al 2008; Goodin 2008). The recommended DMTs for MS are interferon beta, glatiramer acetate, mitoxantrone, natalizumab and fingolimod (National Institute for Health and Clinical Excellence 2003; National Institute for Health and Clinical Excellance 2007; National Institute for Health and Clinical Excellence 2012). These treatments can positively influence the signs and symptoms of the disease, reduce the frequency and severity of relapse rates and minimise accumulation of brain lesions, as evidenced through MRI. Each medication does however have known side effects, which must be considered.

However there is a consensus in all of the above works that a multimodal approach is taken towards management in MS, combining medical, pharmacological and therapeutic intervention. One of which, therapeutic exercise, is the focus of this thesis.

2.2.7 Therapeutic exercise for Multiple Sclerosis

Therapeutic exercise is an integral therapeutic intervention to help manage those with MS (Doring et al 2011), thus it is an important treatment for MS, recommended by health professionals such as physiotherapists.

Physiotherapy is therapy delivered by a qualified physiotherapist, to promote physical, psychological and social wellbeing, based on the needs of the patient/participant established through the physiotherapist's focussed assessment (Thornton 1996; Chartered Society of Physiotherapy 2005). This may include therapeutic exercise or other therapies or modalities such as hands-on treatment, aquatic-based therapy or assisted mobility aids.

Therapeutic Exercise is the "prescription of a physical activity program that involves the client undertaking voluntary muscle contraction and/or body movement with the aim of relieving symptoms, improving function or improving, retaining or slowing deterioration of health" (Taylor et al 2007) .

Within this context Physical Activity is any bodily movement produced by skeletal muscles resulting in energy expenditure. Exercise is a planned, structured and repetitive physical activity with a goal of maintaining or improving physical fitness (Caspersen and Christenson 1985). There is reason to believe that exercising specifically to improve symptoms of MS is worthwhile and, as will be explained during the literature review, may offer a management approach to the deconditioning associated with the disease over time. In addition to managing symptoms, exercise and increased physical activity may go some way to preventing age-related health conditions associated with a sedentary lifestyle.

There are reports in the literature to suggest that those with MS are more sedentary than their healthier peers (Mostert and Kesselring 2002; Motl et al 2005; Sandroff et al 2012). Therefore, those with MS may be at the same, or perhaps greater, risk of age-related health conditions associated with a sedentary lifestyle (Bronnum-Hansen et al 2004; Marrie et al 2008). Consequently increasing the burden on health services and increasing mortality rates, as the combination of inactivity and ageing not only increases the general risk of osteoporosis, diabetes and coronary problems in those with MS, but may worsen the impact of more disease-specific problems, such as fatigue, mobility impairment, balance deficits, weakness and stiffness. All of which are common problems in MS (Ponichtera et al 1992; Matthews 1998; Frzovic et al 2000; Compston and Coles 2008; Motl et al 2008b).

Therefore increased physical activity and exercise should be promoted throughout all stages of the disease, which has not always been the case.

2.2.8 A historical look at therapeutic exercise for Multiple Sclerosis

Historically the importance of therapeutic exercise was not always acknowledged in MS management. McAlpine et al (1955) stated that physiotherapy had previously been prescribed as a placebo until rehabilitation was found to have a “remarkable effect” during the war years in those with traumatic paraplegia, and thus it was used for other causes of paraplegia, such as MS. The progression towards active rehabilitation through therapeutic exercise seen today can be charted by the writings of Douglas McAlpine, Nigel Compston and Charles Lumsden, arguably recognised as the most authoritative authors in MS. In early writings the advice to patients supported healthy activity, with the authors commenting that “on common-sense grounds alone” a normal weight should be maintained (McAlpine et al 1955). Furthermore they acknowledged that routine exercise contributed to maintaining good health, however bed rest (for up to two weeks) during symptom relapse was recommended. Rehabilitation advice for those with more ongoing symptoms was limited to spasticity management, such as positional changes, standing with abducted legs and lying prone (McAlpine et al 1955). Similar to today’s practice it was acknowledged that patients should be discharged from hospital with instructions to help them carry out daily activities; these may have included maintenance exercises.

In the late 1960s Russell and Palfrey (1969) gave specific details of an MS exercise programme, tailored to the individual patient and provided guidance to other therapists and patients on carrying out exercise. Admitting the obvious weakness of assessing short-term improvements of a relapsing remitting disease and chronic progressive disease these authors took a long-term approach to their intervention. Over a period of eight years they encouraged 69 patients with many differing types of MS to exercise daily, provided record cards for them to maintain, and assessed their progress yearly. Their sole outcome measure, a six scale mobility assessment taken from McAlpine & Compston (1955), showed improvement in 41 participants, with no change in the remainder. This study lacked controls, blinding, statistical strength and validated outcome measures and would not withstand contemporary reviewers, nevertheless it illustrates the success of therapeutic exercise treatment of at least one specialist neurorehabilitation centre during the 1960s.

By the 1980s a short section in the McAlpine series of books was dedicated to physiotherapy, with the lack of published data on the merits of physiotherapy treatment being acknowledged (Matthews 1985).

More recently Noseworthy et al (2006) writing in the latest McAlpine publication, acknowledged the importance of exercise in MS management:

> "Patients should be encouraged to enter a graded exercise programme to optimize fitness" (p718)

> "…the introduction of drug treatment in parallel with neurorehabilitation offers a better chance for the rehabilitation intervention to result in sustained benefits to the patients" (p727).

In summary although therapeutic exercise has not always been recommended for those with MS, its importance is becoming increasingly recognised to both manage the symptoms of the disease whilst also addressing the long-term general health of those with MS.

2.3 Therapeutic exercise for Multiple Sclerosis today

Physiotherapy is one of the main health professions involved in the rehabilitation of MS (Khan et al 2008b), with qualitative findings suggesting people with MS would feel more confident exercising with support from a physiotherapist (Dawes et al 2010). Indeed UK-based survey studies suggest that between 21% and 44% of people with MS have contact with a physiotherapist (Freeman and Thompson 2000; Vazirinejad et al 2008). Although it is accepted, that physiotherapy treatment is not only exercise based (see below), prescribing therapeutic exercise is a large aspect of physiotherapy treatment. Furthermore, there is evidence that those with MS want to learn more about exercise options (Somerset et al 2001; Hepworth and Harrison 2004), suggesting a therapeutic exercise intervention may be well received by people with MS.

There is growing evidence and support for therapeutic exercise to be delivered not only by physiotherapists but also other exercise professionals. Indeed cross-organisational options for patient management are encouraged by current guidelines on MS care and general health guidelines (National Institute for Health and Clinical Excellence 2003; Scottish Executive 2007; Scottish Government 2007). With physiotherapy and the fitness industry both playing a role in symptom management and improving the health of those with MS (Figure 2.4). Furthermore, the current social, political and economical landscape encourages community-based rehabilitation where therapeutic exercise can be done in a non-hospital setting (Romberg et al 2004; Romberg et al 2005).

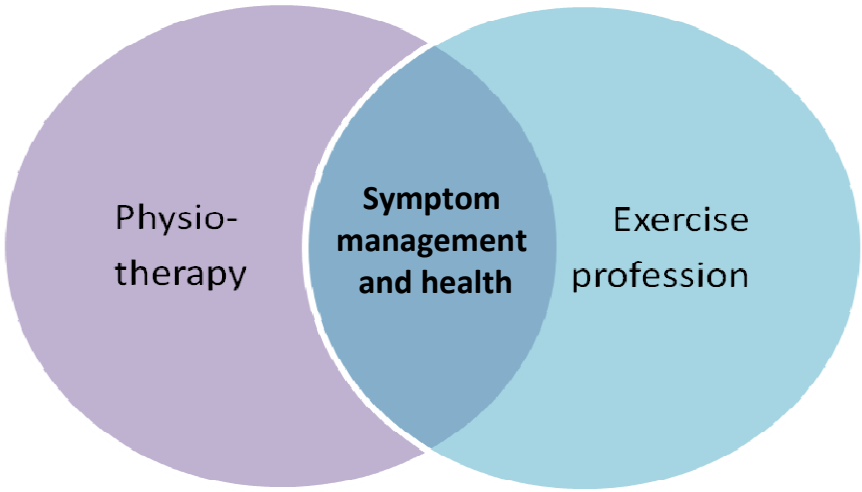

Figure 2.4 Relationship between physiotherapy and the exercise profession in MS management

The following sections review and describe the available evidence for therapeutic exercise interventions in MS.

2.3.1 Identification of studies in the literature review

A systematic method was adopted to identify therapeutic exercise studies discussed in this review of the literature. In addition to relevant textbooks and government publications, online databases including the Cochrane database of Systematic reviews, Ovid-Medline, Ovid-Embase and Google Scholar were searched for published articles.

Key words searched included were Multiple Sclerosis, Rehabilitation, Exercise, Exercise-therapy, Physiotherapy, Physical Therapy, Aerobic, Strength, Resistance, Balance, Focus Groups, Qualitative and Reliability. These were combined and truncated versions of the key words were also used. The main search covered most recent papers (2005 – March 2012), however older papers of interest were also included.

The above searches were carried out on a three-monthly basis throughout the time of the PhD study. Email updates were sent to the thesis author from relevant journals and from Ovid related to the keywords. Social media (i.e. Twitter posts) was also utilised to remain updated on the current literature, by following researchers and charities who posted examples of new research related to MS.

2.3.2 Studies not included in the literature review.

To focus the literature review only studies involving therapeutic exercise with 1) an aerobic exercise intervention, 2) a resistance exercise intervention or 3) a combined exercise intervention methodology were reviewed. As a group and community based methodology was adopted in the study this was also important in the review of the research. As such the following criteria were adopted for exclusion of studies from the literature review.

- Any study involving in-patient therapy, which is classified as any stay over 24 hours in either a specialist rehabilitation centre or hospital ward.
- Any study including an intervention of only one day.
- Any study involving health professionals visiting and delivering interventions in the participants' own home.
- Any study where the intervention was delivered over the internet.
- Any study involving evaluation of a multidisciplinary approach (e.g. physiotherapy, occupational therapy, speech therapy and input from a neurologists and nurses).

- Any study where a hands-on/passive therapeutic approach (when the therapist moves the patient's body whilst they are inactive) was the main component of the intervention.

- Any study where the intervention was mainly pharmacological.

- Any study where the intervention was primarily of a didactic/educational nature.

- Any study whereby the intervention was mainly aquatic based exercise or based on breathing exercises.

- Any study which did not assess functional or psychological outcome measures.

2.3.3 Quality of the literature

Ranking the studies against standardised criteria offers some comparison of quality for researchers and clinicians to use when carrying out evidence based research/practice.

To help establish the quality of the quantitative evidence base, all literature which included a randomised control design was entered into the Physiotherapy Evidence Database PEDro which assesses trials independently for methodological quality. The PEDro is an online tool based on The Delphi List for assessing the quality of randomised clinical trials (Verhagen et al 1998) which can be accessed at (www.pedro.org.au). The PEDro system considers the methodological quality of the study based on "believability" (internal validity) and whether enough detail is provided to interpret the outcome of the study.

For internal validity, criteria are; acknowledging eligibility, random allocation, concealed allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, analysis of intention to treat and adequacy of follow-up (85% for at least one key outcome). For interpretability, criteria are; between group statistical comparisons of at least one key outcome and reports of point and variability measurements for at least one key outcome. Together these criteria provide a total of 11 points.

Utilising the PEDro system has two direct benefits, firstly it allows comparison of the methodological quality across similar studies and secondly it will help in the developmental stage of any new study of an intervention based randomised control trial, to improve methodological quality and reporting. Thus the PEDro system was referred to when developing the main study in this thesis. The PEDro system has been shown to adequately measure methodological quality of clinical trials (de Morton 2009) and to display acceptable reliability of the total score (Maher et al 2003). The total scores for the randomised clinical trials included in this literature review are given, providing comparable evidence on the quality of the background literature.

To help establish the quality of the qualitative evidence, relevant studies were critically appraised using the Critical Appraisal Skills Programme (CASP) qualitative research appraisal tool (available online at www.caspinternational.org). This helps to consider; validity of the results, the results themselves and the relevance of results. Ten questions cover these areas; study aims, appropriateness of methodology, appropriateness of research design, recruitment, data collection, relationship between the researcher and participant, ethical considerations, data analysis, findings and relevance (value) of the research. Unlike the PEDro system, scoring is not absolute and it is not necessary to score the research, however the tool allows comparison of quality between studies.

2.3.4 Systematic reviews and meta-analysis of therapeutic exercise

Many review articles have been written which evaluate therapeutic exercise in MS (Rietberg et al 2004; Karpatkin 2005; Heesen et al 2006a; Dalgas et al 2008; Motl and Gosney 2008; Garrett and Coote 2009; Hogan and Coote 2009; Snook and Motl 2009; Andreasen et al 2011; Dalgas and Stenager 2011).

This section will summarise the reviews of the studies related to exercise therapy. A summary of the reviews, and the reviewed studies discussed within them can be found in Table 2.3. During this section any study included in the reviews, which is not thought relevant to this thesis will not be discussed (refer to Section 2.3.2).

General reviews on the effects of exercise in MS have been written (Karpatkin 2005; Heesen et al 2006b). However Rietberg et al (2004) carried out a review on general therapeutic exercise in MS. In this review only RCT's which concerned rehabilitation, physical therapy, training and home physiotherapy in MS were included (Table 2.3), to ascertain the effects of these on activities of daily living and/or quality of life. All study participants were mild to moderately disabled (EDSS $\leq$6.5). Rietberg et al's (2004) review concluded that exercise based rehabilitation which covers many forms of interventions/exercise types, including more traditional impairment and mobility physiotherapy approaches, as well as aerobic and resistance training can be beneficial for those with MS.

Since then various authors have built on the work of Rietberg and colleagues. Snook and Motl (2009) carried out a meta-analysis of therapeutic exercise related to walking mobility. Interventions and exercise types varied, and included physiotherapy based, aerobic exercise based and resistance exercise based (Table 2.3). The mean effect size of the included studies varied widely. Reporting effect size is becoming more common in studies in MS, they are a scale free measure of the relative size of the effect of an intervention (Coe 2002). Snook and Motl (2009) found the combined estimate of the effect size from the meta-analysis (g=0.19) showed a trend toward exercise being beneficial for mobility, which, at the 95% confidence interval level, which suggests a small effect size.

Studies of physiotherapy interventions (Hogan and Coote 2009) and aerobic and resistance exercise interventions (Hogan and Coote 2009; Garrett and Coote 2009) have been reviewed in people with wide ranging mobility problems. These researchers used the Cochrane criteria for assessing the quality of the literature, but unlike a traditional Cochrane review they aimed to include all studies with a view to reporting on clinical applicability. Hogan and Coote (2009) reported on therapeutic interventions for those more disabled (EDSS≥6); aerobic exercise, resistance exercises and physiotherapy were included (Table 2.3). They reported similar findings to the other reviews; that these interventions have positive benefits for those with MS with mobility problems. Hogan and Coote (2009) highlight the need to carry out similar research in MS, specifically, looking at the effects stratified to level of mobility and disability.

Garrett and Coote (2009) reviewed studies of exercise interventions which included participants who had milder disability (EDSS ≤6). With a focus on making the review clinically relevant, the studies were presented using Frequency, Intensity, Type and Time (FITT) a common acronym used in exercise training (Franklin et al 2000). Garrett and Coote (2009) found that, similar to other reviews, exercise interventions are beneficial for those with MS, who have milder disabilities.

To establish recommendations for the application of resistance, endurance (aerobic) and combined exercise training in MS, Dalgas et al (2008) reviewed many therapeutic exercise studies (Table 2.3). The majority of their reviewed trials looked at aerobic exercise (endurance) (Table 2.3). By choosing to look at exercise as a health promoting intervention, and not a therapeutic approach, Dalgas et al's (2008) review actively excluded physiotherapy. Strict inclusion criteria were also applied to this review; only studies using a longitudinal evaluation of an exercise intervention were included, and only those whose interventions could be categorised as either endurance, resistance or combined exercise were included, in addition this review included one qualitative study.

The authors did not state what the criteria for a longitudinal design were, although trials ranging from 4 – 26 weeks were included. As length of programme was important within Dalgas et al's (2008) review, it is disappointing that the authors failed to comment on the longer term effects of the intervention, following completion of the intervention. However, they did provide information on training regimes studied and basic results. In general the findings suggest that patients mildly to moderately affected by MS can safely tolerate low to moderate endurance training and moderate resistance training; however more evidence is required for combined training. This information however can only be applied to those mildly to moderately affected with MS, as no trials included any participant with an EDSS score of greater than seven. A narrative stance was present throughout the review; some critique was present with the authors concluding that the quality of evidence is poor. However no attempt was made to rank the quality of the studies, which allows more objective comparisons.

Motl and Gosney (2008) took a different stance in an earlier meta-analysis of exercise studies. They looked at the effects of exercise on health-related quality of life and fatigue in those with MS. The majority of trials which were included involved aerobic training for three months or less (Table 2.3). Overall a small improvement in quality of life was found, with more improvement in shorter interventions. When the effect size was calculated and compared with similar meta-analyses, the effect of exercise training was comparable (in magnitude) with the effects of DMTs on reducing exacerbations of MS (Filippini et al 2003). It was also comparable to the effects of long term exercise on mental health outcomes (Colcombe et al 2006) and fatigue (Puetz et al 2006 cited in Motl & Gosney (2008)). However it is unknown which type/level of MS this information applies, as the authors failed to report this, or any demographic data on the participants in the analysed trials. It is disappointing that the disease type was unreported, as direct comparison between DMTs (not given to those with secondary progressive MS) cannot be made without this information.

Asano et al (2009) also carried out a meta-analysis, with the aim of establishing the strength of current evidence guiding regular exercise prescription. One feature of this review different from that of Motl and Gosney (2008) was that only trials whose main outcome was quality of life were included. The benefits of focusing like this mean that, if included trials are statistically powered to show changes in quality of life (as the main outcome) then stronger statements can be made about the overall results. Unfortunately of all the trials included in this meta-analysis none were sufficiently powered to show these effect changes. Two of the trials (Oken et al 2004; Storr et al 2006) attempted to recruit enough patients to show meaningful changes in quality of life, however neither achieved their target recruitment. The remaining five trials did not acknowledge power in relation to quality of life.

A problem, present throughout all the MS exercise literature is the variety of outcome measures used (discussed in more depth in Chapter 3). This is highlighted in the work of Asano et al (2009) which found, across the included trials, seven different tools used to measure quality of life. Realistic comparison, and any attempt to meta-analyse the results across different trials is difficult if numerous different outcome measures are used. Ideally, if a consensus were made on which outcome measures should be used in future trials in MS then true effect changes could be confirmed by the exercise interventions. However with the available data Asano and colleagues could only show that although there is evidence of symptoms improvement after exercise there is insufficient evidence to offer clinical guidelines. With the available evidence only applicable to those mildly affected by MS (EDSS ≤ 5). This is not only due to the differing outcome measures but also due to the varying methodologies and interventions which make it difficult to recommend any specific training guidelines.

However when reviewing the impact of exercise on self-reported fatigue levels in MS Andreasen et al (2011) found more agreement in the fatigue outcome measures used. Only four different outcome measures were used across the 20 reviewed studies; the Fatigue Severity Scale (FSS) was the most common fatigue outcome measure. The review took a descriptive narrative, with limited discussion on the quality of the studies; furthermore the authors did not attempt to calculate the effect of the interventions on fatigue. Two qualitative studies were also included in the descriptions of past studies (Table 2.3). Andreasen et al (2011) concluded that exercise had the potential to improve fatigue, but were unable to draw conclusions as the appropriate FITT of exercise to best help manage fatigue

More recently Dalgas et al (2011) reviewed the potential of exercise to alter the disease progression in MS, much of the work reviewed is based on empirical non-clinical outcomes (such as MRI analysis, relapse rate) or animal studies beyond the realms of this thesis. However the accumulated evidence discussed within the review paper supports a possibility that there is a disease modifying potential to therapeutic exercise in MS.

There is much overlap between the reviews; however no trial appears in all reviews (Table 2.3). This not only reflects the variety of studies in this area, but also the different aims and methodology of the reviews/meta-analyses. The description of the interventions vary slightly throughout the reviews, with some providing more depth of information than others, resulting in some disparity as to the form of exercise. However in general all reviews agree that exercise has been found to be effective, to a certain extent, for those with mild to moderate MS symptoms.

Table 2.3 Chronological summary of reviews and reviewed articles

Author	Short aim	Reviewed studies	
Rietberg et al (2004)	Exercise on daily living and quality of life in MS	Petajan et al (1996)[p a] Mostert and Kesselring (2002)[a r]	O'Connell et al (2003)[a] Debolt and McCubbin (2004)[r]
Heesen et al (2006)	General discussion on exercise in MS	Petajan et al (1996)[p a] Mostert and Kesselring (2002)[a r] Carter and White (2003) [a r c] O'Connell et al (2003)[a]	Debolt and McCubbin (2004)[r] Oken et al (2004)[a] Schulz et al (2004)[a] Romberg et al (2005)[a r]
Karpatkin (2006)	General discussion on exercise in MS	Petajan et al (1996)[p a] Mostert and Kesselring (2002)[a] Rodgers et al (1999)[a]	Harvey et al (1999)[r] Kraft et al (1996)[r]
Dalgas et al (2008)	Exercise recommendations in MS	Schapiro et al (1988)[a] Kasser and McCubbin (1996)[r] Kraft et al (1996)[r] Petajan et al (1996)[p a] Ponichtera-Mulcare et al (1997)[a] Harvey et al (1999)[r] Fisher et al (2000)[r] Mostert and Kesselring (2002)[a] O'Connell et al (2003)[a] Carter and White (2003)[a r c] Debolt and McCubbin (2004)r	Oken et al (2004) [a] Romberg et al (2004)[a r c] Romberg et al (2005)[a r c] Schulz et al (2004)[a] White et al (2004)[r] Gutierrez et al (2005)[r] Kileff and Ashburn (2005)[a] Rasova et al (2006)[a] van den Berg (2006)[a] Dodd et al*(2006)[r] Taylor et al (2006)[r]
Motl and Gosney (2008)	Exercise on quality of life in MS	Petajan et al (1996)[p a] Mostert and Kesselring (2002)[a] White et al (2004)[r] Oken et al (2004)[a]	Schulz et al (2004)[a] Romberg et al (2005)[a r] van den Berg (2006)[a] Rasova et al (2006)[a]
Asano et al (2009)	Exercise on quality of life in MS	Petajan et al (1996)[p a] Harvey et al (1999) [r] Schulz et al (2004)[a] Oken et al (2004)[a] Romberg et al (2004)[a r]	Debolt and McCubbin (2004)[r] van den Berg (2006)[a] Storr et al (2006)[p] Rampello et al (2007)[a]
Garrett and Coote (2009)	Exercise in less disabled MS	Oken et al (2004)[a] Schulz et al (2004)[a] Romberg et al (2004)[a r c] Romberg et al (2005)[a r c] White et al (2004)[r] Gutierrez et al (2005)[r] Kileff and Ashburn (2005)[a] van den Berg (2006)[r]	Taylor et al (2006) [r] Bjarnadottir et al (2007)[p c] Newman et al (2007)[a] Rampello et al (2007)[a] McCullagh et al (2008)[a] Ayan Perez et al (2007)[r]
Hogan and Coote (2009)	Therapeutic interventions in more disabled MS	Harvey et al (1999)[r] Rodgers et al (1999)[a] Mostert and Kesselring (2002)[a] Debolt and McCubbin (2004)[r]	Oken et al (2004)[a] van den Berg (2006)[a] Rasova et al (2006)[p a c]
Snook and Motl (2009)	Exercise on walking in MS	Petajan et al (1996)[p a] Rodgers et al (1999) [a] Debolt and McCubbin (2004)[r] Freeman and Allison (2004)[p] Oken et al (2004)[a] Romberg et al (2004)[a r] Schulz et al (2004)[a] White et al (2004)[r] Gutierrez et al (2005)[r]	Kileff and Ashburn (2005)[a] Romberg et al (2005)[a r] van den Berg (2006)[a] Rasova et al (2006)[a] Taylor et al (2006) [r] Ayan Perez et al (2007)[r] Bjarnadottir et al (2007)[p] Newman et al (2007)[a] Rampello et al (2007)[a]

Author	Short aim	Reviewed studies	
Andreasen et al (2011)	Exercise on fatigue in MS	Petajan et al (1996)[p a] Mostert and Kesselring (2002)[a] Oken et al (2004)[a] Schulz et al (2004)[a] White et al (2004)[r] Gutierrez et al (2005)[r] Kileff and Ashburn (2005)[a] Dodd et al*(2006)[r] van den Berg et al (2006)[a] Rasova et al (2006)[a]	Newman et al (2007)[a] Rampello et al (2007)[a] Fragoso et al (2008)[a r c] McCullagh et al (2008)[a r c] Geddes et al (2009)[a] Plow et al*(2009b)[a r c] Smith et al*(2009)[a r c] Cakt et al (2010)[c] Dalgas et al (2010)[r]
Dalgas et al (2011)	Disease modifying potential of exercise	Petajan et al (1996)[p a] Rodgers et al (1999)[a] White et al (2004)[r] Romberg et al (2004)[a r c] Romberg et al (2005)[a r c]	Kileff and Ashburn (2005)[a] van den Berg et al (2006)[a] Bjarnadottir et al (2007)[p] Dalgas et al (2009)[r] Pilutti et al (2011)[a]

*Qualitative studies [a]aerobic/endurance exercise, [c]combined exercise, [p]physiotherapy [r]resistance exercise [p]physiotherapy intervention, as described by the authors of the review. Please note, due to exclusion of studies as explained in Section 2.3.2 not all studies included in the reviews appear in the above table.

2.4 Therapeutic exercise programmes in MS

The following sections will attempt to place in context the trials pertaining to the studies contained within this thesis, and not replicate the works of previous reviewers. The interested reader is directed to the reviews in the preceding section for greater detail.

Studies involving therapeutic exercise will be discussed in relation to aerobic exercise, resistance exercise and combined exercise (which involves aerobic exercise, resistance exercise and/or another form of exercise). A discussion will then follow on the qualitative literature surrounding therapeutic exercise in MS.

The following literature review discusses many studies; within this, a variety of different outcome measures were used for assessment. Table 2.4 provides a summary of the discussed outcome measures, and a reference to where further information can be found. As can be seen in Table 2.4 physiological, functional and psychological status of participants have been measured in different assessments in past MS therapeutic exercise studies.

Table 2.4 Outcome measures used in the relevant studies.

Outcome Measure (Abbreviation)	Primary outcome assessed	Relevant citation
10-metre Walk Test (10MWT)	Mobility	Collen et al (1991)
3-minute Step Test (3MWT)	Mobility	White et al (2004)
500m Walk Test (500MWT)	Mobility	Schwid et al (1999)
Dynamic Gait Index (DGI)	Mobility	Shumway-Cook and Woolacott (1995)
Multiple Sclerosis Walking Scale (MSWS)	Mobility	Hobart et al (2003)
Rivermead Mobility Index (RMI)	Mobility	Collen et al (1991)
Six-minute Walking test (6MWT)	Mobility	Butland et al (1982)
Timed 25 Foot Walk Test (T25FW)	Mobility	Kalkers et al (2008)
Timed Up and Go (TUG)	Mobility	Podsiadlo and Richardson (1991)
Two-minute Walking Test (2MWT)	Mobility	Butland et al (1982)
Activities-specific Balance Confidence (ABC)	Balance	Powell and Myers (1995)
Berg Balance Scale (BBS)	Balance	Berg (1989)
Dizziness Handicap Inventory (DHI)	Balance	Jacobson and Newman (1990)
Equiscale	Balance	Tesio et al (1997)
Falls Efficacy Scale (FES)	Balance	Yardley et al (2005)
BAECKE Activity Questionnaire (BAQ)	Physical activity	Baecke et al (1982)
PhoneFITT (PF)	Physical activity	Gill et al (2008)
Chalder's Fatigue Scale (CFS)	Fatigue	Chalder et al (1993)
Fatigue Impact Scale (FIS)	Fatigue	Schwartz (1993)
Fatigue Severity Scale (FSS)	Fatigue	Krupp (1988)
Modified Fatigue Impact Scale (MFIS)	Fatigue	Tellez et al (2005)
Multidimensional Fatigue Inventory (MFI)	Fatigue	Smets et al (1995)
Beck Depression Inventory (BDI)	Mood/depression	Beck et al (1961)
Centre of Epidemiological Studies Depression Scale (CES-D)	Mood/depression	Hann et al (1999)
Coopersmith Self-Esteem Inventory (CSEI)	Mood/self-esteem	Coopersmith (1989) cited in Navipour et al (2006)
Hospital Anxiety and Depression Scale (HADS)	Mood/anxiety and depression	Zigmond and Snaith (1983)
Major Depression Inventory (MDI)	Mood/depression	Olsen et al (2003)
Multiple Sclerosis Self-Efficacy-Scale (MSSES)	Mood/self-efficacy	Rigby et al (2003)
Profile of Mood States (POMS)	Mood	Oken et al (2004)
State-trait Anxiety Inventory (SAI)	Mood/anxiety	Spielberger et al (1970)

Outcome Measure (Abbreviation)	Primary outcome assessed	Relevant citation
Functional Assessment of MS (FAMS)	Quality of Life	Cella et al (1996)
Hamburg Quality of Life questionnaire (HQOL)	Quality of Life	Gold et al (2001)
Leeds Multiple Sclerosis Quality of Life scale (LMSQOL)	Quality of Life	Ford et al (2001)
Multiple Sclerosis Quality of Life 54 (MSQOL)	Quality of Life	Morris (2000)
Short-Form 36 Health Questionnaire (SF-36)	Quality of Life	Ware Jr and Sherbourne (1992)
Sickness Impact Profile (SIP)	Quality of Life	Bergner et al (1981)
World Health Organization Quality of Life-Bref (WHOQOL)	Quality of Life	Skevington et al (2004)
Goal Attainment Scale (GAS)	Goal attainment	Kiresuk and Sjherman (1968)
Barthel Index (BI)	Disability	Morris (2000)
Environmental Status Scale (ESS)	Disability	Morris (2000)
Expanded Disability Status Scale	Disability	Kurtze (1983)
Functional Independence Measure (FIM)	Disability	Keith et al (1987)
Guy's Neurological Disability Scale (GNDS)	Disability	Sharrack and Hughes (1999)
Multiple Sclerosis Functional Composite (MSFC)	Disability	Cutter et al (1999)
Mini Mental Status Examination (MMSE)	Cognition	Folstein et al (1975)
Multiple Sclerosis Spasticity Scale – 88 (MSSS)	Spasticity	Hobart et al (2006)
Borg's Rating of Perceived Exertion Scale (RPE)	Exercise capacity	Borg (1982)
Modified Ashworth Scale (MAS)	Spasticity	Bohannon and Smith (1987)
Multiple Sclerosis Impact Scale (MSIS)	Physiological and psychological impact of	Hobart et al (2001)
Multiple Sclerosis Related Symptom checklist (MSRS)	Disease symptoms	Gulick (1989)
Physiological Cost Index (PCI)	Energy use	Bailey and Ratcliffe (1995)

A discussion follows on therapeutic exercise programmes in MS; aerobic exercise, resistance exercise and combined exercise. Due to the large volume of literature in this area a summary of the general literature will be made with depth of detail provided in Table 2.5-Table 2.7. However for those studies with similar methodology to the intervention in this thesis, primarily a combined-exercise class for those with MS, a greater discussion will be undertaken. The RCTs included were compared against the PEDro criteria (Section 2.3.3) for trial quality and their scores, along with other key information and notable limitations of each study are displayed in Table 2.5-2.8.

2.4.1 Aerobic exercise

A focus on studies involving aerobic exercise follows, first, a short explanation of aerobic exercise and aerobic capacity.

Aerobic exercise is used to increase aerobic capacity and aerobic endurance. With aerobic exercise being; any activity that uses large muscle groups, which is maintained continuously and is rhythmical in nature, designed to overload the cardiorespiratory system (Pollock et al 1998). Aerobic capacity describes the functional ability of the cardiorespiratory system to circulate blood around the body, with maximal oxygen consumption, resting heart rate and blood pressure all indicators of aerobic capacity (Katch et al 2001), whilst aerobic endurance; the ability to maintain a continuous rhythmical activity, can be monitored with continuous activities (Dalgas et al 2009), such as walking tests.

Reduced aerobic capacity and reduced aerobic endurance are not clinical features of MS, however may result as secondary symptoms, with reduced aerobic capacity and endurance commonly found in the MS population (Dalgas et al 2009). Thus, strategies designed to improve aerobic capacity and aerobic endurance , such as aerobic exercise are important in MS management. Many studies have looked at the effect of aerobic exercise in MS. These will be briefly summarised, highlighting potential gaps in the literature, with more detail available in Table 2.5. Interventions which utilise mainly aerobic based exercise are the most common in the MS therapeutic exercise literature; they have found that this type of exercise intervention may improve participants' mobility, endurance and aerobic capacity, with fatigue and disability status also showing improvement.

Disability level is not always reported by authors however the majority of studies include participants of milder disability levels (EDSS<4). With some studies stating that they included participants with an EDSS higher than 4, however they did not recruit many participants at this disability level. Two small studies (n=8) (Kileff and Ashburn 2005; Geddes et al 2009) included participants up to EDSS level 6. Another study, which utilised body weight supported treadmill training in six people with MS, recruited participants with a mean EDSS of 6.9 (Pilutti et al 2011). These small trials indicated aerobic training is feasible in those with more disability, however overall the available results are only applicable to those with milder disease, with further, larger studies required in more disabled groups. Interestingly some studies have stratified their results based on disability level, finding that those less disabled have either a better baseline exercise/fitness capacity (Schapiro et al 1988) or an improved exercise capacity, following an aerobic exercise intervention, more so than more disabled study participants (Ponichtera-Mulcare et al 1997).

The majority of studies utilised a static cycle to achieve an aerobic effect in their participants. However other studies have utilised treadmill training (O'Connell et al 2003; van den Berg et al

2006; Pilutti et al 2011), home walking (Geddes et al 2009) or other forms of achieving aerobic exercise, such as an elliptical trainer. There is no evidence to suggest that one aerobic exercise modality is better than another to achieve improvements in MS; however there is no study which compares different aerobic modalities. In the only known aerobic exercise study to be undertaken within a community leisure centre Collett et al (2011) compared different intensities of static cycling in 55 people with MS over 12 weeks. Like other studies the intervention improved mobility compared with baseline results, yet there was no difference found in mobility, strength, quality of life or fatigue between the different intensities of aerobic exercise.

In general, outcome measures and assessments have been taken before and after the intervention, but, as the length of interventions varied from between 4 and 24 weeks, and was delivered one to three times per week, it is difficult to establish the optimal length of intervention to elicit symptom change, with no length of time showing any clear benefit over another.

A small number of studies took measurements at different time points throughout their interventions (Ponichtera-Mulcare et al 1997; Collett et al 2011) but they failed to show any significant changes over time. It may be important to know the optimal number of weeks of training participants would undertake before expecting to see symptom improvements, highlighting a need for further work in this area to better inform the participant and clinician.

Few studies carried out a follow-up, by re-assessing their participants a set period of time after the end of the intervention. However of those that did, symptoms which had shown improvement immediately following the intervention such as walking speed, fatigue levels, exercise capacity and quality of life remained improved at follow-up compared with before the intervention (McCullagh et al 2008; Collett et al 2011). Whilst other improvements such as functional mobility showed decline without the intervention (Collett et al 2011). However, with minimal data on the carry over effect of therapeutic exercise, there is a need for further work reporting on participants' symptoms following completion of an intervention. Establishing the longer term effect of therapeutic exercise is important, particularly as the optimal goal for any therapeutic exercise programme is to improve the health of those with MS and avoid decline of their symptoms and health status long-term, making it beneficial to ascertain the follow-up effects of an aerobic intervention.

In general the interventions were delivered either 2 or 3 times per week, with each session lasting around an hour, which is similar to current exercise guidelines of five 30 minute sessions of aerobic exercise per week (Durstine and Moore 2003). There is no evidence to suggest this is an optimal time for delivering aerobic exercise in MS.

Most exercise interventions have been carried out on an individual basis, supervised by either physiotherapists or exercise professionals. This however may not be the optimal mode of delivery,

particularly in the current healthcare climate, where budgets often drive service provision. Group exercise interventions are another logical option, which may be less costly than individual personal sessions. A group intervention, was carried out by McCullagh et al (2008) who employed a randomised control methodology to investigate the effect of 12 weeks of twice weekly 30 minute aerobic circuit exercises (10 minutes of each of four aerobic machines), these were performed in classes of 4-6 people, led by one physiotherapist. In O'Connell et al's (2003) small randomised control study the aerobic circuit classes were completed in groups, although it is unclear either how many participants were in each group or the level of supervision. There are benefits to both individual and group exercise (particularly regarding level of supervision), however there is a need to establish whether group aerobic exercise is feasible in people with MS, across different disability ranges.

Aerobic intervention studies have taken place in a variety of different venues, from hospital gyms, leisure centres to clinical research laboratories. There is no indication as to whether one is more beneficial than another, and these may be chosen based on the methodology and ease of access. However the work undertaken by Collett et al (2011) has shown aerobic exercise interventions for those with MS can be undertaken in a community leisure setting.

Many different outcome measures have been used across the studies making comparison and review of findings difficult. Mobility, endurance and aerobic capacity have been assessed most frequently in aerobic exercise studies. With the majority of studies finding improvements in these areas, regardless of length of intervention or modality of exercise (treadmill, static cycling etc). Fatigue has often been assessed and although significant improvements have been seen in some studies (McCullagh et al 2008; Huisinga and Stergiou 2011), other studies have reported no change in fatigue (Petajan et al 1996; Schulz et al 2004). Equally, studies including outcome measures to assess disability status and quality of life have found that aerobic exercise may have a significant effect on improving disability (O'Connell et al 2003; Kileff and Ashburn 2005; 2011) and quality of life (Huisinga and Stergiou 2011), whilst Pilutti et al (2011) reported no change in disability with the intervention. Strength, range of movement, spasticity and mood have also been assessed in studies adopting an aerobic exercise methodology however there is little evidence to acknowledge that the intervention is beneficial in these areas. Balance, a common impairment in people with MS, was not assessed in any aerobic exercise study. Furthermore physical activity levels were only monitored in one study (Mostert and Kesselring 2002).

There have been few reported decline in symptoms related to aerobic exercise. However this may be due to reporting bias, whereby authors do not publish negative findings. In the study by Mostert and Kesselring (2002), two participants dropped out due to increased lower limb spasticity during the static cycling intervention. Whilst in Rodgers et al (1999) study the disability levels (as measured with the EDSS) declined in six of their 19 participants following a 24-week cycling

intervention, although overall the study had found non-significant improvements in disability levels, mobility and range of movement in the participants.

Of the studies that included a control group a decline in some symptoms has been noted in the control participants, although not evident in the intervention group; suggestive of the maintenance aspect of therapeutic interventions. Schulz et al (2004) found decline in their control group's mobility after eight weeks, whilst Ponichtera-Mulcare et al (1997) noted reduced exercise capacity in their control group over the 24 weeks of the study (however since only four participants acted as controls, compared with 19 in the intervention group, this is limited evidence). Related to longer term maintenance of symptoms the 12-week follow-up findings from Collett et al's (2011) study suggest many symptoms in MS may be preserved after an intervention, it may be important to highlight the symptom maintenance component of therapeutic exercise in light of the evidence from the above studies.

The quality of the literature in aerobic exercise varies, some studies taking an experimental approach, with no control group (Rodgers et al 1999; Kileff and Ashburn 2005; Newman et al 2007; Huisinga and Stergiou 2011; Pilutti et al 2011). In other studies, a control group was included however these were non-randomised control trials (Ponichtera-Mulcare et al 1997; Rasova et al 2006). Other trials adopted a randomised control design (Schapiro et al 1988; Petajan et al 1996; Mostert and Kesselring 2002; O'Connell et al 2003; Schulz et al 2004; Rampello et al 2007; McCullagh et al 2008; Geddes et al 2009; Collett et al 2011). In these studies the PEDro scores which can be used as a marker of quality vary from five to seven out of a possible eleven. Studies were marked down for not including blinding in their design, not concealing group allocation, not using intention to treat analysis, not including adequate follow-up or not having comparable baseline scores. The benefit of a RCT is that, fundamentally, the design minimises the risk of allocation bias (randomisation) whilst balancing for known prognostic factors, such as demographic details, which may impact on results (controlled) and by doing so more conclusive results emerge. Including a control group may also help balance for unknown prognostic factors (Moher et al 2010).

However, demographic details (e.g. age, gender, disability level) in many past aerobic exercise studies are not always explicitly stated, making comparison between studies difficult. There is also risk of bias in these studies, noted from the PEDro score reported in Table 2.5; generally researchers have been unable to achieve "blinding" of participants and therapists. Other sources of bias include not matching control and intervention groups (based on areas such as gender, age, time since disease onset and disability level), not providing follow-up data or not using intention to treat analysis, which would involve including results from all participants initially recruited into the study (Hollis and Campbell 1999). These are areas which good methodology should aim to overcome.

Aerobic training has been assessed in a number of MS therapeutic exercise studies, where in general it offers benefits to those taking part in the exercise programme with improvements primarily in mobility and exercise capacity. However there is a need for further research in this area particularly regarding;

- Evaluating the effect of aerobic exercise in a more disabled population
- Establishing the feasibility of different exercise modalities to achieve an aerobic training effect
- Establishing the optimal length of time of exercise intervention for change to be seen
- Establishing the optimal frequency of sessions
- Establishing whether a group class delivery is feasible and effective (and what is the optimal modality/equipment to use)
- Standardisation of outcome measures, to allow comparison across studies
    - Utilising outcomes to assess the impact of the intervention on balance and physical activity levels.
- Improved methodology to reduce the risk of bias.
- Undertaking follow-up assessment, a period of time after the intervention, to ascertain the longer term effect of interventions.
- Determining if the venue, where the intervention takes place, or the profession of the exercise instructor is influential on results.

Table 2.5 Aerobic exercise intervention studies

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Lead author, publication date *Country* *Type of study (PEDro score where relevant)* *Follow-up (if included)*	*Number of participants (in each group, where relevant)* *EDSS – Disability score* *Type – MS Diagnosis* *Sex – number of each* *Age – of participants* *Years diagnosed – years since diagnosis with MS* *Completed study – how many participants completed study (reasons for drop out if known)*	*Form of training* *Frequency and time of training* *Venue –where the intervention took place* *Trained – whether participant trained individually or as part of a group* *Led by – Profession of the supervising researcher*	*Outcome measures used (please refer to Table 2.4)*	*The main findings*	*Where appropriate critique was based on;* *Potential areas of bias indicated by PEDro scores.(RCT only)* *Study size, sample description, intervention description and follow-up*
Collett et al 2011 UK RCT (PEDro 7/11) 12 week follow-up.	55 MS participants (20 continuous, 18 intermittent, 17 combined) EDSS - Unclear Type - All Sex F/M – 16/39 Age mean 52 Years diagnosed mean– 13 Completed study – 45 (due to variety of reasons)	Cycling Comparison of continuous, intermittent and combined aerobic cycling. 12 weeks, twice weekly, 20 minute sessions Venue – Community leisure centres Trained – Individually Led by – Exercise professionals	2MWT TUG BI SF 36 FSS MVC quadriceps	Significant increase in 2MWT and non significant improved MVC of quadriceps after 6 weeks. Non-significant improved MVC of quadriceps between weeks 6-12. At follow-up 2MW returned toward baseline scores No clear difference between groups	No; Concealed group allocation Subject blinding Therapist blinding Assessor blinding Follow-up (PEDro requires this to be in 85% of participants)

Geddes et al 2009 USA RCT (PEDro 5/11)	12 MS participants (8 home exercise, 4 control) EDSS range– ≤6 (unclear) Type – All Sex F/M – All F Age range (mean) – 22-64 (95) Years diagnosed – Unclear Completed study – Unclear All	Home walking programme 12 week, thrice weekly for 30 minutes (Intensity 60-80% maximum HR) Venue – Home Trained - Individually Led by – Self-managed	FSS 6MWT PCI	Non-significant improvement in 6MWT and PCI in intervention group	No; Concealed group allocation Subject blinding Therapist blinding Assessor blinding Intention to treat Follow-up
Kileff and Ashburn 2005 UK Experimental	8 MS participants EDSS range 4-6 Type – Unclear Sex F/M – All F Age range (mean) – 33-61 (45) Years diagnosed; range (mean) – Unclear Completed study – Unclear (one dropped out due to knee injury, one due to relapse – unclear if data used)	Cycling 12 week twice weekly 30 minute session Venue - Hospital gym Trained – Individually Led by – Physiotherapist	10MWT 6MWT Functional reach MSRS GNDS FSS MAS	Significant improvement in 6MWT and GNDS. Non significant improvement in FSS and 10MWT	Small sample size Unclear demographic data No follow-up
Huisinga et al 2011 USA Experimental	26 MS participants EDSS mean - 2.7 Type – Unclear Sex F/M – 21/5 Age mean –45.5 Years diagnosed – Unclear Completed study – All	Elliptical trainer. 6 week on 15 occasions, 30minute sessions Venue – University sports facility Trained - Unclear Led by - Unclear	FSS MFIS SF 36 TUG	Significantly improved FSS and SF36 Improved TUG, not analysed for significance	No follow-up Unclear intervention description

McCullagh et al 2008 Ireland RCT (PEDro 5/11) 12 week follow-up	30 MS participants (17 intervention, 13 controls) EDSS – Unclear Type – RR & SP Sex F/M – 24/6 Age mean – 36 Years diagnosed mean – 5 Completed study – 24 (due to symptom relapse, class times, pregnancy, moving home and other personal reasons)	Choice of 10min x 4 of various exercises 12 weeks twice weekly (plus once at home) Venue - Hospital gym Trained – In groups (n=4-6) Led- Physiotherapist	MFIS MSIS FAMS Graded Exercise Test	Significant improvements in MFIS, FAMS, Graded Exercise Test at 3 months. MFIS and FAMS remained improved at 6 month follow-up Adherence to home sessions found poor	No; Subject blinding Therapist blinding Assessor blinding Intention to treat Concealed group allocation Follow-up
Mostert and Kesselring 2002 Switzerland RCT (PEDro 4/11)	59 participants 26 MS participants (13 intervention, 13 controls) EDSS range– 2.5 – 3.5 Type – Majority RR Sex F/M – 21/5 Age mean – 45 Years diagnosed mean - 11 Completed study – 26 (two dropout s due to increased spasticity, two due to symptom relapse, three due to poor motivation) 26 non MS controls (13 intervention, 13 controls) Sex F/M – 21/5 Age range (mean) – (43) Completed study –All	Aerobic Cycling 3-4 weeks of 5 sessions per week 30 minute sessions Venue- Unclear Trained – Unclear Led by - Unclear	Maximum aerobic capacity SF36 BAQ FSS MAS Spirometry-FVC & FEV1	Non-significant improvement in aerobic capacity, BAQ and SF36 in MS intervention group. MS participants were less active, had reduced aerobic capacity, perceived quality of life and higher fatigue compared with non MS controls.	No; Subject blinding Therapist blinding Assessor blinding Concealed group allocation Intention to treat follow-up between group comparison Unclear intervention

Newman et al 2007 UK Experimental	19 MS participants EDSS – Unclear Type – Unclear Sex F/M – 13/3 Age range (mean) – 30-65 (54) Years diagnosed; range (mean) – 7-37 (16) Completed study -16 (unclear why)	Treadmill training 4 weeks thrice weekly, 30 minute sessions Venue - Hospital gym Trained – Individually Led by – Physiotherapist or assistant	Peak oxygen consumption Temporal spatial gait parameters 10MWT 2MWT FSS	Non-significant improved VO2 max, gait parameter. Trend toward improved fatigue	Small sample size No follow-up
O'Connell et al 2003 Ireland RCT (Abstract only)	11 MS participants (Intervention – 5 Control – 6) EDSS range – 0-3 Type - RR Sex F/M - Unclear Age - Unclear Years diagnosed – Unclear Completed study - All	Circuit style classes 12 week, twice weekly, 60 minute sessions (plus one independent session) Venue – Unclear Trained – In groups (unclear numbers) and Individually Led - Unclear	Graded Exercise Test 50 metre walk MSIS FAMS	Significantly improved Graded Exercise Test and FAMS.	Small study No follow-up Unclear demographic data Unclear intervention
Petajan et al 1996 USA RCT (PEDro 5/11) Measurements at Week 5, 10 & 15.	46 MS participants (21 intervention, 25 control) EDSS mean – 3.4 Type – Unclear Sex F/M – 31/15 Age range mean – 40 Years diagnosed mean – 11 Completed study – All	Graded cycle 15 weeks thrice weekly for 30 minutes Venue – Unclear Trained - Individually Led by - Unclear	POMS SIP FSS Graded Exercise test	Significantly improved Graded Exercise test at week 5, 10 and 15.	No; Subject blinding Therapist blinding Assessor blinding Intention to treat Concealed group allocation Intention to treat No follow-up Unclear demographic data

Pilutti et al 2011 Canada Experimental	6 MS participants EDSS mean – 6.9 Type – progressive Sex F/M – 4/2 Age mean – 48.2 Years diagnosed mean – 11.5 Completed study – All	Body weight assisted treadmill walking 12 weeks, thrice weekly 30 minute sessions Venue – Rehabilitation centre Trained – University laborarory Led by – Exercise scientists	EDSS MSFC MSQOL MFIS Treadmill walking speed Required body weight support	Significantly improved walking speed, required body weight support and MSQOL. Non significant improvements in MFIS.	Small study No Follow-up
Ponichtera-Mulcare et al 1997 USA CT Measurements at 15 weeks and 24 weeks	23 MS participants (9 intervention, 4 controls) EDSS mean- 2.44 (stratified into EDSS <3.5 and EDSS>3.5) Type – Unclear Sex F/M – 15/8 Age range (mean) – 31-68 (43) Years diagnosed;– Unclear Completed study -All	Cycling 24 week thrice weekly 30 minute sessions Venue - Clinical research facility Trained - Unclear Led by - Unclear	Graded Exercise test VO_2 max	Non-significant improvements in Graded Exercise Test More so in more ambulatory individuals, not assessed for significance Decline in Graded exercise noted in control group	Unclear demographic data Unclear intervention No Follow-up
Rampello et al 2007 Italy Crossover RCT (PEDro 6/11)	19 MS participants EDSS mean – 3.5 Type – Unclear Sex F/M - Unclear Age range - Unclear Years diagnosed mean - 6 Completed study – 11 (symptom relapse, not adhering to protocol)	Aerobic Cycle (+stretching) Neurorehabilitation Trunk movements, gait re-training and breathing techniques) 8 weeks thrice weekly 1 hour Venue – Unclear Trained - Individually Led by - Unclear	MFIS MSQOL Lung capacity -Forced expiratory volume (FEV1) -Vital capacity (VC) FEV1/VC ratio 6MWT	Significantly improved 6MWT, non-significantly improved MSQOL and MFIS following aerobic exercise intervention. Both interventions improved lung capacity.	No; Subject blinding Therapist blinding Assessor blinding Concealed group allocation Intention to treat Follow-up Unclear intervention

Rasova et al 2006 USA CT	112 MS participants 36 aerobic training 24 neurophysiotherapy 19 combined (aerobic and neurophysiotherapy) 16 controls EDSS mean – 2.7 Type – unclear Sex F/M - Unclear Age range - Unclear Years diagnosed;– Unclear Completed study – Unclear	Aerobic Cycling Neurophysiotherapy Sensory/motor learning/facilitation 8 weeks of twice weekly 60 minute (neurophysiotherapy) or 30 minute (aerobic) sessions Venue - Hospital gym Trained – Individually Led by - Physiotherapist	EDSS BI ESS MSQOL MFIS BDI Spirometry parameters on/off a bicycle ergometer.	Non-significant improvements in fatigue, depression and spirometry parameters in all intervention groups (more so in aerobic group) EDSS improved in both groups receiving physiotherapy	Unclear demographic data No follow-up
Rodgers et al 1999 Ohio Experimental	18 MS participants EDSS mean- 3.6 Type – Unclear Sex F/M – 14/4 Age range (mean) – (43) Years diagnosed– Unclear Completed study - All	Aerobic Cycling 24 week thrice weekly 30 minute sessions Venue - Clinical research facility Trained - Individual Led by - Unclear	Gait analysis -Ground reaction force Lower limb passive range of movement EDSS	Non-significant improved disability level (overall sample) aerobic capacity, hip movement and gait parameters. 6 subjects demonstrated decline in disability level.	Unclear demographic data Unclear intervention No Follow-up
Schulz et al 2004 Germany RCT (PEDro 6/11)	39 MS participants (23 intervention 16 control) EDSS mean – 2.3 Type – unclear Sex F/M – 29/10 Age mean – 41 Years since onset mean – 11.4 Completed study - All	Aerobic Cycling 8 week twice weekly 30 minute sessions Venue - Clinical lab Trained – Individually Led by - Unclear	POMS HADS HQOL MFIS Co-ordination tests -3m plank walk -Figure 8 walk -Static balance Biological/immunological parameters assessed will not be discussed.	Non-significant improved aerobic capacity in both groups. Significant decline in co-ordination in control group.	No; Subject blinding Therapist blinding Assessor blinding Concealed group allocation Intention to treat Follow-up (after the 8 week intervention)

Schapiro et al 1988 Colorado, USA RCT (PEDro 6/11)	50 MS participants (25 intervention, 25 controls) EDSS mean -3.6 Low EDSS ≤3.5, n=32 High EDSS 4-6.5, n=28 Type – Unclear Sex F/M – 27/23 Age range (mean) – 27-62 (47) Years diagnosed; range (mean) – 0-28 (6) Completed study – 91 (Unclear why)	Aerobic Cycling plus health lecture 16 week, 4-5 days per week Venue – Unclear Trained – Individual Led by – Self-managed	Aerobic capacity test	Non-significant improved fitness test. Lower disability group greater fitness capacity	No; Subject blinding Therapist blinding Concealed group allocation Comparable baseline Intention to treat Follow-up (after the 16 week intervention) Unclear demographic data Unclear intervention

EDSS – Expanded Disability Status Scale, F-Female, M – Male, RR – Relapsing-remitting, SP – Secondary Progressive, Outcome measure abbreviations available in Table 2.4.

2.4.2 Resistance exercise

Similar to the previous section on aerobic exercise (Section 2.4.1), a focus on studies involving resistance training will be made. First however an explanation of the mechanisms underlying muscle strengthening follows.

Resistance training is used to improve strength; which is defined as the greatest amount of force a muscle can generate in a single maximum voluntary contraction (MVC) (Lamb D.R. 1984). Strength gains are initially due to adaptations in the CNS; within the CNS the motor unit is comprised of the neuron, originating in the spinal cord, and the muscle fibers which the neuron supplies.

With resistance training, the adaptations to the CNS lead to improved synchronisation of the motor unit, allowing more muscle fibers to be recruited to generate more strength. Following this, hypertrophy (an anatomical increase in muscle fiber size) will occur. In a healthy population, this may occur after a minimum of six weeks of training (Broughton 2011), but there is no clear timeframe (Kraemer et al 2002). It is important that resistance training should be progressed safely at different stages of training to elicit continued improvement; indeed most resistance training studies in this literature review adopt a progressive resistance training model.

Muscle weakness is a common problem in MS and a growing number of studies have included resistance exercises as the main component under investigation. These will be summarised, highlighting potential gaps in the literature, with more detail available in Table 2.6. Results varied across the studies, hampered by many different outcome measures being used, however strength was most frequently assessed. Overall, resistance exercise studies in MS have found improvements in strength, mobility, fatigue, disability and quality of life.

In comparison to aerobic exercise studies fewer resistance exercise studies have included participants with an EDSS score of greater than 5 (Filipi et al 2010; Filipi et al 2011). Filipi et al (2011) stratified the findings from their 78 participants based on disability level. Those with low levels of disability (EDSS of 1-4.5) were able to train at a higher weight/resistance intensity compared to those more disabled. In addition those moderately (EDSS of 5-7) and severely disabled (EDSS >7.5) had similar upper body strength to one another at baseline. In a much smaller study (n=8), Kraft et al (1996) found those less disabled improved mobility more following the resistance exercise intervention, whilst those more severely affected improved their walking speed more. In general however studies have either not reported the disability level of their participants, based on EDSS level, or, only included those less severely affected. Thus, there is a need to establish the effect of resistance exercises across the disability range.

The form of achieving a resistance training effect varies throughout the literature, with many methodologies using resistance machines, some using body weight, and one study using resistance bands. From these no single form suggests particular benefits over the other however access to resistance machines may be limited for some people with MS due to either geographical location or physical ability. Thus, free weights or exercises which use body weight as the form of resistance may offer a more practical solution. The studies by Filipi et al (2010; 2011) used a range of resistance machines, free weights and body weights as part of circuit based programme. Unfortunately however the results are limited, being retrospective, whereby past exercise record-cards were consulted and based on only one outcome measure; strength improvement (Filipi et al 2011) or only based on preliminary data (Filipi et al 2010).

The length of interventions undertaken has been between 6 and 24 weeks, with most outcomes assessed at baseline and at the end of the intervention. General results suggest longer interventions result in more significant changes. For example studies of eight week duration; training at home seven days per week (Harvey et al 1999) or training twice weekly (White et al 2004; Gutierrez et al 2005) resulted in no strength changes. All other studies of a longer duration found gains in strength. However a shorter six week (thrice weekly session) intervention resulted in significant strength gains, albeit using less conventional outcome measures (e.g. ball throwing and leg lifts). Few studies adopted a follow-up approach as part of their methodology. From those that did Dalgas et al (2010) found improvements in fatigue and quality of life were maintained 12 weeks after the intervention whilst Dodd et al (2011) found that improvements following their 10 week intervention were not maintained after 12 weeks. Although expected strength gains, based on time are available for a healthy population where strength gains can be seen in 6-8 weeks (Kraemer et al 2002), further research in this area may establish the effect of time on resistance training in MS. This is important, as the initial mechanism of strength changes occur as a result of neural adaptation, and as the neural system is already compromised in MS it is of interest whether strength changes occur in a similar way to non-MS populations.

Similar to aerobic exercise studies the frequency of resistance exercise sessions in previous studies is either 2 or 3 sessions per week, with some studies following the ACSM's guidelines on progressive resistance training, whereby initially low loads, higher repetitions are progressed to higher loads lower repetitions (Kraemer et al 2002). However no studies have compared intervention frequency, which may be worthwhile.

Supervision during the exercise is not always reported, however it has mainly been by either exercise professionals or physiotherapists. There are examples of interventions which have utilised a group class format successfully, although in all but one of these studies class sizes have not exceeded 3 or 4 participants. In Broekmans et al (2011), Dalgas et al (2009; 2010) and Taylor et al's (2006) studies, groups of three people with MS trained together. More recently Dodd et al

(2011) carried out resistance training classes with up to 12 participants supervised by up to three trainers (physiotherapists and registered personal exercise trainers). Participants in these studies, in general, had low to mild disabilities, although the specific EDSS level was unreported in two of the studies (Taylor et al 2006; Dodd et al 2011). However the description given would indicate an EDSS of less than 5. Thus it is unknown whether a group/class format is feasible in a more disabled group of participants.

The venue of many of the studies has been hospital or university laboratories, however it is possible, and perhaps more conducive for long term continuation of the exercise programme to allow study participants to undertake exercise in a community leisure facility. Doing so also fits well with government guidelines which encourages community rehabilitation (Scottish Executive 2007). Taylor et al (2006) and Dodd et al (2011) have shown this is feasible by carrying out their interventions in community leisure centres.

Results varied across the studies, however strength improvement occurred in almost all studies which assessed strength, regardless of outcome measure, intervention duration, frequency of sessions or modality of exercise. Mobility has been assessed in several studies, with many showing improvement due to the intervention, although some have reported no change in mobility. Fatigue, disability level and quality of life have been assessed in some resistance exercise studies with the majority reporting improvements. Improvements in balance have been found in studies with an intervention of 12 weeks or greater, however as few studies assess balance it is inappropriate to draw any firm conclusions. No study could be found which assessed physical activity levels in their participants. It may be important that a consensus be agreed upon as to what outcomes are assessed to allow for the true impact of resistance exercise training to be established.

No studies reported any adverse effects from any resistance exercises, although in qualitative results, linked with Taylor et al's (2006) study, Dodd et al (2006) found that during the first few weeks of the 10-week programme participants experienced muscle soreness or fatigue. However there is a risk of authors not reporting on adverse event or negative outcomes.

The design and quality of all studies was mixed, one carried out a retrospective analysis as previously discussed (Filipi 2011). Several adopting an experimental methodology with no control group (Kasser and McCubbin 1996; Kraft et al 1996; Fisher et al 2000; White et al 2004; Gutierrez et al 2005; Taylor et al 2006; Ayan Perez et al 2007; Filipi et al 2010; Pryor et al 2011). Another study used a "within subjects" controlled design (de Souza-Teixeira et al 2009). The remainder adopted a RCT design (Harvey et al 1999; Debolt and McCubbin 2004; Dalgas et al 2009; Broekmans et al 2011; Dodd et al 2011; Hughes et al 2011). However, as with the aerobic studies there is a risk of bias with studies often not achieving assessor blinding and failing to use an

intention to treat paradigm when analysing results. For resistance studies PEDro scores ranged from six to nine out of a possible eleven.

As discussed resistance exercise training can result in improved strength, mobility, fatigue, disability and quality of life. However there is a need for further research in this area particularly regarding;

- Including participants across the disability range
- Establishing the optimal length of time for change to be seen
- Whether a group class delivery is feasible and effective
- Establishing the optimal frequency of sessions
- Standardisation of outcome measures, to allow comparison across studies
    - Utilising outcomes to assess the impact of the intervention on physical activity levels.
- Improved methodology to reduce the risk of bias.
- Undertaking follow-up to ascertain the longer term effect of interventions.
- Determining if the venue, where the intervention takes place or the profession of the exercise instructor is influential on results.

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Table 2.6 Resistance exercise intervention studies

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Ayan Perez 2007 Spain Experimental	22 MS participants EDSS – Unclear Type – Unclear Sex F/M - Unclear Age - Unclear Years diagnosed – Unclear Completed study – All	Body weight exercises 6 weeks thrice weekly 30 minutes Venue – Unclear Trained – Unclear Led by – Unclear	9m zigzag run, Clapping test Dynamic flexibility test Explosiveness of arms & legs, Trunk strength Flamingo balance test	Significant improvements in dynamic flexibility/trunk strength, trunk strength, eexplosiveness of arms & legs and 9m zigzag run.	Only Abstract available thus not PEDro rated. Further data available in Garrett and Coote (2009). Unclear intervention Unclear demographic data No follow-up
Broekmans et al (2011) Belgium RCT (PEDro 7/11)	36 MS participants (11 Resistance only, 11 Resistance + EMS, 14 Controls) EDSS mean– 4.3 Type - Sex F/M – 23/13 Age mean – 47.8 Years diagnosed – Unclear Completed study – 33 (Unclear why)	Resistance machines. 20 weeks, 5x 60min session/fortnight Assessed at baseline, week 10 week 20 measurements) Venue – Unclear Trained – In groups (n=3) Led by - Physiotherapist	MVC (knee extension/flexion) TUG T25FW 2MWT Functional Reach RMI	Significant MVC improvement in both resistance training groups compared with control groups. No difference between the two resistance groups.	No; Concealed allocation Subject blinding Therapist blinding Intention to treat Unclear intervention Unclear demographic data No follow-up
Dalgas et al, 2009; 2010 Denmark RCT (PEDro 7/11) 12 week follow-up	38 MS participants (19 intervention, 19 controls) EDSS mean – 3.8 Type – RR Sex F/M - 20/11 Age mean – 48.4 Years diagnosed mean– 7.35 Completed study – 31 (due to musculoskeletal problems, and other personal reasons)	Resistance machines 12 weeks (twice weekly) Venue –Unclear Trained – In groups (n=3) Led by - Unclear	Knee strength MVC leg press Handgrip Functional capacity 10MWT 6MWT FSS MDI SF-36	Significant improvements in knee extensor strength, functional capacity, FSS, MDI SF-36 Many improvements maintained at follow-up.	No; Subject blinding Therapist blinding Intention to treat Follow-up (PEDro requires this to be in 85% of participants) Unclear intervention

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
DeBolt and McCubbin 2004 USA RCT (PEDro 7/11)	36 MS participants (19 intervention, 17 controls) EDSS mean - 3.3 Type - All Sex F/M – 29/7 Age range (mean) – 36-57 (50) Years diagnosed; range (mean) – 1-40 (14.5) Completed study – 35 (symptom relapse)	Body weight exercises (2 weeks supervised then) 8 weeks thrice weekly 1 hour sessions Venue - Participants home Trained – Individual Led by - Self-managed	Static Balance Anteroposterior sway Mediolateral sway Sway velocity TUG Leg extensor power rig MAS	Significant increase in leg strength	No; Subject blinding Therapist blinding Assessor blinding Intention to treat No follow-up
Dodd et al 2011 Australia RCT (PEDro 9/11) 12 week follow-up	71 MS participants (36 intervention 35 control) EDSS – Unclear (mild to moderate walking disability) Type – RR Sex F/M – 52/19 Age mean -49.05 Years diagnosed – Unclear Completed study - All	Resistance machines 10 week twice weekly, 45 minute (plus 30 minute social cool down) sessions Control group; Usual care + 10 1 hour social sessions (e.g. massage, luncheons, educational sessions)	2MWT 1MVC lower body 50% if 1MVC for muscular endurance MFIS WHOQOL MSSS-88	Significant difference between groups for MVC, MFIS and WHOQOL at week 10 At 22 week follow-up No between group differences With all outcomes returning toward baseline	No; Subject blinding Therapist blinding Unclear demographic data
Filipi et al (2010) USA Experimental (Preliminary Data)	33 MS participants EDSS – 1-6.5 (mean) Type – All Sex F/M – 22/11 Age range (mean) – 24-54 (38.8) Years diagnosed – Unclear Completed study – All	Resistance machines, free weights & body weight 6 months, twice weekly, 50 minutes Venue – Unclear Trained - Individually Led by – Exercise trainers	MFIS MFES (Modified Fall Efficacy Scale) BBS TUG MSFC Neurocom Balance Master Gait analysis with Force plate Outcomes at BL, 3 months, 6 months	Non-significant improved MSFC, MFES and muscular power generation with gait analysis.	Only preliminary data reported Unclear demographic data No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Filipi et al (2011) USA Retrospective analysis	67 MS participants EDSS range – 1-8 Low disability; EDSS 1-4.5, n=27, Mild-moderate disability; EDSS 5-7,n=23, EDSS≥7.5, n=17 Type – All Sex F/M – 49/18 Age range (mean) – 24-75 (49.5) (Years diagnosed; range (mean)1-45 Unclear Completed study – All	Resistance machines Progress resistance to address balance and muscle strength (whole body approach) Resistance machines and free weights included (+ balance) 24 week, twice weekly, 50 minutes sessions Instructed by exercise trainers 3:1 subject to trainer ratio. Protocol reviewed by physical therapists for safety Venue – University sports facility Trained - Individually Led by – Exercise trainers	Retrospective analysis of training records during resistance exercise programme. Strength MVC of the following; Leg curls Back rows Leg extensions Lat' pull downs Shoulder Press Chest Press Triceps ext Arm curls Abs crunch Back extension Shoulder raises Wrist curls	Significantly improved MVC on all exercises except Abs crunch. Lower disability group could train at a higher weight intensity. Upper limb strength similar in mild-moderate and more severe group.	No follow-up
Fisher et al (2000) (Abstract only) USA Experimental	16 MS participants EDSS – <6.5 Type – Unclear Sex F/M - Unclear Age range – Unclear Years diagnosed –Unclear Completed study – Unclear	Resistance (unclear details on intensity/progress) 16 week, thrice weekly 60 minute sessions Venue –Unclear Trained – Unclear Led by - Unclear	Muscle strength and power (outcome measures unclear)	Reported improvements in upper and lower limb strength (unclear)	Only Abstract available Unclear demographic data Unclear intervention No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Gutierrez et al 2005 USA Experimental	8 MS participants EDSS mean – 3.7 (self reported) Type – RR Sex F/M – 7/1 Age range (mean) – 25-55 (46) Years diagnosed – Unclear Completed study -All	Resistance machines 8 weeks twice weekly 30 minute sessions Venue - Biomechanics laboratory Trained - Unclear Led by – Exercise professionals	Gait parameters: Knee & ankle muscle strength test 3-minute step test MFIS Self assessed EDSS	Significant improvement in some gait parameters, knee extension strength, MFIS and self-reported EDSS Non-significant improvement in 3-minute step test.	Small sample size Unclear demographic data Unclear intervention No follow-up
Harvey et al 1999 UK RCT (PEDro 7/11)	19 MS participants (6 resistance intervention 6 mobility intervention 5 controls) EDSS – Unclear Type – Unclear Sex F/M – 14/3 Age range (mean) – 36-55 (47) Years diagnosed; range (mean) – 1-15 (7) Completed study – 17 (one dropout due to longstanding back pain, one due to symptom relapse)	Free weights General Mobility Individual programme of stretching, balance, mobility, swimming, cycle sessions 8 weeks of daily exercises Venue - Participants home Trained - Individually Led by – Self-managed	50m timed walk 10MWT Electromyography of quadriceps MVC of quadriceps Timed transfer	Non-significant improved transfer in both intervention groups.	No; Subject blinding Therapist blinding Assessor blinding Intention to treat Unclear demographic data Unclear intervention No follow-up
Hayes et al 2011 USA RCT (PEDro 6/11)	20 MS participants (10 resistance + standard exercise, 10 standard exercise only.) EDSS - mean 5.2 Type – Unclear Sex F/M – 11/8 Age mean – 49 Years diagnosed mean 12 Completed study – 19 (symptom relapse)	Eccentric resistance based work Leg resistance using custom built eccentric ergometer (seated stepper) Standard exercise included aerobic training, stretching and balance exercises. 12 weeks of thrice weekly <60 minute sessions Venue – Unclear Trained – Unclear Led by – Unclear	MVC of 5 lower limb muscles TUG 10MWT 6MWT Stair ascent (SA) Stair descent (SD) BBS FSS (BMI)	Standard exercise only group improved in SA, SD and BBS. No significant differences between groups or over time for other outcomes Overall strength greater in resistance group after 12 weeks	No; Concealed allocation Subject blinding Therapist blinding Assessor blinding Intention to treat Unclear intervention No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Hughes et al 2011 Ireland RCT (Abstract only)	37 MS participants EDSS – Unclear Type – Unclear Sex F/M – Age range (mean) – Unclear Years diagnosed; range (mean) – Unclear Completed study – 25 (unclear why)	Resistance body exercise (squats, calf raises, step-ups, side steps, sitting knee extension) 12 weeks of lower limb strengthening exercises (Intervention group also wore EMS) Venue – Home Trained – Individually Led by – Self-managed	BBS MSWS MSIS	Improvements in all outcome measures across all participants after 12 weeks No significant differences between groups or over time for other outcomes	Only Abstract available thus not PEDro rated. Unclear demographic data No follow-up
Kasser and McCubbin 1996 Cited in Dalgas et al 2008 Experimental	8 MS participants EDSS – Unclear Type – Majority RR Sex F/M – Unclear Age range (mean) – Unclear Years diagnosed; range (mean) – Unclear Completed study – Unclear	Unclear form Whole body approach 10 week, twice weekly Venue - Unclear Trained - Unclear Led by – Unclear	MVC	Non-significant improvements in leg, elbow and shoulder MVC	Only Abstract available Small sample Unclear demographic data Unclear intervention No follow-up
Kraft et al 1996; Kraft et al 1996a (Abstract only) USA Experimental	8 MS participants EDSS – Unclear Type – Unclear Sex F/M - Unclear Age -Unclear Years diagnosed - Unclear Completed study - Unclear	Unclear form Progressive upper and lower body resistance training 12 weeks thrice weekly (time unclear) Venue – Unclear Trained - Unclear Led by - Unclear	Walking speed Stair climbing speed TUG SIP Muscle strength	Non-significant improvements in: walking speed, stair climbing speed and strength.	Only Abstract available Small sample size Unclear demographic data Unclear intervention No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Pryor et al 2011 USA Abstract only Experimental	19 MS participants EDSS – 3.7 Type – RR Sex F/M – Unclear Age range (mean) –(48.2) (Years diagnosed; range (mean) Unclear Completed study – Unclear	Unclear form Progressive intervention (unclear) 16 76week thrice weekly Venue – Unclear Trained - Unclear Led by - Unclear	Self- assessed Disability and fatigue assessed with questionnaire (unreported) T25FW 6MWT	Non-significant improvements in disability, fatigue, T25FW and 6MWT	Only abstract available Unclear demographic data Unclear intervention No follow-up
de Souza-Teixeira et al 2009 Spain Within subjects controlled study	13 MS participants (acted as own control) EDSS mean 3.4 Type – unclear Sex F/M – 9/4 Age range - 43 Years diagnosed – Unclear Completed study – All	Resistance machines 8 week twice weekly, circuits of 40-70 MVC increasing set, and reps Control time – no training (before intervention) Venue – Unclear Trained – Individually Led by – Exercise Specialists	MRI of thighs Quadriceps MVC Quadriceps endurance (40% MVC) TUG	After exercise significant improvement of all outcomes.	Unclear demographic data Unclear intervention No follow-up
de Souza-Teixeira et al 2011 Spain Experimental	16 MS participants EDSS – 3.3 Type – Unclear Sex F/M – 8/8 Age range (mean) – 33-56 (44) Years diagnosed – 9.4 Completed study – 12 (Unclear why)	Resistance Resistance bands 6 week thrice weekly <60 minute sessions Venue – Unclear Trained – Unclear Led by – Unclear	Quadriceps MVC low load (49N) and high load (98N) Quadriceps EMG FSS TUG	Significantly improved MVC low load (49N) and high load (98N) and TUG	Unclear intervention No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Taylor et al 2006 Australia Experimental	8 MS participants EDSS – Unclear Type – Unclear Sex F/M – 7/2 Age range (mean) – 27-61 (45) Years diagnosed mean– 9 Completed study -All	Resistance machines 10 week, twice weekly 60 minute sessions Venue – Community gymnasium Trained – In groups (n=3) Led by – Physiotherapist and Exercise Professional	MVC lower limb Repetitions at 1/2 MVC lower limb Walking speed over 10m 2MWT Timed stair test MSIS	Significant improvement in both MVC and repetition MVC scores Non significant improvement in other outcomes	Small sample size Unclear demographic data No follow-up
White et al 2004 USA Experimental	8 MS participants EDSS mean – 3.7 (self reported) Type - RR Sex F/M – 7/1 Age range (mean) – 25-55 (46) Years diagnosed – Unclear Completed study - All	Resistance machines Lower limb strengthening 8 weeks twice weekly 30 minutes Venue – Unclear Trained – Individually Led by - Unclear	MRI (of the thigh) T25FW 3-minute Step Test MFIS Self-assessed EDSS	Non-significant improvement on MRI assessment and MFIS	Small sample size Unclear demographic data Unclear intervention No follow-up

EDSS – Expanded Disability Status Scale, F-Female, M – Male, RR – Relapsing-remitting, SP – Secondary Progressive, Outcome measure abbreviations available in Table 2.4

2.4.3 Combined exercise

In this section, combined exercise training will be discussed, as will studies directly comparing types of exercise. With combined exercise, training includes a combination of aerobic, resistance or balance exercise; no one type of exercise plays a dominant role in the intervention. Thus, to add to the relevant explanations of aerobic and resistance exercise in Sections 2.4.1 and 2.4.2 respectively, an explanation of the mechanisms underlying balance will be made, with further depth of detail available in Sections 3.9.5 and 3.9.6.

Balance and the ability to maintain ones balance relies on the peripheral sensory systems ability to react to the environment. Vestibular, visual and proprioceptive feedback to and from the CNS is required (Ruhe et al 2010). As discussed in Section 2.2.1, the damage to the CNS of those with MS affects motor and sensory systems with feedback to and from the motor and sensory systems via the CNS being altered (Compston and Coles 2008). Thus, due to damage throughout the CNS of those with MS, visual feedback may be limited, with an altered sensory system unable to provide accurate proprioceptive feedback, leading to balance impairment. Other clinical symptoms of MS, including muscle weakness and fatigue may contribute to increased balance impairment in MS (Motl et al 2008b). Therefore, strategies to improve balance are important in MS management, and combined exercise programmes.

Results from studies which have used a combined exercise intervention have found positive results for a variety of impairments found in MS; mobility, fatigue, aerobic endurance, disability and balance. Details on the studies discussed in this section are provided in Table 2.7, with potential gaps in the literature highlighted. In addition, as the combined exercise doctrine of these studies is similar to that included in this thesis they will be described in more detail where appropriate.

Of the papers reviewed all but one study (Cattaneo et al 2007a) included either an aerobic exercise or resistance exercise component. From these studies only Freeman and Allison (2004) did not incorporate aerobic exercise instead they utilised Pilates and resistance training only. In addition to aerobic and resistance training, balance exercise has been included in some studies (Cakt et al 2010; Vore et al 2011; Motl et al 2012), as has Yoga (Oken et al 2004) and hydrotherapy (Romberg et al 2004; Romberg et al 2005). Flexibility training is often included in the warm-up and cool-down part of the interventions, however Carter and White (2003) and Fragoso et al (2008) made flexibility exercises part of their main intervention. The variety of exercise included in the studies may demonstrate that many exercise different exercise types are feasible for those with MS, however further work is required to confirm this.

The disability level of participants in the majority of combined exercise studies is towards the milder disability level, indicating a need to include those more disabled by MS in future studies of combined exercise. Recently Motl et al (2012) assessed a combined therapeutic exercise

programme in 13 people with MS who had a mean EDSS of 5.6, as will be discussed later in this section, many improvements in mobility were found.

The studies ranged in duration from three (Cattaneo et al 2007a) to 24 weeks (Oken et al 2004; Romberg et al 2004), with outcome measures being taken before and after the intervention. The frequency of the interventions ranged from one to three times per week, with no study comparing different frequencies of exercise. Only one study carried out a follow-up of four weeks (Freeman and Allison 2004), finding that, on average, after a 10 week, weekly balance and Pilates exercise intervention, improvements in balance (Berg Balance Scale - BBS) and mobility/endurance (Six-minute Walk Test -6MWT) were maintained. Therefore there is scope to fill gaps in the literature and by including a follow-up period in future studies.

It is not always reported whether participants trained individually or in groups, however some combined exercise studies have acknowledged that participants trained in groups of 6 (Bjarnadottir et al 2007), 9 (Charlton et al 2010), 10 (Freeman and Allison 2004) or in groups of unreported sizes (Oken et al 2004; Cakt et al 2010). These studies have close similarities to the main intervention included in this thesis, and thus will be discussed individually.

Charlton et al (2010) evaluated a combined aerobic and resistance intervention over 16 weeks, in twice weekly 45 minute sessions. Fourteen participants with MS took part, however their disability level and disease type are unclear, all participants were female and 11 completed the intervention. Participants took part in a modified “Jazzercise-lite” intervention where aerobic and resistance exercises choreographed to music were completed in a circuit format and routines were adapted for those participants more or less able. The class was led by two fitness instructors and held in a community hall. Unfortunately no validated outcome measures were used, instead a nine-item self-designed questionnaire, exploring balance, confidence, coordination, energy, flexibility, mood and strength in addition to motivation to continue attending was completed by nine of the participants at the end of the programme. Results suggest that the intervention improved mood and energy amongst other positive finding. This study is limited by being small, lacking in demographic details, not including established outcome measures nor a control group. Although this study had a relatively poor methodology, it does highlight the feasibility of a group fitness class for people with MS.

Oken et al (2004) carried out a RCT which included 57 individuals with mild to moderate MS symptoms (mean EDSS=3.1), unfortunately other demographic details are unclear. The study compared the effects of group cycling classes with yoga classes on cognitive function, mood, fatigue and quality of life. The participants were divided into three groups; group A attended group cycle classes (n=15), group B attended group yoga classes (n=22) and group C acted as controls (n=20) and were advised not to change their physical activity. For six months participants attended

classes once per week. Sixty-nine individuals began the study, however 12 dropped out, some dropped out for health reasons however six participants dropped out due to being unable to commit to attending the class; highlighting potential adherence problems of a long term intervention. The fatigue aspect of the quality of life measure (SF-36) and the general fatigue aspect of the Modified Fatigue Inventory (MFI) showed significant improvements after six months in both intervention groups. Between-group differences were not reported. Despite the limitations of this study, it offers more long term data than most studies in supervised group exercise.

Another RCT (Cakt et al 2010) sought to establish the effect of aerobic cycling on quality of life and function. The design incorporated three groups; 1) aerobic cycling and combined strengthening and balance exercises performed in small groups twice weekly for eight weeks for 15 participants, 2) a home exercise programme of combined strengthening and balance exercises only (twice weekly for eight weeks) for 15 participants, 3) a control group, not changing their usual habits. A total of 33 participants completed the study, with reasons for attrition being symptom exacerbation in the aerobic cycling group (n=1), the home exercise group (n=2) and in the control group (n=3). A comprehensive battery of outcomes was assessed with the aerobic cycling group showing significant improvement in mobility (DGI and 10MWT), balance (FES and functional reach), mood (BDI) and aerobic endurance and aerobic capacity (tolerated duration and workload of cycling). Those in the home exercise group improved aerobic endurance, aerobic capacity and balance, whilst the control group did not show any significant changes. Between groups the aerobic fitness group improved significantly more than the home exercise group in all but the 10MWT. The study also found adherence was far greater for those in the aerobic fitness class (93% of sessions attended) compared with the home exercise group (60% of session completed).

The ten participants in Freeman and Allison's (2004) study attended one hour sessions once per week for ten weeks. Participants were mildly to moderately disabled by MS (mean EDSS=5), were mostly women (80%), aged 29-69 and on average had been diagnosed with MS for 16 years. The exercise intervention was described as a 15 minute warm-up and 30 minutes of Pilates-based standing and lying stretches. The lack of detail make it difficult to recreate the intervention. No control group was included, although all participants completed the study. Measurements were taken at baseline, following the intervention, and at 4-week follow-up. After the intervention significant improvements in balance (BBS) and mobility/endurance (6MWT and MSWS) were found, these continued to improve at follow-up. Although interesting, the results from this small study cannot be generalised to other groups of people with MS and provide only preliminary data. The results are mainly an audit of a group exercise class already in place.

In a RCT by Bjarnadottir et al (2007) 16 people with mild MS symptoms (mean EDSS=2) and the relapsing remitting form of the disease were included. Six participants took part in the five-week intervention, which, in brief, involved cycling for up to 25 minutes and 13 resistance exercises with

stretching during cool-down. The remaining ten acted as controls, and kept diaries recording any physical activity lasting longer than 20 minutes. The outcome measures included quality of life (SF-36) and oxygen consumption and anaerobic threshold during an exercise test. In the intervention group results suggested an improvement in aerobic capacity after the five weeks, with a trend toward improvements in quality of life. Unfortunately, the study was limited by recruitment problems, with potential participants concerned about participating in physical activity. These are important messages as the education of those with MS about the safety and importance of taking part in physical activity is necessary if it is to be adopted amongst the MS population. The need for quality evidence to inform the clinician and client is very real.

Motl et al (2012) included eight weeks of thrice weekly exercise sessions of aerobic, resistance and balance exercise, delivered in groups of 3 to 4 people. Sessions progressed from initially being 20 minutes long in week 1, to being 60 minutes long by week 8. Thirteen participants with MS were included (EDSS mean= 5.6). The researchers aimed for participants to undertake each exercise type for an equal length of time, with the session supervised by two exercise specialists and was undertaken in a gymnasium. Outcome measures related to mobility were assessed at the baseline and on completion of the intervention, these were Timed 25 Foot walk (T25FW), Timed Up and Go (TUG), MS Walking Scale (MSWS) and temporal spatial parameters of gait (functional ambulation profile (FAP), cadence, velocity, step length, step time, base of support, double support, single support, swing phase). Statistically significant results were found for T25FW, TUG, MSWS and some temporal spatial gait parameters (FAP, velocity, step length, single support, swing phase). As the study did not include a control group or any follow-up assessments it is limited. Furthermore only mobility outcome measures were reported. It does however provide encouraging results for a moderately disabled group of participants undertaking a combined therapeutic exercise intervention.

The intervention for the present study was delivered in a group format (Chapter 4). In addition to the studies just described, aerobic and resistance studies delivered in a group format are of interest. Other group exercise class studies, previously discussed, had a more aerobic basis (O'Connell et al 2003; McCullagh et al 2008) and resistance basis (Taylor et al 2006; Broekmans et al 2011; Dodd et al 2011). All were mainly led by a minimum of two physiotherapists or exercise professionals. Bjarnadottir et al (2007), Freeman and Allison's (2004), Oken et al's (2004) and Motl et al's (2012) combined-exercise classes were led by two professionals, either physiotherapists, physiotherapy assistants or exercise professionals, with many of the interventions designed by physiotherapists. Thus , from a safety point of view group classes be supervised by more than one leader.

The venues where interventions were held varied from study to study; rehabilitation centre/hospital gyms and community leisure halls and gyms, suggesting these are all realistic venues to set exercise class interventions. The study undertaken by Cakt et al (2010) provides the only known

data on a comparison between venue, i.e. an exercise class or home programme, as well as comparison between group and individual exercise, and further investigation here may be worthwhile.

Of interest to any group based intervention, although not evident in the results of these quantitative studies involving group exercise classes, is the social support offered by attending a group class. This may be a confounding factor, which influences results (discussed more in Section 2.5 regarding qualitative literature). A novel approach, taken by Dodd et al (2011) to overcome this potential source of bias, involved the control group attending a "social program" not expected to influence the outcome of interest which was strength (i.e. they attended massage, luncheons and education sessions).

As befits the varying nature of the combined exercise intervention, the outcomes assessed were varied; improvements were seen in mobility, fatigue, aerobic endurance and capacity, disability and balance across the combined exercise studies. During aerobic intervention studies improvements were mainly in mobility and aerobic endurance and capacity (Section 2.4.1), whilst in resistance intervention studies (Section 2.4.2), improvements were mainly in strength and mobility. There is evidence that all types of exercise improve fatigue, disability and quality of life. It may be that if only one intervention is to be utilised, it is logical to suggest a combined intervention may be the most beneficial. Furthermore as those with MS suffer from a variety of impairments (including deficits in strength, mobility, stiffness and fatigue (Motl et al 2008b)), a combined intervention may address these appropriately. However there is minimal research comparing different types of exercise (i.e. an aerobic intervention with a resistance intervention with a combined exercise intervention) future research incorporating this design may be beneficial.

Nevertheless it was partially dealt with in a study by Sabapathy et al (2011) which compared aerobic exercise and resistance exercise in an eight week randomised cross-over trial in sixteen people with MS (unclear disability level). Neither intervention resulted in significant improvements over the other (measurements were taken for grip strength, balance (functional reach), mobility/endurance (TUG, 6MWT), the physiological and psychological impact of disease (MSIS), fatigue (MFIS), depression (BDI) and quality of life (SF-36)). However as the cumulative evidence suggests aerobic exercise may offer benefits for improved mobility and endurance, whilst resistance exercise appears to primarily benefit strength and mobility, thus further comparison studies would be welcomed.

In addition, further work on outcome measures which include balance and physical activity levels would also be beneficial. Cattaneo et al (2007a) and Freeman and Allison (2004) found significant improvements in balance following a three and ten week intervention, respectively, and it would be

of interest if improvements in balance could be recreated in future studies. No studies in the combined exercise literature assessed physical activity levels, a clear gap in the literatue.

Throughout the included combined exercise studies there was minimal evidence of any adverse events, although MS relapses have occurred no study has suggested these were as a direct consequence of the intervention. The 24 week study by Romberg et al (2008) found that the control group deteriorated in their disability scores (measured using the Multiple Sclerosis Functional Composite - MSFC), highlighting the variable nature of MS. When added to the similar evidence from the decline seen in Shulz et al (2004) and Ponichtera-Mulcare et al ‘s (1997) declining control groups (Section 2.4.1). This indicates the need for the use of therapeutic exercise to provide long-term symptom maintenance.

The quality of the literature in combined exercise varies with studies using experimental designs (Freeman and Allison 2004; Fragoso et al 2008; Charlton et al 2010; Motl et al 2012) and randomised control designs (Carter and White 2003; Oken et al 2004; Romberg et al 2004; Bjarnadottir et al 2007; Cattaneo et al 2007a; Cakt et al 2010). As before the risk of bias in the RCTs is highlighted by the PEDro scores where the scores vary from five to eight out of a possible eleven. Indicating a lack of subject, therapist and assessor blinding, follow-up and a lack of utilising intention to treat protocol could be improved upon in future studies.

Combined exercise training may well offer a rounded approach to exercise training, allowing participants to benefit from aerobic exercise, resistance exercise and other forms of exercise such as flexibility and balance re-training. Combined exercise studies have found improvement in participants mobility, exercise capacity, strength, balance, fatigue and disability levels. However there is a need to improve the literature here, particularly regarding

- Including participants more disabled by their MS symptoms
- Establishing the optimal length of time for change to be seen
- Establishing the optimal frequency of sessions
- Standardisation of outcome measures, to allow comparison across studies
- Utilising outcomes to assess the impact of the intervention on physical activity levels.
- Including methodology aimed at improving balance, and relevant outcomes.
- Improved methodology to reduce the risk of publication bias.

- Undertaking follow-up to ascertain the longer term effect of interventions.

Table 2.7 Combined exercise intervention studies

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Bjarnadotter et al 2007 Iceland RCT (PEDro 7/11)	18 MS participants (8 intervention, 10 controls) EDSS mean – 2 Type – RR Sex F/M – 11/5 Age range 37 Years diagnosed 8 Completed study – 16 (symptom relapse)	Combined aerobic and resistance exercise 5 weeks, thrice weekly 60 minutes Cycling Resistance: 13 exercises for major muscle groups 5 weeks thrice weekly 60 min sessions Venue - Rehabilitation centre Trained – Unclear Led by - Physiotherapists	EDSS SF36 Peak oxygen consumption Anaerobic threshold (VO_2 max)	Non significant improvement in Peak oxygen consumption and SF36	No; Subject blinding Assessor blinding Adequate follow-up subjects Intention-to-treat analysis No follow-up
Carter and White 2003 (Abstract only) UK RCT	11 MS participants (6 Intervention 5 Control) EDSS – unclear Type – unclear Sex – unclear Age range – unclear Years diagnosed – unclear Completed study – Unclear	Combined flexibility, aerobic and resistance exercise 12 weeks (twice weekly) Venue – Unclear Trained – Unclear Led by - Unclear	PCI MVC (hip flexors, knee flexors and ankle dorsiflexors)	Non significant improvement in PCI and MVC (hip and knee flexor)	Only abstract available thus not PEDro rated Small sample size Unclear demographic data Unclear attrition No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Cakt et al 2010 Turkey RCT (PEDro – 6/11)	45 MS participants (15 aerobic exercise training [Group 1], 15 lower limb strengthening & balance [Group 2], 15 control [Group 3]) EDSS – Unclear (≤6) Type – All Sex F/M – 23/10 Age range (mean)-38.3 Years diagnosed; range (mean) – 7.33 Completed study - 33	Cycling [Group 1] + combined strengthening and balance exercises 8 weeks twice weekly sessions of around 60 minutes Venue - Unclear Trained – Groups (unclear how many) Led by – Physiotherapist Combined strengthening and balance exercises [Group 2] 8 weeks twice weekly sessions of around 30 minutes Venue – Participants home Trained – Individually Led by – Self-managed	SF36 TUG DGI Functional Reach FES 10MWT FSS BDI Tolerated duration of cycling Tolerated workload of cycling	In Group 1 Significant improvement in all outcomes except SF36. In Group 2 Significant improvement in FES, Tolerated duration of cycling, Tolerated workload of cycling Between Groups 1 & 2 Group 1 Significantly improved in all except 10MWT Control group showed no change	No; Concealed allocation Subject blinding Therapist blinding Follow-up Intention-to-treat analysis
Cattaneo et al 2007 Italy RCT (PEDro 8/11)	44 MS participants (20 combined intervention, 11balance intervention, 13 controls) EDSS unclear Type unclear Sex F/M – 29/13 Age range -46 Years diagnosed 14 Completed study – 32 (discharged early or for other unknown reasons)	Combined 1] Combined balance and motor/sensory 2] Balance exercise 3] Motor/sensory only 3 weeks of 2/3 30 minute sessions per week. Venue – Rehabilitation centre Trained – Individual Led by - Therapists	BBS DGI Fall frequency DHI ABC	Significantly improved balance in groups 1 and 2. Significant BBS between groups 1 and 3 and groups 2 and 3. Significant difference in fall frequency between groups 1/2 and 3	No; Subject blinding Assessor blinding Adequate follow-up subjects

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Charlton et al (2010) Iowa, USA Experimental	14 MS participants EDSS – Unclear Type - unclear Sex F/M – female only Age range (mean) – 32-70 (54) Years diagnosed; range (mean) – unclear Completed study – 11 (9 returned the questionnaire)	Combined aerobic and resistance exercise 16 weeks twice weekly – 45 minutes Venue – Community hall Trained – In groups (of 9) Led by – Exercise professionals	Self –designed self-completed questionnaire regarding symptom improvement and enjoyment of the programme	Confidence, mood & energy improved.	Small sample size Unclear demographic data No follow-up
Fragoso et al (2008) Brazil Experimental	10 MS participated EDSS – mean 2 Type – Mainly RR Sex F/M –9/1 Age range (mean) – 20-49 (35) Years diagnosed – Unclear Completed study – 9 (drop-out not motivated to continue)	Combined flexibility, aerobic and resistance exercise 20 weeks, thrice weekly 60-90 minute sessions 4 weeks progressive stretching 10 weeks stretching + progressive free weights 6 weeks stretching + progressive free weights + walks/runs. Venue – University sports facility Trained - Unclear Led by – Exercise Professionals	CFS HR before/after 3 minute step test	Significantly improved HR (before and after step test) and fatigue.	Small sample size Unclear demographic data No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Freeman and Allison 2004 UK Experimental 4 week follow-up	10 MS participants EDSS mean - 5 Type – Unclear Sex F/M - Unclear Age range (mean) – 35-69 (53) Years diagnosed; range (mean) – 4-28 (10) Completed study - All	Combined body resistance and Pilates exercises. Whole body floor based exercises and Pilates 10 week once weekly 60 minute sessions. Venue - Hospital gym Trained – In Groups (of 10) Led by – Physiotherapist and Physiotherapist assistant	BBS 6MWT PCI FIS MSIS MSWS	Significant improvement in BBS, 6MWT, MSWS At follow-up BBS and 6MWT continued to improve.	Small sample size Unclear demographic data Non controlled
Motl et al 2012 USA Experimental	13 MS participants EDSS mean = 5.6 Type – All Sex F/M – 8/5 Age range (mean) – 23-64 (55.8) Years diagnosed; range (mean) – 2-22 (18.1) Completed study – all	Combined aerobic, resistance and balance 8 weeks , thrice weekly (20 min – 60 min sessions) Venue – Accessible gymnasium Trained – In Groups (of 3-4) Led by – Exercise specialists	T25FW TUG MSWS Temporal spatial gait parameters (FAP, cadence, velocity, step length, step time, base of support, double support, single support, swing phase)	Significant improvement in T25FW, TUG, MSWS, FAP, velocity, step length, single support, swing phase.	Small sample size No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Oken et al 2004 USA RCT (PEDro 5/11)	69 MS participants (15 exercise intervention, 22 yoga intervention, 20 control) EDSS mean - 3.1 Type - Unclear Sex F/M - Unclear Age range - Unclear Years diagnosed – Unclear Completed study – 57 (due to symptom relapse, unrelated surgery, longstanding back pain and poor class attendance)	Aerobic (exercise group) Cycling Yoga Combination of 19 poses 24 week once weekly 60 (aerobic) or 90 (yoga) minute session Venue – unclear Trained – In Groups (Unclear how many/class) Led by – Physiotherapist (exercise intervention) Yoga teacher (yoga intervention)	POMS SAI MFI SF36	Non -significant improvements in MFI and SF36. No clear differences between groups	No; Subject blinding Therapist blinding Assessor blinding Intention to treat Concealed group allocation Intention to treat Follow-up Unclear intervention
Romberg et al 2004; 2005 Finland RCT (PEDro 7/11)	95 MS participants (47 intervention, 48 controls) EDSS mean – 2.3 Type – Unclear Sex F/M – 61/34 Age mean - 43 Years diagnosed; range (mean) – 0-28 (6) Completed study – 91 (Unclear reasons)	Combined aerobic and resistance Hydrotherapy initially and then unsupervised aerobic exercise of choice. Resistance Using resistance bands. 3 weeks of in-patient training followed by 24 weeks of unsupervised home based training. Venue - Physiotherapy department (initially) Participants own home Trained – Individually Led by – Physiotherapist initially.	T25FW 500MWT MVC knee muscles Upper limb weight lifting test Graded Exercise test EDSS FIM MSQOL CES-D Equiscale	Significantly improved EDSS, non-significant improved MSFC, non-significantly improved T25FW.	No; Subject blinding Therapist blinding Assessor blinding Concealed group allocation No follow-up

Author and design	Participants	Key methods	Outcome measure	Findings	Limitations/ potential bias
Sabapathy et al 2011 Australia Randomised crossover	18 MS EDSS - Unclear Type – All Sex F/M – 12/4 Age range (mean) – (55) Years diagnosed; range (mean) – (10) Completed study – 16 (illness, and lack of time)	Combined Aerobic versus Resistance exercise Aerobic whole body aerobic circuits Resistance whole body progressive (8 week washout) 8 week, twice weekly 60 minute sessions Venue – Community Health Centres Trained – Unclear Led by – Exercise physiologists	Grip strength Functional reach Step test TUG 6MWT MSIS MFIS BDI SF-36	Functional reach, step test, TUG and 6MWT improved over the study in both groups No significant differences between groups	Unclear if washout period effective, no control group. No follow-up
Vore et al 2011 New York, USA Experimental	11 MS participants EDSS – Unclear Type – Unclear Sex F/M –9/2 Age range (mean) – (55) (Years diagnosed; range (mean) – (22) Completed study – 10	Combined functional exercise Included combined gait/functional mobility retraining, balance work, aerobic & resistance work 10 week once weekly 60 minute sessions Venue – Hospital gym Trained – Individually Led by – Physiotherapy students	MSQOL ABC MFIS TUG 10MWT Single leg stance	Significant improvements in TUG, 10MWT, MFIS	Small study sample No follow-up

EDSS – Expanded Disability Status Scale, F-Female, M – Male, RR – Relapsing-remitting, SP – Secondary Progressive, Outcome measure abbreviations available in Table 2.4

2.4.4 Summary

There is a growing body of literature surrounding therapeutic exercise in MS, and this has been discussed in relation to aerobic exercise, resistance exercise and combined exercise. The literature varies in methodology and quality and has been summarised, and presented in depth in Table 2.5-2.8. In general therapeutic exercise has been found to be beneficial for those with MS. However, further work would add to our knowledge and should attempt to address some of the following literature gaps

- With many trials investigating group exercise in those mild to moderately affected by their symptoms, future trials should include those more severely affected.

- As few trials have assessed physical activity levels, it is important to monitor this.

- Follow-up, which would allow for assessment of symptom change after cessation of any exercise intervention should be included in future trials.

- As the majority of trials are small and underpowered, larger statistically powered trials should be undertaken.

- Few trials have investigated participants thoughts and beliefs, which may provide an insight into why studies are/are not successful, thus more qualitative methodologies should be included to establish participants' thoughts and beliefs.

- Undertaking interventions at community leisure sites may allow increased participation, and should be included in future work.

2.5 Qualitative research on exercise in people with MS.

As discussed there are a growing number of quantitative studies surrounding the area of rehabilitation and therapeutic exercise for those with MS. Unfortunately there have been few qualitative studies which collect information from the participants' perspective. These may offer an insight into the advantages and disadvantages of exercise interventions, helping guide both researchers and clinicians when establishing exercise related services and interventions.

Studies have gathered opinions, through semi-structured interviews, on exercise from the general MS population and from those with MS who already participated in independent community exercise. Kayes et al (2011) explored the views on engaging in physical activity in 10 people with MS who had a range of disabilities, and were recruited from the general MS population. Whilst Smith et al (2011) interviewed 11 women with MS, who already participated in community based exercise, to establish the impact of exercise specifically on fatigue. Findings in these two studies were similar; it was reported that participating in physical activity and exercise is related to, believing exercise can be beneficial (e.g. the perceived line between benefit and harm) and the emotional response to physical activity and exercise (e.g. previous negative experiences, self-efficacy to control the disease and feeling good whilst exercising). Reported barriers preventing people exercising are exacerbating MS symptoms (particularly fatigue) and feeling misunderstood by the general public or exercise professionals.

However, these studies were not linked to an MS specific exercise intervention and gathering the views and opinions of those taking part in exercise enables the researcher to establish much more than barriers and facilitators. It allows an exploration of the positive and negative outcomes from the exercise intervention, and will gather participants' opinions on improving the intervention.

Three studies have explored the views on exercise of those participating in exercise interventions specifically for people with MS, using semi-structured interviews. The quality of these three studies was considered using the CASP qualitative research critical appraisal tool (Section 2.3.3).

Plow et al (2009b) studied 13 participants who were involved in an individual home exercise programme (of stretching, static cycling and resistance exercises) as part of a larger study. Whilst, in the study by Dodd et al (2006) the nine interviewees had participated in ten weeks of a twice weekly resistance training programme, led by a physiotherapist and exercise professionals in a community leisure centre, the quantitative results of which were reported by Taylor et al (2006). Finally, the ten participants in Smith et al's (2009) study had taken part in an eight week individually tailored exercise programme led by a physiotherapist.

Disability level was not reported based on the EDSS, although disability descriptions were given. Only those participating in Dodd et al's (2006) study included participants with a disability level equivalent to an EDSS score of greater than 5 with the descriptions of participants in the other studies indicating they were of low levels of disability.

Dodd et al (2006) analysed their results using the General Inductive approach similar to that described by Thomas (2006). Dodd et al (2006) explored the positive and negative outcomes of group resistance exercise and established facilitators or barriers to participating. Many positive outcomes of participating were discussed related to physical, psychological and social outcomes. Negative outcomes were related to fatigue and general aches and pains. Extrinsic factors (including leadership, group, venue, cost, time) and intrinsic factors (including determination, positive attitude, seeing progress, novelty and enjoyment) for completing the programme were discussed. The only barrier to participating in exercise was related to the cost of taking part. Participants spoke of the encouraging, supportive and knowledgeable aspects of the leaders making the class easier to complete and that being in a group, in a gym was also worthwhile (Dodd et al 2006). The authors also provided information on the questions they included, which are useful when carrying out similar studies.

The study stood up well to the CASP critical appraisal, however although Dodd et al (2006) justified the use of qualitative research, they did not acknowledge the possibility of using focus groups. The authors did not explain clearly in their articles from the studies what the relationship was between the participants and researchers, which may have been influential.

Smith et al (2009) used an Interpretative Descriptive methodology to analyse their findings. As their aim was to explore the impact of an exercise programme on the participants perception of fatigue many themes surrounding fatigue and exercise emerged. These included, feeling stronger, improved fatigue management and healthy tiredness (improving participants' sleep). Negative impacts of exercise on fatigue were reduced balance and walking ability immediately following exercise. Critical appraisal highlighted some areas where the study quality could improve; Smith et al (2009) provided minimal rationale of the use of qualitative research and interviews and, based on the study's aim, a questionnaire approach may have gathered sufficient information. Minimal explanation was provided on the depth of data analysis; doing so would help inform further research.

Plow et al (2009b) used a General Analytical Induction method to analyse their results and aimed to establish views on physical activity dependent on how active participants were; stratifying their findings based on current physical activity; either physically active (n=3), sometimes active (n=7) or inactive (n=3). Related to these criteria responses were different, with physically active participants displaying more self-efficacy to use exercise for symptom management and a better

ability to self-regulate daily activities to allow them to exercise. Inactive participants presented more barriers to exercise than their more active counterparts. Critical appraisal highlighted that although Plow et al (2009b) justified their methodology, no consideration was given to the use of focus groups, and importantly the researchers did not explicitly acknowledge ethical considerations in their published study.

The studies discussed in this section present interesting messages for any health professional involved in activity prescription for people with MS. They provide an insight into the world of the person with MS which quantitative studies do not. In particular the insights that having greater self-efficacy to control the disease (Plow et al 2009b; Smith et al 2011), being led by knowledgeable professionals (Dodd et al 2006) and being aware of symptom improvements (Smith et al 2009) encourages uptake and continuation of exercise. Fatigue, negative emotional feelings, social situations, inaccurate professional advice and lack of appropriate facilities all emerged as potentially having a negative impact on physical activity and exercise adherence (Dodd et al 2006; Smith et al 2009; Plow et al 2009b; Smith et al 2011). However participants in Smith et al's (2009) study acknowledged that fatigue does not always have a negative effect on exercise, and that it was important that individuals were educated to know when they should be able to exercise.

These papers mainly include the views of those mildly affected with MS, and all use semi-structured interviews to gather data. Gathering data using focus groups is, as yet, an unexplored methodology in a study specific to exercise in MS. However it has been used to gather the views of those with a range of neurological conditions (a small sample of whom had MS) (Dawes et al 2010). Dawes et al (2010) reported that people with neurological conditions would be keener to exercise if they felt it could benefit their symptoms, was provided in a group format (with those of similar disabilities) and was delivered by knowledgeable staff (particularly physiotherapists).

Collecting qualitative data using a focus group methodology, which can be more natural, encourage participant interaction, and allow contrasting opinions to be easily explored (Kitzinger 1994; Wilkinson 1998) are underused in this area of research, these points warrant further investigation.

Thus the views related to exercise of those more severely affected with MS (EDSS>5), who have taken part in a specific MS group exercise programme have not yet been researched.

2.5.1 Summary

Despite the growing area of research related to therapeutic exercise for those with MS there are few qualitative studies. These studies not only provide information on the barriers and facilitators experienced by people with Multiple Sclerosis when considering exercising, but also what effect exercise has on their disease symptoms and other areas of their life, in areas which quantitative studies may not. Thus qualitative research can be used to guide quantitative study into issues

deemed to be important to the participant. The views and opinions of those with Multiple Sclerosis related to exercise is also of interest to any health or exercising professional responsible for organising exercise options for those with MS.

In general qualitative studies have found positive views on therapeutic exercise and physical activity for those with MS, although it has highlighted some problems faced by those with MS when participating in exercise and physical activity. Further work would improve our knowledge in this area and future work should attempt to address some of the following literature gaps;

- As most qualitative research surrounding exercise and MS has not reported disability level, or has only included those described as having an approximate EDSS level 5, opinions and views of those more affected (EDSS greater than 5) should be gathered.

- As semi-structured interviews have mainly been used in MS specific exercise qualitative studies so far, the use of focus groups for gathering data is unexplored.

2.6 Summary and conclusion

There is scope for continued clinically relevant research in therapeutic exercise for those with MS, with an improvement in study quality, leading in part, to improved care and better overall treatment options for those with MS. In particular the lack of community rehabilitation options and qualitative research into MS rehabilitation should be addressed

The aim of this thesis is to address the gaps in the literature. Such gaps include; a lack of studies recruiting those more disabled with their MS symptoms (i.e. an EDSS>5), a lack of follow-up data after the exercise and unclear information as to the optimal duration of the intervention. These areas will be addressed in the main study explained in Chapter 4.

To address the dearth of knowledge regarding the views and opinions of participants taking part in therapeutic exercise interventions for people with MS, qualitative research was undertaken (Chapter 5). These aims will be addressed in the following chapters describing the three studies involved in this thesis.

The following chapter will provide a literature background to the outcome measures used in the main study, and will introduce the rationale behind the reliability of outcome measures used in MS, which will be explained in Chapter 6.

3 Literature pertaining to the methodology.

There are a number of outcome measures used clinically and in research to evaluate the effectiveness of rehabilitation, symptom management and the reduction of disability in patients with MS. Many of these are discussed as part of the literature review in Chapter 2. This chapter provides a literature background to the chosen quantitative and qualitative methods used in the studies undertaken for this thesis.

3.1 Introduction

To answer the research questions of this study (Section 1.5), a mixed methodology approach was used. Three investigations were undertaken related to the theme of therapeutic exercise for those moderately affected with MS. Study 1) The main investigation, was a 12-week exercise intervention, with follow-up assessments 6 and 12 months after the end of the intervention. Study 2) A focus group analysis of the 12-week exercise intervention. Study 3) An assessment of the reliability of the outcome measures used in the main investigation.

Quantitative data were collected through repeated clinical outcome measurement in Studies 1 (Chapter 4) and 3 (Chapter 6). Focus groups were used in Study 2 (Chapter 5) to elicit participants' views on areas related to the exercise intervention in Study 1. This chapter discusses the literature surrounding the chosen methods and puts into context the chosen outcome measures used to achieve the primary aim of establishing the effects of a group exercise class in people with MS of moderate disability. To achieve the aims of Study 1 and Study 3, what will now be described as clinical (quantitative) measurement was undertaken. This will be discussed prior to an examination of the literature which guided the qualitative methods chosen to achieve the aims of the focus group. This chapter complements the methodological details presented in Chapters 5, 6 and 7, providing the background to the methodology sections of these chapters.

3.2 The use of mixed methodology

A mixed methodology gathered both quantitative (Study 1), and qualitative (Study 2) data. This allowed the research to overcome limitations of single methodology studies. For example, quantitative methodology may focus on numerical data and lack the ability to gather data related to understanding the context of participants' behaviour, whilst qualitative methodology may be seen as being subjective and lacking reliability and validity (Taylor 2005; Creswell and Plano Clark 2007).

Primarily quantitative clinical outcomes were used; with qualitative focus group data collected independently of the quantitative results. At the time of collection, one form of data did not influence the other, consequently a mixed methodology triangulation design was used (Creswell and Plano Clark 2007). On final analysis, results from some of the quantitative results were relevant to findings from the focus groups, which in turn complemented some of the quantitative findings, resulting in a greater understanding of the results.

3.3 Gathering clinical measurements

To objectively measure the impact of disease symptoms or a clinical intervention, quantitative measurement is commonly used. There are a number of ways to achieve this, for example, timed tests, instrumental tools or questionnaires (Hammond 2000; Yoward et al 2008). However more than simply measuring, outcome measures must demonstrate practical use (feasibility) whilst being valid and reliable. As such, there are a number of basic concepts when using clinical outcome measures.

3.4 Basic concepts in clinical measurement

Measurement is an important component of healthcare: used to establish the impact of treatment and monitor change in clinical performance (Streiner and Norman 2008). A reliable and valid outcome measure which accurately monitors significant changes is important both in research and clinical practice (National Institute for Health and Clinical Excellence 2003).

Reliability is an indicator that the outcome measure can produce consistent results, while validity is an indicator of whether the outcome measure is appropriate for its intended purpose (Bowling 2005). Furthermore the outcome measure, and, where possible, its established reliability and validity, should be relevant and feasible for use within the MS population.

Establishing test re-test reliability involves repeatedly testing the same variable to determine if a similar score is found (Bowling 2005). Within reliability assessment, it may be important that both intra-and inter-rater reliability be established. Intra-rater reliability establishes the rate of agreement of two, or more, scores taken by the same assessor. Whilst inter-rater reliability establishes the agreement of two, or more scores taken by two, or more different independent assessors (Bowling 2005). Error may be minimised through training and experience (Richards et al 2000), thus more experienced clinicians (with more practice using the outcome measure, correctly) are perceived to provide more reliable results (Streiner and Norman 2008). However, if time consuming and costly training of a clinician is required for an outcome measure, the clinical applicability of the outcome measure may be undermined.

Statistical tests measuring correlation are commonly used to estimate the reliability of the outcome measure. Simple correlation models are, however, limited as they only examine a linear relationship, not reliability. A commonly used, and more appropriate statistical method is establishing reliability using the Intraclass Correlation Coefficient (ICC), where scores closer to unity (1) are deemed more reliable (Denegar and Ball 1993).

It is important to establish validity to determine whether an outcome measure is appropriate for its intended use. Validity can be established in one of two ways. The most common method compares the outcome measure against other established outcome measures (the so called “gold standard”) that assess similar attributes. Statistical analysis is used to determine if there is a strong correlation between the two results. Alternatively, if no similar outcome measure is available, the outcome measure must be compared against relevant hypothetical concepts (Streiner and Norman 2008).

Other statistical tests similar to the ICC, such as the Pearson correlation (commonly denoted as *r*), may also be used in the literature to describe validity. For both, scores closer to unity (1) suggest a stronger correlation between the outcome measure of interest and the established outcome measure, indicating they are measuring the same factor (Denegar and Ball 1993).

Related to the validity of the measurement is the influence of “floor” and “ceiling” effects, terms which indicate that scores are either very high or very low resulting in the mean score approaching the maximum or minimum score possible (Streiner and Norman 2008). Theoretically any outcome measure which has a maximum or minimum score may be vulnerable to a potential “floor” or “ceiling” effect.

A “floor effect”, is deemed problematic if, for example, a participant is unable to achieve the basic requirements to score lower than the minimum score on a measurement. A “ceiling effect”, is deemed problematic when, for example, a participant achieves a top score on a measurement. For both these situations, any change in clinical status may not be clearly captured (Nunnally and Bernstein 1994). Thus, the outcome measure will not indicate a true representation of what it is attempting to measure. In this case the use of secondary outcome measures may compensate for a potential floor or ceiling effect.

Less well-known properties such as the clinical significance/precision of an outcome measure are important. Determining clinical significance will help determine any change in score is clinically significant and not due to an error in the measurement. One interpretative value for clinical significance, calculated from scores distributed across a group of participants repeating the same outcome measure, is Minimal Detectable Change (MDC). MDC is defined as the minimal amount of change that is not likely to be due to chance variation or error in the measurement (Haley and Fragala-Pinkham 2006), thus it is independent of any change seen on, for example, the EDSS scale.

However within the literature similar statistical calculations, such as Minimal Important Difference (MID) (Guyatt et al 2002) and Minimally Important Clinical Difference (MICD) (Coleman et al, 2011) may be used. All are indications of clinical significance.

In addition it is important to know how precise the measure is, this can be described using the Standard Error of Measurement (SEM); calculated from the standard deviation of the distributed test scores and the reliability of the measure (Denegar and Ball 1993).

It is a recommendation that, in addition to reporting results of statistical tests, effect sizes or difference of means are also reported (Them and Be 2008). Doing so provides an indicator of the effect of the intervention without the requirement to consider the number of participants (Coe 2002).

The available MS literature reveals that the reliability and validity of outcome measures is not well established. Furthermore, using statistical methods, such as those described above to determine the clinical significance and precision of outcome measures used to assess therapeutic exercise is rare.

3.5 Feasibility in clinical measurement

When deciding on an outcome measure for either clinical or research purposes the practicalities of how it will be used is an important consideration. Indeed the outcome measures used should be convenient for the clinician as well as acceptable to the client (Hammond 2000). Past studies questioning physiotherapists on what factors they consider when choosing outcome measures highlight the importance of them being practical and feasible (Chesson et al 1996; Copeland et al 2008). Findings suggest that cost, time, patient expectations, service prioritisation, clinical decision making, audit requirements and clinicians knowledge of outcome measures are all important factors when choosing an outcome measure. With space and patient burden also important considerations (Bethoux and Bennett 2011).

3.6 Outcome measurement in MS

Both generic and MS-specific outcome measures exist. Generic measures can be used in a wide range of disease populations, making the data generated from them comparable across different groups. However they will not focus on areas specific to MS, where the recommendation is that, where available, MS specific outcome measures should be used in MS therapeutic exercise studies (Motl and Gosney 2008).

Data can be generated from both assessor rated outcome measures and self-report questionnaires. These can be chosen based on whether the outcome of interest can be observed (e.g. walking or balance) or whether the outcome is better captured from the patients thoughts and feelings (e.g. fatigue and mood). However, data on outcomes which may be readily observed may also be captured with self-report measures (e.g. balance). Self-reporting may be difficult for those with MS, if for example they have difficulties in manual dexterity or cognitive problems which may impact speed of information processing and memory (Matthews 1998; Bruce et al 2010), influencing both the time to complete self-reported outcome measures and the accuracy of the data.

Similarly, in those with MS, performance may fluctuate throughout the day and from day to day, irrespective of any new disease activity (Finlayson and van Denend 2003). Quantitative research has been conducted to establish the influence of time of day on symptoms; however, no conducive findings have emerged. With Morris et al (2002) and Feys et al's (2012) participants reporting increased fatigue in the afternoon compared with the morning. Although participants in Crenshaw et al's (2006) study did not report any significant changes in fatigue throughout the day. Mobility was also assessed in these studies, with no indication that fatigue influences mobility, perhaps suggesting that time of day may not be influential on mobility.

3.7 Outcome measures used for study inclusion

Before a fuller discussion on the outcome measures used in the study, information is provided to the reader on the measurement tools used to establish participants' eligibility to the study. Three outcome measures were used; the Mini Mental Status Examination (MMSE), the Expanded Disability Status Scale (EDSS) and a Fitness Screening form based on the Physical Activity Readiness Questionnaire (PAR-Q). Copies of these are available in Appendix 1 and 2.

3.7.1 The Mini Mental State Examination

In MS, cognitive deficiency may be problematic (Compston and Coles 2008). The studies in this thesis required a level of comprehension which would allow participants to follow instructions, complete questionnaires and attend scheduled appointments. Thus, determining sufficient cognitive functioning was important. To ensure participants were of adequate cognitive function the Mini Mental Status Examination (MMSE) (Folstein et al 1975) was used.

The MMSE measures cognitive aspects of mental status, primarily; arithmetic, memory and orientation, providing a total score out of 30, with higher scores indicative of better cognition. The MMSE has been found to be reliable and valid in populations where cognitive impairment may be common (Folstein et al 1975; Kim and Caine 2002). In MS its validity and reliability has not been fully established. However the MMSE has been used in previous studies related to

therapeutic exercise in MS (Patti et al 2002; Patti et al 2003; Finkelstein et al 2008) where scores of 24 or greater were used for study inclusion. Therefore, a score of 24 or greater was required for inclusion in the present studies.

The MMSE is not without its limitation, as it can be influenced by age and education level (Tombaugh and McIntyre 1992), however it is easy to administer and does not require a high level of assessor skill, therefore appropriate to the studies in this thesis.

3.7.2 The Expanded Disability Status Scale

Created by Kurtze (1983), the EDSS evaluates neurological impairment in MS, and is used as a measure of disability. The scale quantifies neurological impairments, in each of eight neurological Functional Systems (FS); pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other. These are combined with ambulation ability and give a measure of disability on a scale from normal (0) to death due to MS (10) (Figure 3.1).

The EDSS scale has been used in the majority of studies involving therapeutic exercise for those with MS, as discussed in Chapter 2. Theoretically, its use allows comparison between or within those with MS. It is a widely recognised scale; however problems have been highlighted, such as a poor response to change (Sharrack et al 1999) and scores clustered around 3/4 and 5/6 (Whitaker et al 1995; Jacobs et al 1999). Grades above three are heavily reliant on mobility, thus at the higher end of the scale a newly acquired FS problem may not necessarily modify the EDSS score with the scale lacking any sensitivity to cognitive changes. Other acknowledged restrictions of the EDSS are the limitations of a nominal scale, when ordinal scales may be a more valid method (Hobart et al 2000). Step changes are not reflective of an equal change in disability and the concentration on impairment (for the lower levels of the scale) and mobility (for the higher levels of the scale) (Rossier and Wade 2001; Bethoux and Bennett 2011) suggest the scale may not capture true disease progression.

The literature review indicated that there is a literature gap surrounding therapeutic exercise for those moderately affected with MS, thus, an Expanded Disability Status Scale (EDSS) of 5-6.5 was required for study inclusion. This description of moderate MS has been used in the past by researchers undertaking similar MS rehabilitation studies (Freeman et al 1997; Freeman et al 1999).

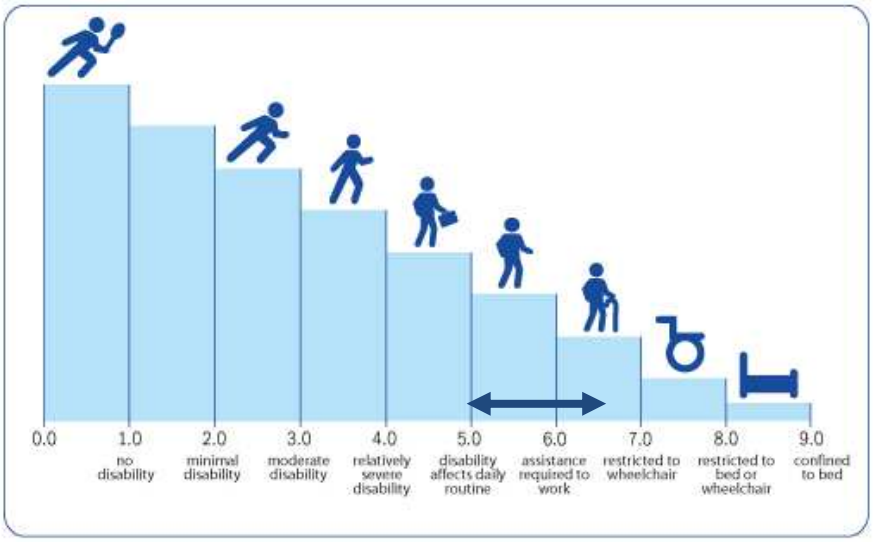


Figure 3.1 Pictorial representation of the EDSS Scale

Level of those in study indicated by arrow (MSActiveSource 2010)

Despite it's acknowledged limitations the EDSS scale was used in this study as it is the most widely accepted measure of disability used throughout the MS literature. At present no consensus has been reached as to whether another measure of MS disability should be used, consequently to allow for comparison between the results of this study and the work of others the EDSS scale was used.

3.7.3 Fitness Screening form

Study 1 included an exercise intervention, thus it was appropriate to establish potential participants' fitness to exercise. A Fitness Screening form was used based on the Physical Activity Readiness Questionnaire (PAR-Q) (Shephard 1988).

Modified versions of the PAR-Q are common in exercise research and in the exercise industry to screen individuals for their suitability to exercise (Warburton et al, 2011). However, there are limitations to the use of the PAR-Q, for example, it is vulnerable to false positives and may not be used consistently. Despite this it does highlight potential risks to exercise participation e.g. heart conditions or pain during exercise. Unlike the MMSE and the EDSS score there was no cut-off score for eligibility. If on completion of the PAR-Q any issues were highlighted which would suggest exercise may be contra-indicated this would be discussed with the research team, and the potential participant excluded as necessary.

3.8 Choosing the outcome measures in this study

A discussion follows of the main outcome measures used in Study 1 and Study 3. By reviewing the literature, acknowledging outcome measures used clinically in rehabilitation and by considering the feasibility, reliability and validity of the outcome measure, a range of outcome measures were considered and chosen. For practical reasons the availability of equipment was also important when choosing the outcome measures. The outcome measures chosen were based on, 1) the research aims and 2) the International Classification of Functioning (ICF) (World Health Organization 2001). The ICF is a framework which can be used to categorise the assessment of different components of health, it will be described in more detail in Section 3.8.2. In Study 3, the test re-test reliability of four of the outcome measures used in Study 1 was investigated in more detail.

3.8.1 The outcome measures relevant to the research aims

To meet the aims of the research, outcome measures were chosen to measure the physiological, functional and psychological status of participants. As discussed in Section 2.2 there are many clinical features and symptoms found in MS. A decision was made to focus on some of these (such as those which have been studied in the past therapeutic exercise literature), in particular, outcomes that gathered information on mobility, balance, leg strength, activity participation, fatigue, mood, quality of life and body composition, all of which may be compromised in MS.

Information was gathered using the following outcome measures. Most were gathered by the assessor, whilst four were self-completed questionnaires (these are notated by an *).

Mobility	The Timed 25 Foot Walk (T25FW)
	The Six-minute Walk Test (6MWT)
	Temporal Spatial parameters of gait
	Timed Up and Go test (TUG)
Balance	The Berg Balance Scale (BBS)
	Activities Balance Confidence scale (ABC)*
	Overall Stability (OS)
Leg strength	Strongest (SLS) and weakest (WLS) leg strength
Activity participation	PhoneFITT (PF)

Fatigue	Fatigue Severity Scale (FSS)*
Mood	Hospital Anxiety and Depression Scale (HADS)*
Quality of Life	Leeds MS Quality of Life (LMSQOL)*
Body Composition	Body Mass Index (BMI)

Some of the above outcome measures will gather data on one, or more, aspect of physiological, functional or psychological status. For example, the TUG will provide data on functional balance and global leg strength.

The rationale behind each outcome measure will be explained in the following sections. For reference, the data collection sheets, which include all assessor rated outcome measures are provided in Appendix 3. The participant rated questionnaires are provided in Appendix 4.

3.8.2 The outcome measures relevant to the International Classification of Functioning

Outcome measures chosen linked to the International Classification of Functioning (ICF). The ICF is a model of describing health related conditions, and their impact on the individual. The concept was developed by the World Health Organization (2001) and offers a framework to describe the interaction between the different domains of a health condition; body functions and structures, activity and participation and environmental factors. Recently a comprehensive core set of categories, based on the ICF have been developed for MS (Coenen et al 2011), helping researchers and clinicians monitor MS appropriately.

Due to the primary focus of the study being a physical intervention, outcome measures in Study 1 and Study 2 were chosen to measure the impact of the intervention across the domains of body functions and structures, activity and participation. Whilst domains related to contextual factors, which are Environmental and Personal factors, were not measured, as these relate to areas out with the primary focus of this research. The interaction between the problems faced by those with MS, the domains of the ICF and the relevant outcome measures used to capture the information in the study are displayed in Figure 3.2. These were informed by the ICF guideline (World Health Organization 2002) and the core Set for MS (Coenen et al, 2011). Throughout Section 3.9 examples of the relationship between each outcome measure and the ICF is provided.

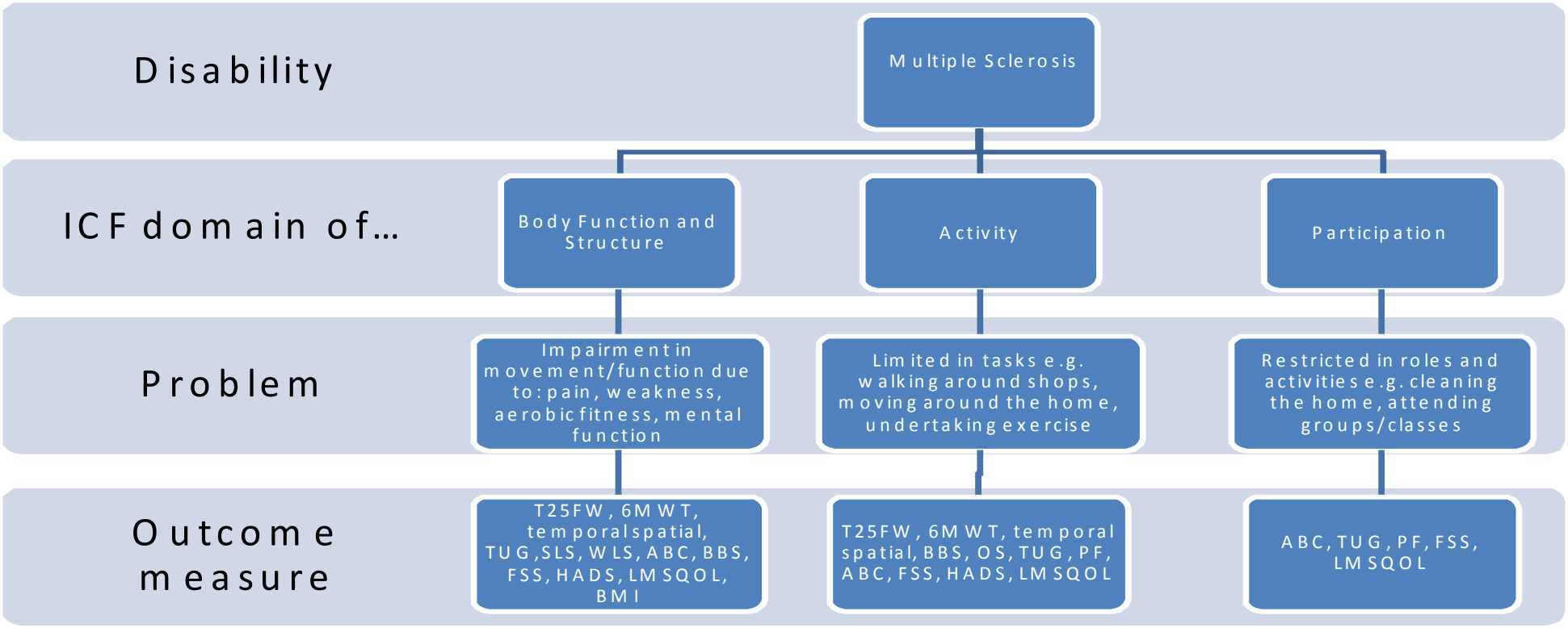


Figure 3.2 Outcome measures related to the International Classification of Functioning

T25FW–Timed 25ft Walk, 6MWT–Six-minute walk test, temporal spatial gait paramters, BBS-Berg Balance Scale, TUG-Timed up and Go test, SLS–strongest leg strength, WLS–weakest leg strength, PF-PhoneFITT, ABC-Activities Balance Confidence, FSS-Fatigue Severity Scale, HADS-Hospital Anxiety and Depression Scale, LMSQOL-Leeds MS Quality of Life).

3.9 The outcome measures used in this study

There are many different outcome measures used to investigate the effect of therapeutic exercise in MS, some of which have been discussed in Chapter 2 (Tables 2.6 -2.8). These vary in terms of validity, reliability and feasibility. A discussion on the different outcome measures used in the present study and, where relevant, other similar outcome measures will follow. The reader is referred to Table 2.5 where a list of outcome measures, and references to the original works, where available, can be found.

3.9.1 Timed 25 Foot Walk

Altered mobility, and reduced walking speed are common symptoms in MS (Motl et al 2008b). Measures of mobility, such as short timed walks are used by physiotherapists in neurological rehabilitation (Yoward et al 2008). These can include the 10-metre Walk Test (10MWT) or the Timed 25-Foot Walk (7.62m) (T25FW). Both are popular in MS literature and are similar in that they require minimal equipment and measure mobility over a set distance. As both need additional space for acceleration and deceleration they require more room than is suggested by their name. However, the T25FW was chosen in this study as it is accepted as the mobility measure used in the Multiple Sclerosis Functional Composite (MSFC) (Kalkers et al 2000), a measure of disability in MS. The MSFC includes a mobility component (T25FW) a cognitive and an upper body component. In addition, the T25FW is shorter that the 10MWT and due to space limitations the 10MWT could not be easily carried out within the testing area used for this study.

The T25FW is a timed walk (measured in seconds (s)) over a marked 25-foot course (7.62 metres (m)). The T25FW is also a relevant outcome measure when used independently. The origins of the T25FW are difficult to locate, however the study by Cutter et al (1999) is one of the earliest uses of the T25FW in MS research.

The T25FW was chosen for both Study 1 and Study 3 as it has been used commonly in MS therapeutic exercise studies (White et al 2004; Romberg et al 2004; Romberg et al 2005; Pryor et al 2011). In addition, it has now been proposed, by the European Rehabilitation in MS network (RIMS) for best practice and research, as a core outcome measure to assess walking in MS (Gijbels et al 2011).

Feasibility

The T25FW is a practical tool, easy to perform and relevant for both clinical and research purposes. Taking less space than the 10MWT it may be more practical if assessment space is limited.

Reliability and validity

Cohen et al (2000) found intra-rater and inter-rater reliability of the T25FW to be high as part of the MSFC. When tested over six testing sessions (two sessions per day) completed over two weeks, an intra-rater ICC of 0.93 and an inter-rater ICC of 0.95 were reported. Schwid et al (2002) looked at the reliability of changes in T25FW scores in 63 participants (EDSS 0-6.5), measured over five consecutive days, finding the measure reasonably reliable, however they found that scores may varied by up to 16%. Coleman et al (2012) looked at the clinical significance of T25FW scores during a 14 week clinical trial of Dalfampridine (medication prescribed to those with MS to improve walking). They found that in participants (mean EDSS=5.8) who were judged to have minimally improved, a 17.2% improvement in T25FW was recorded, for those judged to have shown no change a 7% change in T25FW was found.

The test is discussed as having good validity, and as being the standard for correlation of other walking and mobility measures (Bethoux and Bennett 2011). In MS, as part of the MSFC the T25FW has been shown to correlate moderately with the EDSS (Rudick et al 2002).

ICF domain and category

The T25FW captures data on body functions and structures, such as; muscle function, gait pattern functions and structure of the lower extremity. It also captures data on activity and participation, such as; walking and moving around (World Health Organization 2002; Coenen et al 2011).

Strengths and limitations

The test offers an ordinal score where progress and decline can be monitored on a continuous scale. Changes in score have been found to compare with both clinical observation and patients' perception of change (Kaufman et al 2000; Hoogervorst et al 2004). The test has shown good validity and feasibility. Furthermore there is a need to clarify instructions for the test, as these may impact the assessment (Bethoux and Bennett 2011).

Further work required

There is a need to validate the test in MS when used as a stand-alone measure, outwith the MSFC. With more work required to establish the reliability, clinical significance and precision of the T25FW in those with MS who are clinically stable. To do so the T25FW was assessed as part of Study 3 (Chapter 6).

3.9.2 Six-minute Walk test

As discussed, mobility is often compromised in people with MS and this is not only over short distances, such as 25 feet. Measuring walking over longer distances provides information on both mobility and aerobic endurance. Longer walking tests, such as the 500m walk test, the Two-minute Walk test (2MWT) and the Six-minute Walking Test (6MWT), may measure endurance. The 500m walk requires participants to walk the measured distance. Therefore would only be appropriate for those with an EDSS of 4.5 (i.e. EDSS 1- 4.5). The 2MWT, like the 6MWT, is time limited, and thus all participants below an EDSS score of 6.5 or less should realistically be able to complete these. The 2MWT is shorter than the 6MWT, and may be thought of as having more clinical applicability, with less burden on the patient (Bethoux and Bennett 2011), however this may also limit its ability to capture data on aerobic endurance, whereas a test lasting a longer length of time may bring participants closer to their aerobic capacity. Furthermore there is limited evidence of the psychometric properties of the 2MWT in MS research. As such neither the 500m walk or 2MWT were used in this study.

The 6MWT, common in MS literature and used by 14% of British Neurophysiotherapists (Yoward et al 2008) was chosen for this study. It has the ability to capture data on mobility and endurance, with recent work suggesting its strength as a measure of endurance in MS (Bethoux and Bennett 2011). First described by Butland et al (1982), the original use of the 6MWT in respiratory disease has expanded into neurological conditions such as MS (Freeman and Allison 2004; Paltamaa et al 2005; Rampello et al 2007; Coote et al 2009). For the 6MWT participants are asked to walk as far as possible, under controlled conditions, in six-minutes. Although different protocols are available, the American Thoracic Society (2002) guidelines were used in this study; this involved the participant walking a 30m course in a corridor with the assessor providing specific verbal cues and instructions to standardise the protocol.

Feasibility

With minimal costs and training required the 6MWT is feasible for both clinical use and research. Indeed walking for a reasonable length of time is an ubiquitous activity, which may be carried out by all ambulatory persons with MS. As such the 6MWT is a highly functional outcome measure, which has been found to correlate strongly with community ambulation (Gijbels et al 2010b).

Reliability and validity

Paltamaa et al (2005) assessed the inter-rater reliability of the 6MWT in nine participants with MS and reported the ICC to be 0.93. In part of the same study, the test re-test reliability was established in 19 participants with MS, four of whom had an EDSS score of 4 to 6.5, the ICC was reported as 0.96. The physiotherapy assessors had different levels of experience using the outcome measure,

further supporting the reliability of this outcome measure. The good intra-rater reliability found by Paltamaa et al (2005) was confirmed by Fry and Pfalzar (2006) in a study of 12 people with MS who had a mean EDSS score of 3.6. The ICC was 0.96 when the testing was done one week apart, similar to Paltamaa et al's (2005) study. Goldman et al (2008) carried out three tests over one day finding good inter-rater (ICC=0.91) and intra-rater reliability (ICC=0.94) of the 6MWT.

Although clinical significance has not been statistically determined for the 6MWT in MS, it has been established in other conditions. For example in Parkinson's disease MDC scores for the 6MWT were reported to be a change of 82m (Steffen and Seney 2008). In Steffen and Seney's (2008) study the mean 6MWT score was 316m (SD 142m), thus the MDC was more than 25% of the mean score, suggesting a reasonably large change in score is required, in the Parkinson's disease population, to indicate a clinically significant change.

In an MS population, Paltamaa et al (2005) found a SEM of 30.65m in an ambulatory MS population. With a mean score in this study's participants being 538m at baseline, the narrow SEM score does suggest the 6MWT is precise in those with mild-moderate MS.

In studies involving MS participants, it has been shown that the 6MWT correlates well with disability (measured with EDSS, r=0.73; MSFC r=0.72), quality of life (measured with the Short Form–36 (SF-36) *r*=0.69) and mobility (measured with the MS Walking Scale *r*=0.81) (Goldman et al 2008).

There are a variety of different 6MWT protocols available in the literature mainly related to instructions and length of corridor to be used. Altering these constants does affect the reliability and validity of the outcome measure. For research purposes, standardised protocol should be stated and followed.

ICF domain and category

The 6MWT captures data on body functions and structures, such as; exercise tolerance function, muscle function, gait pattern functions and structure of the lower extremity. It also captures data on activity and participation, such as; walking and moving around (World Health Organization 2002; Coenen et al 2011).

Strengths and limitations

In addition to showing good reliability and validity the 6MWT has been found to correlate strongly with community ambulation (Gijbels et al 2010a). It offers an assessment of mobility, providing a test of endurance, which is feasible in most locations. The literature suggests it may be limited by

fatigue and exhaustion (Bethoux and Bennett 2011), however this implies the test is capturing data on aerobic endurance. As suggested an open area, or long corridor is required for the test which may not be practical for all assessment situations.

Further work required

There is reasonably strong evidence as to the psychometric properties of this test in MS, however further work on the reliability and validity of the 6MWT across the disability range in MS is warranted. To confirm the previous work on reliability and to determine the clinical significance and precision of the 6MWT in a population moderately affected with MS, the 6MWT was included in Study 3.

3.9.3 Temporal Spatial parameters of gait

The T25FW and 6MWT provide good clinically applicable measures of mobility; however with specialist equipment it is possible to more accurately measure different components of gait. Doing so may provide data on which component of the participants gait is compromised. Measuring gait accurately can be done by using motion analysis systems or measuring temporal (e.g. time taken per step) and spatial (e.g. distance covered per step) parameters of gait through computerised walkways.

Motion analysis provides comprehensive three-dimensional data on gait kinematics. However as expensive and bulky equipment is required, with training and time required to understand the complex data produced, computerised motion analysis is limited to use in research laboratories (Bethoux and Bennett 2011), and would not be feasible in the clinical surroundings of this study.

Computerised walkways to measure temporal and spatial parameters of gait are embedded with sensors to identify the pressure from footfall. These walkways can be transported easily and taken to different study sites. By combining temporal and spatial parameters, a functional ambulation profile, provides a quantifiable measurement of gait (Walsh 1995). Consequently, information is generated to help identify gait abnormality in individuals.

One system to measure gait parameters is the GAITRite system (CIR Systems), which is a 4.5m carpet embedded with sensors and linked to a computer. More recent MS literature, shows that computerised walkways, such as the GAITRite system are becoming more popular (Smedal et al 2006; Newman et al 2007; Givon et al 2009; Motl et al 2012). Givon et al (2009) showed that the GAITRite system can highlight compromised gait patterns in those with MS who have a very low level of disability.

For this study, temporal parameters of gait were established including; walking cadence (WCa), walking velocity (WVel) and step time. As were spatial parameters of gait; left (LSL) and right leg step length (RSL). Gait cycle, single support time and double support time were also recorded although not included in this thesis. Finally overall walking performance was established with Functional Ambulatory Performance (FAP). The measured parameters are similar to those assessed by past authors using the GAITRite system (Newman et al 2007; Givon et al 2009; Motl et al 2012). A description of each parameter is provided in Table 3.1.

Table 3.1 Temporal Spatial gait parameter measured with the GAITRite system.

Variable	Description
Cadence (WCa)	Number of steps per minute
Velocity (WVel)	The distance walked divided by the ambulation time
Step length (left LSL & right RSL)	The distance from the heel point of the current footfall to the heel point of the previous footfall in the opposite foot (this would be a negative value if the participant does not clear the first foot with the second).
Step time (left LST & right RST)	The distance from first contact of one foot to the first contact of second foot
Functional Ambulation Profile (FAP)	Numerical representation of gait (overall walking performance)

(CIR Systems 2010)

Feasibility

Measuring temporal spatial parameters using the GAITRite system presents a quick and easy assessment, producing quantitative data on gait patterns which many other walking tests do not. The system is quick to set-up and requires minimal analysis. However, its expense and requirement for training indicate that the outcome measure is best suited for research purposes. The literature does not specify whether shoes should remain on or off for testing (Newman et al 2007; Givon et al 2009), however consistency is recommended.

Validity and Reliability

Limited reliability data on temporal spatial gait parameters, which have been established with the GAITRite system, is available. However in an MS population (n=13, mean EDSS = 6) temporal spatial parameters, measured with the GAITRite system, have been found to correlate well with both the T25FW and the TUG. Sosnoff et al (2011) found that walking velocity scores correlated with the T25FW (ICC=0.93) and the TUG (ICC=0.93) and that FAP scores correlated with the T25FW (ICC=0.82) and TUG (ICC=0.88).

ICF domain and category

The data gathered from the temporal spatial gait analysis captures information on body functions and structures, such as; gait pattern functions and structure of the lower extremity. It also captures data on activity and participation, such as; walking and moving around (World Health Organization 2002; Coenen et al 2011).

Strengths and limitations

In summary, assessing temporal spatial gait parameters provide a comprehensive quantitative gait analysis. There is limited data available on the psychometric properties, in comparison with more traditional outcome measures, although evidence suggests it correlates well with other short mobility outcome measures. The expense and training required for this system may limit its use although its use is recommended within the MS literature (Bethoux and Bennett 2011).

3.9.4 Timed Up and Go

Mobility is only one aspect of function. Other components of function, such as balance and orientation around objects are not collected with straightforward mobility assessments, such as the T25FW. Therefore the Timed Up and Go (TUG) test, a functional measure of mobility, global leg strength and balance ability was also used in this study. The TUG, is a generic outcome measure originally designed for use in the elderly population (Podsiadlo and Richardson 1991). Participants are timed standing up from a chair, walking around a cone (placed 3 m from the chair) and sitting back onto the original chair. It is reportedly used by over half of surveyed British neurorehabilitation physiotherapists (Yoward et al 2008) and is used in MS research (Nilsagard et al 2007; Cakt et al 2010; Sabapathy et al 2011; Vore et al 2011).

Feasibility

The test is simple and cheap to perform, with minimal training required, although as with all the outcome measures it is important to follow standardised protocol.

Reliability and Validity

In a test re-test study of 43 participants with MS (EDSS 3-6) (Nilsagard et al 2007), reliability was found to be good (ICC=0.91) when tested one week apart. An ICC of 0.86 was found for the 24 participants in the study with an EDSS greater than 4. Although four physiotherapy assessors collected data, the same physiotherapist tested the same participant at both time points. Unfortunately, the experience level of the physiotherapists was unreported; this is regrettable as experience of assessor may influence results (Richards et al 2000). Clinical significance of the

TUG, indicated by the MDC score, has not been determined in the MS literature. However for those with Parkinson's disease the MDS score has been found to be 11 seconds (s) the mean score for the TUG was 15s (10s SD) (Steffen and Seney 2008), highlighting that the score required to indicate a clinically significant change was very large, relative to the mean score. There are no reports of the precision of the TUG, measured with SEM, in the MS literature.

In an MS population Nilsagard et al (2007) found good correlation (ICC=0.83) between the TUG and the 10MWT, which supports the validity of the TUG as a mobility outcome measure.

ICF domain and category

The TUG captures data on body functions and structures, such as muscle functions, and control of voluntary movement function. It also captures data on activity and participation, for example changing body position, walking and moving around (World Health Organization 2002; Coenen et al 2011).

Strengths and limitations

As stated, the test is simple to perform, and has reasonable psychometric properties. However depending on the focus of the TUG's use, its ability to capture data on both mobility, strength and balance can be both a strength and weakness. The TUG may be a good functional measure however it may be limited as a measure of individual impairments.

Further work

Further work on the reliability, clinical significance, precision and validity of the TUG would strengthen the previous findings of other authors. Thus to add to the current knowledge on the reliability of the TUG, and to determine clinical significance and precision in a group of people moderately affected with MS the TUG was included in Study 3.

3.9.5 Berg Balance Scale

The ability to maintain balance during physical activities is important in daily life. It is based around an individual's peripheral sensory system's ability to react to the external environment and provide vestibular, visual and proprioceptive feedback to the CNS and back, via the peripheral motor system, to the postural muscles in the body (Ruhe et al 2010). However, as has been discussed in Section 2.2.3 a deficit in balance is common amongst the MS population (Frzovic et al 2000; Cattaneo et al 2007a).

There are different outcome measures to assess balance, in this section a focus will be made on those which are task orientated, and assess functional dynamic balance.

Some balance measures to assess functional dynamic balance have been used in the MS therapeutic exercise literature, such as the Equiscale. However, the Equiscale, based on other measures of balance (the Berg Balance Scale (BBS) and the Tinetti Balance assessment) has been rarely used in the MS therapeutic exercise literature. Furthermore as the Equiscale is not freely available, it would havelimited clinical applicability. The Tinetti balance assessment (Tinetti 1986), includes nine-items on balance and eight-items on gait), it is used by 17% of physiotherapists working in neurology in the UK (Yoward et al 2008), however it is not common in any MS therapeutic exercise studies. Moreover, with a focus on both balance and gait, the Tinetti assessment does not focus solely on balance. Since these scales are not commonly used, it would be difficult to compare findings, and hence reach conclusions from the study results.

The more commonly used measure of balance in MS, the BBS, was therefore chosen for this study. In the survey of commonly used outcome measures 71% of neurophysiotherapists used the BBS (Yoward et al 2008). It is a generic, assessor rated measure of functional balance, originally designed for use in the elderly population by Berg (1989). The participant performs 14 tasks (of increasing difficulty e.g. “Sitting to standing”, “Standing unsupported”, “Standing unsupported with eyes closed”, “Standing on one leg”), measured on a 5-point ordinal scale. A maximum score of 56 can be achieved, with higher scores indicating better balance.

Feasibility

The BBS is cost effective and requires minimal equipment and training; however it may take 15-20 minutes to complete, longer than other balance measures (Tyson and Connell 2009).

Reliability and validity

In 19 people with MS (EDSS <6.5) test re-test reliability of the BBS measured one week apart was found to be good (ICC=0.99), with inter-rater reliability also good (ICC=0.85) (Paltamaa et al 2005). In Paltamaa et al’s (2005) study, the physiotherapy assessors had different levels of experience using the outcome measure. This not only strengthens the findings but also improves the clinical applicability of the BBS.

In a less disabled MS population (where only one third of participants used a walking aid – EDSS unclear) similar results were found when two experienced neurorehabilitation physiotherapists, assessed the reliability of the BBS 3 days apart. Inter-rater reliability was found to be high (ICC=0.96) (Cattaneo et al 2007b).

No studies reporting the clinical significance (MDC) of the BBS could be found in the MS literature, however in Parkinson's disease a clinically significant change of 5 points was indicated, with the mean score being 50 points (SD=7) (Steffen and Seney 2008). In a post stroke population the MDC for the BBS was 7 points when the mean score was 43 points (Stevenson 2001). Paltamaa et al (2005) established precision (SEM) of the BBS to be less than 1 point in a group of people moderately (EDSS mean=5.26) affected with MS.

Cattaneo, Regola and Meotti (2006) validated the BBS with other measures of balance in people with MS and found a moderate correlation (r=0.48) with the Activities Balance Confidence scale (ABC), although this correlation does suggest the two outcome measures are capturing different information. This is of interest as the ABC was also used in this study (Section 3.9.9). The BBS is an assessor rated measure, whilst the ABC is a self-rated measure, which may explain the correlation. Like any scale with a maximum score, the BBS may be vulnerable to a ceiling effect, whereby participants may achieve the top score, and any improvement will not be captured by the scale

ICF domain and category

The BBS captures data on body functions and structures, such as; vestibular function and proprioceptive function. It also captures data on activity and participation, such as; maintaining and changing body position (World Health Organization 2002; Coenen et al 2011).

Strengths and limitations

The BBS has reasonable reliability and validity and has practical clinical use.

Further work

There is a need to clarify the psychometric properties of the BBS across the disability range in MS. The reliability of the BBS would strengthen the results found by Paltamaa et al (2005) and Cattaneo et al (2007b) and would strengthen results of studies using this outcome measure. As such the BBS was included in Study 3 (Chapter 6).

3.9.6 Assessment of Overall stability

Overall postural stability is important for maintaining an upright posture and for maintaining balance during normal activities of daily living. With deficits in balance, such as those found in MS, reducing the body's ability to maintain a static posture and leading to an increased body sway from the centre point (Karlsson and Frykberg 2000). In this study, static balance is defined as the

ability of the participant to maintain their Centre of Pressure (COP – the central point of pressure applied to the foot during contact with the ground (Winter 1995; Ruhe et al 2010)) in static stance.

When attempting to maintain static stance, any movement by the participant, resulting in movement of the COP anteroposteriorly, mediolateraly or an axis between these movements, provides an indicator of Overall Stability (OS) (Winter 1995; Arnold and Schmitz 1998).

This data can be determined using static force-plates or moveable balance plate analysis. Force plates are rigid electronic plates, on which the participant stands; the plate records the position of the COP when is then, through software packages, used to calculate the net COP and the displacement of the COP from this reference point during the test (Gibbs 1997). However, the use of force-plates is somewhat limited as they may not challenge static stance, and hence may not provide the best data on OS (Karlsson and Frykberg, 2000).

However, a moveable balance plate provides an unstable platform on which a participant stands, which captures similar data to a force plate. Therefore a balance plate may replicate more challenging environments. For example, the moveable platform may mimic the challenge of maintaining balance whilst standing on a train or bus. For this reason and due to the availability of equipment, a moveable balance plate was used in this study, this collected data on the movement of the COP as an indicator of OS.

In this study, the Biodex Stability System (Version 1.3) balance plate was available to provide an objective measure of overall stability (OS). The balance system comprises a freely moving platform, connected to a computer, which measures overall stability (Figure 3.3). The participant stands on the platform, and attempts to maintain a static posture (and maintain the balance plate in a horizontal position), whilst doing so the balance plate and computer calculate any movement of the COP from the central point, and record this movement in degrees, providing the OS. Lower scores indicate a better ability to maintain the COP, and from this indicate better overall balance stability.

Figure 3.3 Maintaining static stance on balance plate

The stability of the balance plate can be predetermined to one of eight different levels, the most stable test (level 8) permits minimal movement (from horizontal) of the platform. The protocol for the static balance assessment in this study was designed based on past literature (Aydog et al 2006; Ghoseiri et al 2009) and pilot work (Section 4.2.11).

Feasibility

Once installed the system is quick to set-up and requires minimal analysis. Its expense and requirement for training indicate that this outcome measure is best suited for research purposes.

In addition to its research use, it can be used as a rehabilitation tool, offering biofeedback on the patient's balance performance, and thus has clinical use. It is suggested that more than two trials be performed and that fatigue may impact performance (Cachupe et al 2001). In this study, testing was limited to three 20 second trials (further protocol detail can be found in Section 4.2.11).

Reliability and Validity

The Biodex balance system has been found to be reliable in those with Parkinson's disease (Ghoseiri et al 2009) and rheumatoid arthritis (Aydog et al 2006). Unfortunately no formal validity study could be found using the Biodex balance system in Multiple Sclerosis.

ICF domain and category

The assessment for OS captures data on body functions and structures, such as; vestibular function and proprioceptive function. It also captures data on activity and participation, such as maintaining a body position (World Health Organization 2002; Coenen et al 2011).

Strengths and limitations

In summary, capturing data on overall stability using the Biodex system provides a continuous scale of balance. However there is limited evidence of its past use in MS, this may be due to its expense making the outcome measure appropriate mainly for research use.

3.9.7 Quadriceps strength

Deficits in strength, particularly in the lower limb are common in MS (Matthews 1998; Motl et al 2008b). In addition the deficits may be more evident on one side of the body (Confavreux and Vukusic 2008). Assessing strength in MS is made more complicated by other confounding factors related to the damage found within the nervous system and physical fatigue. For example, muscle tone (spasticity) may be altered in those with MS leading to joint contractures (Tripp and Harris 1991) causing pain and limiting movement.

There are a number of different outcome measurement tools used in the MS therapeutic exercise literature to assess strength and changes to the properties of participants' muscles. This makes comparison of results difficult. Testing muscle strength using electromyogram (EMG) methodology has been used in some studies (Harvey et al 1999; de Souza-Teixeira et al 2009), EMG measures the electrical conduction across muscle fibres during a muscle contraction. Electrodes are placed on the skin, directly over the muscle of interest with the signal sent to a computer. However the quality of the information gathered from this outcome measure can be affected by the thickness of the skin and subcutaneous fat and the contact between the skin and electrodes (Day 2002). Unfortunately, the equipment required for the EMG method of assessing muscle properties was not available for this study. Other therapeutic exercise studies have used large-scale resistance equipment (such as the static weight machines found in exercise gyms) (Dodd 2011; Filipi 2011; Taylor 200; Dalgas 09/10), or large-scale dynamometers (Gutierrez et al 2005; de Souza-Teixeira et al 2009; Broekmans et al 2011; Hayes et al 2011) to assess strength. Unfortunately these methods were impractical for the clinical setting of this study. Instead a Hand-held Dynamometer (HHD) which would provide an accurate measurement, whilst also being practical for the clinical setting, was used in this study.

In general most studies have used a maximum voluntary contraction (MVC) to assess muscle strength deficits, in this study the strength of participants' quadriceps was assessed using a MVC

measured with a HHD. The technique involves positioning the participant and HHD to isolate the muscle group of interest. A MVC was assessed using a "make-test", which is preferred for those with neurological conditions where spasticity may be problematic (Bohannon 1995). To ensure reliability in all assessments the length of the lever arm was also recorded (from the apex of the patella to the anterior of the Medial Malleolus where the HHD was placed), from this, torque was calculated, providing a quantitative measure of leg strength.

In addition, the following points were considered in the design of the protocol. To avoid an increase in muscle tone during testing, past literature on strength training in persons with spastic hemiparesis was consulted. Tripp and Harris (1991) compared the reliability of five "make tests" using an isokinetic dynamometer in 20 people post stroke. Although this testing was not carried out using a hand-held machine the rest period between each trial was of interest. In Tripp and Harris' (1991) study, the rest period was dictated by the readiness of the participant to carry out the next trial. This resulted in good reliability across the five trials and no increase in muscle tone. To minimise the risk of increased muscle tone during this study, and allow for the impact of physical fatigue the MVC was recorded three times, with a minimum of 30 s rest between each trial, once the participant was ready.

The Lafayette HHD (Model 01163) was used, with higher scores, representing increased strength. In MS leg weakness often presents asymmetrically (i.e. unilateral weakness) (Confavreux and Vukusic 2008), thus weaker (WLS) and stronger leg (SLS) strength was assessed to allow comparison between the two.

Feasibility

The Lafayette HHD is portable (Figure 3.4), affordable and requires minimal training. Morris et al (2008) suggests that three trials are adequate to establish reliable strength values. An initial cost will be involved. However, the HHD can be used both clinically and for research purposes. As with all outcome measures strict protocol must be used to ensure good reliability.

Figure 3.4 Hand-held Dynamometer

One pence coin provided to demonstrate scale.

Reliability and Validity

Bohannon et al (1995) discussed that HHDs have been found to be reliable in a range of neurological conditions, mainly post stroke. Unfortunately there is minimal research on the reliability and validity of this method of measuring quadriceps strength in MS. Morris et al (2008) assessed reliability of HHD quadriceps testing using the Lafayette model, in a group of patients following traumatic brain injury. Test re-test scores were good (ICC = 0.92). The protocol, regarding sitting position, used in Morris et al's (2008) was adopted in this study (Section 4.2.5) .

In healthy adults Martin et al (2006) assessed the validity of the Lafayette (model 01163) HHD by comparing its performance with the Biodex isokinetic dynamometer, described as the "gold-standard" of muscle strength measurement in healthy adults. Results suggested that the Lafayette HHD correlated well (r=0.91) with results from the Biodex isokinetic dynamometer.

ICF domain and category

Measuring quadriceps' strength captures data on body functions and structures, such as; muscle power functions, muscle tone functions, motor reflex functions and structure of lower extremity (World Health Organization 2002; Coenen et al 2011).

Strengths and Limitations

Measuring both weaker and stronger leg quadriceps strength using the HHD provides a good measure of strength. The Lafayette model is practical and has diverse application as it can be easily carried around and used to measure strength on a number of different muscle groups.

In general, measuring muscle strength in those with MS is vulnerable to increased muscle tone and fatigue affecting results; however an effort was made to allow for this in the assessment protocol. There is a need to clarify the best outcome measure to monitor strength in MS with more data required on the reliability and validity of this outcome measure in MS research.

3.9.8 The PhoneFITT

Monitoring activity is important; with past research suggesting those with MS may be less active than the general population (Mostert and Kesselring 2002; Motl et al 2005; Sandroff et al 2012), increasing the risk of health problems associated with inactivity (Motl et al 2011). Different methods are available for reporting physical activity behaviour including; activity diaries (Ghione et al 1993), physical activity questionnaires (Mostert and Kesselring 2002) or electronic motion detection/accelerometers (Motl et al 2009b; Weikert et al 2010). Despite this, levels of physical activity are not well reported in the MS literature.

Activity diaries may be limited as there are no standardised activity diary formats available, thus self-designed diaries would require piloting and validation before being used in an intervention trial such as this. Furthermore, they rely on participants' remembering to complete the diary on a regular basis and much time may be required to input/interpret the responses from study participants.

Accelerometers are small (matchbox size) electronic devices, worn on the body to accurately measure motion (Hale et al 2008), they are becoming more prevalent in the MS literature (Hale et al 2008; Snook et al 2009; Motl et al 2009b; Weikert et al 2010). They have, for example, been used in cross sectional studies lasting seven days (Snook et al 2009; Motl et al 2009b) or in one off testing occasions to access their psychometric properties (Hale et al 2008; Weikert et al 2010). However, to the author's knowledge they have not been included in any MS therapeutic intervention studies. For this study, which had an intervention of 12 weeks and follow-up of up to a year it was not practical to expect participants to wear an accelerometer for this length of time.

However, self-reporting questionnaires are a simple, cheap method used to report physical activity. In MS therapeutic exercise literature the BAECKE Activity Questionnaire (BAQ) was used by Mostert and Kesselring (2002). However, this outcome measure may suffer a floor effect by being

aimed at a more active population, with many questions about activities at work. Thus was less appropriate for the participants in this study.

The PhoneFITT (PF) (Gill et al 2008) activity questionnaire is a generic outcome measure initially designed to be administered easily over the telephone and be applicable to an elderly population. Unlike the BAQ it also captures data on basic activities of daily living (such as carrying light loads) and exercise activity (such as bicycling), thus is more appropriate in a less active population.

The PF questions physical activity in relation to Frequency, Intensity, Type and Time (FITT) (Franklin et al 2000). Participants recount the time spent, and how often, in a typical week in the past month, they undertake particular activities. The option to include other personal activities is provided. To establish intensity; participants comment on their breathing during discussed activities. An example of a typical question is provided in Table 3.2. For analysis in this study, scores were totalled according to the original author's protocol. In summary, the number provided at Q2, plus the number (1-4) chosen at Q3 and the number (1-3) chosen at Q4. The scale has no upper limit, and thus it is not vulnerable to a ceiling effect, with higher scores representative of more activity.

Table 3.2 Example of typical PhoneFITT question

Activity	**Q1 Participated**	**Q2 Frequency (number of times per week)**	**Q3Duration**	**Q4 Intensity**
(In a typical week in the past month have you done) Walking for exercise	1□Yes 2□No		1□1 - 15 min 2□16 - 30 min 3□31 - 60 min 4□1 hour +	1□Breathing NORMALLY and able to carry on a conversation 2□SLIGHTLY out of breath BUT still able to carry on a conversation 3□TOO out of breath to carry on a conversation

Feasibility

The questionnaire is administered as an interview, it is a multidimensional scale and some assessor training is required on its use. The scale can be completed in five to ten minutes, and is appropriate for both clinical and research purposes.

Reliability and validity

To the author's knowledge no data is currently available on the use of the PF in MS. In a preliminary study in a group of older adults the PF was found to be moderately reliable (ICC=0.74) when tested one week apart (Gill et al 2008). However, much work is required on this relatively new outcome measure.

ICF domain and category

The PF captures data on activity and participation, such as; carrying out daily routine, undertaking tasks, recreation and leisure and moving around (World Health Organization 2002; Coenen et al 2011) .

Strengths and Limitations

The PF captures data on simple activities of daily living through to exercise based physical activity using both a nominal and ordinal score, with the potential to gather information on additional participant activities. However, this makes comparison between participants difficult. The reliability and validity of the PF requires further research.

3.9.9 Activities Balance Confidence scale

In addition to assessor rated (BBS) or instrumented (OS) measures of balance, participants' self-reported balance, and their balance confidence whilst undertaking activities of daily living is important. Two self-reported measures of balance are used in the therapeutic exercise in MS literature, the Dizziness Handicap Inventory (DHI) and the Activities Balance Confidence scale (ABC) (Powell and Myers 1995). Cattaneo et al (2006; 2007b) have assessed the validity and reliability of both , finding the ABC to have better reliability and validity. The ABC is also shorter and gathers information particularly on balance, consequently for this study the ABC was used.

Fifteen items, related to balance confidence, are included in the ABC questionnaire (e.g. "How confident are you that you will not lose your balance or become unsteady when you... walk up and down the stairs") and asks participants to rate these on a 10-point scale. The ABC was developed by Powell and Myers (1995) and was initially used in an older adult population.

Feasibility

The scale can be completed in five minutes and as such can be used in both clinical and research settings

Reliability and Validity

In addition to the above work by the original authors Powell and Myers (1995), the test-retest reliability has been assessed in a study of 25 individuals with MS who were hospital in-patients (Cattaneo et al 2007b), with reliability reportedly good (ICC=0.92) when repeated three days apart. In an earlier study with 51 MS participants the ABC was found to correlate moderately (r=0.48) with the BBS (Cattaneo et al 2006), as discussed in Section 3.9.5.

ICF domain and category

The ABC captures data on body functions and structures, such as perceptual function. It also captures data on activity and participation, for example undertaking multiple tasks and lifting and carrying objects(World Health Organization 2002; Coenen et al 2011).

Strength and limitation

The reliability and validity of the ABC have been found to be reasonable in an MS population. The outcome measure is self-completed and thus vulnerable to patient reporting (for those who may have cognitive or manual dexterity problems).

3.9.10 Fatigue Severity Scale

Fatigue is an important symptom found in many people with MS (Motl et al 2008b). Fatigue in MS is different to fatigue experienced in a healthy population. Krupp et al (1988; 1989), found that fatigue experienced in MS (more so than in the healthy control group in their study) may prevent sustained physical functioning, be worsened by heat, have a sudden onset and cause frequent problems. Furthermore, quantitative measurement of fatigue in MS can be difficult as descriptions of fatigue may vary across the MS population; a single person may have difficulty describing their fatigue and report it in a number of ways (Chipchase et al 2003).

Despite this, self-reporting outcome measures are thought to be one of the best methods of gathering fatigue information as it is the respondent's own report of what they are experiencing. A number of different fatigue outcome measures are available. For example the Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS) or the Multidimensional Fatigue Inventory (MFI). The MFIS and the MFI are longer questionnaires and used less frequently in the therapeutic MS literature (Andreasen et al, 2011). Thus the Fatigue Severity Scale (FSS), developed for use in MS (Krupp et al 1989) was used in this study. Participants rate their agreement to nine items related to fatigue on a seven-point Likert scale (e.g. "I am easily fatigued"). Scores are totalled and divided by nine, higher scores are indicative of fatigue being more severe.

Feasibility

The FSS may be completed in less than five minutes. It requires no training and minimal explanation and is therefore feasible for use both clinically and in research.

Reliability and Validity

The FSS has been found to have good test re-test reliability (ICC=0.84) when measured after an average of 10 weeks in a sample including those with MS (Krupp et al 1989). The FSS showed good discrimination between those with MS and healthy controls with the differences in scores highly significant (Chipchase et al 2003).

There are however, reports of both floor and ceiling effects in an MS population (Kos et al 2003), which must be considered when analysing the results of this outcome measure.

ICF domain and category

The FSS captures data on body functions and structures, such as; energy and drive functions, other specified (fatigue). It also captures data on activity and participation, such as; carrying out a daily routine, focusing attention and recreation and leisure (World Health Organization 2002; Coenen et al 2011).

Strengths and limitations

The FSS has been used often in MS therapeutic exercise literature, and has shown reasonable reliability in MS. Although it is a short test, being self completed it may be vulnerable to problems with participant self-reporting (for those who may have cognitive or manual dexterity problems). Furthermore, the outcome measure may be vulnerable to a floor or ceiling effect.

3.9.11 Hospital Anxiety and Depression Scale

Similar to the assessment of fatigue, mood is highly subjective to each individual; thus, self reported questionnaires are commonly used. In the therapeutic exercise in MS literature the Beck Depression Inventory, CES-D, Coopersmith Self-esteem Inventory, Major Depression Inventory, Multiple Sclerosis Self-Efficacy-Scale, Profile of Mood States (POMS) and the State-trait Anxiety Inventory have all been used. However, all except the POMS focus on one particular aspect of mood. The Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983), which was created based on clinical experience, and developed for use in the general population, captures information on both depression and anxiety. The HADS has previously been used in the therapeutic exercise in MS literature (Schulz et al, 2004), and has wider application in other MS literature (Janssens et al 2003). Containing only 14-items it is shorter, and quicker to administer than the 65-item POMS. As such, the HADS was used in this study to quantify mood, more specifically levels of anxiety and depression.

Participants are asked to rate each of the 14-items on a 4-point scale producing a total score of 42. Seven items refer to anxiety (e.g. “I get sudden feelings of panic”) and seven to depression (e.g. “ I feel cheerful”), with participants asked to rank their agreement, in relation to how they have been

feeling in the past week. A score of eight or above for either anxiety or depression has been suggested to indicate anxiety disorders or clinical depression respectively (Honarmand and Feinstein 2009).

Feasibility

The test has previously been found to be easily understood and acceptable to both patients and clinicians (Bowling 2005). Taking less than five minutes to complete it is appropriate for both clinical and research purposes; however, the measure may be vulnerable to a floor or ceiling effect.

Reliability and validity

In MS the validity of the HADS has been assessed against a structured psychiatric assessment and found to correlate well (Honarmand and Feinstein 2009). The original authors of the scale claimed good reliability when used with hospital inpatients, however further work should be done, particularly in relation to MS.

ICF domain and category

The assessment for mood using the HADS captures data on body functions and structures, such as temperament and personality functions. It also captures data on activity and participation, such as handling stress and other psychological demands (World Health Organization 2002; Coenen et al 2011).

Strengths and limitations

There is reasonable evidence of the validity of the HADS, it has been widely used in past MS research, being unidimensional and reasonably short the test is easy to understand. However, as the HADS is a self-completed outcome measure it may be difficult for those with cognitive or manual dexterity problems to complete. Furthermore it may be vulnerable to a floor or ceiling effect, although there is no report of this.

3.9.12 Leeds MS Quality of Life

Health related quality of life is reportedly studied more in MS than any other neurological condition (Mitchell et al 2005). Although there are a number of quality of life outcome measures available it is recommended that an MS specific scale be used in intervention studies (Motl and Gosney 2008). The Leeds MS Quality of Life Scale (LMSQOL) was designed specifically for MS by Ford et al (2001), and has been used in previous MS studies. Although Motl and Gosney (2008) did not include it in their review of quality of life outcome measures, from which they

recommended that intervention studies use disease specific quality of life scales (such as the MSQOL or the MSIS). They later went on to use it in a number of studies related to quality of life and physical activity in MS (Motl et al 2008a; Motl and McAuley 2009; Motl et al 2009a) , suggesting their support for this outcome measure in studies related to physical activity.

For the above reasons and as the LMSQOL is shorter than both the MSQOL (54 items) and the MSIS (29 items), the LSMQOL was used in this study. Participants' rate eight-items, on a 4-point scale, related to health and quality of life (e.g. "I have worried about my health") in relation to the past month. Lower scores are indicative of higher quality of life.

Reliability and validity

Ford et al (2001) found in people with MS (n=199, EDSS level unclear) that the LMSQOL scale showed good internal consistency and moderate test re-test reliability (ICC=0.75) when tested one month apart. The authors also provided evidence of moderate validity with general quality of life (measured with the SF-36 where the ICC equalled 0.68). In addition the LMSQOL was also able to differentiate between relapsing remitting MS and more progressive MS (Ford et al 2001).

ICF domain and category

This assessment of quality of life captures data on body functions and structures, such as temperament and personality functions. It captures data on activity and participation, such as carrying out daily routine and relationships (Coenen et al 2011).

Strengths and limitations

The scale is unidimensional, and was developed for use in MS, it has not been shown to be vulnerable to floor or ceiling effects. However, evidence of the reliability and validity of the LMSQOL are limited to the original authors work, unlike that of other MS specific outcome measures. The outcome measure is self-completed and thus vulnerable to poor patient reporting.

3.9.13 Body composition

Body composition, in particular fat distribution, is an important indicator of health, and risk of developing other health problems such as obesity and coronary heart disease, musculoskeletal problems and some cancers (World Health Organization 2000). Measuring body composition can be difficult, with special techniques required to accurately measure fat mass (Katch et al 2011). However BMI is commonly used, calculated from height and weight. Normative values are available whereby a BMI of;

- <18.5 is underweight with a low disease risk (although at increased risk of other health problems)
- 18.5<25 is normal weight, with an average disease risk
- 25<30 is overweight, with an increased disease risk
- >30 is obese with an increasing disease risk between moderate to very severe.

(World Health Organization 2000)

Body composition, measured with Body Mass Index (BMI) is rarely reported in MS therapeutic exercise literature, when it is acknowledged it is mainly as a demographic descriptor. Few studies have reported on the effect of an exercise intervention on BMI in MS, of those that have reported BMI before and after an intervention no significant changes have been found (Petajan et al 1996; Hayes et al 2011).

Feasibility

Measuring BMI is based on participant's height and weight, which can easily be measured clinically.

Reliability and Validity

As discussed there is limited evidence of the use of BMI in MS research, thus there is no data on its reliability and validity in this patient group. Like all outcome measures, strict protocol and calibration of tools (i.e scales and stadiometer) are required to ensure validity and reliability.

ICF domain and category

BMI captures data on body functions and structures, such as weight maintenance functions. This does not appear in Coenen et al's (2011) core set for MS, however is an important descriptor of health status.

Strengths and limitations

BMI is a simple clinical test, which provides a crude representation of body composition. The outcome measure has well known limitations in the exercise literature. For example, those with a higher bone or muscle mass may be incorrectly classified. Furthermore the numerical value provides no information on body proportion (important, as the distribution of fat around the body is a predictor of disease risk) (Katch et al 2011).

3.9.14 Goal Attainment Scale

The Goal Attainment Scale (GAS) (Kiresuk and Sherman 1968) was used to assess achievement of participants goals. Although it is not commonly used in research, clinically it can be used to compare between individuals and different forms of health services (Playford et al 2009). A list of relevant goals are created, by the researching healthcare professional, from this list the participant and researcher consider what goals the participant may like to achieve (commonly three goals). Once chosen the participant and researcher discuss and decide the chosen goals in order of importance (from 1-3) and weigh the possibility of achievement (from 1-3). The overall goal attainment scale score, on completion of the intervention, is calculated using an automated Microsoft Excel spreadsheet (Turner-Stokes 2009), which applies a standard mathematical formula, as described below;

$$\text{Overall GAS} = 50 + \frac{10\Sigma(W_i X_i)}{\sqrt{(0.7\Sigma W_i^2 + 0.3(\Sigma W_i^2))}}$$

Where:

wi = the weight assigned to the *i*th goal (if equal weights, wi = 1)

xi = the numerical value achieved (between –2 and + 2).

Earlier MS literature has suggested that the GAS should be used alongside other outcome measures (Khan et al 2008a), such as those described in this chapter. A modified version was used in this study, based on past recommendations to improve the practicalities of its use (Turner-Stokes 2009).

Reliability and Validity

Unfortunately no literature on the psychometric properties of the modified GAS could be found, however the scale is unique and modifiable to the individual, this may explain the difficulties in assessing these properties. Further work is required in this area.

Feasibility

The outcome measure requires groundwork on the part of the researcher or clinician to establish relevant goals, discussion is also required to establish the unique goals of each participant. Details of how the GAS was used in this study are given below.

In accordance with the methods of Turner-Stokes (2009) a list of 12 possible goals (with a 13th 'personal' goal) was created related to the outcome measures discussed in this chapter.

To establish "Best anticipated outcome" (the +2 score) it was important that achievement of the chosen goal was based on the literature or expert clinical judgement. Thus a thorough search of the relevant literature was made to establish what changes in each outcome measure would be required to indicate clinical improvement. Where possible the "Best anticipated outcome" (the +2 score) score was based on MS literature, and/or where reliability studies had been carried out to determine relevant clinical change. A discussion with the Consultant MS physiotherapist was carried out to provide expert advice on what clinical improvement may be anticipated in the patient population of interest. This created the recommended 5-point scale (between -2 and +2) for each goal;

- +2 Best anticipated outcome
- +1 More than expected outcome
- 0 Expected outcome
- -1 Less than expected outcome
- -2 Unfavourable outcome

A brief explanation follows as to the rationale from the literature regarding the "Best anticipated outcome (+2)" for achievement of the 12 chosen goals. Achievement of the other parameters (+1, 0, -1 and -2) were chosen through discussion with the Consultant MS physiotherapist, based on the +2 score. It is acknowledged that these are limited in many cases by 1) the evidence being in a disease population where symptoms and management are different to those experienced in MS, 2) the participants in this study presenting with a wide range of disability levels. However, this later point was addressed by use of percentage changes in scores for each individual, rather than a finite score.

Establishing the Best Anticipated Outcome (+2 score)

For the T25FW past studies in MS have suggested a clinical change of 16% would indicate a clinically relevant change (Kaufman et al 2000; Schwid et al 2002; van Winsen et al 2010) . As such, relevant values were chosen to establish +2 achievement (with lower scores a percentage of this), these are provided below. The Best anticipated outcome (+2) score will be provided for the other outcome measures discussed overleaf.

- Best anticipated Outcome (+2 score) - Reduction in time to walk 25 ft by >16%
- More than expected outcome (+1 score) - Reduction in time to walk 25 ft by 10-15%
- Expected outcome (0 score) - Reduction in time to walk 25 ft by 1-9%
- Less than expected outcome (-1 score) - No reduction in time to walk 25 ft
- Unfavourable outcome (-2 score) - Increase in time to walk 25 ft

For the 6MWT, work done in Alzheimer 's disease was used (Ries et al 2009), where a 4% difference in walked distance implied clinical change. Thus, the +2 achievement score was based on this.

To determine achievement of improving quadriceps' strength, (i.e. +2 achievement) a change of >26% was found in the Traumatic Brain Injury literature (Morris et al 2008), this was used as a basis to determine goal achievement. Achievement of TUG performance was based on work done in Alzheimer 's disease by Ries et al (2009); where an improvement of 17% indicated clinical change.

The Best Anticipated Outcome score for the BBS was established from studies involving participants with Parkinson's disease (Steffen and Seney 2008), where for those requiring walking aids a change of 7 points (12.5%) would imply clinical change. Improvement in OS was difficult to determine, as minimal literature is available on the outcome measure (Biodex balance system), therefore a percentage overall improvement was linked to work done by Steffen & Seney (2008) for the BBS, with a 12.5% improvement considered to imply a clinical change.

For the ABC scale the 13% value to indicate clinical change in a study on Parkinson's disease was used (Steffen and Seney 2008). For the FSS MS literature which involved therapeutic exercise (similar to that of this research) was used (Newman et al 2007; Dalgas et al 2010), where an 8% improvement may indicate clinical change, and thus the +2 score. Similar rationale was used for the HADS, where a physiotherapy exercise intervention for people with MS found a change of 10% (Wiles et al 2001).

To determine if participants had improved in a goal to "improve quality of life" (based on the LMSQOL) results from a past physiotherapy study (Miller et al 2011), which noted an improvement of 10%, were used to determine +2 goal achievement.

A goal related to social interaction was included, as this has been found to be an important outcome in group exercise classes (Dodd et al 2006; Smith et al 2009). To determine achievement of this goal an arbitrary outcome based on making contact with others outwith the class was chosen as the +2 outcome. Finally a goal related to attendance at the exercise programme was based on an attendance of 80%, as past studies with similar weekly classes reported class attendance of 80% or more (Taylor et al 2006; McCullagh et al 2008; Dalgas et al 2009).

Strengths and limitations

The GAS captures data on participants' unique goals and can be used to guide and motivate an intervention, it allows for both over and under achievement of goals.

Calculation of goal attainment is based on establishing different levels of expected outcomes, this requires knowledge and experience. Furthermore, it may be difficult to predict outcomes in a heterogeneous disabled population, as each individuals capacity to achieve a goal may be different. In this study, goals were linked to outcome measures assessed at baseline and also week 12, where achievement of goals was based on percentage changes rather than an actual score. This was judged a pragmatic solution to allow for those with different abilities to be compared on a similar scale. However, the limitations of this are accepted.

3.10 Focus groups

A secondary aim of this work was to elicit participants views on exercise and the exercise intervention, including; personal goal attainment, positive and negative outcomes associated with the intervention, and intrinsic and extrinsic factors to participation in, and completing, the intervention. To achieve this aim focus groups were undertaken for the qualitative study (Study 2) discussed in Chapter 5.

3.10.1 Gather the views and opinions from study participants

There are options available to gather study participants views, questionnaires could be completed, or qualitative methodology such as one to one interviews or focus groups could be undertaken.

Self-designed questionnaires with topics specific to the intervention would be one method to gather views and opinions from participants in this study, with a need to pilot and validate the questionnaire prior to its use. Questionnaires limit the depth of explanation in a participant's answer, and answers are limited to pre-determined questions only. Furthermore, unless questionnaires are returned to the researcher immediately they are vulnerable to respondents not returning the questionnaire at a later date. In addition, discussion is not possible meaning there is less opportunity to gain insight into different viewpoints (Denscombe 2007).

One benefit of questionnaire based research is that it can gather concise information from a large group of people. However, as small numbers were anticipated for this study, it was felt that qualitative methodology should be adopted. There are examples of qualitative research, using one to one semi-structured interviews, in the MS therapeutic exercise literature (Dodd et al 2006; Smith et al 2009; Plow et al 2009b). The studies by Dodd (2006) and Plow (2009b) are the qualitative part of mixed methodology studies, whereby qualitative data complements other findings (Creswell and Plano Clark 2007).

However one to one interviews are limited in that discussion is restricted to one participant, with analysis of other interviews (with different participants) done by the researcher later. In addition

they can be time-consuming and may not produce natural responses from participants (Creswell and Plano Clark 2007; Denscombe 2007).

The intent of the study was to stimulate discussion and debate between participants, as groups were already formed from the group nature of the intervention, focus groups were a practical and sensible choice to gather the views and opinions of the study participants. Focus groups are a well established qualitative method of gathering views and opinions from a group of people (Morgan 1998). Undertaking focus groups had other advantages such as participants being able to relate to one another's views, whilst questioning, challenging or agreeing with each other (Kitzinger 1995).

Credibility of focus group data

As with the clinical (quantitative) outcome measures previously described, it is important that rigor and validity be preserved when undertaking focus group research. There is much debate in the health sociology literature about the relevance of establishing rigor and validity (Rolfe 2006; Freeman 2006). At a basic level Fern (2001) discusses that, fundamentally, the methods employed, such as; the group composition, the number of groups and participants, the location, the moderator (researcher) and the analysis can all impact validity. He also contests that validity is to be judged by the reader. Fern's (2001) rationale was used when establishing the methodology for Study 2 (Chapter 5).

Strengths and limitations

There are a number of advantages to focus groups. They work well to "focus" the opinions of those with a commonality or who are undertaking a collective activity (Kitzinger 1994), for example those with MS who have undertaken a group exercise class together. The well conducted focus group can encourage participation from those who are reluctant to partake in one-on-one interview or who may feel their views are not relevant (Kitzinger 1995) . They can gather differing views and opinions, can help establish motivations, are deemed to be reasonably quick and easy to set-up and can be used both to educate the group, and gather opinions on service improvement (Morgan 1996). In comparison with one-to-one interviews, focus groups may be more natural; encourage participants to interact, exchange anecdotes, whilst questioning and commenting on shared experiences (Kitzinger 1994; Wilkinson 1998). Thus Focus Groups were appropriate for the group nature of this study.

Nevertheless, there are also some limitations to focus groups. Unlike other forms of data collection confidentiality is compromised with all group members aware of others' views, once expressed. Furthermore the more articulate group member may perhaps silence a less confident participant (Kitzinger 1995). The research is difficult to recreate, even with the most skilled moderator leading

the group, furthermore the risk of the moderator influencing the group may be regarded as creating a bias, which has been described as a "cardinal sin" in qualitative research (Fern 2001). In comparison with one-to-one interviews it is difficult to establish depth to participants' opinions (Wilkinson 1998).

3.11 Summary and conclusion

By reflecting on the outcome measures used in the therapeutic exercise studies described in Chapter 2, and the outcomes discussed in this Chapter it is clear that there are many available outcome measures to assess the range of limitations and consequences of MS. Thus, much empirical data can be gathered to guide rehabilitation and exercise prescription.

For this study, outcomes were chosen which would capture data on the physiological, functional and psychological status of participants. Outcome measures which showed the best feasibility, reliability and validity in relation to both the study population and the methodology were chosen to capture the wide range of areas the intervention sought to address.

This chapter provided a literature background which focused on the methods chosen to establish the aims of the study. An initial discussion on the clinical outcome measures chosen, and why was followed by a discussion on the use of focus groups. It was highlighted, however, that there is a need to address the lack of data on the strength of outcome measures used in MS therapeutic exercise literature, particularly for those who have moderate MS (e.g. EDSS 5-6.5). The next three chapters will describe the studies undertaken as part of this thesis. Before a discussion of how all three studies may guide future clinical practice and research agendas.

4 Study 1

The effects of a 12-week leisure centre based, group exercise intervention for people moderately affected with Multiple Sclerosis

Three investigations were completed as part of this thesis, the first and main investigation assessed the impact of a twelve week combined exercise intervention, for people with moderate MS. Participants from the main investigation (described in this Chapter) were also participants in the other two studies. Some outcome measures used in the main investigation were assessed for reliability, with this work discussed in Chapter 6 of this thesis.

4.1 Introduction and rationale

A number of studies have used exercise interventions to manage the clinical symptoms associated with MS (Section 2.4). This evidence is mainly in those mildly affected with MS, with less known about the effects of therapeutic exercise in those with an EDSS greater than 5. Studies have looked at the effects of exercise over several weeks and months, indicating a need to establish if there is an optimal length of time to ascertain any effect of an exercise intervention. Furthermore, most studies report findings at the end of the intervention period, thus there is a need to look at the effects of exercise beyond the end of the formal exercise intervention. Additionally, the majority of past studies focus on an aerobic-only or resistance-only approach. Although there is evidence to suggest an exercise approach combining aerobic and resistance components may be beneficial, further work is required to confirm this.

To address these gaps in the literature, summarised in Section 2.4.4) the main project in this study (Study 1) was designed to establish the effects of a 12-week combined exercise intervention for those with moderate MS (EDSS 5-6.5). Assessments were carried out up to one year after the end of the intervention. To determine the impact of time on the chosen outcomes, and to determine the impact of taking part in an exercise programme on the chosen outcomes over a longer period of time.

Following the main aim, hypothesis and overview of the design a description of the methods, results and a discussion of the findings are presented.

4.1.1 Study aim

To deliver and evaluate, over both the short and longer term, the effects of a 12-week community based group exercise class for people moderately affected with MS, against controls matched for disability level who received usual care.

4.1.2 Research questions

What are the short and longer term effects of a 12-week community based group exercise class in people moderately affected with MS, compared to controls with MS of a similar age, gender and disability level who received usual care?

Is a 12-week community based group exercise class effective in improving the physiological, functional or psychological status of people moderately affected by MS?

4.1.3 Hypothesis

The null hypothesis for this study is that there will be no statistically significant difference in any of the assessed outcomes between the two groups, and further that there will be no statistically significant difference in assessed outcomes over time.

4.1.4 Study Design

A longitudinal single-blind randomised control trial (RCT) was undertaken with each participant being involved over 15 months. The study compared two groups, one receiving the intervention and one acting as a control group. Thirty-two participants were randomly allocated (refer to Section 4.2.3) to receive either the group exercise intervention or usual care as part of the control group.

To determine the short term effect of the intervention, assessments were undertaken at baseline, after eight weeks and after twelve weeks of the intervention. After which time all participants were free to participate in any form of exercise they would like. To determine the longer-term effect of the intervention, follow-up assessments were done six and twelve months after completion of the 12-week intervention (Figure 4.1).

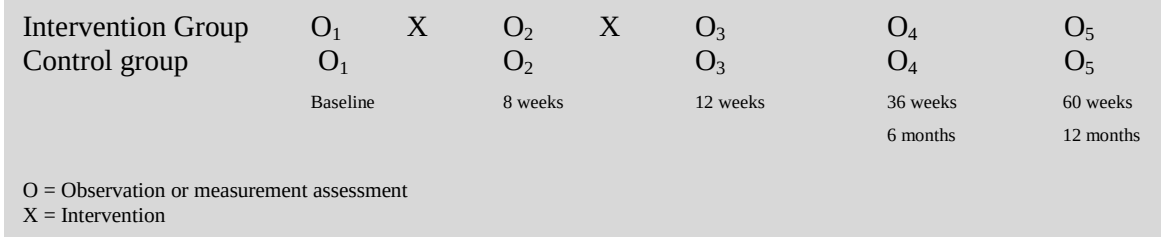


Figure 4.1 Symbolic representation of Study 1 design

4.2 Methodology

4.2.1 Ethical considerations

Ethical approval was obtained from the West of Scotland Research Ethics Committee in December 2009 (Appendix 5) and Research and Development approval from NHS Ayrshire and Arran Research and Development Management in January 2010 (Appendix 6).

4.2.2 Recruitment and participants

The subjects were recruited from the Managed Clinical Network (MCN) for MS within NHS Ayrshire and Arran. They were all patients of the consultant in rehabilitation medicine, Douglas Grant Rehabilitation Centre, Ayrshire Central Hospital, Irvine. All participants had to have a confirmed diagnosis of MS, and fit the inclusion criteria to take part.

Inclusion criteria

- Clinically or paraclinically diagnosed MS, based on the most recent additions to the diagnostic criteria (Table 2.1).
- An Expanded Disability Status Score between 5 (ambulatory without aid or rest for about 200 m) to 6.5 (constant bilateral assistance required to walk about 20m without resting)
- Stable rehabilitation and drug therapy within the past 30 days.
- Adequate cognitive function, assessed by achieving a score of 24 or greater on the Mini Mental State Examination.

Exclusion criteria

- An exacerbation of their MS symptoms within the past three months.
- A rapidly progressive disease
- A history of cardiovascular, respiratory, neurological or metabolic disease, or any other medical condition which may prevent participation in the study.
- Inability to complete the protocol for the outcome measures or the exercise class, as measured by a fitness screening form

Before the onset of the study the number of participants required to achieve the necessary statistical power was calculated, based on the previous work of Romberg et al (2004). It was determined that to achieve a significant difference at the 5% level and a desired clinical effect of a 20% improvement in the Timed 25 Foot Walk outcome measure, 23 participants would be required in

each group in order to achieve an estimated power of 80%. Thus in total for the intervention group and the control groups 46 subjects were required.

4.2.3 Screening for inclusion

To be accepted into the study participants went through several stages of screening (Figure 4.2). Initially a list of all patients on the MCN database for MS in NHS Ayrshire and Arran who lived within a commutable distance of Sites A or B (Section 4.2.10) was generated; people on this list were sent a letter and participant information sheet inviting them to take part (Appendix 7 and Appendix 8). Instruction was provided to contact the main researcher by telephone or email should they require further information or would like to take part. Reminder letters were sent after one month and healthcare professionals working in the Rehabilitation Centre who dealt with MS patients who may qualify for the study were asked to make relevant patients aware of the study.

Forty-three patients contacted the main researcher. They were asked over the phone if they had any further questions and what their availability and transport options were for attending the twice-weekly class. They were also asked about their current mobility level (Do you use a wheelchair? Are you able to walk with/without a walking aid? Are you able to walk without a rest or walking aid for 300m or more?). These questions provided a crude screening, as those unable to commit to the class time, venue, or who were more or less disabled than the inclusion criteria allowed were not invited to the main screening assessment at the hospital rehabilitation unit. At this stage seven interested participants were not invited for screening. One was suffering a relapse of symptoms and six had mobility problems deemed too mild for inclusion in the study.

Thus, 36 potential participants were invited for screening, which took place within the physiotherapy department of the NHS rehabilitation centre. This screening was done by the Consultant MS physiotherapist and included an open discussion about the study and the following screening outcome measures (refer to Section 3.7);

- The Mini Mental State Examination (Folstein et al 1975)
  Subjects answered questions, and performed tasks as part of the examination, and were eligible to take part in the study if they scored more than 24 points.

- The Expanded Disability Status Scale (Kurtzke 1983)
  Subjects were assessed by a the Consultant MS physiotherapist and EDSS level was recorded. Participants were eligible if they were deemed to have an EDSS score of 5-6.5

- Fitness screening form
  Fitness to exercise, based on the Physical Activity Readiness Questionnaires (Shephard 1988); to ascertain general levels of fitness with a bias towards cardiovascular and

respiratory function. The questionnaire was used as a means to highlight any health requirements of participants, thus answering “yes” to any questions did not automatically exclude potential participants

Following screening, thirty-two participants were eligible to take part, with four excluded at this stage due to having an EDSS of less than 5, undergoing symptom relapse or now being unable to commit the time to take part. A summary of the important stages of recruitment is provided in Figure 4.2. This figure includes the patient journey, through to the month 12 assessments, further details on attendance and attrition are discussed in Section 4.4.2.

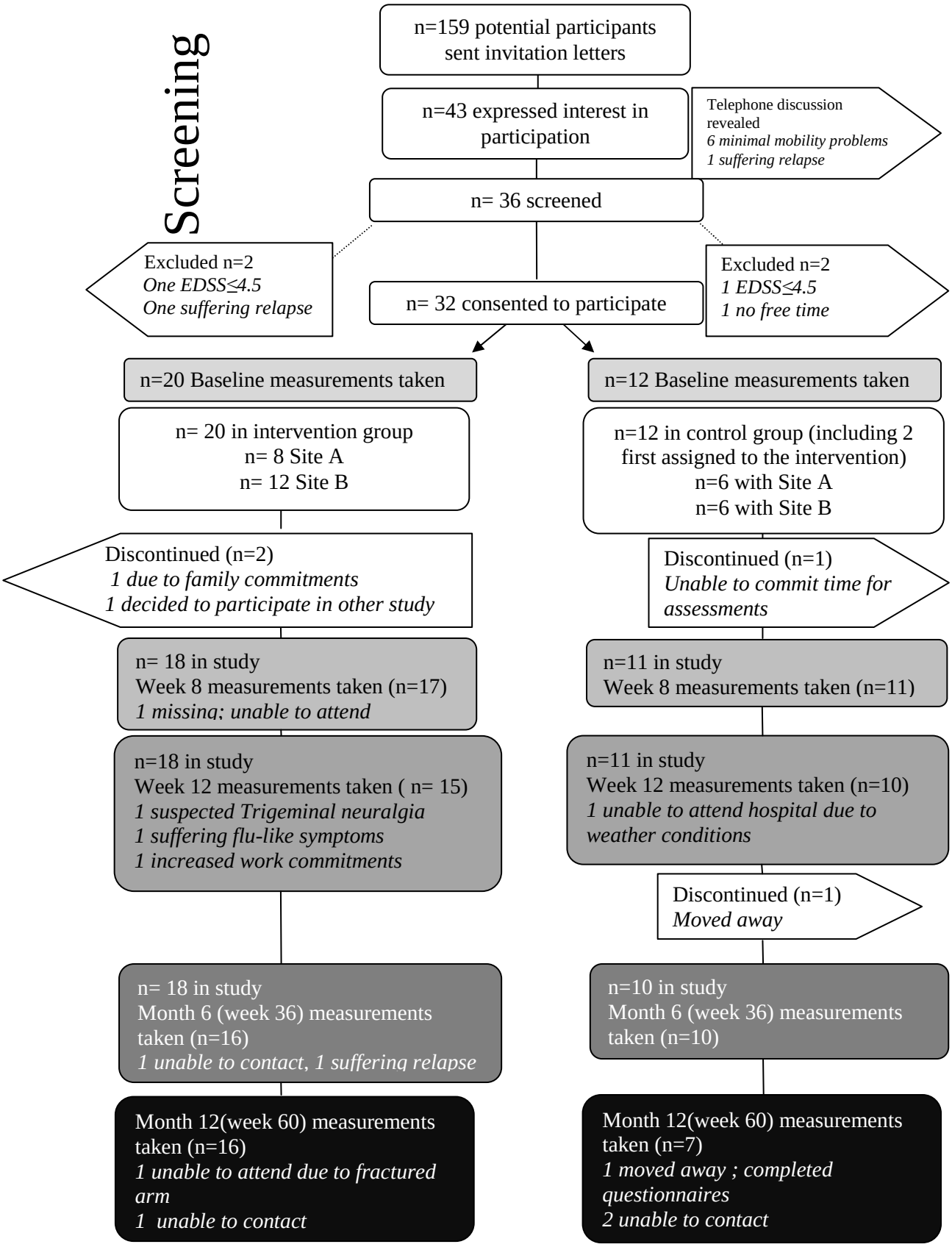


Figure 4.2 Flowchart of recruitment, group allocation and patient journey.

Reason for discontinuation are explained in italics, please note not all outcome measures collected for all participants at all time points due to individual mobility issues, and technical problems.

A total of 32 participants consented to take part (Table 4.1). These participants were randomly selected (see below) to either receive the intervention or be in the control group. The intervention took place at one of two venues (Site A and Site B – see Section 4.2.10), each site had a maximum class capacity of 10 to 12 participants. Participants at Site A received the intervention first. Fourteen participants were eligible for participation at Site A (i.e. lived within a 15 mile radius of Site A); ten of these participants were randomly selected to begin the class. Early in the intervention, two participants could no longer commit the time, and were transferred to the control group, as they had attended less than 4 classes. Data from these two participants are considered in the control group, along with the other original four controls.

Eighteen participants were eligible for Site B. From these, twelve were randomly selected for the class, with six controls.

It was necessary for those randomised to all begin the intervention at the one time, and it was initially felt that more control participants may be sought later, however this was not achieved.

Table 4.1 Baseline characteristics of subjects in the longitudinal study.

Group	Number of subjects	Gender M:F	Age (years) Mean (SD)	EDSS Mean	Years since onset Mean (SD)
Intervention	20 Site A = 8 Site B = 12	5:15	51.4 (8.1)	6	13.4 (6.4)
Control	12	4:8	51.8 (8)	6	12.6 (8.1)

Randomisation method

Randomisation was achieved with a computer programme (Microsoft Excel, 2007). The following example describes the method for Site A (repeated at a later date for Site B). On a blank spreadsheet a "Group" column of 10 "I" were placed (denoting the intervention group), followed by 4 "C" (denoting control group). In the next "Random number" column the RAND function on the computer programme randomly provided a number. The "Random number" column was then sorted in ascending order, thus changing the order within the "Group" column. This later column was then copied and pasted over to a second spreadsheet containing an alphabetical (by surname) list of the potential participants.

4.2.4 The research team

The main team consisted of the Chief Investigator (Thesis author), an assessor, fitness instructors and the Consultant MS physiotherapist. The Chief Investigator is a physiotherapist and fitness

instructor who had some experience in exercise classes for those affected with MS, she co-ordinated the study and jointly led the exercise classes.

The assessor was a physiotherapist, recruited in January 2010. To improve the assessor's knowledge of the outcome measures three hours of formal training was given, with relevant articles on the outcome measures supplied. Training involved observation, formal practice and discussion. An instruction manual for all outcome measures was also provided Appendix 9. The assessor was blind to group allocation, to avoid the risk of study bias discussed in the literature (Schulz and Grimes 2002; Maher et al 2003).

Fitness instructors were employed by either East Ayrshire Leisure or KA Leisure. Contact was made in August 2009 with leisure staff, and meetings were held to discuss the possibility of classes taking place. Commitment to the project was strong with leisure staff aware of a "gap" in the service for those with MS. The staff involved in the intervention all had experience leading exercise classes with disabled clients. In addition they had completed a training day organised by the Chief Investigator and the Consultant MS physiotherapist related to exercise prescription in MS.

4.2.5 Assessment protocol

The assessor took written consent from those who met the inclusion criteria and agreed to take part. Contact details, were also taken at this time (Appendix 2).

Following screening (Section 4.2.3) each participant underwent baseline assessment; this and all follow-up assessments took place within the hospital rehabilitation unit. A private room was used and attempts were made to keep the room temperature at or below 22° Celsius. Similar methodology to that described below was carried out at all five assessments points. On arrival at the rehabilitation unit participants were led to a quiet room where they completed the four self-rated questionnaires which gathered data on balance (ABC), fatigue (FSS), mood (HADS) and quality of life (LMSQOL). On completion of the questionnaires the assessor rated outcome measures were completed.

As discussed in the previous chapter (Section 3.7) eight different assessor rated outcome measures were collected by the assessor at each assessment (with the addition of the Goal attainment scale at baseline only). These collected data on; mobility (T25FW, 6MWT, Temporal spacial parameters of gait and TUG), balance (BBS, OS), strength (SLS/WLS), activity levels (PF) and body composition (BMI). Three separate assessment protocols were created (Protocol 1 provided in Appendix 3), which varied the order of the outcome measures, altering the order of mobility, balance and strength assessments. Participants were randomly assigned a protocol order and followed this order for every assessment. This was arranged to minimise the effect of tiredness and

fatigue potentially affecting results of the later outcome measures, as well as the overall results. As some participants wore functional electrical stimulation devices on their legs, ankle foot orthotics, or ankle supports inside their shoes participants kept their shoes on during this process. The mobility aid used by the participant was noted for each outcome measure and was kept consistent at all assessments.

Timed 25 Foot Walk test (T25FW)

The 25FWT (Cutter et al 1999) was repeated three times at each session. More fully described in Section 3.9.3 participants were given instructions. These included being told to walk at a normal pace and to walk past the cone (cones were placed 25ft apart, Figure 4.3). Participants were given the opportunity to rest between walks, if required. The time taken to walk 25 feet was recorded and the average of the three walks included in the analyses). To minimise walking participants walked across the GAITRite carpet used to assess temporal spatial parameters (Section 4.2.5)

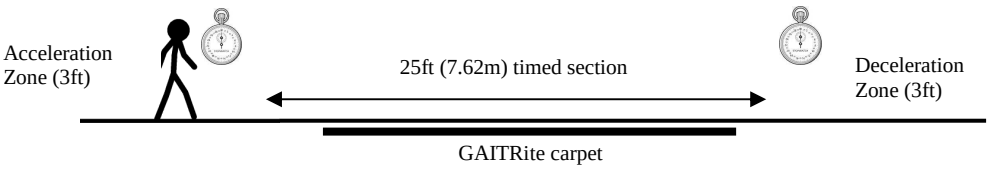


Figure 4.3 Diagram of 25foot walk

Temporal spatial parameters of gait

To determine walking patterns, temporal spatial walking parameters were collected as each participant walked over a computerised carpet; the GAITRite system (CIR Systems – Model K648-D8). Discussed in Section 3.9.3 this instrument is a 4.6 m (15 foot) carpet, embedded with electronic sensors positioned in a grid-like fashion through the length of the carpet which is linked to a computer with dedicated GAITRite software (CIR Systems – version 3.8A). The sensors detect foot-fall and accurate gait parameters are recorded (CIR Systems 2010).

Three separate walks over the GAITRite were performed by each participant as part of the T25FW (Figure 4.3) To ensure steady state gait, approximately three feet at either end of the carpet provided an acceleration and deceleration zone. Participants' leg length was required for the temporal spatial measure, and was measured for each leg, in centimetres, from the anterior superior iliac spine to the floor at the first assessment.

Computer analysis of the walks was accomplished with the data transformed and relevant parameters saved. This analysis involved using the GAITRite software's FootFall Editor to erase

any “footfalls” from walking sticks or walking frames, ensuring only participants’ footfalls were analysed. Analysed temporal parameters were; walking cadence (WCa), walking velocity (WVel) and left (LST) and right step time (RST) (with, gait cycle, single support time and double support time recorded, but not included in this thesis). Analysed spatial parameters; left (LSL) and right leg step length (RSL) were analysed as was overall walking performance; Functional Ambulatory Performance (FAP) (as explained in Section 3.9.3).

Six-minute walk assessment (6MWT)

Participants completed a 6MWT (Butland et al 1982) (Section 4.2.5) once per session. The guidelines written by the American Thoracic Society (2002) were used. To summarise, the test was carried out in a quiet corridor, with two cones placed 30 m apart. Precisely worded encouragement was given every minute and rests permitted if required (Appendix 9).

Timed Up and Go (TUG)

The TUG (Podsiadlo and Richardson 1991) assessment was carried out three times at each assessment. The test (previously discussed in Section 3.9.4) started and ended with participants sitting on a standard chair (seat height 40cm from the floor) with armrests. They were instructed to stand up, walk around a cone placed 3 m away, and sit back down in a safe/fast manner. The time from their back leaving and returning to the chair was recorded with the average of the three trials analysed.

Berg Balance Scale (BBS)

To measure balance the BBS (Berg et al 1989) was completed once per session. The BBS is more fully described in Section 3.9.5. The assessor evaluated 14 functional balancing tasks of increasing difficulty, on a 5-point scale. Equipment used for this test included a Reebok step 16cm high, and two chairs (one with armrests) both height 40cm.

Overall Stability (OS)

To assess Overall Stability participants were assessed on the Biodex balance system (Biodex Stability System – Version 1.3). More fully described in Section 3.9.6. At the baseline assessment participants’ foot position was recorded, and the same position was used for all follow-up assessments. At each assessment participants were tested three times (with more than 1 minute rest between each test) at stability level eight (the most stable) for 20s. To avoid biofeedback, the screen was covered during testing with participants asked to look at and focus on a cross marked on the wall in front of them. Participants were instructed to avoid holding onto the support handles

during the 20s of each trial. The average, of the three readings for overall stability (OS) index score was used for analysis.

Quadriceps strength

Quadriceps strength was assessed using a MVC "make-test" following standardised protocol (Bohannon 1997), the method is discussed in more depth in Section 3.9.7. To establish positioning for all subsequent assessment, at the first assessment the Lafayette HHD (Model 01163) was placed anterior to the participants' Medial Malleolus, and the distance from here to the apex of the patella was measured and recorded (Figure 4.4). This distance constituted the "lever-arm", and to improve reliability was kept the same for all assessments.

Participants sat on a raised plinth, with their back unsupported and their feet not touching the floor . They were asked to cross their arms over their chest to avoid recruiting other muscle groups during testing (Figure 4.4). With their knees at 90 degrees, the "lever-arm" distance was marked with a semi-permanent marker pen. The HHD was positioned on this mark. The HHD was set to sound a beep at the start and end of 3 s (during this time the HHD was recording the force produced by the participant). Participant were instructed to "push as hard as you can after you hear the first beep, stop pushing when you hear the second set of beeps" (constituting a three second MVC). This was repeated with three trials on each leg, with a minimum of 30 s rest between each trial. The average of the three readings of each leg was analysed. Torque (Nm) was used to quantify strength; calculated for each leg by multiplying the force (kilogram output) by 9.81 and multiplying this by the lever arm length. The weaker leg and stronger leg were established from baseline measurements, and in all subsequent analysis the weaker leg remained the reference leg (i.e if the left leg was deemed the weaker at baseline, all subsequent analysis of the weaker leg was from left leg results).

Figure 4.4 Image of leg strength assessment.

Note HHD placement, anterior toMmedial Malleoli, and participant sitting position.

The PhoneFITT (PF)

To measure functional activities of daily living and leisure activity the PF was used (Gill, Jones, Zou, & Speechley 2008). Discussed in Section 3.9.8 this self-report interview questionnaire asks for "frequency, intensity, type and time" of six functional activities of daily living and ten exercise based leisure activities. Participants provide information on six specific common household tasks and eleven particular forms of physical activity in a typical week in the preceding month. They are asked to provide details on the time spent doing each activity, how often they undertake each activity and provide information on their breathing during each activity. There is the option to include other personal activities not included in the questionnaire.

Activities Balance Confidence scale (ABC)

To measure participants' confidence in their balance the ABC (Powell and Myers 1995) was used, discussed previously in Section 3.9.9. Fifteen questions related to functional and everyday activities which challenge balance were rated on a 10-point Likert scale to determine participants' confidence in performing these activities. This yielded a score of 0-150 which was used for analysis, with higher scores indicative of more balance confidence.

Fatigue Severity Scale (FSS)

To establish fatigue, the FSS (Krupp et al 1989) was used, previously discussed in Section 3.9.10. Participants self-reported their agreement with nine fatigue-related questions on a seven-point Likert scale, based on their experiences in the past week. Producing a mean score between 0 and 7, this score was used for analysis, with higher scores suggestive of higher fatigue.

Hospital Anxiety and Depression Scale (HADS)

To assess mood, more specifically anxiety and depression, the self-reporting HADS (Zigmond and Snaith 1983) was used, discussed in more depth in Section 3.9.11. Participants respond to fourteen questions; seven related to anxiety, seven related to depression on a 4-point scale, in relation to the past week. Thus generating a mean score between 0-42, which was used for analysis. The mean scores (0-21) for each aspect; anxiety and depression, were also analysed. Higher scores are deemed to suggest more anxiety and depression.

Leeds Multiple Sclerosis Quality of Life scale (LMSQOL)

The LMSQOL scale (Ford et al 2001) was used to assess quality of life, previously discussed in Section 3.9.12. Participants were are asked to rate eight health related questions on a four-point scale, in relation to the past month. This too was self-reported and resulted in a score 0-24, which was used for analysis with lower scores indicative of a higher quality of life.

Body composition (BMI)

To gather data on body composition Body Mass Index (BMI weight (kg)/height (m^2) was calculated based on height and weight, previously discussed in Section 3.9.13. Height was measured in metres (m), using a Leicester stadiometer. Weight was measured in kilograms (kg), using seated scales on each of the five assessments.

The Goal Attainment Scale

To establish what goals participants would like to achieve over the duration of the study the Goal Attainment Scale (Kiresuk and Sherman 1968) was used on the first assessment. The rationale for the Goal Attainment Scale is discussed in Chapter 3 (Sections 3.9.14). Participants choose three of 12 possible goals (or a 13^{th} personal goal), which they hoped to achieve by the end of the 12-week intervention. They then graded their chosen goals in order of importance (from 1-3). Goals were chosen by all 32 participants, as these were discussed prior to participants being allocated to either the intervention or control group.

The overall Goal Attainment Scale score for each of the participants in the intervention group was calculated using an automatic Microsoft Excel spreadsheet, applying a standard mathematical formula (Turner-Stokes 2009).

4.2.6 The exercise intervention

It is recommended that for those with MS a well-balanced exercise programme be undertaken to improve health and manage symptoms (Mulcare 2003; White and Dressendorfer 2004). Achieving this was the main aim of the intervention for the main study, with the following section discussing the rationale for the intervention methodology.

Acknowledgement of special considerations in the MS population (Mulcare 2003) was at the forefront of the design of the intervention. As such the following was considered, with a brief outline of how they were incorporated provided in parenthesis;

- possible cognitive deficit (verbal, written and pictorial explanation of each exercise),
- fatigue (no expectation to complete all exercises, rest sessions provided, intensity monitored),
- mornings an optimal time (classes late morning),
- balance problems (option of seated exercises),
- daily fluctuation in symptoms (no expectation to match or exceed previous classes exercises),
- variation in symptoms and ability (options provided within each exercise)

Within the MS therapeutic exercise literature interventions vary from three weeks to 24 weeks. As yet there are no guidelines as to the optimal length of an exercise intervention. Indeed, change (or no change) has been seen regardless of the length of the intervention. In the general exercise literature, optimal improvements in fitness variables will result from interventions carried out over several weeks, allowing the participant to adapt to the training regime (Pollock et al 1998). For a healthy population strength gains from resistance training may take six to eight weeks, although this may vary with the individual and type of training (Kraemer et al 2002; Broughton 2011). It was judged that, to compare the results of this study with the therapeutic exercise in MS literature and to follow the guidelines for healthy populations the intervention would be undertaken for 12-weeks. Furthermore, to establish if this length of intervention is required, assessments were taken after 8 and 12 weeks.

The commonly accepted FIIT acronym; Frequency, Intensity, Type and Time of exercise (Franklin et al 2000) will now be discussed in relation to the intervention.

Frequency

Exercise guidelines suggest that healthy adults undertake a well-rounded exercise programme which totals 150 minutes per week. If this cannot be met, benefits can still be achieved from some activity (Pollock et al 1998, Garber et al 2011).

The frequency of classes varies in the MS therapeutic literature; from one to three sessions per week (Table 2.5-6). However, there is no evidence comparing different frequencies, thus the optimal number of sessions per week remains unknown. Many 12-week interventions, include two sessions per week (Kileff and Ashburn 2005; McCullagh et al 2008; Dalgas et al 2009; Dalgas et al 2010). This approach remains popular (Collett et al 2011) and is recommended (White and Dressendorfer 2004).

To allow comparison with the therapeutic exercise literature the intervention was carried out twice weekly. Furthermore the leisure staff involved in the study could provide a venue and staff twice weekly.

Intensity

The Borg RPE scale (Borg 1982) to monitor exercise intensity has been used in the MS literature (Bjarnadottir et al 2007; Morrison et al 2008; McCullagh et al 2008; Motl et al 2012), finding it a simple way of monitoring exercise intensity.

During physical activity RPE was first discussed by Borg (1970) as a means to rate perceived exertion during activity. Two scales are available; the original with values ranging from 6 to 20, chosen to denote heart rate values of 60 to 200 beats/min, the newer scale attempts to offer a general ratio scale with values ranging from 0 to10 (Borg 1982). The later scale was chosen in this study.

Participants were asked to maintain a “moderate” (RPE 3) to “somewhat-hard” (RPE 4) intensity, as is recommended by White and Dressendorfer (2004).

In the general exercise literature safe progression of exercise training is recommended to allow for continued benefit (Pollock et al 1998; Kraemer et al 2002; Garber et al 2011). This rationale is adopted within the MS therapeutic exercise literature, particularly for resistance training programmes (Section 2.4.2). There are also examples of progressive exercise training in the combined exercise training literature (Fragoso et al 2008; Sabapathy et al 2011). Thus, to allow for progression in this study different levels were available for each exercise (Table 4.2), this ensured participants were able to work at an intensity appropriate to them. The level chosen was based on discussion between the participant and the Chief Investigator or supervising leisure staff. A similar approach was adopted by Sabapathy et al (2011).

Type

The study aimed to assess the impact of the intervention on the physiological, functional and psychological status of participants.

Within this study physiological and functional outcomes primarily guided the intervention i.e. mobility/aerobic endurance, leg strength and balance. Therefore the type of exercises included were designed to improve these areas, consequently the type of exercise was a combination of aerobic/mobility, resistance and balance exercises. Hence the type of exercise is described as combined exercise.

The Chief Investigator and the Consultant MS physiotherapist chose the exercises for the intervention. These were based on the available literature, their personal knowledge of physiotherapy and fitness training and through discussions with neurophysiotherapy colleagues and supervisors. The included exercises are described in Section 4.2.7. A whole body approach was adopted, thus although in Section 4.2.7 exercises are defined as primarily aerobic, resistance or balance exercises there may be overlap between types of exercise.

Time

Classes in past studies, which have used alternating or combined exercises, have been undertaken for around an hour at a time (Freeman and Allison 2004; Taylor et al 2006; McCullagh et al 2008). As there have been no reports of this being problematic an hour long session was also chosen for this study. However, it is acknowledged that two one hour classes does not meet the 150 minutes of recommended exercise per week for healthy adults (Pollock et al 1998, Garber et al 2011). It was judged that two, one hour, classes per week were a good initiation into exercise for participants, many of whom were very sedentary.

The main circuit component lasted 35-40 minutes and was aimed at improving the participants' aerobic endurance/mobility, strength and balance. The exercises in the circuit each lasted one minute, chosen for pragmatic reasons based on pilot work (Section 4.2.11). A similar format has been used successfully in the past (Taylor et al 2006). After each minute the participants moved to the next exercise station, once the slowest participant was ready the group began a new exercise (allowing a minimum of two minutes rest between each exercise).

4.2.7 The exercises in the programme

The main exercises were delivered in a circuit component, with everyone completing the same exercises as they were able. During the study, prior to each session the Chief Investigator chose 8-10 exercises from Table 4.2, this varied from session to session.

The exercises were chosen to benefit those with moderate MS, with it anticipated that the exercises would have a carryover effect on the different outcome measures used in the study. An explanation of the exercises and examples of the hypothesised impact each may have on the outcome measures follow in the sections explaining aerobic exercises, resistance exercises and balance exercises.

Cards, with pictures and verbal instructions, for each exercise were placed around the room, alongside the relevant equipment. Four levels for each exercise allowed for those with differing abilities and progression through the weeks. At week nine, a fifth level was added to some of the exercises to offer variety. Progress cards were completed by participants at the end of each exercise. An explanation of the chosen exercises will be discussed based on what was judged to be the main exercise type, i.e. primarily aerobic, resistance or balance.

Table 4.2 Circuit components of the exercise class.

Exercise	Main Type	Description of each exercise and option at each level.
Runner's arms	Aerobic	Near a chair 1.Sitting down, moving arms in a running style. 2. Sitting down, moving arms in a running style, holding weights. 3. Standing, moving arms in a running style. 4. Standing, moving arms in a running style, holding weights.
Shuttle walk	Aerobic/ Mobility	Chairs set 10m apart 1.Rest at each end of the shuttle (having a seat) 2.Walk continuously without resting at each end 3.Walk continuously with a small weight in each hand 4.Walk continuously with a small weight in each hand, swinging arms
Side steps	Aerobic/ Mobility	Near supporting surface 1. Holding onto a stable surface, take one step to the side, and bring feet together, step back. 2. Not holding on, take one step to the side, and bring feet together, step back. 3. As 3, lifting arms out to the side, in time with step. 4.As 4, but taking two-steps to the side before changing direction * 5. Grapevine (two steps crossing one leg behind the other)
Static bike	Aerobic	On exercise bike or foot pedals 1.Sitting down, use pedals only. 2. Sitting down, use pedals, and lifting arms up and down too. 3. Sitting on bike pedalling with no resistance. 4. Sitting on bike pedalling against resistance. *5. As above, standing out of saddle
Step-ups	Aerobic/ Mobility	Using 20cm step 1.Sit down, with step in front, lift alternate legs up/down 2.Standing, step alternate feet forward and back (not on step 3.Standing, step alternate feet forward and back onto step 4. As 3, but lifting opposite arms up to the sky (e.g. right arm/left leg). *5. Straddle step
Calf raises	Resistance	Near supporting surface 1.Holding onto a stable surface, lift heels from floor, repeat as able. 2. Lift heels from floor, not holding on, repeat as able.

Exercise	Main Type	Description of each exercise and option at each level.
		3.Lift heels from floor, holding a light weight, repeat as able 4. Lift heels from floor, holding a heavier weight, repeat as able.
Up and go	Resistance	Sitting on a chair 1. In a chair (with arms) stand up fully, and sit down again, repeat as able. 2. Stand from chair, walk to other chair and sit down, repeat as able. 3. Stand from chair, walk around other chair, and return to sit in first chair, repeat as able. 4. As 3, but with arms folded when standing.
Leg extensions	Resistance	Sitting on a chair 1. Straighten leg as best as possible, point your toes to the sky, hold for a second then swap legs. Repeat. 2. As above, hold for a FIVE seconds then swap legs. Repeat as able. 3. As above, hold for a TEN seconds then swap legs. Repeat as able. 4. As above, hold for a FIFTEEN seconds then swap legs. Repeat as able. *5. As above, small pulses at the end.
Squats	Resistance	Near a chair 1.Holding on, bending legs half-way to ground 2.Not holding on, bending legs half-way to ground 3.As above holding light dumbbells 4.As above, slightly heavier dumbbells *5. As 4, when standing straight, going up on toes
Side-kicks	Resistance	Near supporting surface 1. Holding onto a stable surface, lift one leg out to side (as wide as is safe) swap legs, hold for a second swap legs. Repeat. 2. As above, hold for a FIVE seconds then swap legs. Repeat as able. 3. As above, hold for a TEN seconds then swap legs. Repeat as able. 4. As above, hold for a FIFTEEN seconds then swap legs. Repeat as able. *5. As above, small pulses at the end.
Upper body	Resistance	Near a chair 1.In sitting, shoulder raises (no dumbbells) 2.As above, with light dumbbells 3.In standing, shoulder raises (no dumbbells) 4.As above, with light dumbbells
Single leg stance	Balance	Near supporting surface 1.Hold onto a stable surface and stand on one leg (aim to maintain for 10 seconds) 2.As above, not holding on, with arms out to side for balance 3. As above, not holding on, with arms into side. 4. As above, with arms into side, slightly bending supporting leg, and then stand up straight, repeat as able.
Take-off	Balance	With balance cushion 1. Sitting on chair (with a back), lean forward (simulating 1st part of standing up), and reach forward with arms. 2. As above sitting on stool. 3. As above sitting on sit fit, on chair. 4. As above sitting on sit fit, on chair, lifting one leg (swap legs after 30 secs).
Tick-tack toe	Balance	Near supporting surface 1. Walk between tramlines, using wall if required, turn and repeat as able. 2.Walk between tramlines, not using wall 3.Walk on line, using wall if required 4. Walk on line, not using wall.

Exercise	Main Type	Description of each exercise and option at each level.
Cushion standing	Balance	Near supporting surface 1.In the corner of the room, try and maintain your balance without holding on. 2. As 1 standing on a mat. Come off, then go back on, when required. 3. As 2, standing on sit fit. Come off, then go back on, when required. 4. As 3, moving straight arms slightly (about 4 inches) at sides.

*Week 9 onward

Primarily aerobic exercises

Past literature has found aerobic interventions and combined exercise interventions to improve mobility and endurance (Section 2.4.1 and 2.4.3), thus to improve mobility and aerobic endurance, exercises were chosen which were judged to have an impact on aerobic endurance and functional mobility.

Five exercises were primarily aimed at improving aerobic endurance and mobility, with it anticipated that these exercises may have an impact on the 6MWT (Section 3.9.2) and the T25FW (Section 3.9.1) outcome measures. The aerobic exercises were continuous and rhythmical, and thus demanded effort from the cardiorespiratory system. As the aerobic exercises were undertaken twice weekly for the duration of the study it was anticipated that this would be at a training intensity sufficient to increase aerobic endurance (Section 2.4.1) and therefore have a positive effect on the 6MWT. In addition, the "shuttle walk" exercise mimicked the T25FW and therefore it was anticipated that this would influence the T25FW outcome measure.

These exercises were named using "lay terms" to help remind participants of what each would involve. Exercises included "Shuttle walks", "Step-ups", "Runner's arms", "Side-steps" and "Static bike", with exercises chosen based on discussions with neurophysiotheapists and the relevant literature. An example of the "Step-ups" exercise is displayed in Figure 4.5.

There are examples of variation of these exercises in earlier literature. In past studies previous authors have described some of the exercises similar to those classified as primarily aerobic exercise in this study as being resistance or balance exercises; highlighting the diverse nature of whole body exercise, targeting; aerobic, resistance and balance components;

- "Step-ups" in past studies where they are described as being aerobic (Sabapathy et al 2011), resistance (Debolt and McCubbin 2004; Hughes et al 2011) or balance exercise interventions (Motl et al 2012)

- "Side-steps" incorporated into the resistance component of Sabapathy et al's (2011) and Hughes et al (2011) work.

- A "Static bike" has been used in many past aerobic and combined exercise studies (Bjarnadottir et al 2007; Cakt et al 2010; Hayes et al 2011; Motl et al 2012).

- Treadmill walking has also been included in past aerobic and combined exercise studies (van den Berg et al 2006; Newman et al 2007; Pilutti et al 2011; Sabapathy et al 2011;

Motl et al 2012), but as treadmills were not available at both intervention sites (facilities at the two sites varied, Section 4.2.9), the "Shuttle walk" was included.

- "Runner's arms" was chosen to achieve an increased aerobic workout, whilst resting the legs, and is not dissimilar to the upper body aerobic work utilised in Sabapathy et al's (2011) study.

Step-ups. Levels

1.Sit down, with step in front, lift alternate legs up/down

2.Standing, step alternate feet forward and back (not on step)

3.Standing, step alternate feet forward and back onto step

4. As 3, but lifting opposite arms up to the sky.

Figure 4.5 Example of an "aerobic" exercise used during the intervention.

With instructive pictures and text with options for progression provided.

Primarily resistance exercises

As weakness is a common symptom in MS, strength was part of the physiological and functional outcomes assessed in this study, thus exercises to improve strength were included. Past literature

has found resistance interventions and combined exercise interventions improve strength (Section 2.4.2 & 2.4.3).

To improve strength six exercises were available, five focused on lower body strength. By including resistance exercises twice weekly, for the duration of the programme (12 weeks) it was anticipated that adaptations to muscle fibre recruitment, and hence improvements in strength would emerge (Section 2.4.2). The main measurement of leg strength was quadriceps strength (Section 3.9.7); with the "leg extension" exercise assumed to target quadriceps strength specifically.

In addition, as a pragmatic/functional approach was taken in the design of the exercise programme, many different exercises which trained an array of lower body muscle groups were included, some of which were similar to the outcome measures. For example the "Up and Go" and "Squats" exercises offered specific training which mimicked components of the TUG (Section 3.9.4) and the BBS (Section 3.9.5) outcome measures. Thus repeated completion of these two exercises was anticipated to affect these outcome measures. Finally, the "side-kicks" exercise whilst primarily strengthening abductor muscles of the hip also required participants to stand on one leg, and therefore this exercise may have a carryover effect to improve balance, and, if so, would be evident in results of the balance outcome measures.

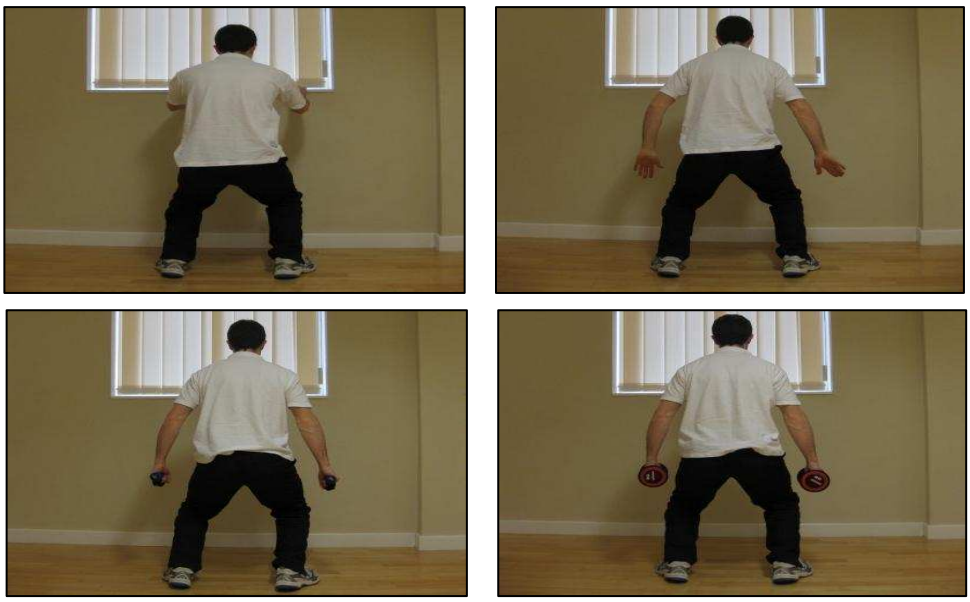
One upper body exercise was included to provide variety and improve participants' whole body strength. Within the resistance and combined therapeutic exercise literature in MS the intervention components are not always provided, with large gym-based machines often the resistance modality chosen The use of machines was inappropriate for this study as the facilities at the leisure sites varied (Section 4.2.9). Thus, it was decided that mainly body weight exercises would be utilised, with the addition of free-weights and time to increase intensity.

Some resistance exercises were more functional in nature, such as the "Up and Go", "Squats" and "Calf Raises". Whilst others focused more on strengthening general muscle groups such as the shoulder muscles with "Upper Body", the quadriceps muscles with "Leg Extensions" and the leg abductor muscles with the "Side-kicks". Variations of these exercises are to be found in past literature;

- "Up and Go" (Debolt and McCubbin 2004; Sabapathy et al 2011),
- "Squats" (Hughes et al 2011; Sabapathy et al 2011; Motl et al 2012),
- "Side-kicks" (Hughes et al 2011; Sabapathy et al 2011),
- "Upper Body" (Sabapathy et al 2011),

- "Calf Raises" (Cakt et al 2010; Hughes et al 2011; Sabapathy et al 2011)
- "Leg extension" (Harvey et al 1999; Hughes et al 2011; Motl et al 2012).

An example of the "Squats" exercise is shown in Figure 4.6.



Squats; Level

1. Holding on, bending legs half-way to ground
2. Not holding on, bending legs half-way to ground
3. As above holding light dumbbells
4. As above, slightly heavier dumbbells

Figure 4.6 Example of a "resistance" exercise used during the intervention,

Primarily balance exercises

Using a combined exercise intervention which included exercises for balance was another important aim of the study since there is less literature including balance as the main intervention in MS therapeutic exercise studies (Cattaneo et al 2007a). Balance exercises have been included in combined exercise, or as part of resistance exercise interventions. Similar to aerobic and resistance studies, the actual exercises included in the intervention are not always provided in past literature.

To challenge balance four exercises were available; for safety these were performed either under closer supervision or near a wall/chair. Balance impairment in MS may be directly related to the underlying pathophysiology of MS; as a result of damage in the CNS the motor and sensory systems cannot accurately provide feedback required to maintain good balance (Section 2.4.3). Thus, within the 12 week time frame the exercises chosen in the programme were not anticipated to have a direct effect on the underlying pathophysiology cause of balance impairment in MS. However, it was anticipated that continued challenge to participants balance, through the chosen

balance exercises, would improve coping strategies and participants' confidence in their balance. Some of the included balance exercises offered specificity of training as they were designed to mimic components of the outcome measures selected to assess balance; with "Cushion standing" being similar to the static balance assessment involved in the OS (Section 3.9.6) outcome measure. Similarly "Single leg stance" and elements of "Tick-tack toe" are assessed in the BBS (Section 3.9.5) and thus it was anticipated that continued practice of these exercises may have a carryover effect on overall balance as evidenced in the BBS.

Exercises included "Take-off", "Single Leg Stance", "Cushion standing" and "Tick-tack toe". Versions of some of these exercises appear in past MS therapeutic exercise literature;

- "Take-off" (Cattaneo et al 2007a),
- "Single Leg Stance (Sabapathy et al 2011; Motl et al 2012),
- "Cushion Standing" and "Tick-tack toe" (Cakt et al 2010; Sabapathy et al 2011; Motl et al 2012).

An example of the Tick-tack toe exercise is shown in Figure 4.7.

Tick-tack toe; Levels
1. Walk between tramlines, using wall if required, turn and repeat.
2.Walk between tramlines, not using wall
3.Walk on line, using wall if required
4. Walk on line, not using wall.

Figure 4.7 Example of a "balance" exercise used during the intervention.

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4.2.8 Education

There was no formal educational component during the intervention. However, both instructors frequently gave general exercise advice during the class and answered any specific questions the participants may have had regarding exercise and their symptom management. If any issues were raised outwith the skill level of the instructors advice was sought from the Consultant MS physiotherapist.

4.2.9 Warm-up and Cool-down

A warm-up and cool down is recommended as part of all exercise interventions (Kraeman 2010; McKardle et al 2010; Pollock 1998; Garber 2011). Past therapeutic exercise literature has included a warm-up and cool down of around 10 minutes in a one hour class (Debolt and McCubbin 2004; Freeman and Allison 2004) . Thus, the leisure assistant led a 10-minute group warm up. Aerobic (e.g. marching, toe taps) and stretching (e.g. side bends and trunk twists) exercises were done sitting or standing. The instructors were free to change the content of the warm-up as appropriate.

The cool-down followed a similar pattern to the warm up and lasted 5-10 minutes, with aerobic components and stretching. Participants were given the option of doing the warm-up or cool-down seated or standing.

4.2.10 Venue

The exercise classes were held twice weekly (Tuesday and Thursday). Participants did not have to pay for classes during the 12-weeks of the study. They were held in one of two venues with classes at Site A beginning first, classes at Site B followed the same format one month after completion of Site A classes.

Site A

Site A was a leisure centre comprising a swimming pool, exercise studios and leisure gym. The site had good transport link with local buses. Disabled parking and on street parking were available, although minimal. The room used for the venue was upstairs behind the main gym, and participants were able to use a lift to access the floor. The room contained no equipment and had mirrors around the walls. Chairs, an aerobic step, a static bike (Pulse Spin Cycle) and dumbbells of varying sizes (1kg-5kg) were provided. The room temperature was maintained at or below 22° Celsius by air conditioning. Music was played throughout the class, and was the choice of the instructor.

Located 300ft from Site A, a community hall, was used for the first two weeks of classes, due to room bookings at Site A.

Site B

Site B was a local authority leisure centre comprising a swimming pool, exercise studios and adult and youth leisure gyms. The site had good transport links with local buses. Disabled parking was available. The room used for the venue was on the ground floor of the centre and accessible within 50m of the car park. The "Shokk" youth gym was used, where scaled-down gym equipment was found, but not used for the class. Chairs, an aerobic step, a static bike (Shokk Xtreme spin cycle) and dumbbells of varying sizes (1kg-5kg) were provided. The room temperature was maintained at or below 22° Celsius by air conditioning. Music was played throughout the class, and was the choice of the instructor.

4.2.11 Pilot work

Pilot work was done at the hospital rehabilitation unit before beginning the study.

Assessment pilot and resultant methodological changes.

From the pilot work an estimated time to complete the assessment and to establish whether those most disabled (EDSS 6.5) would be able to complete the assessment was confirmed.

Two participants (EDSS 5.5 and 6.5) took part in the pilot for the assessments, neither of whom took part in the main study. The study was explained, and consent taken. The participants were asked to complete the self-rated questionnaires; the ABC, FSS, HADS and LMSQOL, and it was established that this would take approximately 10 minutes. The physical assessments and PhoneFITT were then carried out, following protocol order 1 (Section 4.2.5) taking between 50 and 70 minutes dependant on the participants disability level.

Following pilot work, protocol changes were made as follows;

- To avoid difficulties with participants who wore ankle foot orthosis, or a Functional Electrical Stimulator (FES) machine on their foot, footwear was to remain on throughout all testing. During the main study participants were reminded to wear the same shoes for assessments.

- The initial protocol for the overall stability assessment (perfomed on the Biodex balance machine was based on past work in disabled populations, which had found stability Level 8 to be more appropriate than a more challenging level of stability (Aydog et al 2006) and tested for 20 s (Aydog et al 2006) and 30 s (Ghoseiri et al 2009). Following pilot work the stability level remained at level eight (the most stable) and the length of each test was shortened from 30 s in the pilot to 20 s.

Feedback from the participants was positive regarding the ordering of tests and the difficulty.

Exercise class pilot and resultant methodological changes.

Two participants took part in the pilot exercise class; both were included in the main study (participants 1 and 9 Table 4.4). It was judged that no training effect would occur sufficient to disqualify the pilot participants' inclusion in the main study; since the one hour exercise pilot was done only once, five weeks prior to the start of the exercise class. It is acknowledged that the pilot participants may have started with some slight advantage, i.e. prior knowledge of the class content, however this would likely become insignificant over the 12-week duration of the intervention.

The pilot class lasted about one hour, and involved a seated warm up and seated cool down, led by one of the fitness instructors. Thirteen exercises were trialled, word-explanations and photographs were provided (similar to those in Table 4.2) and discussed with the participants.

Following pilot work, exercise modifications were made;

- In the "upper body" exercise Level 1 changed from using small weights, to no weights.
- In the "cushion-standing" exercise Level 1 changed from standing on a mat, to standing on the floor.
- Name changes were made to some exercises e.g. "Side kick" (originally "Hip Abduction") as their names were deemed too technical.

Feedback from the participants was positive regarding the format, difficulty/intensity and variation in the class.

4.3 Statistical Analysis

Data were analysed using Minitab (v. 16) and SPSS (v. 16) statistical packages. Independent sample t-tests were used for demographic outcomes found to be parametric (e.g. Body Mass Index) and for non-parametric variables (e.g. Age) a Mann-Whitney *U* test was used. All outcome measures were analysed on the basis of Intention to Treat, with all variables summarised and comparisons made between groups and over time. When three trials were taken for an outcome measure, at each time point, (i.e. T25FW, TUG, SLS, WLS, OS and temporal spatial outcomes) intraclass correlations were run to assess for reliability across the three trials. In doing so moderate to high reliability was found suggesting the values were consistent, accordingly the mean of the three readings was used for analysis.

The outcome variable data were analysed using a univariate General Linear Model Analysis of Variance (ANOVA) which allowed for missing data and possible interaction effects over time (baseline, week 8, week 12, month 6 and month 12) and between groups (intervention and control) to be assessed. All tests were at the 5% ($p<0.05$) level of significance (Norman and Streiner 2007). Where results of the ANOVA indicated significance between groups (Group effect), over time Tukey's Post Hoc analysis was carried out, to establish whether, over the five time points, significance could be found between particular stages (e.g. between weeks 8 and 12, between week 8 and month 6 etc.).

A Kolmogorov-Smirnov test was used to assess the distribution of the data; any results found not to be normally distributed were transformed to Natural Logarithms and these are presented. Baseline variables were checked for normality using SPSS (v. 16), and as many of the outcomes were not found to be normally distributed, a Mann-Whitney U test was performed to check for significance. Normally distributed data was analysed with a two-sample t-test.

The effect of the intervention was calculated, using Cohen's *d* analysis, to establish effect size at each time point. This showed the difference between the two groups and provided a numerical value used to interpret the size of the effect of the intervention. They were calculated for the intervention group only. These values were interpreted as a small effect size (d <0.5), moderate effect size (d=0.5<0.8) or a large effect size ($d\geq$0.8) (Tyson and Connell 2009). Unlike tests of statistical significance, effect size indicates the size of the difference without confusing it with sample size (Coe 2002). It is found in both meta-analysis of MS therapeutic studies (Motl and Gosney 2008; Snook and Motl 2009) and in primary studies of therapeutic exercise in MS (Huisinga and Stergiou 2011)

Clinical effectiveness was also calculated, independently, for both groups as percentage change for all outcome measures at all time-points from baseline. The formulae and worked examples for both effect size and percentage change are available in Appendix 11.

4.4 Results

4.4.1 Baseline demographic characteristics

Thirty-two participants began the study. Twenty subjects were allocated to the intervention group with twelve subjects to the control group. Data will be presented as a whole data set, with those attending the intervention at site A and site B being regarded as one intervention group, similarly the control participants will be considered as one group.

The intervention group comprised of five men and fifteen women, with four men and eight women in the control group. Demographic details of both groups are given in Table 4.3, including their baseline scores for the main outcome measures. Table 4.3 shows that at baseline there were no statistical differences between the two groups in terms of age ($p=0.893$), years since disease onset ($p=0.687$) or any of the assessed outcome measures.

Table 4.3 Demographic and baseline characteristics of participants in Study 1.

Variable/Outcome measure	Intervention group	Control group	Test	p-value
Number of subjects	20	12	-	-
Gender M:F	5:15	4:8	FE	0.696
Age (years)	51.4 (8.06)	51.8 (8)	MW	0.893
EDSS	6.1 (0.36)	5.8 (0.5)	MW	0.387
Years since onset	13.4 (6.4)	12.6 (8.1)	MW	0.687
T25FW (sec)	22.1 (21.8)	16.1 (13)	MW	0.289
6MWT (m)	191.1 (102.2)	221.2 (120)	MW	0.431
WCa (steps/min)	84.3 (24.4)	123.5 (102.5)	T-test	0.068
WVel (cm/sec)	67.4 (24.2)	105.9 (69.2)	T-test	0.251
FAP	69.8 (14.4)	78.6 (15.6)	T-test	0.506
LSL (cm)	40.85 (14.9)	47.97 (19.7)	T-test	0.559
RSL (cm)	44.33 (15.9)	48.4 (20.2)	T-test	0.663
TUG (sec)	6.3 (8.4)	4.8 (3.3)	MW	0.723
BBS	41.4 (11.8)	44.7 (11.1)	T-test	0.822
OS	6.3 (8.4)	4.8 (3.3)	T-test	0.506
SLS (Nm)	84.3 (24.4)	123.5	MW	0.187
WLS (Nm)	67.4 (24.2)	105.9 (69.2)	T-test	0.106
PF	53.3 (20.6)	54.6 (26.6)	T-test	0.155
ABC	56.2 (16.6)	51.8 (23.5)	MW	0.578
FSS	5.3 (1.7)	5.7 (1.2)	T-test	0.108
HADS	15.9 (6.5)	15.8 (9.3)	MW	0.578
LMSQOL	12.9 (4.9)	14.1 (3.9)	T-test	0.481
BMI	41.4 (11.8)	44.7 (11.1)	MW	0.289

Mean, (standard deviation) and significance details are presented where appropriate

FE – Fisher's Exact, MW – Mann-Whitney, T-test – Independent samples t-test, EDSS-Expanded disability Status Scale, T25FW – Timed 25ft Walk, 6MWT – Six-minute walk test, BBS, Berg Balance Scale, TUG-Timed Up and Go test, SLS-strongest leg strength, WLS-weakest leg strength, BMI-Body Mass Index, PF-PhoneFITT, ABC-Activities Balance Confidence, FSS-Fatigue Severity Scale, HADS-Hospital Anxiety and Depression Scale, LMSQOL-Leeds MS Quality of Life, OS-Overall stability, WCa-walking cadence, WVel-walking velocity, FAP – Functional Ambulatory Perfomance/Overall walking performance. LSL – Left leg Step Length, RSL – Right leg Step Length.

4.4.2 Attendance and attrition.

Baseline data were taken for 32 subjects who began the study. Attendance and attrition is summarised in Figure 4.3. Reasons for attrition will be explained, with relevant participants identified in parenthesis based on participant number provided in Table 4.4.

At the week eight assessments three subjects discontinued participation (7, 8 & 32), with missing data for a further three continuing subjects (5, 25 & 31). At week twelve one other subject discontinued participation (45), with four participants unable to attend for assessment, although they remained in the study (25, 24, 6 & 28). At month six, one participant had moved away and discontinued participation (14), one could not be contacted (26) and one was suffering increased mobility problems and was unable to attend (24). At month twelve another participants had moved away from the area, however they completed the questionnaires at home (12), three could not be contacted (1, 10 & 13) and one had fractured her dominant arm and could not attend or self complete the questionnaires (4).

Over the course of the study there was missing data for some outcome measures. If the assessing physiotherapist or Chief Investigator deemed it clinically unsafe to perform the outcome measure, for example balance or mobility outcome measures, the outcome measure was not completed; with a 0 score recorded for missing data. This occurred on different occasions with two of the participants (25 and 29), who had an EDSS score of 6.5.

Attendance at the exercise class was taken for the intervention groups. Attendance rates were calculated to include attendance of those who discontinued participation. Overall attendance at the intervention was 71%, 340 out of a possible 480 sessions (Site A 62%, Site B 80%). Other studies who report attendance rates often exclude those who discontinued study participation (Taylor et al 2006; McCullagh et al 2008; Dalgas et al 2010), thus for this study if attendance from those who officially discontinued participation (n=3) is excluded, overall attendance was 77% (Site A 72%, Site B 81%).

Table 4.4 Demographic details of all subjects at baseline

Participant	Site	Group	Age (years)	Sex	Years since onset	EDSS
1	A	I	45	M	14	6
2	A	I	58	F	11	6
3	A	I	48	F	18	6
4	A	I	58	F	16	6.5
5	A	I	62	F	15	6
6	A	I	49	F	18	6
7	A	I	40	F	7	6.5
8	A	I	43	F	2	6
9	A	C	54	F	16	5.5
10	A	C	45	F	16	6.5
11	A	C	45	M	12	6.5
12	A	C	54	M	8	6
13	A	C	53	F	13	6
14	A	C	52	F	27	5
15	B	I	68	M	33	6
16	B	I	40	F	12	6
17	B	I	58	F	15	6
18	B	I	41	F	4	6.5
19	B	I	53	M	17	6.5
20	B	I	49	F	16	6
21	B	I	54	F	12	6
22	B	I	53	M	10	5
23	B	I	49	M	15	6.5
24	B	I	47	F	16	6.5
25	B	I	63	F	12	6.5
26	B	I	45	F	7	6
27	B	C	64	F	22	5.5
28	B	C	58	M	1	6
29	B	C	59	M	7	6.5
30	B	C	34	F	5	6
31	B	C	51	F	6	6
32	B	C	58	F	2	6

Site refers to site which before randomisation subjects could have been allocated to attend had they been selected to the intervention group. I-Intervention, C-Control group, M-Male, F-Female.

4.4.3 Overall results and trends

Mean data from the assessed outcome measures at baseline, week eight, week twelve, month six and month twelve is presented in Table 4.5.

The mean scores varied for all outcome measures across the different time-points of the study. These will be discussed in more depth in the next section of this chapter. Results showed large standard deviations throughout the whole data set, for example in the intervention group baseline mean scores for the T25FW were 22.1 s with standard deviation being 21.8 s.

Although there was no statistically significant differences between any outcome measures (Table 4.5), better baseline scores were seen for the control group in all assessor rated mobility and balance measures (Table 4.5).

At baseline there was no difference in leg strength between the intervention and control group. Across the sample as a whole, for 14 of the participants their left leg was stronger, whilst the right leg was stronger for the remaining 18 participants tested at baseline. T-test analysis was performed to determine whether there was a difference between weaker and stronger leg strength. A statistically significant result emerged ($p<0.01$).

Table 4.5 Group means (SD) for the main outcome measures.

Outcome Measure	Baseline	Week 8	Week 12	Month 6	Month 12
T25FW (sec)					
Intervention	22.1 (21.8)	14.8 (9.3)	14.9 (13.6)	21.7 (22)	16.4 (18.1)
Control	16.1 (13)	15.4 (10.1)	13.1 (8.6)	12.79 (8.5)	23.6 (26.9)
6MWT (m)					
Intervention	191.1 (102.2)	228.6 (118.7)	262.2 (127.4)	226.5(134.4)	252.3 (115)
Control	221.2 (120.1)	260 (128.9)	215.8 (175.7)	233.89(98.1)	260.3 (159.2)
WCa (steps/min)					
Intervention	84.3 (24.4)	91.7 (25.6)	97.2 (28.7)	89.1 (26.8)	92.8 (27.7)
Control	123.5 (102.5)	100 (18.1)	93.3 (22.9)	82.1 (33.2)	93.4 (32.2)
WVel (cm/sec)					
Intervention	67.4 (24.2)	77.6 (33.9)	85.4 (35.4)	77.1 (32.2)	80.4 (31.2)
Control	105.9 (69.2)	87.7 (28.8)	98.8 (71.6)	68.7 (32.6)	80.7 (38.8)
FAP					
Intervention	69.8 (14.4)	73.7 (17.3)	78.1 (17.3)	76.87 (15.4)	79.5 (14.9)
Control	78.6 (15.6)	81.1 (13.3)	74.7 (17.4)	77.8 (11.6)	71.9 (15.1)
LSL (cm)					
Intervention	40.9 (14.9)	42.7 (17.1)	49.9(12.6)	49.6 (10.1)	49.6 (9.3)
Control	48 (19.7)	52.7 (10.3)	42.9 (8.6)	46.9 (9.7)	49.2 (11.8)
RSL (cm)					
Intervention	44.3 (15.9)	47.5 (18.2)	53.7 (11.7)	50.3 (11.2)	51.4 (10.2)
Control	48.4 (20.2)	52.4 (10.1)	45.9 (6.9)	47.9 (9)	47.3 (11)
LST (s)					
Intervention	0.8 (0.6)	0.71 (0.5)	0.73 (0.6)	0.81 (0.59)	0.84 (0.8)
Control	0.61 (0.3)	0.62 (0.22)	0.67 (0.2)	0.67 (0.2)	0.76 (0.4)
RST (s)					
Intervention	0.78 (0.5)	0.73 (0.5)	0.76 (0.53)	0.81 (0.52)	0.8 (0.6)
Control	0.61 (0.3)	0.61 (0.14)	0.69 (0.2)	0.68 (0.2)	0.77 (0.4)
TUG (sec)					
Intervention	22.3 (16.9)	19.7 (14.6)	18.4 (15)	27.2 (26.3)	20.9 (20)
Control	19.7 (14.93)	19.5 (12.1)	16.2 (11)	16.03 (11.5)	28.7 (29.8)
BBS					
Intervention	41.4 (11.8)	47.4 (9.7)	46.7 (10.6)	46 .4(10.8)	40.3 (17.2)
Control	44.7 (11.1)	47.9 (8.1)	40.9 (15.2)	43.3 (16.7)	42.4 (16.3)
OS					
Intervention	6.3 (8.4)	4.1 (2.9)	3.7 (2)	4.4 8 (2.2)	4.4 (2.2)
Control	4.8 (3.3)	4.1 (2)	4.6 (1.9)	5.38 (5.86)	4.1 (2.2)
SLS (Nm)					
Intervention	42.4 (21.6)	40.2 (18.4)	67.7(41.3)	73.6 (42.9)	75.5 (43.2)
Control	45.5 (14.4)	48.6 (15.8)	41 (38.4)	86.8 (27.5)	95.2 (25.5)
WLS (Nm)					
Intervention	27.9 (16.1)	36.3 (20)	54.5 (49)	70.2 (39.6)	71.6 (37.9)
Control	28.3 (14.7)	33.6 (16.5)	34.3 (24.6)	66.2 (35.2)	70.6 (35.6)
PF					
Intervention	53.3 (20.6)	69.7 (23.6)	78.2 (35.5)	61.08 (34.8)	60.7 (34.1)
Control	54.6 (26.6)	38.3 (23.1)	54.6 (16.7)	47.3 (30.4)	48.8 (24.2)
ABC					
Intervention	56.2 (16.6)	69.7 (23.6)	79.8 (28.3)	62.56 (32)	54.1 (30.6)
Control	51.8 (23.5)	58.7 (35.6)	60.9 (35.6)	57.8 (41.2)	57.4 (41.2)
FSS					
Intervention	5.5 (1.7)	5 (2)	5 (1.8)	5.07 (1.7)	5.4 (1.4)
Control	5.7 (1.2)	5.7 (2.1)	6.2 (0.7)	5.28 (1.56)	5.33 (1.7)
HADS					
Intervention	15.9 (6.5)	11.6 (5.4)	11.7 (5.9)	12.13 (2.7)	12.8 (6.6)
Control	15.8 (9.3)	14.2 (7.9)	13.8 (6.6)	13.4 (4)	18.9 (9)
HADS Anx					
Intervention	7.95 (4.1)	5.6 (3.5)	6.2 (3.3)	6.3 (3.1)	5.9 (4)
Control	7.92 (5.2)	8.4 (5.1)	6.5 (4)	7.5 (4.4)	9.4 (5.1)

HADS Dep					
Intervention	7.4 (3.7)	6 (2.4)	5.5 (3.4)	8.2 (3.5)	7 (3.6)
Control	7.9 (4.9)	8 (4.6)	7.3 (3.5)	6.8 (4.7)	9.5 (3.6)
LMSQOL					
Intervention	12.9 (4.9)	11 (4.22)	10.9 (3.9)	12.13 (2.7)	12 (3.3)
Control	14.1 (3.9)	12.3 (4.1)	12.4 (3.1)	13.4 (4)	15.4 (4)
BMI (kg/m^2)					
Intervention	28.7 (5.1)	27.9 (5.1)	27.5 (6)	27.6 (4.3)	45.3 (8.7)
Control	31.4 (5.9)	30.7 (6.7)	29.6 (6.2)	29.9 (5.5)	53.6 (9.9)

T25FW – Timed 25ft Walk, 6MWT – Six-minute walk test, BBS, Berg Balance Scale, TUG-Timed Up and Go test, SLS-strongest leg strength, WLS-weakest leg strength, BMI-Body Mass Index, PF-PhoneFITT, ABC-Activities Balance Confidence, FSS-Fatigue Severity Scale, HADS-Hospital Anxiety and Depression Scale, HADS Anx-Hospital Anxiety and Depression Scale Anxiety; HADS Dep-Hospital Anxiety and Depression Scale depression LMSQOL-Leeds MS Quality of Life, OS-Overall stability, WCa-walking cadence, WVel-walking velocity, FAP – Functional Ambulatory Perfomance/Overall walking performance. LSL – Left leg Step Length, RSL – Right leg Step Length.

4.4.4 Results of the study

The results of the study were calculated in three ways;

- To compare results between groups and over time a General Linear Model Analysis of Variance was performed (ANOVA).

- Effect sizes were calculated for all outcome measures for the interventions group (Table 4.6).

- Percentage change, from baseline, was also calculated, for all outcome measures in both groups.

The primary outcome measure, the T25FW is explained in the Section 4.4.5. Results of the ANOVA (Section 4.4.6), Effect sizes (Section 4.4.7) and clinical effectiveness (Section 4.4.8) for the secondary outcome measures are discussed in respective sections.

4.4.5 Primary outcome measure results

The primary outcome measure was the T25FW, however ANOVA results of the T25FW demonstrated no statistically significant difference over time (Table 4.6). Effect sizes were calculated based on Cohen's *d*. For the T25FW small effect sizes occurred at all time points. However, after the twelve weeks of the intervention the mean scores improved by 7.2 s (a percentage change of 33% - Table 4.7) compared with the 3 s (19%) in the control group. At follow-up however, there was no similar pattern. Six months after the intervention the mean scores for the T25FW in the intervention group had regressed back toward baseline scores (1.8% clinical change), a further six months (12 months) after the intervention the intervention group showed a clinical improvement of 20.6%.

In the control group a clinical improvement of 20.5% was seen at 6 months. This compared with scores at 12 months where values were less than baseline (-46.5%), suggesting deterioration over time. It is important to note that large standard deviations across the sample were present in both groups (Table 4.5), leading to considerable variability within the results.

In summary, the intervention did not lead to any statistically significant findings or significant effect sizes in the primary outcome measure, the T25FW. Although there was evidence of positive percentage change scores.

Table 4.6 Differences between group and over time, including effect sizes and clinical effect.

Outcome Measure	Group effect p-value	Time effect p-value	Group/time interaction p-value	Effect size at;			
				Week 8	Week 12	Month 6	Month 12
T25FW *	0.645	0.948	0.702	0.30	0.23	0.22	0.1
6MWT	0.422	0.684	0.747	0.02	0.68	0.01	0.69
WCa*	0.820	0.392	0.134	0.49	0.68	0.72	0.65
WVel *	0.102	0.267	0.565	0.61	0.54	1.01~	0.65
FAP *	0.146	0.846	0.696	0.1	0.81~	0.52	1.09~
LSL *	0.077	0.821	0.183	0.16	0.81~	0.57	0.43
RSL*	0.135	0.906	0.295	0.05	0.65	0.35	0.45
LST	0.324	0.217	0.663	0.22	0.28	0.22	0.15
RST	0.2	0.376	0.722	0.18	0.15	0.1	0.35
TUG *	0.541	0.922	0.938	0.15	0.03	0.62	0.19
BBS	0.255	0.985	0.352	0.25	0.80~	0.5	0.69
OS*	0.177	0.764	0.699	0.32	0.7	0.48	0.63
SLS*	0.255	<0.001^	0.302	0.23	1.65~	0.69	1.32~
WLS *	0.717	<0.001^	0.613	0.20	1.33~	1.9~	0.72
PF	<0.001^	0.531	0.079	1.37~	1.05~	0.55	0.86~
ABC	0.006^	0.194	0.539	0.33	0.94~	0.77	0.28
FSS	0.601	0.889	0.219	0.30	0.67	0.01	0.2
HADS	0.01^	0.254	0.683	0.02	0.08	0.38	0.52

HADS Anx	0.019^	0.223	0.462	0.62	0.07	0.28	0.31
HADS Dep	0.011^	0.545	0.936	0.34	0.31	0.28	0.49
LMSQOL	0.002^	0.128	0.759	0.34	0.27	0.21	0.19
BMI	0.065	0.791	0.893	-0.02	0.17	0.11	0.05

T25FW – Timed 25ft Walk, 6MWT – Six-minute walk test, BBS, Berg Balance Scale, TUG-Timed Up and Go test, SLS-strongest leg strength, WLS-weakest leg strength, BMI-Body Mass Index, PF-PhoneFITT, ABC-Activities Balance Confidence, FSS-Fatigue Severity Scale, HADS-Hospital Anxiety and Depression Scale, LMSQOL-Leeds MS Quality of Life, OS-Overall stability, WCa-walking cadence, WVel-walking velocity, FAP – Functional Ambulatory Perfomance/Overall walking performance. LSL – Left leg Step Length, RSL – Right leg Step Length. *Data transformed to Natural Logarithm for group effect, time effect and group/time interaction. ^ $p<0.05$, ~ $d \geq 0.8$,

4.4.6 Analysis of Variance statistical test results

There was no significant differences between the groups in any of the outcome measures at baseline. Overall the ANOVA results did not reveal statistically significant results for many outcome measures. However, significant differences between groups was found for perceived activity levels (PF), perceived balance confidence (ABC), mood (HADS) and quality of life (LMSQOL).

Regarding activity levels (PF) the ANOVA revealed a statistically significant difference between the groups ($p<0.001$), there was no evidence of a time effect ($p=0.53$). However group behaviour, over time, demonstrated a trend towards significance ($p=0.079$). Post hoc analysis, did not reveal any statistically significant differences, between time points.

The ANOVA results for perceived balance confidence (ABC) revealed a statistically significant difference between the groups ($p=0.006$), however no significant time effect ($p=0.194$) or group time interaction ($p=0.539$) emerged.

Similarly the ANOVA revealed a significant difference in mood (HADS) ($p=0.01$); both anxiety (HADS Anx) and depression (HADS dep) ($p=0.019$ and $p=0.011$ respectively). However ,no significant time effect or group time interaction was found for this outcome measure (Table 4.6).

The ANOVA results revealed a statistically significant difference ($p=0.002$) between the groups for perceived quality of life (LMSQOL). No significant time effect ($p=0.128$) or group time interaction ($p=0.759$) emerged.

As group time interactions were not suggestive of any interaction post hoc analysis was not run for the ABC, HADS or LMSQOL results.

A significant difference between time points was seen for leg strength (as measured by torque) of both the stronger ($p<0.001$) and weaker ($p<0.001$) leg. As the group behaviour over time was not significant (Table 4.6), results imply this was over the sample as a whole, with no clear difference between groups. Furthermore no significant group time interaction emerged for either stronger ($p=0.302$) or weaker leg strength ($p=0.613$). Despite this ICCs were run post hoc, however no significant difference was seen between time points, implying at no single time point were strength results statistically improved.

In summary, there was no evidence from the results of the ANOVA that the intervention had any statistically significant effect on the other outcome measures assessed in the study (Table 4.6).

4.4.7 The effect of the intervention

It is recommended that statistical analysis (ANOVA results) and the effect of the intervention (effect sizes) be considered together (Them and Be 2008). The key findings from the ANOVA (Section 4.4.6) and the effect sizes are important descriptors of the overall study results. To ascertain the effect of the intervention effect sizes were calculated, in the intervention group only, based on Cohen's *d* (Table 4.6). This calculation uses means from both the intervention and control group (Appendix 11). Thus, as positive effect sizes emerged for all outcome measures (with the exception of BMI at week 8) these results suggest the intervention group improved more than the control group over all outcome measures.

After eight weeks, a good effect was seen for perceived physical activity (PF; $d = 1.37$), with moderate effects seen for anxiety scores and walking velocity.

On completion of the intervention, i.e. week 12, a large effect size was found for dynamic balance (BBS; $d=0.8$), stronger (SLS; $d=1.65$) and weaker (WLS; 1.33) leg strength, perceived physical activity (PF; $d=1.05$), balance confidence (ABC; $d=0.94$), overall walking performance (FAP; $d=0.81$) and left leg step length (LSL; $d=0.81$). Moderate effect sizes were seen for walking endurance (6MWT), fatigue levels, stability, walking cadence and walking velocity.

Six months after completion of the intervention large effect sizes were seen in the intervention group for weaker leg strength (WLS; $d=1.9$) and walking velocity (WVel; $d=1.01$). Moderate effect sizes were seen for dynamic balance, mobility (TUG), stronger leg strength, perceived physical activity, perceived balance confidence, walking cadence, overall walking performance and left step length.

Twelve months after the intervention, large effect sizes were seen for stronger leg strength (SLS; $d=1.32$), perceived physical activity (PF; $d=0.86$) and overall walking performance (FAP; $d=1.09$). Moderate effect sizes emerged for walking endurance (6MWT), dynamic balance, weaker leg

strength, mood, stability, walking cadence and walking velocity. Results of this for the main outcome measures appear in Table 4.6, further temporal spatial results are available in Appendix 12.

Over all four time-points (following baseline) no clear pattern emerged to demonstrate a good effect was maintained. Some outcomes showed the greatest effect size after 8 weeks (T25FW, PF, HADSAnx & LMSQOL), whilst for other outcome measures the greatest effect size was after 12 weeks (BBS, SLS, ABC, LSL & RSL) or after a further 6 months (TUG, WLS, FSS, WCa, WVel) and some on completion of the study (6MWT, HADS, HADS depression, FAP). In addition, at week 12, month 6 and month 12 moderate or large effect sizes were seen for measures of leg strength, balance and perceived physical activity.

4.4.8 Percentage change results

Percentage change was calculated, from mean baseline scores, for the outcome measures at all the time-points independently for both groups (Table 4.7). Overall more improvement was seen in the majority of the outcome measures in the intervention group, which supports the positive effect sizes discussed in Section 4.4.7.

The improvement seen was particularly true for the assessments taken during and immediately following the intervention (Week 8 and 12). At the follow-up assessments the control group appeared to improve more in some of the outcome measures (such as stronger leg strength, perceived balance confidence and fatigue levels) although the intervention groups still improved to a greater extent in most outcome measures.

In addition, the results of percentage change indicate where participants performance on the outcome measures worsened when compared with the initial baseline scores. This was most common in the control group, where at month 6 dynamic balance (BBS), perceived physical activity (PF), stability (OS), mood (HADS and HADS Anx), walking cadence (WCad), velocity (WVel) and overall walking performance (FAP) had lower scores. This regressive pattern continued at month 12 for these outcome measures and mobility (T25FW & TUG), body composition (BMI), anxiety and depression (HADS). In the intervention group a regression to scores below baseline was seen at month 6 for mobility (TUG) and at month 12 for dynamic balance (BBS) and body composition (BMI).

Table 4.7 Percentage change in intervention and control group.

Outcome Measure	Intervention group				Control group			
	Week 8	Week 12	Month 6	Month 12	Week 8	Week 12	Month 6	Month 12
T25FW	24%	33%	1.8%	26%	4.2%	19%	20.6%	-46.5%
6MWT	19%	37%	18.5%	32%	18%	-2.4%	5.7%	17.7%
WCa	9%	15%	5.7%	10%	-19%	-24%	-33.5%	-24.4%
WVel	14.3%	26.6%	14.4%	20.3%	-17.3%	-6.7%	-35%	-23.8%
FAP	5.6%	12%	10.1%	13.9%	3.2%	-5%	-1%	-8.5%
LSL *˚	4.6%	22%	22%	22%	9.8%	-10.6%	-2.3%	-2.5%
RSL* ˚	7.2%	21%	13.5%	16.7%	8%	-5.2%	-0.5%	-2.3%
LST	11%	8.7%	-2.3%	-3.8%	-1.6%	-9.8%	-9.8%	-26%
RST	-6.4%	-2.6%	-3.8%	-2.6%	0	-13%	-12%	-26%
TUG	12%	17%	-22.1%	6.2%	0.8%	17%	18.5%	-46%
BBS	15%	12%	12.1%	-2.6%	7%	-8.5%	-3.1%	-5.1%
OS	8%	12%	28.9%	30.2%	6%	2%	-12.1%	14.6%
SLS	5.2%	60%	73.5%	78%	68%	-10%	86.8%	95.2%
WLS	29%	95%	152%	157%	19%	21%	90.7%	109%
PF	31%	47%	14.6%	13.9%	-29%	0.2%	-13.4%	-10.6%
ABC	24%	42%	11.3%	3.7%	13%	8%	11.5%	11.3%
FSS	7.9%	9.2%	3.6%	1.8%	-0.5%	-8.2%	7.4%	6.5%
HADS	27%	26%	23.7%	19.5%	10%	13%	15.2%	-19.6%
HADS A	29%	22%	21%	26%	-6%	17.9%	5.3%	-18.7%
HADS D	19%	26%	10%	5%	<-1%	7.5%	14%	-20%
LMSQOL	15%	16%	6%	7%	13%	12%	5%	-9.2%
BMI	2.7%	3%	3.8%	3.9%	2.2%	5.9%	4.8%	-<1%

Grey shading represents better improvement compared with the other group.
T25FW – Timed 25ft Walk, 6MWT – Six-minute walk test, BBS, Berg Balance Scale, TUG-Timed Up and Go test, SLS-strongest leg strength, WLS-weakest leg strength, BMI-Body Mass Index, PF-PhoneFITT, ABC-Activities Balance Confidence, FSS-Fatigue Severity Scale, HADS-Hospital Anxiety and Depression Scale, HADS A-Hospital Anxiety and Depression Scale anxiety; HADS Dep-Hospital Anxiety and Depression Scale depression; LMSQOL-Leeds MS Quality of Life, OS-Overall stability, WCa-walking cadence, WVel-walking velocity, FAP – Functional Ambulatory Perfomance/Overall walking performance. LSL – Left leg Step Length, RSL – Right leg Step Length.

4.4.9 Fatigue Severity Scale, possible ceiling effect

As discussed in Section (3.9.10) the FSS has previously been found to be vulnerable to a ceiling effect. There was evidence of this during the present study, the FSS at baseline are displayed in Figure 4.8. A good distribution of scores was found, however five participants recorded the maximum score, indicated a ceiling effect.

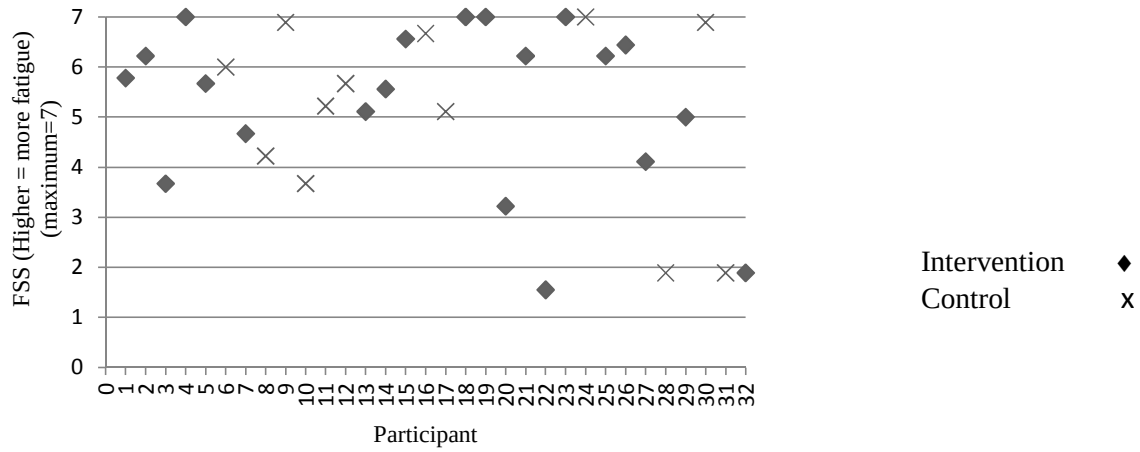

Figure 4.8 Scatterplot of FSS at baseline

(Participant number refers to number in Table 4.4)

There was no indication of either a floor or ceiling effect from the results of any other outcome measure.

4.4.10 Goal attainment

All participants were asked to choose three goals which they would like to achieve by the end of the intervention period (Table 4.8). Improving fatigue scores and balance stability was the priority goal for most participants (n=7 for both), with improving mobility endurance (n=6) and dynamic balance (n=5) also common. Many participants choose to improve the strength of their weaker leg (n=17) and improving fatigue scores (n=16).

Table 4.8 Goals (and related outcome measures) chosen by the participants

Related outcome	Goal 1	Goal 2	Goal 3	Total
Fatigue (FSS)	7	4	5	16
Balance stability (OS)	7	3	2	12
Mobility/endurance (6MWT)	6	2	5	13
Dynamic Balance (BBS)	5	7	1	13
Attend class	2	5	4	11
Mobility (T25FW)	2	1		3
Leg strength (WLS)	1	8	8	17
Balance (ABC)	1	1	2	4
Quality of life (LMSQOL)		1	1	2
Mobility/function (TUG)	1		1	2
Anxiety and depression (HADS)			1	1
Single leg balance**			1	1
Weight loss**			1	1

No participant chose the goal related to social interaction.
FSS-Fatigue Severity Scale, *S-Overall Stability), 6MWT – Six-minute walk test, BBS- Berg Balance Scale, Timed 25ft Walk, WLS-weaker leg strength, ABC-Activities Balance Confidence, LLMSQOL-Leeds Multiple Sclerosis Quality of Life, TUG-Timed Up and Go test, HADS-Hospital Anxiety and Depression Scale, **Personal (12^{th}) goal.

Achievement of chosen goals was calculated for those in the intervention group, using the formulae described in Section 3.9.14. The basic results are presented in Figure 4.9. This result considers all three of the chosen goals. In this figure scores further from the fulcrum are larger, thus it can be seen that for all but two of the participants, their GAS score was larger at the end of the intervention, indicating a move towards achieving their goals. However t-test analysis did not reveal any significant difference (p=0.7) between the mean scores at baseline and following the intervention.

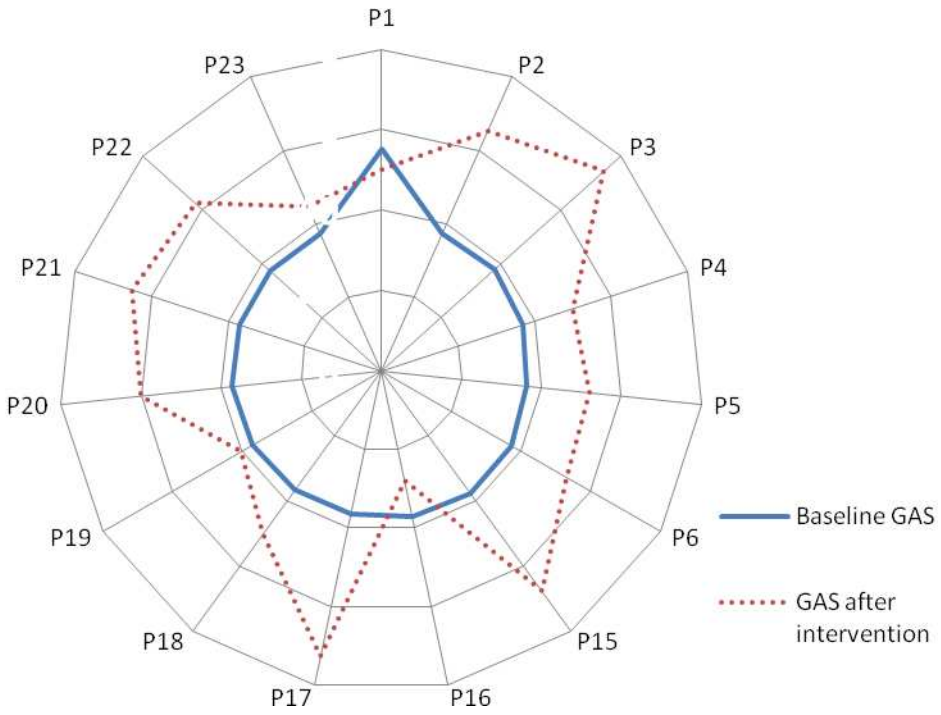

Figure 4.9 Radar diagram of intervention group GAS scores

Larger scores are indicative of improvement. P – Participant number (Participant number refers to number in Table 4.4)

4.4.11 Summary of results

Results from this study suggest that there was no statistically significant results or large effect sizes for the primary outcome measure (T25FW), despite this, percentage changes were seen. Of the secondary outcome measures, statistically significant differences emerged between groups for the perceived physical activity, perceived balance confidence, mood and quality of life. However, no interactions were found for any outcome measures, thus, there was no indication, from the ANOVA results, that the intervention had a significant effect. The calculated effect sizes at each time point provided evidence that the intervention had a large effect on many of the assessed outcome measures, furthermore there were many more clinical improvements seen in the intervention group compared with the control group. In addition, results suggest that most participants improved in outcome measures related to goals they chose to improve.

4.5 Discussion

The aim of the study was to deliver and evaluate, for up to one year, the effects of a 12-week therapeutic exercise class, against a control group matched for disability level who received usual care, and establish the effects of participation after a further six and twelve months. In doing so, the following results emerged:

A 12-week community based group exercise class for people moderately affected with MS results in many physiological (strength, mobility, fatigue and body composition), functional (mobility, balance and activity participation) and psychological (mood and quality of life) improvements in those who take part. However, there was no statistically significant difference in these outcomes for those undertaking the 12-week exercise intervention when compared to a control group of people moderately affected with MS not taking part in the exercise intervention.

4.5.1 General findings

There was no evidence that the therapeutic exercise intervention had any statistically significant effect on the primary outcome measure the T25FW, thus confirming the null hypothesis for the primary outcome measure (Section 4.1.3). Small effect sizes were also found for the T25FW. However positive percentage change was seen, with those in the intervention group improving more so than the control group at three of the four time-points. Within the MS therapeutic exercise literature, similar non significant improvements in T25FW times have also been found in less disabled MS populations; undertaking 16 weeks of resistance training (Pryor et al 2011), and undertaking 24 weeks of home based combined aerobic and resistance training (Romberg et al 2004; Romberg et al 2005). However Motl et al (2012) found that after eight weeks of thrice weekly combined (aerobic, resistance and balance) therapeutic exercise T25FW scores significantly improved in study participants (n=13, EDSS mean=5.6). Although similar, their participants were slightly less disabled than the participants in this study (EDSS mean (intervention group) = 6.1). In addition, the intervention took place three times a week, which may have encouraged greater change.

For the secondary outcome measures, the results of the ANOVA did not indicate any statistically significant improvements due to the intervention (i.e. there was no statistically significant difference between groups over time), and thus the null hypothesis (Section 4.1.3) cannot be rejected. However, the ANOVA indicated that statistically significant changes in perceived physical activity levels (PF), perceived balance confidence (ABC), mood (HADS) and perceived quality of life (LMSQOL) did occur, but it was not clear that this was in one particular group only.

Effect sizes, were also considered as part of this study, although these are not as powerful as the ANOVA statistical tests they are recommended to provide a clearer explanation of the data (Coe 2002; Them and Be 2008). From the effect sizes it emerged that the intervention group improved in all outcome measures; physical, functional and psychological. However, no clear pattern emerged to demonstrate that a particular physiological, functional or psychological improvement resulted at a particular time point. Moderate or large effect sizes were seen in the intervention group, for measures of leg strength, balance and perceived physical activity at all time-points following completion of the intervention .

Finally, at each time-point percentage change was calculated separately for each group, as the change from baseline. Overall, those in the intervention group improved more at all time points in most outcome measures. The results also highlighted that the control group regressed below baseline at varying time-points for measures of mobility, balance, activity levels, body composition and fatigue. This observation may be an indication of the potential symptom deterioration seen in MS.

In summary, the results were analysed using an ANOVA statistical test. The ANOVA did not indicate that any improvements emerged as a direct result of being in the intervention group. In addition to the ANOVA, effect sizes were calculated as was percentage change (from baseline). There was an indication from the results of the calculated effect sizes that many outcome measures improved in the intervention group. Percentage change results indicated the majority of outcomes improved more in the intervention group than in the control group. The following sections will discuss these results for each outcome measure.

4.5.2 Physical activity levels

Amongst the key findings from this study is that of improved physical activity levels (as measured by the PF (Gill et al 2008) which considers a variety of activities of daily living and exercise activities). Improved physical activity from participating in the intervention is suggested by results from the ANOVA, where a trend towards a significant difference between groups over time emerged. The moderate (month 6) and large (week 8, 12 and month 12) effect sizes seen in the intervention group also support the premise that physical activity improved as a result of participating in the intervention. Furthermore, the intervention group displayed a positive percentage change at all time-points, whilst the control group either maintained their levels of activity (week 12) or displayed less physical activity (week 8, month 6 and 12). This result, in the intervention group at least, may be unsurprising as participants were taking part in an intervention. However, there was no obligation to continue remaining active post 12-week intervention, and thus it is encouraging that taking part in the exercise class promoted a long term increase in physical activity, despite this being less than during the period of the intervention. Results, of percentage change, in the control group imply that, despite having the opportunity to engage in the same

physical activity options following the initial 12-weeks, the majority of the control group were not able to maintain those physical activity levels.

As previously discussed (Section 1.1), therapeutic exercise is one aspect of physical activity, thus the improvements in physical activity levels noted are interesting, as only one past study could be found in the therapeutic exercise MS literature, which assessed physical activity levels (Mostert and Kesselring 2002). Mostert and Kesselring (2002) used the Baecke Activity Questionnaire (BAQ) to investigate the effect of aerobic exercise on activity levels. In their study, activity levels increased by, on average, 4%, less than in the present study (where at week 12 a 47% increase was seen, and at month 12 a 13.9% increase from baseline was still maintained). It is important to remember, however that comparisons between different outcome measures are limited.

As discussed in Section 3.6 there are limitation in using self-report outcome measures, this may be particularly problematic for those with MS, who may have minor cognitive problems which may influence the accuracy of data, a potential limitation of this key finding. The author does acknowledge the growing trend in monitoring activity using electronic motion detection or accelerometers in those with mild MS (Weikert et al 2010; Weikert et al 2011), using these technologies or monitoring attendance at activities may, dependant on the study design, be utilised in future studies.

An increase in physical activity may be beneficial to those with MS, as people with MS have previously been found to be more sedentary than the general population (Mostert and Kesselring 2002; Stuifbergen et al 2003). It is important to not only encourage exercise, but also encourage general daily physical activity in people with MS. Increasing physical activity may go some way to improving MS-related symptom deterioration, such as muscle weakness and reduced balance, whilst also aiding prevention of other co-morbidities associated with inactivity, including reduced aerobic endurance, cardiovascular problems, obesity, diabetes, psychological ill-health and cancer (Chief Medical Officers 2011). Future studies could aim to move beyond establishing the impact of therapeutic exercise on symptom management in MS and look at the wider implications on overall physical activity and health.

4.5.3 Balance

Improving balance was an important goal for many participants in the study (Table 4.8), thus it is important, not least from the patients' perspective that positive improvements in balance emerged during the study. Statistically significant improvements in balance confidence (ABC) emerged from the ANOVA results of this study, although this was in both the intervention and control group. Statistically significant differences were not seen for the other two balance outcome measures (BBS and OS). However, moderate to large effect sizes were seen at the end of the intervention for all measures of balance, the positive effect was maintained at month 6 and month

12 follow-up. After eight weeks, only small effect sizes were seen across the balance outcome measures, this finding may imply that a longer exercise intervention is required to modify changes to balance in those with moderate MS .

In this study the ANOVA results from the ABC, found a statistically significant difference between the groups (p=0.006), Despite this, in the intervention group a large effect size at week 12, and a moderate effect size at month 6 (Table 4.6) was found. The percentage change results indicated that for the intervention group the greatest percentage change was seen after 12 weeks, however percentage change differences were higher for the control group at months 6 and 12 than the intervention group. Overall, these results imply that the intervention had positive benefits for balance confidence, and that 12 weeks may be required to achieve better results, which may not be maintained long term after the end of an exercise intervention. In Cattaneo et al's (2007a) study, participants followed a three-week, thrice weekly inpatient programme; no significant differences in ABC scores were found. As the ABC includes many questions related to everyday experiences (e.g. get into or out of a car"), it may not have been appropriate outcome measure for the methodology of Cattaneo et al's (2007) study. As the participants were inpatients during the study, they would not have had the chance to experience getting into or out of a car, for example, between answering the questions at baseline and then again at follow-up.

Despite no statistically significant finding emerging for the BBS in this study, a large effect size was seen at week 12, whilst moderate effects were maintained at months 6 and 12. Percentage change was similarly positive after week 8, week 12 and month 6, however BBS scores regressed towards baseline at the month 12 follow-up. Indeed those in the control group showed a higher percentage change at month 6 and 12 than the intervention group.

Relevant past studies, which have used the BBS, have found significant improvements. Freeman and Allison (2004) found a significant improvement in BBS results (p=0.02) at the end of their 10 week, once weekly combined exercise programme in a single cohort of patients with lower disability levels (mean EDSS=5) than participants in the present study. Hughes et al (2011) found a significant improvement in BBS scores ($p<0.001$) after a twelve week home exercise programme in participants who all used walking aids. When Hayes et al (2011) studied two cohorts of participants (mean EDSS=5.2) for 12 weeks of thrice weekly combined training (one group undertaking combined exercise, one undertaking combined exercise plus intense resistance training), they found a significant difference in BBS between groups (p=0.049). Those in the "combined intervention group only" improved whilst those in the other group regressed in their BBS scores. Results from these studies, alongside results from the present study, may suggest longer interventions are needed for balance improvements. However, this combined evidence also suggests, training stimulus, disability level and type of exercise may be influential to the outcome

of an intervention. Therefore, no strong conclusions can be drawn and further research on balance in those with MS is warranted.

As with the BBS, no statistically significant results emerged for balance stability (OS), although moderate effect sizes were seen at all time points (week 12, month 6 and month 12) after the intervention. Furthermore, in the intervention group, a positive clinical change was seen at all time points, improving at each subsequent assessment; more so than in the control group. Thus, similar to the discussion on the BBS above the duration of the therapeutic exercise intervention may be important in influencing balance results. However, as no past studies in the therapeutic MS literature were found which utilised a stability balance plate similar to that used in this study, results cannot be compared with past research.

4.5.4 Mood

There is evidence of increased anxiety and depression amongst those with MS, compared with a healthy control group (Zorzon et al 2001). In this study the ANOVA results indicated a statistically significant difference in mood, measured with the HADS, as a result of participating in the study, although it was not evident that this was as a result of the intervention. The intervention group improved more than the control group; as represented by the positive effect size and the results of percentage change for the HADS. Some aspects of mood declined in the control group, particularly at the month 12 follow-up.

In other studies researchers who have used different outcome measures to capture data on anxiety and depression have found statistically significant results due to the a aerobic exercise intervention. Petruzzello et al (2009) found a statistically significant improvement in anxiety (measured using the STAI) after a single 20 minute session of aerobic exercise. On completion of the eight week aerobic cycling exercise programme a significant improvement in depression (measured with the BDI) emerged ($p<0.05$). However in the same study, the comparison group, undertaking a resistance/balance intervention, did not show a significant change in depression scores Cakt et al (2010). Yet the 12-week resistance intervention in Dalgas et al's (2010) study resulted in a significant improvement in depression (measured with the MDI), with scores being maintained at the 12 week follow-up.

There are other examples of aerobic-based exercise interventions having a positive effect on mood (Petajan et al 1996; Schulz et al 2004; Rasova et al 2006), but the results were less significant. Accordingly further work is required to ascertain the potential effect of exercise on mood in MS.

4.5.5 Quality of Life

Quality of life is reportedly lower in those with MS than their healthier peers (Mostert and Kesselring 2002). Statistically it was found by the ANOVA that perceived quality of life results, as measured by the LMSQOL (Ford 2001), were significantly different ($p=0.002$) between groups across the duration of the present study. Despite only small effect sizes at each time point the percentage change results indicate that the intervention group improved more so than the control group.

The LMSQOL is an MS specific quality of life measure. It has been used in a home based MS-specific physiotherapy intervention (Miller et al 2011), and a number of studies have shown an association between physical activity and quality of life measured with the LMSQOL (Motl et al 2008a; Motl and McAuley 2009; Motl et al 2009a).

Past literature in therapeutic exercise in MS, has measured quality of life using MS specific quality of life scales, such as the MSIS (O'Connell et al 2003; Freeman and Allison 2004; Taylor et al 2006; Sabapathy et al 2011) or the MSQOL scale (Romberg et al 2005; Rasova et al 2006; Rampello et al 2007; Vore et al 2011; Pilutti et al 2011). With more generic quality of life scales, such as the SF-36 (Ware and Sherbourne 1992; Sabapathy et al 2011; Dalgas and Stenager 2011) and the WHOQOL (Skevington et al 2004) used in other MS therapeutic exercise studies. The number of different quality of life scales used makes comparison difficult, not only with results in this study, but between results of past studies.

In general, results have found small improvements in quality of life following therapeutic exercise interventions for those with MS. Pilutti et al (2011) showed a significant change in quality of life following a 12 week, thrice weekly aerobic based study, however the lack of control group in this study limits the impact of these results. Dalgas et al (2010) found that improved quality of life was maintained three months after completion of their resistance training programme. Conversely Dodd et al (2011) found that three months after their resistance training programme quality of life improvements were not maintained. Thus, the significance of the findings in this study, that improvements in quality of life were found and were maintained at the follow-up assessments suggest there is a need to establish the impact of exercise interventions on quality of life further.

4.5.6 Muscle strength

Reduced strength is a common symptom for those with MS (Matthews 1998), furthermore for participants in this study improving strength was an important goal (Table 4.8). This study's results suggest that a statistically significant difference over time emerged for leg muscle strength, when both groups were considered together, for both stronger leg ($p<0.001$) and weaker leg ($p<0.001$). Large effect sizes were seen in the intervention group after 12 weeks of the intervention,

with moderate and large effects seen at the six and 12-month follow-up assessments. Looking at percentage change in each group, both groups improved, with the intervention group improving most at the 12 week time-point whilst the control group improved more at other time-points. It is difficult to explain this finding, although, as indicated in Section 4.5.2, control participants were free to increase their physical activity levels, and doing so may have improved their leg strength.

Improvements in strength initially occur because of neural adaptation (increased recruitment of motor units originating in the spinal cord and stimulating muscle fibers), which is followed by muscle hypertrophy (Section 2.4.2). In healthy individuals these neural adaptations may take place within the first 6 weeks of training, before hypertrophy is seen, although the time for improvements in strength to emerge does vary in the literature (Kraemer et al 2002). In an already altered neural system, as is found in MS, adaptations required for improvements in strength may be different to those of a healthy population. This may explain why strength gains were not found at week 8, yet were found at all subsequent time-points, and perhaps why improvements were found long term in the control group. Establishing the influence of neural adaptations on strength gain would add an interesting perspective to the therapeutic resistance exercise literature, and provide worthwhile clinical guidance to the length of training required.

In this study a maximum voluntary contraction (MVC), for 3 s, was assessed, using a "make-test" where the assessor matched (but did not "break") the force generated by the participants' quadriceps muscles (Bohannon 2001). In other studies, different methodologies have been used to assess strength; making comparison with others results difficult. In past literature strength gains in participants' leg muscles are found by almost all studies where resistance training was the main intervention (Section 2.6.2). In these mainly resistance training studies the intervention methodology is different to the combined exercise nature of the present study. Only one third of the intervention in this study was primarily resistance based, thus training specificity may have an important role in outcome. Therefore, the findings from resistance only studies are acknowledged but not directly relevant.

In the combined therapeutic exercise literature in MS, strength is not commonly assessed, making comparison difficult. However Romberg et al (2004) used a MVC (5 s) to measure quadriceps strength using a dynamometer (a different model to that of this study). Similar to in this study, no statistically significant results occurred in their intervention group following their six-month home based exercise study. Further work in establishing the effects of a combined exercise programme on participants strength is warranted.

In addition, all previous studies, to the author's knowledge have reported strength differences based on either left leg or right leg scores. This however does not reflect that weakness may be more evident in one lower limb compared with the other, in those with MS, i.e. monoparesis

(Confavreux and Vukusic 2008). The approach in the present study, which reported weaker leg and stronger leg strength differences (based on leg strength at baseline) is novel and revealed statistically significant differences between weaker and stronger leg, at baseline. As a proposal, future authors may be interested in adopting this approach.

4.5.7 Fatigue

Fatigue is amongst the top five most commonly experienced symptoms experienced by people with MS (Mathews, 1998), and in this study improving fatigue was the main goal (alongside improving balance stability), which participants wanted to achieve by the end of the intervention (Table 4.8). For many years those with MS were advised not to undertake exercise, as it has been suggested that exercise may worsen symptoms of fatigue (Sutherland and Andersen 2001). In this study no statistically significant changed in fatigue levels emerged, measured using the FSS, over time or between groups. Thus, there was no evidence of increased fatigue from participating in exercise.

A small effect size (d=0.3) was seen at week 8 whilst a moderate effect size (d=0.67) was seen at week 12. This compares to the small effect size (d=0.43) reported by Huisinga et al (2011) after 6 weeks of aerobic exercise training. In the present study, percentage change indicated that fatigue levels improved most during the intervention time (week 8 and 12). At the follow-up assessments these improvements in fatigue regressed back towards baseline. This compares to one previous study where the FSS follow-up results three months after the end of resistance training interventions remained improved (Dalgas et al 2010), although they regressed back towards baseline in Dodd et al's (2011) study. The relationship between exercise and fatigue is unclear, however if exercise has a positive carryover effect on other areas of participants lifestyle, fatigue management may be improved, with further investigation required related to exercise and fatigue in MS.

When Andreasen et al (2011) carried out a meta-analysis of therapeutic exercise in MS, two relevant conclusions emerged. The FSS is the most commonly used outcome measure for fatigue in the relevant literature and therapeutic exercise has the potential to improve fatigue. Although, from this study there is no statistically significant results to support the latter point, it is noted that fatigue levels improved most during the intervention phase of the study, with no evidence that exercise had a detrimental effect on fatigue levels.

In the literature, mainly aerobic based therapeutic exercise studies have assessed fatigue using the FSS. Statistically significant changes have been found (Huisinga and Stergiou 2011), while some authors reported improvements which failed to reach significance (Kileff and Ashburn 2005; Newman et al 2007). Other authors have reported no change in FSS scores following a therapeutic exercise intervention change (Petajan et al 1996; Geddes et al 2009; Collett et al 2011). In the resistance and combined exercise literature both Cakt et al (2010) and Dalgas et al (2010) found

statistically significant improvements in fatigue in studies lasting 8 weeks and 12 weeks respectively. Further suggesting there is a need for more research in this area.

Past MS literature found the FSS to be vulnerable to a floor and ceiling effect; in a study of 51 women with MS (EDSS mean 6.5) 1 participant recorded the lowest possible score (demonstrating a floor effect), whilst 1 participant recorded the highest score (demonstrating a ceiling effect) (Kos et al 2003). In the present study, there was no indication of a floor effect, however a ceiling effect was demonstrated, particularly at baseline, when five participants recorded the highest possible score. Thus the FSS, for these five participants, may not be recording a true reflection of their fatigue, limiting results. Future studies monitoring fatigue, in a group of people moderately affected with MS must be aware of a potential ceiling effect with the FSS, and perhaps utilise a different fatigue outcome measure.

4.5.8 Mobility

Mobility problems are common in those with MS (Motl et al 2008b). In this study mobility was assessed in a number of ways; over a short distance (T25FW), over a longer distance to gauge endurance (6MWT), functionally (TUG) and by measuring temporal and spatial parameters of gait. No statistically significant findings emerged, despite past MS therapeutic exercise studies reporting significant improvements in mobility following their intervention (Freeman and Allison 2004; Kileff and Ashburn 2005; Newman et al 2007; de Souza-Teixeira et al 2009; Cakt et al 2010; Vore et al 2011).

Results of the T25FW, which showed non-significant improvements have been discussed in Section 4.5.1. It emerged from the ANOVA that none of the other mobility outcome measures showed statistically significant changes. Moderate effect sizes were seen for the 6MWT (Week 12 and Month 12), the TUG (Month 6) and for various temporal spatial parameters throughout the time-points, this provides some indication of a positive effect, on mobility, from participating in the study.

Past MS therapeutic exercise studies have found significant improvements in 6MWT times. With Kileff and Ashburn's (2005) 12 week, twice weekly cycling intervention and Freeman and Allison's (2004) 10 week, once weekly balance and Pilates-based exercise intervention, both showing statistically significant improvements. It seems logical that Kileff and Ashburn's (2005) aerobic intervention would have resulted in increased endurance and the significantly improved 6MWT. However Freeman and Allison's (2004) intervention did not have a strong aerobic endurance component, yet still produced improvements in endurance measured with the 6MWT. In comparison to the present study Kileff and Ashburn's (2005) and Freeman and Allison's (2004) studies were smaller, included participants who were less disabled and did not include control groups. These findings, combined with the effect sizes noted in the present study suggest further

work is required to establish the impact of different types of exercise interventions on walking endurance in MS.

The TUG is common in MS therapeutic exercise literature. Minimal changes in TUG scores have been found in some studies (Debolt and McCubbin 2004; Filipi et al 2010; Hayes et al 2011), other studies have shown non-statistically significant improvements (Collett et al 2011; Huisinga and Stergiou 2011; Sabapathy et al 2011), whilst the following studies have found statistically significant improvements. Resistance exercise interventions (de Souza-Teixeira et al 2009; Vore et al 2011) and combined exercise training interventions (Cakt et al 2010; Motl et al 2012) have resulted in statistically significant changes in TUG scores. The main differences between these studies and the present study are that participants' disability level was lower and the intervention was delivered to individual participants (not in a group).

Finally, temporal spatial gait parameters showed improvement throughout the study, detected by effect sizes and percentage change. Results from a recent experimental study (Motl et al 2012) found that many temporal spatial gait parameters improved significantly following a combined exercise programme, however, as discussed in Section 4.5.1 the intervention was delivered thrice weekly. Thus participants in Motl et al's (2012) study may have both a better training stimulus (three times per week) allowing them to improve. In a different study, involving four weeks of treadmill training by 16 people with MS (EDSS unreported), statistically significant improvement were seen in step length, but improvement in cadence did not reach significance (Newman et al 2007). The focus on a walking intervention in this older study, which was also delivered thrice weekly, may explain the difference in results, as it may be expected that a walking intervention may improve gait parameters.

4.5.9 Body composition

Body composition is an important indicator of health status and long term disease prevention (World Health Organization 2000). In this study BMI was used to indicate body composition. Throughout the study, average BMI remained in the overweight to obese category for both groups, indicating that the study participants, as a group are at an increased risk of developing other diseases. These include obesity and coronary heart disease, musculoskeletal problems and some cancers (World Health Organization 2000). Small improvements were seen in both groups BMI scores. This is similar to a past 12-week exercise intervention study (Hayes et al 2011).

Although addressing the impact of therapeutic exercise on long term disease prevention is beyond the scope of this thesis it is becoming established, in the literature, that therapeutic exercise can have a beneficial effect not only on the symptoms of MS. Therefore, it may now be important to establish the impact of therapeutic exercise on disease risk and long term disease prevention for

those with MS. This is relevant as those with MS have been found to be at the same risk as the healthy population of developing long term health problems (Bronnum-Hansen et al 2004).

4.5.10 Changes over time

The study sought to establish whether 8 or 12 weeks of the exercise intervention would result in clinical improvement in the assessed outcome measures and whether any improvement would be maintained (by assessing at 6 month and 12 month follow-up). As no statistically significant or effect size patterns emerged it is difficult to draw conclusions as to recommendations regarding duration of a combined exercise intervention. Beyond that, long-term continuation of an exercise program may prevent further deterioration, although there is no evidence of this from present results.

Due to the longevity of the study, the opportunity to monitor the natural progression of symptoms, in the control group, was realised. In therapeutic exercise MS studies, assessing participants over six months provides the opportunity to monitor symptom progression over a reasonable length of time. If control groups are advised to not change their usual routine, this will also provide information on natural symptom progression. In this study there was no evidence of any clinically significant change in any outcome measures in the control group. However the clinical effectiveness results (Section 4.4.8) indicated that in the control group some outcomes (related to mobility, balance and physical activity) had regressed below baseline by month 6, whilst many outcomes (related to mobility, balance, body composition, physical activity and anxiety and depression) regressed below baseline at month 12. There are no reports of statistically significant regression of symptoms in relevant past studies (Ponichtera-Mulcare et al 1997; Romberg et al 2005; McCullagh et al 2008) which is similar to the results in this study. However, the results hint at the progressive nature of the disease over a period, and may highlight some of the progressive symptoms which may be affected in those who have moderate MS (EDSS 5-6.5). Although further work which addresses a longer follow-up may be required, particularly as those with a higher EDSS (e.g. 6-6.5) may progress at a different rate to those with a lower EDSS (e.g. 5-5.5).

4.5.11 Goal attainment

The GAS was used to capture data on all participants priority goals, achievement of goals and as a motivational tool to encourage achievement of goals (in the intervention group), by the end of the 12-week intervention. Participants were asked to choose three of a possible 12 goals related to the outcome measures and the exercise class, with the option to choose another personal goal. It emerged that improving fatigue, balance, mobility/endurance and weaker leg strength were the most commonly chosen goals for all participants. Knowledge of the goals of individuals with MS is very important, as it could help lead future research agendas, and it is disappointing that there is minimal evidence within the literature on the exercise “goals” of those with MS.

All but two participants improved in their three chosen goals, thus the majority of those in the intervention group improved in the outcomes they chose as goals. There are no previous examples within the relevant literature to compare these results; however, it provides a further indication of the success of the intervention.

In order to establish achievement of goals for the study sample it was necessary to base these on expected changes. To do so the author sought guidance from the Consultant MS physiotherapist and any clinical significance in the relevant literature (Section 3.9.14). The difficulties establishing values for relevant clinically significant change scores, by the need to obtain values from both other disease populations and exercise interventions is a limitation of this outcome measure, implying a need for further work. This finding in part led to the development of Study 3 (Chapter 6) to establish what a clinically significant change for common outcome measures used in MS may be. Thus although these results and the outcome measure itself is of interest, more work is required to ascertain its potential as an outcome measure in MS therapeutic exercise.

4.5.12 Influence of different EDSS levels

This study recruited participants with an EDSS of between 5 and 6.5, which translates to four different levels on the EDSS scale. Fundamentally, these are categorised based on ability to walk a set distance. The results were analysed as a whole data set, i.e. results were not analysed for individual disability levels. It was found that, in general, larger standard deviations were seen in the more disabled group. However the small number of participants in the less disabled range (i.e. EDSS 5 and 5.5, n=4) make it difficult to confirm this. Large standard deviations have been reported in past studies of therapeutic exercise in people with MS where studies have recruited participants of a similar, or slightly lower, disability level to in this study (Mostert and Kesselring 2002; Debolt and McCubbin 2004; Freeman and Allison 2004; Freeman et al 2010). Suggesting that, even with a narrow EDSS (5-6.5) heterogeneity of the sample is still problematic. Thus, it may be necessary for future studies to narrow the EDSS level further. This however limits the applicability of the results to a smaller proportion of the MS population.

Based on results from this study, if narrowing the EDSS to only include participants with an EDSS score of 5 to 6, 30 participants would be required in each group to achieve a power of 92% (with significance set at $p<0.05$), for an improvement of more than 2 s on the T25FW to be significant. However, narrowing the recruitment levels as such may jeopardise recruitment and make the results less relevant to the wider disease population.

4.5.13 Recruitment, attendance and attrition.

When recruiting for the study initial interest was minimal, follow-up invitation letters were sent and healthcare professionals within the rehabilitation unit were reminded to discuss the study with

potential participants at the time of clinic visits. However, although the study failed to recruit a large number of participants, leading to both the study being underpowered for statistical significance (refer to Section 4.2.2) and fewer participants in the control group, which may have influenced results. It is comparable in participant number to many similar studies (Table 2.5-Table 2.7) The level of recruitment achieved may have been due to the commitment of a 12-week, twice-weekly exercise programme, the many outcome measures assessed, transport difficulties accessing the venue or the invitation letter not inspiring interest in the study. Furthermore as discussed by Bjarnadottir et al (2007) potential participants may have had concerns about increasing physical activity. Ethical restraints restricted the Chief Investigator being onsite to recruit participants, or advertising the study through posters, although doing so may have positively influenced recruitment. Ethical restraints also prevented the research team from contacting non-responders to establish their reasons for not taking part.

Attendance at the 12-week class was analysed on an Intention to Treat basis. Attendance was found to be 71%. Attendance was similar to another group combined exercise class (67-75% (Charlton et al 2010)), although lower than other aerobic (McCullagh et al 2008) and resistance (Taylor et al 2006; Dalgas et al 2010) group exercise intervention, where attendance rates were >83%, 94% and >80% (in Dalgas et al's (2010) attendance of <80% resulted in exclusion from the study) respectively. This may be explained by the relatively high disability level of participants in the present study, with higher disability there may be more effort or logistics involved in attending a twice-weekly class. However, attendance rates are more comparable if, in the aforementioned better-attended studies, participants who discontinued participation are excluded from analysis. In future studies participant retention may be improved by offering transport options and encouraging participants to "buddy" with another participant, or indeed encourage able-bodied peers to participate to encourage adherence as has been successful in a past study into exercise adherence in youths with disabilities (Temple and Stanish 2011).

Not all participants completed the full study, at week 12 three participants had discontinued participation, and data was only collected from 25 individuals with participants unable to attend for assessment for a variety of reasons; e.g. adverse weather conditions, increased work commitment, relapse or other illness. At the end of the study, one further participant had discontinued participation, with data collected from 23 participants. In addition, not all outcome measures were assessed in all participants at all time points, as clinical judgement deemed it inappropriate to do so with two of the most disabled participants, if for example, a participant was having more severe mobility problems. This is a limitation of the study, and highlights the problems of long-term data collection. Future studies could seek to increase recruitment, thus allowing for attrition having a minimal effect on the results.

4.5.14 Appropriateness of a community venue

There is a move towards healthcare within the community, with many government papers and publications promoting activity for those with disabilities in the community (Department of Health 2005; Scottish Executive 2007). The exercise intervention for this study took place at local authority community leisure centres and were part-led by local authority leisure staff. To the author's knowledge only one other study in the UK (Collett et al 2011) has reported on a MS therapeutic exercise intervention being carried out in community leisure centres. This and the present study show that the community model is feasible and adds to international evidence, that organised exercise in community venues is safe and appropriate for many different disability levels of MS (Taylor et al 2006; Charlton et al 2010; Dodd et al 2011).

4.5.15 Limitations

This study adds unique knowledge to the growing body of research in therapeutic exercise in MS. Despite this, it is not without its drawbacks. Study limitations, which have not previously been acknowledged, will now briefly be discussed and, when appropriate, potential solutions to overcome them will be offered for future research.

The modest sample size for the study was problematic, perhaps leading, to outcome measures not reaching statistical significance. Future studies should be powered appropriately, and utilise improved recruitment methods (as discussed in 4.5.13) to increase participation. These future studies may utilise more modern forms of communication, when ethically appropriate, to notify a wider range of potential participants. Establishing effective methods to both increase initial and continued participation would be important for much rehabilitation-based research, and time spent on this area would be worthwhile.

The control group continued usual care, as such they did not receive an "active" intervention. Thus, the benefits of the intervention, which may have been influenced by the social dynamic of a group exercise programme must be factored into the results. Past literature provides examples of how an active control group can be incorporated into the study design, allowing the outcome to be more directly identified as being due to the variable of interest (i.e. the therapeutic exercise intervention). For example in Dodd et al's (2011) study the control group undertook a "social program" in groups. Whilst in Harvey et al's (1999) study the control group undertook a "general home exercise programme", this is of interest but would not encourage social interaction .

Although the study provides worthwhile long term data on the effect of a 12 week therapeutic intervention. It is a limitation that data were not collected on participants' exercise behaviours following the end of the intervention (i.e. whether they continued to exercise). Doing so would

strengthen, and help explain the long term results. Thus future studies should seek to include this in their methodology.

Randomised control trials which incorporate blinding of either assessors, therapists and participants is often seen as the *sine qua non* for clinical trials (Schulz and Grimes 2002) and not doing so carries a risk of biased results. Furthermore these aspects of blinding are incorporated into the PEDRO criteria to assess the quality of RCTs in rehabilitation (Section 2.3.3). In this study, the assessor was blind to group allocation; however, neither "therapists" (those leading the intervention) nor the participants were blind to group allocation, leading to a potential bias in the results. Achieving triple-blinding would strengthen the findings, although it would be difficult to achieve in an active intervention such as therapeutic exercise.

4.5.16 Critique of methods

An effort was made to ensure the outcome measures and methodology were appropriate to the research, piloting of the outcome measures was done on several occasions prior to the study, with the components of the exercise intervention also piloted (refer to section 4.2.11). Despite this, there are areas whereby, in retrospect, improvement was possible.

At baseline all participants successfully completed the outcome measures, however at subsequent assessment points some participants were unable to complete some outcomes. For example, the mobility level of two participants deteriorated as the study progressed resulting in them no longer being able to complete the 6MWT or T25FW, despite two physiotherapists being available to provide safe supervision. Thus mobility measures which can be used in a more disabled population may be required.

The temporal spatial walkway was unable to gather data from participants who used a wheeled walking frame (as the GAITRite system was unable to differentiate between footfall and wheel tracks). This is unreported in the literature, and may present a barrier to using this outcome tool in future studies with participants of a higher disability level.

In general, there is a need to establish the psychometric properties of the chosen outcome measures in those moderately affected with MS, as discussed in Chapter 3. This was addressed for the T25FW, 6MWT, TUG and BBS in Study 3 (Chapter 6). It is also recommended that further outcomes to assess balance, physical activity, body composition and goal attainment in future MS research may be beneficial to our understanding of the benefits of therapeutic interventions for those with MS.

4.6 Summary and conclusion

Multiple Sclerosis results in many clinical symptoms, and there is increasing evidence that therapeutic exercise plays a role in addressing these symptoms. This chapter describes a single-blinded RCT investigating the short and longer-term effects of a 12-week community based exercise class, in people moderately affected with MS, comparing them to a control group receiving usual care.

The study was unique in a number of areas and as such adds substantial knowledge to the literature surrounding therapeutic exercise in MS. This study was the first to assess the impact of an exercise intervention delivered in community leisure centres, in a group format to those with MS. Furthermore it is one of a small number of studies which have delivered a combined (aerobic, resistance and balance) exercise intervention to those moderately affected with MS. Despite a lack of statistically significant data to suggest the intervention resulted in any changes, there were positive results overall.

Although results from the primary outcome measure, the T25FW, did not show statistically significant changes, positive benefits were found, as indicated by the positive percentage change scores. No statistically significant results emerged as a result of the intervention, although improvements were seen overall. Calculated effect sizes implied the intervention had a positive effect on all outcome measures. A single study rarely provides enough evidence to guide clinical and research practice, nevertheless the results of this study add to the findings of other studies and the systematic reviews discussed in Chapter 2. Therapeutic exercise can improve physical activity levels, balance and quality of life, despite, in many cases, using different outcome measures to those used in the present study.

Results from this study, which gathered information on the goals of those with MS, regarding participation in a therapeutic exercise programme are, to the author's knowledge, new, and previously unreported. Furthermore, other findings regarding the degenerative nature of the physiological, functional or psychological status of people moderately affected with MS, who are maintaining their usual routine (i.e. the control group), are of note. During the study group there was evidence that the control group deteriorated in clinical outcomes , with some scores regressing below baseline scores in areas related to mobility, balance, body composition, physical activity and mood) suggesting the need for long term maintenance perhaps utilising therapeutic exercise.

Like other similar studies, the study did not find that the exercise intervention had a detrimental effect on participants fatigue levels, which has important clinical and research implications.

Overall no statistically significant changes over time emerged from the results of this study, thus further work is required in this area to determine the long-term impact of therapeutic exercise interventions for people with MS.

The results of this study are unique in that they were the first to establish over a year follow-up the impact of the intervention on physiological, functional and psychological status of participants.

The following chapter will describe a qualitative study of the views and opinions from the intervention group in the chapter. Before, in Chapter 6, a description of a study to establish the reliability of outcome measures used in this chapter's study. An explanation of how the three studies (Chapters 4, 5 and 6) influence each other and how this may guide future research agendas will be done in Chapter 7.

5 Study 2

A qualitative analysis of a 12-week group exercise intervention for people with Multiple Sclerosis

The previous chapter describes the main intervention undertaken as part of this thesis, this involved a twelve week exercise intervention, for people moderately affected with MS. This chapter will investigate the views and opinions of those who participated in the exercise intervention. Focus groups were undertaken after the intervention, which were then analysed using a general inductive method.

5.1 Introduction and rationale

There is increasing evidence that participating in physical activity and therapeutic exercise plays a beneficial role for those with MS (Chapter 2). To strengthen research findings, it is important that any therapeutic exercise intervention be analysed using both quantitative and qualitative methods, with Dodd et al (2006) acknowledging that doing so in their study allowed data to be gathered which would not have been established using a quantitative methodology alone. Using mixed methodology is supported in guidance texts on qualitative literature, i.e. by utilising a qualitative methodology the views and opinions of study participants can be gathered in a way which quantitative methods are unable to achieve (Webb and Kevern 2001). Furthermore, establishing the views and opinions of those taking part in research is important to help ensure the relevance and quality of research undertaken in healthcare

As evidenced in Chapter 2 there are a growing number of studies investigating MS therapeutic exercise, some of which have utilised a qualitative methodology (Section 2.5). These qualitative studies have gathered views on exercise and physical activity in the general MS population (Kayes et al 2011). An MS population who habitually participated in exercise (Smith et al 2011), or where the participants were undertaking a new therapeutic exercise intervention related to the study (Dodd et al 2006; Smith et al 2009; Plow et al 2009a). These studies provide information on barriers and facilitators those with MS experience when considering exercise, whilst also providing detail on the opinions of how exercise can affect participants' disease symptoms and other areas of their life. All of these previous studies have captured the views on exercise through semi-structured interviews. They have found positive views on physical activity and therapeutic exercise from those with MS, whilst also gathering details on some problems faced by those with MS related to exercising. The studies were, in general, in those who were mildly to moderately disabled by MS, although specific EDSS levels were not defined.

This chapter will discuss the methodology and results of a study to establish the views and opinions of those moderately affected with MS (EDSS 5-6.5) who took part in the exercise intervention as part of the main study (Chapter 4). Within the results section consideration will be given to important findings. The study will then be discussed to explain the relevance of the results and place the research within the context of the main study findings and the relevant past literature. Thus, this qualitative study will address the following literature gaps established in Chapter 2;

- As most qualitative research surrounding exercise and MS have not reported disability level, or have only included those described as having an approximate EDSS level of 5, opinions and views of those more affected (EDSS greater than 5) should be gathered.

- As semi-structured interviews have been used in all MS specific exercise qualitative studies thus far, the use of focus groups for gathering data is unexplored.

5.1.1 Study Aim

To establish the views and opinions on exercise and a therapeutic exercise intervention of those who had undertaken a therapeutic exercise intervention.

5.1.2 Research question

What are the participants' views on exercise and a therapeutic exercise intervention? These included; personal goal attainment, positive and negative outcomes associated with the intervention, and intrinsic and extrinsic factors to participation in, and completing, the intervention.

5.1.3 Study design

A qualitative focus group design was utilised. Two focus groups were undertaken, these were moderated by the same independent physiotherapist, who used semi-structured questions to facilitate the group. The Chief Investigator then transcribed the recorded focus groups and analysed the transcripts using a general inductive method. Analysis was verified independently by a second physiotherapy researcher, and emergent themes were refined to establish key themes. The specific design will be discussed in the following methodology section.

5.2 Methodology

The fundamental methodology was based on the guidelines of Fern (2001), who advises on ensuring rigor and validity when undertaking focus groups. In his guidelines he highlights five main areas which may influence results and thus should be acknowledged. These include; the *number of groups and participants*, the *group composition*, the *moderator*, the *location* and the

analysis. An explanation of the rationale of the above five areas is acknowledged within the following section.

5.2.1 Ethical considerations

Ethical approval was obtained from the West of Scotland Research Ethics Committee in December 2009, Research and Development approval from NHS Ayrshire and Arran Research and Development Management in January 2010. Participants had provided consent to take part in this study when consenting for the main study and prior to each focus group discussion participants were reminded their comments would be recorded, and subsequently analysed.

5.3 Recruitment and participants

Fern (2001) acknowledges that the *Number of groups and participants* and the *Group Composition* are areas which must be acknowledged when undertaking qualitative research.

It is recommended in the literature that the number of focus groups be dictated by the number of new themes emerging from the data, known as data saturation (Morgan and Scannell 1998). In this study due to participant numbers two focus groups were conducted, one for each intervention site (Section 4.2.10) used in the main study. Therefore data saturation may not have been reached.

Some authors recommend that there be 6 to 10 participants in a focus group (Morgan and Scannell 1998), however it is not unreasonable for there to be 4 to 8 participants (Kitzinger 1995) with Tang and Davis (1995) discussing that anything between 4 and 12 participants is acceptable. Smaller groups may allow more in-depth views to be explored with larger groups perhaps providing less opportunity for participants to voice their opinions (Carey 1994).

Practicalities of this study dictated the number of participants. The inclusion and exclusion criteria were as previously described (section 4.3), in addition only those who had participated in the intervention group of the main study were eligible for this study. Participants in this study had all attended the 12-week exercise class, thus a "naturally occurring" group composition was utilised. Kitzinger (1995) discusses that a "naturally occurring" group will allow participants to relate to one another's views, while at the same time expressing challenging views, participants may be able to contradict what one has said by reminding them of previous experiences together (e.g."Yes you have, you have lost weight"). By using focus groups, participants will also be able to relate to one another, as they have similar problems associated with their MS and all followed the same 12-week exercise programme.

From the 20 people who took part in the intervention group of the main study (Chapter 4) 14 agreed to take part in the focus groups. All had moderate MS (EDSS 5-6.5), four were men whilst ten were women. Five people took part in the focus group at Site A, whilst nine people took part in the focus group at Site B (refer to Section 4.2.10). The demographic details of the participants along with the site where the focus group took place is displayed in Table 5.1. The qualitative analysis will be reported using illustrative quotes from participants within the results section, each participant was provided with a number indicated in Table 4.4.

Table 5.1 Demographic description of participants in Study 2.

Focus Group Site	Number of participants	Mean age (years)	Sex (M:F)	Mean years since disease onset	EDSS
A	5	54.2	1:4	14.8	6.1
B	9	51	3:7	14.8	6.1

5.3.1 Similarities and differences between the two focus groups

There were similarities between the two groups. All participants had taken part in the same intervention which was delivered at a community leisure site, with the same physiotherapist at both sites. In addition, the exercises and format of the class (e.g. length of warm-up, time for each exercise, and length of cool-down) were identical at both sites (Section 4.2.6 and 4.2.7). The intervention sites differed in ease of access and type of room used (Section 4.2.10). Fewer participants attended the class at Site A, where there were five regular attendees, with one person attending less than half of the classes. At site B there were 10 regular attendees, with two people attending less than half of the classes.

All participants were aware that the MS exercise class was funded for the 12-weeks of the intervention and that on completion of the class they were all being referred to their local authorities exercise referral schemes. The scheme included discounted access to exercise facilities and exercise classes aimed at those with disabilities. At Site B, this also included the current exercise class which was being maintained once a week, funded by the local authority.

As indicated in Table 5.1 both focus groups included men and women, with participants being of a similar age (Site A mean age= 54.2 years, Site B mean age =51 years) and had been diagnosed for a similar length of time (mean time since diagnosis=14.8 years). The EDSS level of participants was similar in both focus groups (mean EDSS =6.1).

5.3.2 The research team

Fern (2001) acknowledges the importance of the *Moderator* in qualitative research. The moderator (or researcher) is the linchpin of all focus group methodologies and can influence and structure the topics of discussion and spark or stifle debate (Gibbs 1997). An experienced moderator will help ensure the quality of the data collected, with Morgan (1998) (p47) attesting that the moderators experience "will be most valuable when it is directly relevant to the topics and participants" involved in the study.

The moderator chosen for this study, was otherwise independent from the study, she had experience as a physiotherapist, rehabilitating people with MS, and had a special interest in what motivates those with MS to exercise. Furthermore, she had several years qualitative research experience and had acted as moderator in similar studies.

In addition, to establish any changes in participants' body language, a second independent research physiotherapist acted as scribe. This researcher also verified topics and themes during analysis of the focus groups. This researcher had experience in qualitative research related to exercise participation. Neither researcher was known to the participants prior to the focus group.

5.3.3 Questions

There is a risk of bias inherent in the role of the moderator, as the moderator can influence the discussion. This may be seen as a disadvantage of focus group research. To combat this, a interview schedule of semi-structured questions and prompts was developed for this study. Questions were determined by the Chief Investigator, based on past qualitative literature in MS and exercise studies (Dodd et al 2006; Smith et al 2009), from general literature on focus groups (Webb and Kevern 2001) and areas of interest from the more general exercise in MS literature. The moderator aimed to stay within these topics, however if participants explored other areas of interest the moderator was free to use her judgement to allow this.

Questions included in the interview schedule are displayed in Table 5.2. Results from the focus group at Site A were preliminary analysed prior to the focus group at Site B and, as it was felt that areas regarding barriers to exercise and exercising in a group could be explored more, modifications were made to the interview schedule for Site B (Table 5.2).

Table 5.2 Focus group interview schedule

Site	Questions
Site A & B	Can you tell me about any positive benefits from attending the classes? Can you tell me about any problems you had attending the classes? What did you think about the exercises themselves? What motivated you to participate in the study/classes? What motivated you to complete the classes? Tell me how you felt about exercising in a group? What would you change to make the classes better? Do you feel you have achieved the goals you set out at the start of the programme of exercise? Tell me what you thought about the instructors taking the classes?
Site B (additional questions)	Can you tell me what your views on exercise were before beginning the study? Have these views changed? Can you tell me about anything you have learned about how exercise can help? How do you feel about exercising with those without Multiple Sclerosis, who may have similar disabilities? How do you feel about exercising with those without Multiple Sclerosis, who have no disabilities?

5.3.4 Location

The *Location* where the focus group takes place is deemed to be of importance to the results of qualitative research (Fern 2001). The value of an easily accessible venue is important both for the researcher and the participants (Morgan 1996). For the research team a quiet room where all the views of participants are heard, with participants and the moderator sitting in a circle to allow good communication would be recommended; for participants an impartial, accessible venue, with refreshments may be helpful (Kitzinger 1995; Morgan and Scannell 1998).

These points were considered in arranging the location of the focus groups. Both focus groups took place in the final week of the 12-week intervention. The focus groups were undertaken in a private room at the intervention site, 20-30 minutes after completion of the exercise class. Participants, moderator and scribe were provided with refreshments and all sat around a large table. The focus groups were recorded on an Olympus WS-321M Digital Voice recorder.

5.3.5 Analysis of focus groups

After the focus group has been completed, *Analysis* is performed. This is the final area of methodology which Fern (2001) deems of high importance in focus group methodology. It is acknowledged that the use of traditional qualitative interview analysis may be inappropriate for focus group analysis (Myers and MacNaghten 1999; Webb and Kevern 2001). It is recommended that the focus group be analysed like a conversation, as the groups' views come in bits and pieces; participants are interrupted by others, respond to different views and refer back to others' answers (Webb and Kevern 2001; Krueger 2006). Although an analytical approach to data analysis is

encouraged, no specific method of analysis is advocated in the relevant MS exercise literature. Authors conducting similar studies have used a general inductive approach (Dodd et al 2006).

Thus, in this study the data was analysed using a general inductive approach similar to that described by Thomas (2006), and processed following the recommendations of Kitzinger (1995) and Webb and Kevern (2001) with the following steps taken;

1. The two focus groups were initially analysed independently from each other.

    (i) Areas of interest emerging from Site A, not questioned on the interview schedule, were added to the interview schedule for Site B (Table 5.2)

2. The main researcher listened to the recording of the focus groups, read the transcripts several times and cross referenced data with the scribed notes.

3. The data was coded to identify initial topic areas.

4. A further level of analysis was incorporated to refine the coding framework.

5. Emerging themes were identified with representative quotations.

6. In order to improve the reliability of coding and identified themes a second physiotherapy researcher independently read the transcripts and identified codes and themes.

7. Both researchers discussed emergent themes. These were refined to identify similar coding and themes, leading to the presented themes and subthemes.

5.4 Results

5.4.1 Demographic characteristics

Of the 32 people who participated in the main study, 20 were randomly allocated to the intervention group and from this group 14 participants took part in Study 2. The study sample consisted of four men and 10 women, a demographic description of the sample is provided in Table 5.1.

5.4.2 General findings

At both focus groups participants interacted well. However, there were differences noted between the two groups in terms of response to questions and interaction with each other.

At Site A participants took it in turns to speak, with an even spread of comments from all five participants. A close group dynamic was evident as participants often completed one another's

sentences and expanded on each other's comments, speaking at length on the importance of the social aspects of the exercise intervention.

At Site B more dominant members of the group dictated the answer to many of the questions, thus, some participants did not comment very often. However, the participants at Site B also spoke at length of the importance of the social aspects of participating in the intervention.

During both focus groups the moderator did not have to ask all the questions on the interview schedule, as many areas were addressed naturally. However the moderator had more impact during Site B's focus group, this was in response to the dominant group members' behaviour, as the moderator made an effort to include all participants in the discussion.

As has been discussed additional questions were added to Site B's interview schedule, which covered some areas discussed at Site A which were not part of Site A's interview schedule. No new themes emerged from Site B suggesting that data saturation may have been achieved. The duration of both focus groups was approximately one hour, with both coming to a natural completion with the moderator feeling all areas had been covered.

5.4.3 Emergent themes

Similar themes emerged in both groups, and thus results are presented from both focus groups together. Three key themes were identified from the two focus groups, and were;

- Benefits of the class
- The exercise class
- Barriers to exercise

The three key themes emerged from a number of different subthemes, themes and subthemes were interdependent as can be seen in Figure 5.1. Findings are summarised in Table 5.3 and will be discussed under the three key themes. Overall, the exercise class emerged as a bridge to allow participants to overcome barriers to exercise and benefit from the class.

Illustrative quotes will be used to report findings, with the study site and individual participant number provided in parenthesis (refer to Table 4.4). Conversations between participants are represented with quotes with minimal line spacing between. Individual quotes are separated from one another with larger line spacing

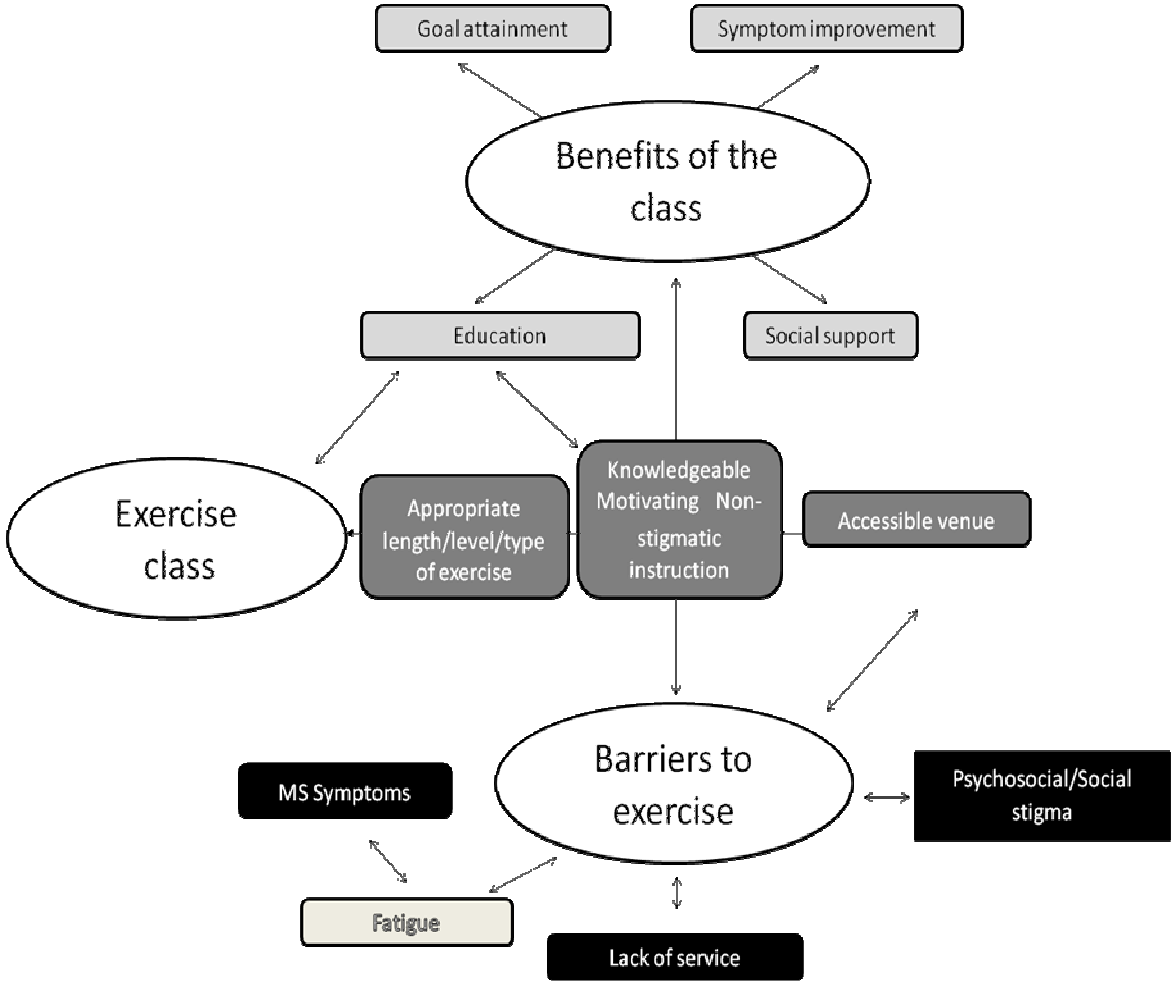

Figure 5.1 Main themes and subthemes emerging from the focus groups.

Table 5.3 Key themes and subthemes emerging from the focus groups

Theme	Subtheme	Topic area
Benefits of the exercise class	Symptom change	Balance Mobility Fatigue Sleep Activities of daily living Healthy lifestyle behaviours
	Goal attainment	Improvements in some areas
	Social support	Meeting others Working in a group
	Education	Appropriate exercise Positive views of exercise now Inspired to continue
The exercise class	Instruction	Knowledgeable Motivating Non-stigmatic
	Venue	Accessibility
	Class structure	Length of class Length of each exercise Level of difficulty Type of exercise
Barriers to exercise	Psychosocial factors/Social stigma	Inappropriate professional advice Exercising with able-bodied people Attitudes of general public
	MS Symptoms	Unable to do the same as before Progressively more disabling symptoms
	Symptom change	Fatigue
	Lack of service	Few other exercise options for people moderately affected with MS
	Venue	Accessibility

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5.4.4 Benefits of the exercise class

Symptom change

It emerged from both focus groups that one of the most positive outcomes from participating in the class was the improvement of many of the participants' symptoms. The participants commented on improvements in their balance, mobility/walking and management of their fatigue. In addition the participants remarked that the therapeutic exercise helped to improve their sleeping patterns, activities of daily living and had a positive influence on healthy lifestyle behaviours.

> "..for the last couple of weeks I've been coming up the stairs and down the stairs." (A1)

> "I feel a lot more energetic...really I feel much more alert, my head feels clearer I can think things through better." (A2)

> "I can use a dust pan and brush, I couldn't do that before." (B24)

> "Yes you have, you have lost weight" (A5 to A1)

However, although some participants made positive comments about their levels of fatigue, some participants noted suffering from post-exertional fatigue immediately after the class. This was seen by some as a negative outcome, but not by all participants.

> "My fatigue's got worse, but my balance has improved" (B22)

> "I think it's helped me, because the different exercises that you're doing is helping me to do things round about the house…but like [B22] was saying, sometimes you go home and you just want to go to sleep or something, you don't want to do the housework" (B24)

> "I do feel the benefit, and ... I go home and I fall asleep for an hour or two" (A1)

Goal attainment

At the start of the main study (Chapter 4) participants were asked to choose three goals which they would like to improve by the end of the intervention. The participants were asked whether they felt they had achieved these, or any other personal goals. Some participants felt they had done so.

> "My confidence is getting better as well, and my balance is getting better. The goals I set myself… I'm achieving some of them" (A1)

> "My balance has got a lot better. That was one of mine [A5's goals], my balance" (A5)

" Well I personally feel I've reached my goal to a point". (B17)

Participants in both groups were keen to continue exercising and participants commented that they would still like to work toward achieving their goals.

"We could all do better yet…." (A3)

The focus group format allowed participants to explore each other's views, this was apparent when participants were discussing improvement. In doing so participants were able to appreciate the variation in their symptoms from day to day.

"..we all improved a lot. Even our balance and thing"(B15)
"I don't think I have, I think I've got worse" (B21)
"Do you not?"(B15)
"I think I've got worse"(B21)
"I don't think my balance has got better"(B23)
"I think generally we have"(B15)
"But I think you can get good days"(B17)
"I think I'm just having a bad day today" (B21)

Social support

All of the participants spoke favourably about participating in a group exercise class. It became apparent that the class format, with all participants having similar symptoms provided an environment that allowed participants to support and encourage one another, helped to motivate and improve participants attitudes surrounding their own disability and MS symptoms. It also provided an environment which facilitated new friendships. Thus providing both extrinsic (meeting other people) and intrinsic (motivation, enjoyment, acceptance) factors to facilitate participation.

"I think because everyone is in the same boat, it stops you from feeling sorry for yourself, feeling oh I can't do this, you see everybody else getting on with it and it inspires you to try harder" (B24)

It was suggested, by the quality of the interactions between the participants in the Site A focus group, that a better "group-dynamic" was evident in Site A's focus group. For example, during Site A's focus group participants strongly agreed about the importance of group exercise with those who have similar experiences.

"Good to get out and about and meet people...We're all the same, there is nobody any different, which was a bonus, because sometimes it's quite, when you see super fit people, it's a wee bit..." (A4)
"Depressing, maybe?" (A5)

"quite nice to come in and do it all together, which has been a good group" (A2)
"it's been great, hasn't it?" (A5)

In addition, some participants had never met others with MS. The opportunity to do so, by taking part in the exercise intervention was deemed to be a positive benefit of group exercise in a disease specific class.

> "I've had Multiple Sclerosis for 16 years …this is the first time, we've had, well, I've had this opportunity to come, and meet, and be.." (A2)
> "with others" (A4)
> "as a group" (A2)

> "[when comparing with before the class] I hadn't met anyone on a similar sort of level of MS" (B18)

Education

The participants acknowledged that many of them had learned new things during the 12-weeks of therapeutic exercise.

> "I've found it really enjoyable, and I've been shocked that an improvement could be made by exercising at a much gentler level" (B20)

> "They [the instructors] were saying, don't do it like that, do it like this because that's getting the air into your lungs and you know, while you were doing it.. They're telling you well, that's good for your lungs...Good for your heart" (A4)

Some participants described how they used what they had learned in the class and applied it elsewhere,

> ".. in the kitchen when you're at the work top, again you can add a wee exercise" *(B17)*

> "... they [the instructors] explained it, and then when you got home you would do them [the exercises] a wee bit" (A4)

5.4.5 The exercise class

Instruction

Partly linked with the previous results surrounding education, the participants felt that having exercise instructors who were specifically trained to teach those with MS, as was the case in this study, allowed them to feel safe and understood. It emerged that this extrinsic factor to participation helped the participants to enjoy and benefit from the class.

> "[the instructors] have been very professional and their knowledge has been outstanding…. always there for moral support" (A1)

Venue

Some of the participants acknowledged that they had no problems accessing the venue where the exercise intervention took place. However, others commented on the lack of disabled parking spaces or mentioned that lack of personal transport may have been problematic. These discussions provided an insight into the external barriers which may prevent people who are moderately affected with MS from taking part in exercise.

> "Well I would have had transport problems but [another participant] lives around the corner from me and...he brings me down" (B24)

Class structure

There was positive feedback regarding the range of exercises included in the exercise class, which included a range of aerobic, resistance and balance exercises, these could be performed at differing levels of difficulty. The participants liked the varied levels of difficulty available for each exercise.

> "I was really impressed with the fact that there were [exercise] options for different levels of difficulty and because you were writing things down [progress cards] at what level you had been exercising at. It was encouraging because after a few weeks you could look back and see, oh, yes I am getting better" *(B20)*

Some of the participants discussed that they felt ready to progress to different types of exercises, it emerged that this was to both alleviate boredom but also allow participants to challenge themselves further.

> "...I'd quite like a Pilates class for people with MS; I think that would be quite good because it is concentrating on your core muscles" (B11)

As discussed in Section 4.2.6 the exercise class lasted around one hour, including a warm-up, the main circuit component (one minute of each exercise) and a cool down. This was discussed during the focus group with participants suggesting that this format could be improved by including a longer cool down section and/or a longer duration on some of the exercises. However, these views were not shared by all participants as some felt that the class timings were appropriate.

> "The minute on the bike for me is quite good at the moment, but for doing the shuttle walks and the upper body strength or the running arms. Things like that, I feel as if I could go on" *(A1)*

> "I think the hour is actually just long enough." *(A2)*

5.4.6 Barriers to exercise

Psychosocial factors/Social stigma

A strong theme, which emerged frequently throughout both focus groups, was the attitude of other people (as perceived by the participants) towards the participants, as people with MS. This was judged to be an extrinsic barrier to participation (the attitudes of others).

There was discussion on previous experiences with exercise instructors which had been less successful than the instruction in the present study. Participants gave examples of negative experiences they had previously had with leisure professionals who may have had minimal knowledge of MS and exercising with MS. For some participants it emerged that this had prevented them exercising in the past

> "I felt that the individual trainers [in previous exercise experiences], although they were very sympathetic they didn't really have an understanding, they were frightened as well… they were sort of saying well you can't do this and you can't do that. I would be like, oh well, I won't go at all" (B18)

It was also suggested, by participants' comments, that health professionals provide them with health advice, but perhaps may not be able to provide practical advice on how to achieve improvements in their health.

> "when I was at the doctors about my knee, they basically said, you need to lose weight…it must be something that every doctor…" (A1)
> "I think that they say that to everyone" (A5)
> "They get it ingrained into their head" (A1)

When participants discussed exercising in an environment with healthy people, it emerged that this could also be a barrier preventing them exercising. Participants discussed that when exercising in the past they had felt different from healthy people and that they had to explain their illness or their symptoms to others. Some participants did not enjoy having to provide these explanations to members of the public.

> "…if you were in with another class you would feel out of the ordinary" *(A2)*

> "[When exercising previously] I'd get off the exercise bike and quite often stagger across the room to the weights machine or whatever and you'd see people sort of staring and I'd think "God, am I going to have to say it all again?"" *(B10)*

The participants' understanding of how healthy people act around those with MS may be linked with acceptance of their own illness, and thus this may be an intrinsic barrier to participation. Some participants discussed avoiding activities where they had to confront their condition; imposing self-limitations.

> "I think working in the pool would be good for people" (B21)
> "No I wouldn't go to that [the pool], I've tried things like that before and I know I wouldn't. I'm not being funny or that. I'm just being realistic. I wouldn't go to something that was just all able-bodied people and me." (B24)

MS Symptoms

The participants in the focus groups discussed that the symptoms they experienced due to their MS were a barrier to them exercising, in the past many had participated in exercise or had been more active than they were now. However, it emerged that the class gave them the confidence and opportunity to exercise again, helping overcome this barrier. Furthermore the class gave them the opportunity to challenge their imposed self-limitations, and do new things, or exercises they hadn't done for a while.

> "Pre MS, I was fairly fit... I did do a programme of exercise, a lot of swimming and sit-ups to build the muscles up. But MS kicked in and I wasn't able to do any of that anymore, well I just kind of stopped doing anything. This has got me coming back and doing something, at a much lower level, but it's something, and even getting up in the morning and getting ready to come [to the class] is a reason to get moving" (B13)

> "I'm doing things that I've never, that I haven't been able to do for years." (A3)
> "Yes, I know I know." (A5)
> "Like silly things like, standing on one leg." (A3)

Lack of services

There was a general agreement amongst all participants that there was a lack of services and opportunities to exercise for those with MS; deemed to be an extrinsic barrier to participation. The participants were keen to continue active involvement in the MS exercise class, and other forms of exercise after the study. However, they discussed the difficulties in doing so. The comments made, surrounding the subtheme of lack of service and participants feeling there are not many exercise options for those with MS, link with past comments under the theme of Benefits of the Exercise Class (Section 5.4.4). When participants expressed that they enjoyed exercising in a group with those with a similar condition.

> "I feel with MS you need it [exercise] all the time, you need it either once a week, or once a fortnight. You can't stop because.. you need to do this, you know all the time. [The NHS rehabilitation centre] couldn't obviously do that for us. This is a wee outlet for us all, and I think it would be good for us all if it continued" (A5).

Fatigue

As discussed in the section on *Symptom improvement* (Section 5.4.4) some participants acknowledged feeling post-exertional fatigue which had a negative effect on other activities of

daily living following the class. This emerged as the main negative outcome from participating in the exercise intervention.

Venue

There was also negative comments regarding accessing the class, in particular participants discussed disabled parking problems and potential transport problems accessing the venue. Illustrative quotes have previously been provided in Section 5.4.5.

5.4.7 Summary of results

Results from this study suggest that the therapeutic exercise class acted as a bridge to help participants overcome barriers to exercise allowing them to benefit from taking part in the exercise intervention. Benefits to taking part included symptom improvement and social support. Barriers to exercise related to participants symptoms and a lack of exercise services appropriate for the participants.

5.5 Discussion

This qualitative study aimed to establish the views on exercise and the therapeutic exercise intervention, undertaken as part of the main study (Chapter 4), in people moderately affected with MS. The following research question was addressed.

What are the participants' views on exercise and the therapeutic exercise intervention? These include; personal goal attainment, positive and negative outcomes associated with the intervention, and intrinsic and extrinsic factors to participation in, and completing, the intervention.

To answer this question focus groups were undertaken at the end of a 12-week exercise intervention study for people with MS (Chapter 4). The methodology was guided by five main areas; *number of groups and participants*, the *group composition*, the *moderator*, the *location* and the *analysis* (Fern 2001). A general inductive approach to analysing findings was adopted, which included verification of emergent themes by two researchers.

5.5.1 General findings

The exercise intervention, discussed in Chapter 4, was delivered at one of two sites, at each site a focus group was undertaken. Despite there being slight differences between the groups, common themes and subthemes emerged from both focus groups.

Three key themes emerged, these were 1) Benefits of the exercise class, 2) the Exercise class and 3) Barriers to exercise. These will be discussed in relation to the results from the quantitative findings of the main study and will be compared with results in similar past research.

5.5.2 Differences between focus groups

Findings from both focus groups were similar, with participants interacting well with one another and being positive about the exercise intervention. However, it seemed that there was a stronger group dynamic amongst participants at Site A, evidenced by participants agreeing with each others' views and finishing one another's sentences more than in the focus group at Site B. In addition there was an equal spread of conversation amongst participants at Site A, whilst at Site B more dominant members of the group appeared to dictate the conversation, perhaps limiting the views of others from being expressed. To elicit views from all participants at Site B the moderator played more of a role, in an attempt to include everyone.

The two groups differed in number of participants (n=5 at Site A; n=9 at Site B). It is suggested in the literature that the moderator may find smaller groups easier to manage (Morgan 1996). Whilst Carey (1994) suggests that the fewer people in a focus group the greater the likelihood that they will interact. This was the case in the present study, when the smaller focus group interacted better than the larger focus group.

The difference in group size may have influenced findings in the present study, however each group's size was dictated by the main study, and the numbers participating in the exercise intervention. Although, it is acknowledged as a limitation of this study, it is unknown if focus groups of a similar size would have altered the discussion between participants. Future research which includes more than one focus group may benefit from keeping numbers of participants similar. Tang and Davis (1995) suggest four important factors which may help dictate group size. These are the number of questions, the time provided for each question, the format of the focus group and the duration of the focus group. In summary more time is required for a focus group with more participants or if there are more questions or if the format of the focus group is not structured with ideas and views being freely discussed. For structured focus groups (e.g. using semi-structured questions) they recommend on average 2 minutes per question for each person, but advise pilot work is undertaken.

5.5.3 Emergent themes

Three key themes emerged from the study, these traversed both focus groups, were interlinked by a number of different subthemes and answered the research question. The three themes were;

- Benefits of the class; symptom change, goal attainment, social support and education. This theme addressed the research question on personal goal attainment, positive outcomes associated with the intervention and intrinsic and extrinsic factors in participating and completing the intervention.

- The exercise class; instruction, venue and class structure.
  This theme addressed the research question on intrinsic and extrinsic factors to participating in, and completing, the intervention.

- Barriers to exercise; psychosocial factors/social stigma. MS Symptoms, symptom change, lack of service and venue.
  This theme addressed the research question surrounding negative outcomes associated with the intervention and intrinsic and extrinsic factors in participating and completing the intervention.

Many positive outcomes from participating in the exercise intervention were discussed during the focus groups, some positive outcomes were related to participants' MS symptoms. It emerged from the focus groups that participants had found improvements in balance, mobility and fatigue management. This was similar to benefits found in past qualitative studies after participants with MS had participated in resistance exercises or combined exercise interventions (Dodd et al 2006; Smith et al 2009). As different types of exercise were delivered in past studies compared with the present study (Section 4.2.6) results suggest that participants taking part in many types of exercise perceive symptom benefits. The positive comments from the present study participants on symptom improvements also links with the quantitative findings in the main study (Chapter 4); where it emerged that the intervention had a non-significant effect on participants balance, some aspects of mobility and fatigue levels (Section 4.7.5).

Other positive outcomes of the exercise intervention emerged, which were not captured by the quantitative outcome measures used in the main study, highlighting the benefits of mixed methodology. For example, participants spoke of improvements in their ability to undertake activities of daily living, that they were now sleeping better and that there was a positive effect on other healthy lifestyle behaviours. Participants in studies which have explored the benefits of prescribed therapeutic exercise (including aerobic, balance, resistance and stretching exercises) (Smith et al 2009) and independent community exercise (which included cycling, gym programmes, swimming or walking) (Smith et al 2011) also commented on improvements in activities of daily living and sleep patterns. The similarities in the positive outcomes and benefits found in this and past studies, in less disabled MS groups, suggest that benefits from taking part in therapeutic exercise can be found across a range of disabilities and, as discussed, are not specific to one type of exercise.

Goal attainment was briefly discussed during the focus groups, with improving balance a goal that had been met by some participants. This links with the goal setting used as part of the main study, where improving balance was a priority goal for some participants at the start of the exercise intervention (Table 4.8). However, there was disparity amongst participants in the focus group as to whether they felt they had attained their personal goals by taking part in the 12-weeks of exercise. Some participants felt they had achieved their goals, whilst others were less positive. In addition, there was also discussion that participants felt they would improve more if they continued exercising. In past MS therapeutic exercise literature there is no discussion on achieving personal goals, making it difficult to compare these results. However, Dodd et al (2006) acknowledged that participants in their study stated that seeing signs of progress motivated them to continue exercising.

It emerged that the social support dynamic of participating in the exercise intervention was important to participants, providing both extrinsic facilitators (meeting new people) and intrinsic facilitators (motivation, enjoyment and acceptance). This subtheme of social support may have been strengthened by the group nature of both the exercise class and the focus group. Participants were all positive about meeting others, and exercising with people who had a similar condition; with many new friendships being made. This finding supports that found in similar past studies. For example Dodd et al's (2006) study involved semi-structured interviews, undertaken at the end of a group exercise intervention and found that exercising with others with MS instilled a feeling of acceptance and understanding. This helped the participant feel "normal", encouraged an "enjoyable environment" and facilitated group "camaraderie".

Furthermore, the social benefits of group exercise has been found to encourage maintenance of exercise amongst those with MS (Smith et al 2011). Indeed people with a range of neurological diseases, including MS, have previously stated that they would like to exercise with a group of people with similar disabilities (Dawes et al 2010). This knowledge may be important for service provision.

It was encouraging that participants reported continuing the exercises learned in the class at home, and equally encouraging that all planned to continue exercising and trying new forms of exercise. Different levels of each exercise were available, and during the focus groups, participants acknowledged that this was good, allowing them to progress with their own routine. In addition participants completed progress cards at each session. Using progress cards has been acknowledged in past literature as an intrinsic motivator to exercise (Dodd et al 2006). Indeed participants in this study deemed them to be encouraging, discussing that it was good that they could chart their progress and look back upon it. Being aware of symptom improvement has also acted as an internal motivator for participants in other studies (Smith et al 2009; Smith et al 2011)

In general participants in the present study were happy with the format of the class although they gave examples of how the class could be improved. With some participants ready to move on to trying new types of exercise, such as Pilates. This is similar to the participants in Dodd et al's (2006) study who felt that at the end of the intervention they would like to progress to different types of exercise and exercise equipment. There is no known qualitative literature on preferred types of exercise for people with MS, although a variety of exercise types, have been studied in past therapeutic exercise studies (Chapter 2). It may be pertinent that future mixed methodology studies in MS therapeutic exercise seek to establish preferred types of exercise. As this knowledge may improve adherence and therefore direct service provision effectively.

The results of the focus groups suggest that some participants may impose self-limitations on physical activity due to their MS. This may be considered an internal barrier to participating in an exercise intervention, and thus was related to the Barriers to Exercise theme. Furthermore, the Barriers to Exercise theme provided details on the impact health professionals and members of the general public may have on the willingness of those with MS' to exercise. Participants also agreed that a lack of knowledge regarding MS in health and exercise professionals and members of the general public had a negative impact on them.

The attitudes of others, including health professionals, and participants' views of exercising with able-bodied people were explored under the subtheme of Psychosocial factors/Social stigma. During the focus groups participants discussed they had experienced a lack of knowledge, regarding MS, by exercise professionals they had encountered in the past, presenting a potential barrier to exercise participation. This has also been acknowledged in other MS research undertaken in New Zealand (Kayes et al 2011) and in the general neurology research undertaken in the UK (Dawes et al 2010), which sought to elicit views on exercise. Thus a lack of understanding and knowledge of neurological conditions in exercise professionals may be a problem across different geographical locations. Exercise professionals knowledge of working with those with neurological conditions should be investigated further. It may be recommended that improved training on the part of those involved in delivering exercise for those with neurological disabilities may ultimately increase exercise uptake and continuation of exercise for those with MS.

Regarding self-imposed limitations, it emerged that through exercising during the class, participants challenged their thoughts on their own capabilities. This resulted in them trying new (and old) things which they had not done before (or for a long time). Therefore, it could be suggested that they felt empowered and more confident in their own capabilities. Similar attitudes were found in those less severely affected with their symptoms, who habitually participated in independent community exercise (Smith et al 2011). This is an important finding as using therapeutic exercise to challenge perceived self-limitations may help those with MS take control throughout the varying stages of their disease.

Linked with how participating in exercise may help MS sufferers become more empowered in their symptom management is the importance of education, good instruction and healthcare advice. In Thorne, Con, McGuinness, McPherson and Harris's (2004) qualitative study exploring issues surrounding communication between those with MS and healthcare providers it emerged that those with MS felt empowered by healthcare providers who offer a supportive and facilitative attitude. The quality of the instruction during the exercise class was one of the extrinsic facilitators which helped participants in this study take part in, and complete, the exercise intervention. This is similar to previous findings; that leadership (which was encouraging, supportive and knowledgeable), alongside group classes and venue, may be important (Dodd et al 2006). Quality instruction was also important as some participants in the focus groups had felt previous fitness instruction had been delivered by non-knowledgeable staff, a view echoed in a previous study (Kayes et al 2011).

Although there was no formal educational component delivered during the exercise intervention, there was an implied educational component, with instructors giving advice on exercise and general advice on managing symptoms. It emerged from the focus groups that this resulted in participants realising that therapeutic exercise can be gentle and can help improve their mood. Participants learned from other participants and instructors, that there is a balance to be found between exercise, energy levels/fatigue and activities of daily living. Indeed, in the main study there was quantitative evidence that the intervention had a beneficial effect on participants' levels of anxiety. This "wellness-philosophy" has been found by past authors looking at the relationship between fatigue and exercise in study participants who habitually exercised independently in their community (Smith et al 2011). Thus to help those with MS realise the many positive outcomes from participating in an exercise intervention an educational component should be integral to any MS exercise service to help participants better understand their symptom management. Indeed, even during the focus groups participants were learning from others. Perhaps giving an indication that a group workshop (led by an expert tutor, with participants also informing the content), may be a potential format for any future educational component.

The exercise intervention delivered in this study (Chapter 4) was designed by physiotherapists and was jointly led by a physiotherapist and an exercise professional. This combination may have been beneficial to the success of the programme. There are few examples of previous MS studies which have utilised this combination in leading exercise classes for those with MS (Dodd et al 2006; Taylor et al 2006; Dodd et al 2011). With most therapeutic exercise interventions being led by physiotherapists (Freeman and Allison 2004; Kileff and Ashburn 2005; Newman et al 2007; Bjarnadottir et al 2007; McCullagh et al 2008; Cakt et al 2010; Broekmans et al 2011) or by exercise professionals who had consulted with physiotherapists (Filipi et al 2011). Furthermore, as physiotherapy input is preferred by those with MS in exercise and physical activity provision (Dawes et al 2010; Kayes et al 2011), specialist physiotherapists and exercise professionals should consider working together when developing and initially delivering safe and effective MS exercise

classes. This collaboration is currently recommended for exercise delivery in other neurological diseases such as stroke (Scottish Intercollegiate Guidelines Network 2008).

From the comments raised during the focus groups barriers to exercise emerged. Some were clearly extrinsic (over which the participants may have minimal control), for example a lack of services and difficulties accessing the venue. Others could be judged to be both extrinsic and intrinsic (areas where participants may not initially feel they have control, however it could be argued that these areas may be linked with their acceptance of their own illness), for example the attitudes of others and exercising with able-bodied people. Other barriers were more internal (influenced by the participant, or symptoms suffered by the participant), for example their MS symptoms.

A lack of exercise services and the venue where exercise took place was discussed, and emerged as potential external barriers to exercise participation. Participants did not feel there was enough exercise services available for them to access. This is similar to the findings in Kayes et al's (2011) study, undertaken in the UK, where it was discussed that a lack of potential exercise services appropriate for those with neurological conditions may be a barrier to exercise participation.

In addition, some participants in this study who did not have their own car or were unable to access the intervention sites using public transport, stated that they may have had problems attending if other participants had not provided transport. Similar findings emerged in Kayes et al's (2011) study, where it was reported that physical activity may be limited by transport options. In addition, in Plow et al's (2009b) study, which took place in America, it was acknowledged that problems accessing exercise facilities were barriers to participating in exercise.

As a range of disability levels were represented in Kayes et al's (2011) and Plow et al's (2009b) studies, these results suggest that transport options may be an important area for service provision for those with MS. It seems that this may be a global issue, both geographically and across the disability spectrum found in MS. Thus governments and healthcare providers may be required to improve transport provisions for those with MS to help encourage an inclusive society.

It emerged that participants in this study did not want to exercise with able-bodied people, with participants providing examples of when they had felt uncomfortable by the attitudes of others. Similarly, participants in the study by Smith et al (2011) commented upon feeling self-conscious that their symptoms may be misinterpreted by the general public, resulting in them choosing to exercise at quieter times or away from others. This emphasises that being accepted into a social-network may encourage people with MS to exercise, which should be addressed in future service provision.

This study found that other intrinsic barriers to participating in exercise for study participants were related to their MS symptoms. Participants acknowledged that as their symptoms worsened they were unable to do the same type of exercise as before. However, for some participants taking part in the exercise class resulted in them doing exercises and activities which they hadn't been able to do for a long time. There are links here between the implied self-limitations which participants discussed imposing on themselves and their symptoms being a potential barrier to exercise and consequently highlighting that those with MS may benefit in a number of ways, both physical and psychological, by being given the opportunity to exercise. This strengthens the physiological, functional and psychological results found in the main study (Section 4.4).

There was a discussion that suggested fatigue may be an intrinsic barrier to prevent some participants from exercising. This was the only negative outcome which emerged and was only for a small number of study participants. Stronger suggestions of the limiting effect of fatigue and exercise in MS have emerged from past qualitative studies related to exercise and MS (Dodd et al 2006; Smith et al 2009; Plow et al 2009b; Smith et al 2011), where fatigue was found to be a barrier or negative outcome for some people with MS. However, as in other studies (Dodd et al 2006; Smith et al 2009), participants in the present study agreed with each other that this may be a "healthy tiredness", helping their fatigue management, with few commenting on the problems of fatigue.

Although fatigue is reportedly problematic for many with MS (Chipchase et al 2003), the present results, in a more disabled population than previous studies (Dodd et al 2006; Smith et al 2009), provides limited evidence to support this. Researchers are therefore encouraged to adopt qualitative methodology and questioning to capture details on other barriers to exercise, to better equip health professionals overcome barriers to exercise for people with MS.

5.5.4 Limitations

This study adds much to the qualitative research in therapeutic exercise in MS. However it is not without its limitations. Where appropriate potential solutions to overcome these limitations will be provided to aid future research.

The number of focus groups, and the number of participants was guided by the main study, in that only two focus groups were carried out, one for each site. Thus, the main limitation of this study was the small sample size, although it was comparable to past similar studies. Due to this it is unknown if true data saturation was reached. However, the same themes emerged in both groups, and both researchers who analysed the findings believed that no new themes, related to the research questions, were emerging. Future studies may benefit from recruiting more participants and undertaking more focus groups to establish if all relevant issues are raised. Similarly the number of participants was based on the main study, and no formal method was adopted to establish the

optimum number of participants in each group (such as that provided by Tang and Davis (1995)), this led, in part, to group numbers not being equal.

The semi-structured questions used in the focus groups were based on past literature of relevance and areas of interest from the wider MS therapeutic exercise literature, and as such were judged to be relevant. However, as modifications were made after the first focus group, based on areas of interest which had emerged from the first focus group it is acknowledged that the questions chosen may have been limited. This does suggest that it is a limitation of the study that pilot work was not undertaken as part of this study. Therefore, to establish the appropriate number of participants, number of questions and time required and, to establish if questions are appropriate it may be advised that pilot work be undertaken.

Although data analysis was verified by a second researcher, it is a limitation that member checking was not carried out, whereby participants are sent a typed transcript of the focus group and asked to confirm/verify the discussion. This would have strengthened analysis of the results and should be incorporated into future study design.

Only the views of those who agreed to participate in the focus groups were obtained. Therefore the views of those who; did not continue to attend the exercise class, were in the control group of the main study (Chapter 4) or, more generally, did not have moderate MS, were not included. Thus these findings cannot be generalised. Future work may benefit from getting views from those who had not taken part in a formal intervention and from those either more or less severely affected with MS. In doing so a greater depth of results may emerge.

In addition, although focus groups were appropriate for the group nature of the study, in the focus group at Site B the more dominant members of the group dictated the discussions, thus the views of some group members were not heard. Follow-up one to one interviews may better capture views of those who are less comfortable speaking in a group format.

5.6 Summary and conclusion

Establishing the views and opinions of those taking part in research is important to help ensure the relevance and quality of research undertaken in healthcare. This Chapter described a study which utilised focus group methodology and a qualitative analysis of the views and opinions of participants in a 12-week exercise study, all of whom were moderately affected with MS. The results indicated there were many positive outcomes from participating in the intervention, and also established barriers and facilitators to undertaking exercise for those moderately affected with MS.

The findings support the quantitative results from the main study, such as improvements in balance and fatigue with focus group participants acknowledging they had improved in these areas with evidence of psychological benefits emerging in both this study and Study 1. The findings also support previous qualitative literature in people with MS, and acknowledge the potential of exercise to help people with MS have a positive influence on their disease management. Facilitators to exercise participation which were important to the participants included, the social support offered by group exercise, an accessible venue, appropriate exercise and knowledgeable instruction. Potential barriers to exercise participation also emerged; these were psychosocial factors (such as poor instructor knowledge and not feeling comfortable exercising with able-bodied people), lack of exercise services, or the participants' symptoms.

The results of this study are unique as, they are the first to utilise focus group methodology to capture opinions of exercise participation in a group of people moderately affected with MS.

The following chapter will discuss the results of a test-retest reliability study designed to assess four mobility and balance outcome measures used in Study 1 (Chapter 4). In Chapter 7 the over conclusion will include clinical and research recommendations emerging from the work.

6 Study 3

Reliability and clinical significance of mobility and balance assessments in Multiple Sclerosis

Chapter 4 describes the main investigation (Study 1) undertaken as part of this thesis, which assessed the impact of a twelve week combined exercise intervention, for people with moderate MS. This chapter will describe a study investigating the reliability, Minimal Detectable Change (MDC) and Standard Error of Measurement (SEM) of four outcome measures used in Study 1.

6.1 Introduction and rationale

To ensure that accurate measurement is carried out in healthcare, the use of reliable outcome measures, to accurately monitor changes in clinical performance is important for both research and clinical practice (National Institute for Health and Clinical Excellence 2003; Streiner and Norman 2008).

In the therapeutic exercise studies reviewed as part of this thesis (Chapter 2) many different outcomes are used (Table 3.1). From these a number of different outcome measures to capture data on the physiological, functional and psychological status of participants were assessed as part of Study 1 (Chapter 4). However, when reviewing the literature regarding the methodology (Chapter 3), and in particular when developing the Goal Attainment Scale (3.9.14) it was found that there was minimal evidence as to the reliability and clinical significance of many outcome measures used in MS rehabilitation. Particularly for those with a higher level of disability (e.g. EDSS>5).

Thus, from the different outcome measures included in Study 1 (Section 3.9) those that gathered data on mobility and balance were assessed further. The primary outcome measure from Study 1 (T25FW) was assessed in this study, as were the 6MWT, TUG and BBS which are common in the therapeutic exercise literature and recommended as practical outcome measures (Crow and Harmeling 2002; Gijbels et al 2010b). They were also recommended clinically within the West of Scotland MS Physiotherapy Network (NHS Scotland and 2003) and were used within the NHS rehabilitation locality where the study was undertaken, and thus the study had direct clinical applicability.

This chapter will describe the methodology and results from the study assessing the reliability of four of the mobility and balance measures used in Study 1; the Timed 25 Foot Walk test (T25FW), Six-minute Walk test (6MWT), Timed Up and Go test (TUG) and the Berg Balance Scale test

(BBS). A discussion will follow, to place the results within the relevant clinical and research context. Accordingly, the study will address the literature gaps, described in Chapter 3, below;

- There is minimal evidence as to the reliability of mobility and balance outcome measures used in MS literature regarding therapeutic exercise.

- There is minimal evidence as to the clinical significance and precision of mobility and balance outcome measures used in MS research.

In addition, the findings from this study will allow a more accurate analysis of some of the results found as part of Study 1 (i.e regarding Clinical Effectiveness Section 4.4.5), where relevant this will be highlighted in the results and discussion section of this chapter.

Important concepts to this chapter are discussed in Chapter 3, which provides the main literature pertaining to this study. In particular, the basic concepts in clinical measurement (Section 3.4) and the rationale for each outcome measure (Sections 3.9.1, 3.9.2, 3.9.4 and 3.9.5). Chapter 4 describes in more detail the use of each outcome measure in this study (Section 4.2.5).

6.1.1 Study aim

The aim of this study was to establish the test re-test reliability, clinical significance and precision of commonly used mobility and balance outcome measures (T25FW, 6MWT, TUG and BBS) in people moderately affected with MS

6.1.2 Research question

What are the reliability, clinically significant minimal detectable change and standard error of measurement scores of outcome measures (T25FW, 6MWT, TUG and BBS) used in people with moderate MS?

6.1.3 Study design

A test re-test reliability study of measurements assessed seven days apart by a single physiotherapist assessor was undertaken. Twenty-four people moderately affected with MS (EDSS 5-6.5) took part. Study 1 involved outcome measures being taken at five different time points (Figure 4.1), for this reliability study, participants were asked to return seven days after one of these scheduled appointments. On this second occasion, four of the outcome measures were repeated. To control the influence of diurnal changes in clinical performance participants attended at a similar time of day on both occasions. The outcome measures were performed in the same order on both days. To encourage consistency within this reliability study, participants were asked to avoid starting a new exercise routine, having an unusually busy day before the second

assessment to standardise their clothing, footwear and food and drink consumption on both testing days.

6.2 Methodology

6.2.1 Ethical considerations

A substantial amendment to the original ethical application for the main investigation was submitted to the West of Scotland Research Ethics Committee and Research and Development approval from NHS Ayrshire and Arran Research and Development Management. Approval was granted in July 2010.

Slight amendments were made to the participant information sheet, to reflect the inclusion of the reliability study, with the consent form updated to reflect the new version number of the participant information sheet.

6.3 Recruitment and participants

For this study the inclusion and exclusion criteria were as previously described for Study 1 (section 4.3). It was verified that participants had read and understood the participant information sheet, and all read and completed the consent form.

Before beginning the study the number of participants necessary to achieve the required statistical power was calculated, based on the reliability results of Paltamaa et al (2005), Fry and Pfalzer (2006) and Nilsagard (2007). All of which found high reliability scores higher (ICC>0.8) for the 6MWT, TUG and BBS. Therefore it was determined from power estimation tables for the design of reliability studies (Walter et al 1998) that, where good reliability was anticipated (i.e. between 0.7 and 0.9), a sample of 19 was required to achieve a power of 80% at the 5% level of significance

The study recruited 24 participants; with an EDSS 5-6.5 (mean 5.75). The majority (n=17) were female, the average age was 51.8 years and the average time since diagnosis was 13.7 years. The demographic details of the participants are displayed in Table 6.1, as is a breakdown of demographic details based on disability level.

Table 6.1 Demographic description and disability level of participants in Study 3.

Number of Participants	EDSS	Gender M:F	Age (SD)	Years since disease diagnosis (SD)
2	5	1:1	43.5 (13.4)	8 (2.8)
2	5.5	0:2	59 (7.1)	19 (4.2)
13	6	5:8	52.7 (7.1)	14.1 (7.6)
7	6.5	2:5	50.6 (7.9)	13.1 (4.5)
24	**5-6.5**	**7:17**	**51.8 (7.9)**	**13.7 (6.5)**

EDSS – Expanded Disability Status Score. Overall sample indicated in bold.

6.3.1 Assessed outcome measures

One physiotherapy assessor measured all outcome measures; having undertaken more than 50 similar assessments, she was familiar with the protocol. Further details on each outcome measure is available in Sections 3.9 and 4.2.5.

The 25 foot walk (T25FW)

To measure mobility over a short distance the T25FW (Cutter et al 1999) was assessed following the protocol described in Section 4.2.5.

The Six-minute walk (6MWT)

To measure endurance and mobility over longer distances participants completed a 6MWT (Butland et al 1982) (described in Section 4.2.5).

The Timed Up and Go (TUG)

The TUG (Podsiadlo and Richardson 1991) assessment was carried out following the protocol described in Section 4.2.5.

Berg Balance Scale (BBS)

To measure balance the BBS (Berg et al 1989) was completed once per session and is more fully described in Section 4.2.5.

6.3.2 Statistical analysis

The study aimed to establish reliability, clinical significance (through MDC scores) and precision (through SEM) scores for all four outcome measures. Data were analysed using the SPSS (v.16) statistical package. Assumptions of normality were assessed using the Kolmogorov-Smirnov test. A paired Wilcoxon rank test was used to assess sequential shift over the two time-points for variables found not to be normally distributed (the 25FW, TUG and BBS). Data for the 6MWT was normally distributed, thus a paired sample t-test was used to assess sequential shift over time. Significance was set at $p < 0.05$. For the BBS Cronbach Alpha correlation was used to check for internal consistency and α was found to be 0.96, therefore other tests of reliability were appropriate to perform.

To assess test re-test reliability Intraclass Correlations Coefficients (ICC) were calculated for all measures, the appropriate intra-rater ICC mixed models were used to compare the variability of different scores from the same subject (Denegar and Ball 1993). Scores closer to 1 indicate stronger reliability, with a score 0.60 - 0.79 suggesting moderate reliability and a score of greater than or equal to 0.8 suggesting good reliability (Tyson and Connell 2009).

Minimal Detectable Change (MDC) was calculated at the 95% confidence interval, to determine what scores would fall outside the measurement error of the assessment tool (based on the test/re-test reliability scores). To determine this, the Standard Error of Measurement (SEM) was first calculated using the equation below (where SD denotes Standard Deviation, ICC denotes Intraclass Correlation Coefficient & day 0 indicates the first day of assessment):

$$SEM = SD_{day\ 0} \times \sqrt{(1\text{-}ICC)} \qquad \text{(Streiner and Norman 2008).}$$

Similarly, MDC was calculated using the equation below:

$$MDC = 1.96 \sqrt{2} \times SEM \qquad \text{(Altman and Bland 2011).}$$

In addition, the calculated MDC score for each outcome measure was used to determine clinical significance in the findings from Study 1. To do so, the MDC score was calculated as a percentage of the Study 1 baseline score for the four outcome measures during Study 1. To determine whether clinical significance was achieved at the week 8, week 12, month 6 or month 12 follow-up time points this percentage MDC was compared to results found in study 1.

6.4 Results

6.4.1 Demographic characteristics

Of the 32 participants in Study 1, 24 participants took part in this study, this comprised seven men and seventeen women, demographic details are described in Table 6.1.

6.4.2 General findings

The mean scores, standard deviations and 95% confidence intervals for all four tests on both time points are displayed in Table 6.2.

The study found no significant difference between the scores for each of the outcome measures when participants were tested one week apart. The reliability (ICC) analysis revealed a high correlation between the Day 0 and Day 7 scores for all four of the outcome measures, values ranged from 0.94 to 0.97. Together these two observations suggest good reliability. In addition narrow confidence intervals were found for all ICCs, further supporting the strength of the reliability results.

Standard Error of Measurement (SEM) scores were calculated for all outcome measures. These provide an indication of the precision of the outcome measure. For the T25FW the SEM was 4.6s, for the 6MWT the SEM was 27.5m, for the TUG the SEM was 3.6s and for the BBS the SEM was 2.4 (a change of score of 3 points).

By using the above SEM scores the MDC was calculated for each outcome measure with results displayed in Table 6.2. It emerged that for the T25FW, a change of 12.6s would be required before a change in score would suggest a clinical improvement or decline in a person's walking performance across a population of people with MS who had an EDSS of 5 to 6.5. Similarly, the following MDC results would suggest a clinical change; 76.2m for the 6MWT, 10.6s for the TUG, and 7 points (rounded up from 6.5) for the BBS. These results should be considered alongside the mean day 0 scores, displayed in Table 6.2.

Table 6.2 Results from each outcome measure assessed for reliability

Test	Day 0 mean (SD)	Day 7 mean (SD)	95% CI day 0	95% CI day 7	p-value	ICC	95% CI ICC	SEM	MDC_{95}
T25FW[a] (s)	17.98 (18.6)	19.98 (28.9)	10.12 – 25.83	7.78-32.18	0.153[1]	0.94	0.86-0.97	4.6	12.6
6MWT[b] (m)	246.88 (135.7)	238.12(125.1)	189.56 – 304.19	185.32– 290.93	0.262[2]	0.96	0.91-0.98	27.5	76.2
TUG[a](s)	22.01 (21.6)	24.49 (29.5)	12.87 - 31.15	12.02 - 36.95	0.241[1]	0.97	0.93-0.99	3.8	10.6
BBS[b] (score)	45.92 (12.4)	46.38 (13.3)	40.66 – 51.17	40.76-51.99	0.115[1]	0.96	0.92-0.98	2.4	6.5

T25FW- Timed 25 foot walk, 6MWT- Six-minute walk test, TUG-Timed Up and Go,BBS-Berg Balance Scale.

p-values calculated between mean scores at day 0 and day 7, ICC – Intraclass correlation coefficient, SEM – Standard error of the measurement, MDC – Minimal Detectable Change.

[a] Intraclass correlation coefficient (2, 3), [b] Intraclass correlation coefficient (2, 1), [1]Results of Wilcoxon Ranks test, [2]Results of paired samples t-test.

6.4.3 Clinical significance related to Study 1.

The clinical significance (MDC) is relevant to results from Study 1, in particular the scores for percentage change (Section 4.4.5). By using the MDC score from the T25FW, 6MWT, TUG and BBS (Table 6.2) it was possible to calculate, based on the mean baseline scores taken during Study 1 (Table 4.5), whether a clinically significant change (MDC) had occurred at the week 8, week 12, month 6 or month 12 assessments. To ease comparison with results already described (section 4.4.5), the MDC was calculated as a percentage of the baseline score in Study 1 (for each of the four outcome measures) with results displayed in Table 6.3.

For example; the MDC for the T25FW was 12.6s, in Study 1 the mean baseline score for the T25FW was 22.1s (Table 4.5), therefore any change of 12.6s (57% of the baseline score) or greater may indicate a significant clinical change in the whole sample.

It can be seen in Table 6.3 that no clinically significant change occurred at any time point in either the exercise intervention group, or the control group during Study 1. However, improvements at week 8 for the BBS and week 12 for the 6MWT in the intervention group were nearing a clinically significant change. Conversely, at the 12 month follow-up for the TUG the control group were nearing a clinically significant decline in performance.

Table 6.3 MDC score (%) related to results from Study 1.

Outcome Measure	Intervention group					Control group				
	MDC	Percentage change				MDC	Percentage change			
		Week 8	Week 12	Month 6	Month 12		Week 8	Week 12	Month 6	Month 12
T25FW	57%	24%	33%	1.8%	26%	78%	4.2%	19%	20.6%	-47%
6MWT	38%	19%	37%*	18.5%	32%	33%	18%	-2.4%	5.7%	17.7%
TUG	48%	12%	17%	-22%	6.2%	54%	0.8%	17%	18.5%	-46%*
BBS	17%	15%*	12%	12.1%	-2.6%	16%	7%	-8.5%	-3.1%	-5.1%

Data incorporated from Section 4.4.8
T25FW- Timed 25 foot walk, 6MWT- Six-minute walk test, TUG-Timed Up and Go, BBS-Berg Balance Scale. *Nearing a clinically significant change.

6.4.4 Standard deviations

In the present study (Study 3), large standard deviations were seen for all four tests; in particular the T25FW test and the TUG test Table 6.2. In general, the higher standard deviations in all measures were in the most disabled group (Table 6.4). One of the more extreme examples of this emerged in the most disabled group of participants (EDSS= 6.5) for the follow-up T25FW score. The mean time to walk 25-foot was 45.28s, with the standard deviation being 46.18s.

Table 6.4 Mean reliability scores, comparison between EDSS .

Test	EDSS	n	Day 0 mean (SD)	Day 7 mean (SD)
T25FW (s)	5	2	8.4 (0.6)	8.1 (0.4)
	5.5	2	10 (1.7)	9.2 (0.9)
	6	13	11 (3)	9.8 (2.5)
	6.5	7	35.9 (28)	45.3 (46.2)
6MWT (m)	5	2	415 (161.2)	358.5 (57.3)
	5.5	2	272.5 (38.9)	262.5 (14.9)
	6	13	276.6 (76)	277.9 (74.4)
	6.5	7	136.3 (168.4)	123 (156.2)
TUG (s)	5	2	10.7 (2.9)	11 (1.1)
	5.5	2	13.1 (0.2)	13 (1.2)
	6	13	13.3 (3.9)	13.1 (3.4)
	6.5	7	44 (31)	52.6 (44.9)
BBS (score)	5	2	55 (1.4)	55 (1.4)
	5.5	2	50 (5.7)	51.5 (2.1)
	6	13	50.9 (5.1)	51.9 (5.3)
	6.5	7	33 (16)	32.3 (17.1)

T25FW- Timed 25 foot walk, 6MWT- Six-minute walk test, TUG-Timed Up and Go, BBS-Berg Balance Scale

6.4.5 Summary of results

Results from this study suggest that when the T25FW, 6MWT, TUG and the BBS are assessed by a single assessor seven days apart the outcome measures are reliable, producing high ICC scores. MDC change scores and SEM scores for each outcome measure were calculated and should be considered alongside the SDs which emerged across the study population.

6.5 Discussion

Motivated by a need to establish the clinical significance of changes seen in outcome measures used in MS, this study used quantitative analysis to investigate the reliability of four outcome measures used in Study 1 (Chapter 4), the T25FW, 6MWT, TUG and BBS. All four outcome measures have been used in past MS physiotherapy and therapeutic exercise research (as can be seen in Tables 2.5-2.7). The results of this study found good test-retest reliability for the T25FW, 6MWT, TUG, BBS in a group of 24 clinically stable people with MS who had an EDSS score of 5-6.5.

Clinically significant change (MDC) was established for all four outcome measures. For the T25FW a change of 12.6s was found to indicate a clinically significant change, similarly for the 6MWT a 76.2m change would indicate a clinically significant change, whilst for the TUG the MDC was 10.6s, and for the BBS the MDC was 7 points. These results allow for more detailed analysis of the results found in Study 1 (Chapter 4).

The precision of the four outcome measures was calculated based on the SEM. For the T25FW a SEM of 4.5s emerged, for the 6MWT the SEM was 27.5m, for the TUG the SEM was 3.8s and for the BBS the SEM was 3 points.

6.5.1 Test re-test reliability

High correlation (ICC) scores were found for all four measures with no significant differences between the mean scores, indicating that in a group of people moderately affected with MS (EDSS 5-6.5), the outcome measures are reliable. This finding is generally similar to other studies that have calculated test re-test reliability for the 6MWT, TUG and BBS. However for the T25FW, where results indicated good reliability (ICC=0.94) no study could be found testing reliability one week apart and thus there are no studies with which to compare results.

Results from the 6MWT (ICC=0.96) were comparable to the two previous studies which established reliability using similar methodology to this study (Paltamaa et al 2005; Fry and Pfalzer 2006). In people less disabled by their MS symptoms Paltamaa et al (2005) reported an ICC of 0.96 (mean participant EDSS=5.26), whilst Fry and Pfalzer (2006) reported a similar ICC of 0.96 (mean participant EDSS=3.6). Thus, these combined results indicate the 6MWT is a reliable outcome measure across a wide disability range in people with MS.

The present study indicates that reliability of the TUG appears to be good (ICC=0.97). This finding supports the data provided by Nilsagard et al (2007), who found that in those with MS (EDSS>4),

test re-test reliability one week apart produced an ICC of 0.88. Taken together these results also suggest the TUG appears reliable in a moderately disabled MS population.

The BBS also appears reliable in people with moderate disability in MS, where the high reliability results (ICC=0.96) found in this study add to Paltamaa et al's findings (ICC=0.85), in a smaller group (n=10) of people with MS, who were slightly less disabled than those in this study.

Taken together with findings from past studies, in a clinically stable MS population of moderate disability, the T25FW, 6MWT, TUG and BBS appear reliable when assessed by one physiotherapist one week apart. This strengthens the findings from the main investigation (Study 1), as test-retest reliability is confirmed.

6.5.2 Clinical Significance (Minimal Detectable Change)

To determine clinical significance of the four assessed outcome measures, MDC values were calculated. MDC values should be considered alongside the mean scores and the resultant standard deviation scores (Table 6.2 and Table 6.4). Using the formula described in the methods section (6.3.2) it was possible to calculate MDC values from the relevant past literature, as this value has not previously been calculated by many authors. Thus, the MDC values found in this study can be compared with past literature whilst also indicating the clinical significance (based on baseline scores in Study 1 and the MDC) from the results in Study 1 (Chapter 4).

For the 6MWT the MDC was 73.2m. Clinically this would mean that if a person with moderate MS were initially assessed in the clinic using the 6MWT, and then on reassessment the distance walked following the 6MWT protocol was 73.2m greater or lesser, this would be an indication that a clinically significant change had occurred. This result can be compared with past studies where the MDC scores were 85m (Paltamaa et al 2005) and 106m (Fry and Pfalzer 2006). Participants in these past studies were less disabled, suggesting that varying levels of disability may influence the MDC scores for the 6MWT.

Relative to the mean 6MWT scores at baseline in Study 1, at no time point did the intervention or control group as a whole sample achieve a clinically significant score. The overall finding indicates that the exercise intervention in Study 1 did not result in a clinically significant change in mobility/endurance measured with the 6MWT, with no clinically significant change seen in the control group.

Results from the BBS found a MDC of 7 points. In comparison, the results of the study by Paltamaa et al (2005), in participants who had a mean EDSS of 5.26, were calculated to be lower (MDC=3 points). This suggests that further work is required to indicate whether disability level will influence MDC scores. A larger change in the BBS may be required to show clinically

significant change in those more disabled with MS. In relation to results from Study 1, at no time point did the results of the intervention and control groups, as a whole sample, achieve a clinically significant change. However, at week 8 the mean change in the intervention group's BBS score was near that which would indicate a clinically significant change.

Whilst analysing the results for the BBS, a very high Cronbach's α (α=0.96) was found; indicating that some of the items tested with the BBS may be measuring the same aspect of balance more than once (Norman and Streiner 2007). However further clinical and statistical analysis would be required to verify the importance of this finding and to establish which items on the BBS may be repetitive.

For the TUG the MDC was 10.6s. This is high relative to the mean score (22.01s) at day 0. It was calculated in Nilsagard et al's (2007) study of 43 participants that the MDC was 12.2s. Relative to the mean day 0 score (13.9s) for their participants' TUG score, the MDC is also high. Thus, further work is required to determine whether calculating MDC scores for the TUG in a moderately disabled group of people with MS are an appropriate indicator of clinical change.

However, by utilising the MDC score found in this study (10.6s), and comparing it with results from Study 1 it was possible to establish if any clinical significant change occurred at any specific time point. Overall, at no time point during Study 1 did a clinically significant change in TUG score occur in either group, on average, based on the calculated MDC score.

As has been acknowledged reliability has not been established for the T25FW in the past MS research and thus clinical significance results from the present study, which found a high MDC of 12.6s that cannot be compared with other work. As with the TUG score, the MDC score is high considering the mean T25FW score (17.98s) at day 0. In addition, by considering the MDC for the T25FW with the results from Study 1 at no time did the mean score, from either the intervention or the control groups achieve the MDC score. This suggests that the intervention did not result in a clinically significant change, across the whole sample, in mobility measured with the T25FW and that there was no clinically significant change in the control group.

The practicalities of using the MDC score as an indicator of clinical significance may be strongly influenced by large standard deviations found across a group of participants; although the established MDC scores may be useful when assessing the individual. In this study high standard deviations were found which may have led to the high change scores indicated for the T25FW and TUG. Large standard deviations may have also led to the lack of clinically significant findings, based on the MDC score, from results of Study 1. Using the MDC as an indicator of clinical significance has been shown to be problematic in other studies looking across a similarly heterogeneous group of disabled children (Haley and Fragala-Pinkham 2006) and people with

Parkinson's disease (Steffen and Seney 2008); where high change scores were established for some outcome measures, including the TUG. These suggestions coupled with findings from the present study suggest it would be advisable therefore, to establish particularly for the T25FW and TUG, MDC scores in narrower disability ranges and perhaps seek additional means of determining clinical significance.

6.5.3 Precision (Standard Error of Measurement)

By calculating the SEM scores, it was possible to suggest the precision of the four outcome measures in those with an EDSS of 5-6.5. There has been little work published in this area, making comparison difficult. Paltamaa et al (2005) calculated a SEM score for the 6MWT to be 30.7m, which is similar to results in the present study; where the SEM was 27.5m. For the BBS, which has a total score of 56, Paltamaa et al (2005) found the SEM to be 1 point, similar to the 3 points (rounded up from 2.4) in the present study, suggesting the BBS is reasonably precise in those with MS who have an EDSS of 5 to 6.5.

For the T25FW and TUG the SEM was calculated as 4.6s and 3.8s respectively. These results are reasonable low, and suggest that the outcome measures are precise in this sample population, although further work is required to confirm this.

6.5.4 Limitations and critique of methods

This study adds new knowledge to the body of research surrounding outcome measures used to monitor the clinical impact and clinical progress in those with MS. The study however is not without its limitations. These will now briefly be discussed and, when appropriate, potential solutions to overcome these limitations will be suggested for future research.

The study is limited in that the methodology incorporated a test re-test style, using only one assessor. Thus future studies should incorporate inter-rater reliability, similar to the methodology adopted by Nilsagard et al (2007) whereby more than one assessor assesses the outcome measure. The sample size in this study was relatively small, however, power estimation tables for the design of reliability studies (Walter et al 1998) would suggest that, where good reliability was anticipated (i.e. between 0.7 and 0.9), a sample of 19 could achieve a power of 80% at the 5% level of significance. As the study recruited 24 participants, the study was adequately powered.

The results can only be applied to those with MS who have an EDSS score of 5 to 6.5, recruiting participants with a different EDSS score would improve our understanding of these outcome measures in those with MS. In addition, the study participants were recruited from a larger study, all of whom had completed the outcome measures previously on a minimum of two occasions. This may have had an impact on the results, thus it may be appropriate to assess reliability in a group of

participants less familiar with the outcome measures. In addition the results can only be applied to the assessed outcome measures following the standardised protocol (Appendix 9).

The finding of a high Cronbach's α for the BBS is a limitation of the BBS. It suggests that some of the tasks performed as part of the BBS outcome measure may be capturing similar data to other tasks; avoiding duplication when assessing outcome measures is important in a disease population known to suffer from fatigue, where succinct outcome measure assessment may minimise the impact of fatigue on results. It would be pertinent to investigate this finding further in other groups of people with MS.

6.6 Summary and conclusion

Accurate measurement of health outcomes is important in both research and clinical practice. This Chapter described a test re-test reliability study, where a single physiotherapy assessor assessed mobility and balance outcome measures, one week apart, in people moderately affected with MS. The results indicate that the assessed outcome measures; the T25FW, 6MWT, TUG and BBS were reliable when tested under these conditions. The study also established clinically significant change scores for each of the outcome measures alongside establishing the precision of these outcome measures in a group of people moderately affected with MS. The calculated MDC scores, from this study, for the T25FW, 6MWT, TUG and BBS allowed the results from Study 1 in this thesis (Chapter 4) to be more fully described; with no clinically significant changes (using MDC) emerging for these four outcome measures at any time during Study 1.

However, this study also highlighted that using the MDC solely to evaluate the clinical significance of the four measures may not be recommended when assessing a heterogeneous MS population. For example the heterogeneity of the group, even within the EDSS score 5-6.5 results in much variation in balance and mobility, due in part to confounding factors such as gait speed, walking aid, or spasticity.

The results of this study will go some way to help guide future research and clinical practice, and add to the current knowledge of outcome measurement in clinical practice and research in people with MS. They are unique in that they are the first to describe the reliability, clinical significance and standard error of measurement of mobility and balance outcome measures in a group of people moderately affected by MS.

7 Final conclusions and recommendations

The aim of this thesis was to investigate the impact of therapeutic exercise on those moderately affected with MS. Motivated by the need to establish whether therapeutic exercise had an impact on the clinical symptoms and lives of those with MS. Although there is accumulating evidence that therapeutic exercise has a beneficial effect in those with MS, there are still unanswered questions in this area. The studies in this thesis were designed to address some of these unanswered questions, with the following specific aims:

- To deliver and evaluate, over both the short and longer term, the effects of a 12-week community based group exercise class in people moderately affected with MS, against controls matched for disability level who received usual care

- To establish the views and opinions on exercise and a therapeutic exercise intervention from those who had undertaken a therapeutic exercise intervention.

- To establish the test re-test reliability, MDC and SEM of commonly used mobility and balance outcome measures (T25FW, 6MWT, TUG and BBS) in people moderately affected with MS

The conclusions of this investigation and recommendations from each study's findings will now be discussed.

7.1 Overall conclusion

The study found that participating in a 12-week therapeutic exercise intervention specifically for those moderately affected with MS (EDSS 5-6.5) resulted in a number of benefits, although compared to a control group of similar participants results were not statistically significant. During focus groups, following the 12-week intervention, participants acknowledged that taking part helped them to overcome barriers to exercise and benefit in a number of ways.

Furthermore the study found that the T25FW, 6MWT, TUG and BBS are reliable when assessed by the same assessor one week apart in those with MS who have an EDSS score of 5 to 6.5

7.1.1 Complementary studies

Both the focus group study (Study 2) and the reliability study (Study 3) complemented the main study, the long-term exercise intervention study (Study 1).

The findings from Studies 1 and 2, add to the growing evidence that therapeutic exercise is beneficial. There was both quantitative and qualitative evidence of the benefits of participating in the therapeutic exercise intervention. In Study 1 despite no statistically significant results (measured with an ANOVA) to suggest the intervention had a positive effect, other statistical tests to quantify a change (effect sizes and percentage change from baseline) provided evidence that the intervention had a positive effect. The results from the qualitative study supported some of these findings, in that participants felt improvements in balance, some areas of mobility and fatigue, whilst also highlighting the importance of the social benefit of the exercise intervention.

Study 3 established that the four assessed outcome measures (T25FW, 6MWT, TUG and BBS) were reliable. Finding that the calculated clinical significance values were large in relation to the mean group score for the T25FW and TUG outcomes. In both Study 1 and 2 there was evidence, of large standard deviations found for many of the outcome measures. This may explain why no statistically significant results emerged in Study 1 and why large clinical significance results occurred in Study 3, highlighting the difficulties when undertaking research in a heterogeneous disease population such as MS.

7.1.2 Innovative studies

All three studies add unique knowledge to the literature and were innovative in a number of ways.

- Study 1 was different to past studies as it was the first to assess the effect of an exercise intervention, delivered in the community, in a group format, to those with MS.

- Study 2 was the first to capture views and opinions from a group of people with MS using focus group methodology.

- Study 3 was unique as it reported the reliability of mobility and balance outcome measures in a group of people with MS all of whom had an EDSS score of 5 to 6.5. Furthermore, it was the first to report clinical significance of the four outcome measures, measured by minimal detectable change scores, in those with MS.

The overall investigation contributes unique knowledge to therapeutic exercise for those with MS and a number of clinical and research recommendations have emerged.

7.2 Recommendations from Study 1

Clinical recommendations

- Community leisure centre based group exercise is a feasible option for those moderately affected with MS.

- Combined; aerobic, resistance and balance exercise has a positive effect on people with MS, particularly in areas related to physical activity levels, balance, quality of life and muscle strength, with no detrimental effect on fatigue.

Research recommendations

- Narrowing the EDSS level of study participants in future studies will improve the significance of results found in therapeutic exercise studies. This should be based on power calculations to determine recruitment.

7.3 Recommendations from Study 2

Clinical recommendations

- Those with MS would like exercise options which would allow them to exercise in an environment with others who have similar levels of disability

- When establishing a therapeutic exercise intervention for those with MS, an educational component may help participants. A focus group format may be a potential format for this.

- A basic understanding of neurological conditions should be expected from those delivering exercise interventions to this group of people.

Research recommendations

- Adopting qualitative methodology to gather data on the outcome of intervention studies in MS will strengthen research findings and offer an insight into new areas which quantitative analysis may not capture.

7.4 Recommendations from Study 3

Clinical recommendations

- When following a standardised protocol the T25FW, 6MWT, TUG and BBS are reliable outcome measures to assess mobility and balance in people moderately affected by MS. Thus these outcome measures should be used in this patient population.

Research recommendations

- Establishing the reliability, clinical significance and precision of these outcomes measures across the disability range found in MS should be done.

- By stratifying participants, based on level of disability, the impact of disability level on the clinical significance and precision of these outcome measures may be better established.

- Standardised methods to calculate both the SEM and MDC should be used in future studies.

7.5 Key recommendations for rehabilitation practice

- A community based group exercise class should be one service available as part of an Integrated Care Pathway for MS.

- To ascertain what may be required to run such a service, and to establish whether it is a feasible option for care pathways in MS consultation between patient representatives, physiotherapists and community exercise professionals should be done locally.

- Personnel involved in service delivery should be trained in exercise delivery to neurological populations.

- Class content should be varied, from a bank of exercise options designed by physiotherapists and chosen to benefit each participant's needs, capabilities and goals.

- Classes should be available two to three times weekly, for around 60 minutes, be delivered by a minimum of two leaders and should be associated with an education component.

7.6 Key recommendations for future research

- Researchers in MS rehabilitation should seek to recruit sufficient numbers of participants to enable appropriately powered analyses to be conducted, including allowing for stratification of results based on, for example, different levels of disability.

- Power calculations, to determine recruitment should be based on outcome measures appropriate to both the population of interest and the aims of the study.

- Mixed methodology studies, to include both quantitative and qualitative outcomes would enhance understanding of rehabilitation literature in MS.

Appendices

Appendix 1 Expanded Disability Status Scale

0 – Normal neurological exam (all grade 0 in all Functional System (FS) scores*)

1 – No disability, minimal signs in one FS* (i.e. grade 1)

1.5 – No disability, minimal signs in more than one FS* (more than 1 FS grade 1).

2 – Minimal disability in one FS (one FS grade 2, others 0 or 1)

2.5 – Minimal disability in two FS (two FS grade 2, others 0 or 1)

3 – Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four (three or four FS grade 2, others 0 or 1) though fully ambulatory

3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1)

4 – Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting on one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous levels; able to walk without aid or rest some 500 metres

4.5 – Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterised by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous levels; able to walk without aid or rest some 300 metres

5 – Ambulatory without aid or rest for about 200 metres; disability severe enough to impair full daily activities (e.g. to work a full day without special provisions); Usual FS equivalents are one grade 5 alone, other 0 or 1; combinations of lesser grades usually exceeding specifications for level 4.

5.5 Ambulatory without aid for about 100 metres; disability severe enough to preclude full daily activities; (usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for level 4.

6 – Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 metres with or without resting; (usual FS equivalents are combinations with more than two FS grade >3)

6.5 – Constant bilateral assistance (canes, crutches, braces) required to walk about 20 metres without resting; (usual FS equivalents are combinations with more than two FS grade >3)

7 – Unable to walk beyone approximately 5 metres even with aid, essentially restriced to wheelchair, wheels self in standard wheelchair and transfers alone; up and about in wheelchair some12 hours a day; (usual FS equivalents are combinations with more than one FS grade >4; very rarely pyramidal grade 5 alone)

7.5 – Unable to take more than a few steps; restricted to wheelchair; may need aid intransfer; wheels self but cannot carry on in standard wheelchair a full day. May required motorised wheelchair (usual FS equivalents are combinations with more than two FS grade >4)

8 – Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self –care functions; generally has effective use of arm; (usual FS equivalents combinations, generally grade >4 in several systems)

8.5 – Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions; (usual FS equivalents are combinations, generally >4 in several systems)

9 – Helpless bed patient, can communicate and eat (usual FS equivalents are combinations, generally >4 in several systems)

9.5 – Totally helpless bed patient; unable to communicate effectively or eat/swallow; (usual FS equivalents are combinations, generally >4 in several systems)

10 – Death due to MS

*Excludes cerebral function grade 1

Note 1 – EDSS levels 1 to 4.5 refer to patients who are fully ambulatory and the precise level number is defined by the FS score. EDSS levels 5 – 9.5 are defined by the impairment to ambulation and usual equivalents in FS scores are provided.

Note 2 – EDSS should not change by 1 level unless there is a change in the same direction of at lease one level in a least one FS.

Appendix 2 Screening Form

Demographic Data

Today's date _____
Participant ID _____

Participants name _____

Date of Birth _____ Age _____ Sex F_____M____

Disease diagnosis 007 (please choose only 1)
Relapsing/Remitting (RR) ____
Primary Progressive (1P) ____
Secondary Progressive (2P)____

Number of year since original diagnosis (whole years only) _____

EDSS Score _____ MMSE Score _____
(See additional form) (See additional form)

Eligible for inclusion in study (see page 2) Yes _____ No _____

Mini Mental State Examination

Instructions: ***Ask the questions in the order listed. Score one point for each correct response within each question or activity.***

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Physical Activity Readiness Questionnaire; Fitness screening form

	Yes	No
Are you physically active at the moment		
Have you suffered from any form of heart trouble?		
Do you frequently have any pains in your heart or chest?		
Do you often feel faint or have spell of severe dizziness?		
Have you fallen more than twice in the past month?		
Has your doctor ever said that your blood pressure was too high or too low?		
Has your doctor ever told you that you have bone or joint problems such as arthritis, back problems etc which may be aggravated by exercise?		
Are you currently on any prescribed drugs for any heart condition problems or blood pressure?		
Are you recovering from an illness (other than your MS) or operation		
Do you know of any reason why you should not do any physical activity?		
At this point please remind the participant what the class will involve, and establish if they think they will be able to manage it.		
Do you feel you will be able to manage the exercise class for this study?		

Comments

_____

_____

Any advice given

_____

_____

Inclusion Criteria Does this patient have….	Yes	No
Clinically or paraclinically diagnosed MS, based on the most recent additions to the diagnostic criteria?		
Primary or secondary progressive MS?		
An EDSS score between 5 and 6.5? (See additional sheet)		
Stable rehabilitation and drug therapy within the past 30 days?		
Adequate cognitive function, assessed by the Mini Mental State Examination of 24 or over? (See additional sheet)		
Access to either the Galleon Leisure centre or Magnum centre using with own transport or patient transport		

If <u>No</u> to any of the above, do not complete the rest of this form.

Exclusion Criteria	Yes	No
Has this patient suffered a recent exacerbation of their MS symptoms within the past three months?		
Does this patient have a rapidly progressing disease?		
Does this patient show any signs of severe cognitive deficits?		
Does this patient have a history of cardiovascular, respiratory, neurological, metabolic disease, or any other medical condition which may prevent participation in the study?		
If other what?		
Is this patient unlikely to be able to complete the protocol for the outcome measures or the exercise class, as measured by a fitness screening form?		

If <u>Yes</u> to any of the above, do not complete the rest of this form.

Appendix 3 Assessment form

Protocol & Data collection sheets for Quantitative Assessments

Today's date _____
Participant ID _____ Participant Initials ___ ___
Date of Birth _____ Age _____ Gender_____
Weaker Leg left [ ] Right [ ]
Height (cm)_____ Weight (kg)_____

Leg Length (cm) (L)_____ (R)_____

Timed 25ft walk test shoes on.

Test	Time (mins:sec)	Time (sec)	Comments (not necessary)
Test 1			
Test 2			
Test 3			

Did participant wear AFO Yes____ No ___
Was an assistive device used Yes ___ No ___
If Yes, what?
Unilateral Assistance Cane (UCa)_____ Crutch (UCr) _____
Bilateral Assistance Cane (BCa) _____ Crutch (BCr) _____
Walker/Rollator (WR) _____

Any other comments (not necessary)_____

Temporal Spatial walking assessment.

The participant will walk with shoes on across the Gaitrite carpet whilst they are performing the 25 ft walk test. Measurements will be recorded on the computer.

Any other comments (not necessary)_____

Overall Stability Assessment using a balance plate Biodex
with shoes on.

Patient position:
Left heel [ ] Co-ordinates [ ] Left foot angle [ ]
Right heel [ ] Co-ordinates [ ] Right foot angle [ ]

Test 1
Comments _____
% Time in zone
A [ ] B [ ] C [ ] D [ ]
% Time in quadrant
I [ ] II [ ] III [ ] IV [ ]

Stab indx [ ] *AP Indx* [ ] *ML* [ ]
Mean Deflect [ ] Mean AP def [ ] Mean ML def [ ]
StDev [ ] StDev [ ] St Dev [ ]

Test 2
Comments _____
% Time in zone
A [ ] B [ ] C [ ] D [ ]
% Time in quadrant
I [ ] II [ ] III [ ] IV [ ]

Stab indx [ ] *AP Indx* [ ] *ML* [ ]
Mean Deflect [ ] Mean AP def [ ] Mean ML def [ ]
StDev [ ] StDev [ ] St Dev [ ]

Test 3
Comments _____
% Time in zone
A [ ] B [ ] C [ ] D [ ]
% Time in quadrant
I [ ] II [ ] III [ ] IV [ ]

Stab indx [ ] *AP Indx* [ ] *ML* [ ]
Mean Deflect [ ] Mean AP def [ ] Mean ML def [ ]
StDev [ ] StDev [ ] St Dev [ ]

Berg Balance Scale

Record the lowest possible score for each item

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if:
• the time or distance requirements are not met
• the subject's performance warrants supervision
• the subject touches an external support or receives assistance from the examiner
Subject should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Scoring

1 SITTING TO STANDING

INSTRUCTIONS: Please stand up. Try not to use your hand for support.
( ) 4 able to stand without using hands and stabilize independently
( ) 3 able to stand independently using hands
( ) 2 able to stand using hands after several tries
( ) 1 needs minimal aid to stand or stabilize
( ) 0 needs moderate or maximal assist to stand

2 STANDING UNSUPPORTED

INSTRUCTIONS: Please stand for two minutes without holding on.
( ) 4 able to stand safely for 2 minutes
( ) 3 able to stand 2 minutes with supervision
( ) 2 able to stand 30 s unsupported
( ) 1 needs several tries to stand 30 s unsupported
( ) 0 unable to stand 30 s unsupported
If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

3 SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A

STOOL

INSTRUCTIONS: Please sit with arms folded for 2 minutes.
( ) 4 able to sit safely and securely for 2 minutes
( ) 3 able to sit 2 minutes under supervision
( ) 2 able to able to sit 30 s
( ) 1 able to sit 10 s
( ) 0 unable to sit without support 10 s

4 STANDING TO SITTING

INSTRUCTIONS: Please sit down.
( ) 4 sits safely with minimal use of hands
( ) 3 controls descent by using hands
( ) 2 uses back of legs against chair to control descent
( ) 1 sits independently but has uncontrolled descent
( ) 0 needs assist to sit

5 TRANSFERS

INSTRUCTIONS: Arrange chair(s) for pivot transfer. Ask subject to transfer one way toward a seat with armrests and one way
toward a seat without armrests. You may use two chairs (one with and one without armrests) or a bed and a chair.
( ) 4 able to transfer safely with minor use of hands
( ) 3 able to transfer safely definite need of hands
( ) 2 able to transfer with verbal cuing and/or supervision
( ) 1 needs one person to assist
( ) 0 needs two people to assist or supervise to be safe

6 STANDING UNSUPPORTED WITH EYES CLOSED

INSTRUCTIONS: Please close your eyes and stand still for 10 s.
( ) 4 able to stand 10 s safely
( ) 3 able to stand 10 s with supervision
( ) 2 able to stand 3 s
( ) 1 unable to keep eyes closed 3 s but stays safely
( ) 0 needs help to keep from falling

7 STANDING UNSUPPORTED WITH FEET TOGETHER

INSTRUCTIONS: Place your feet together and stand without holding on.
( ) 4 able to place feet together independently and stand 1 minute safely
( ) 3 able to place feet together independently and stand 1 minute with supervision
( ) 2 able to place feet together independently but unable to hold for 30 s
( ) 1 needs help to attain position but able to stand 15 s feet together
( ) 0 needs help to attain position and unable to hold for 15 s

8 REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING

INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can. (The recorded measure is
the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)
( ) 4 can reach forward confidently 25 cm (10 inches)
( ) 3 can reach forward 12 cm (5 inches)
( ) 2 can reach forward 5 cm (2 inches)
( ) 1 reaches forward but needs supervision
( ) 0 loses balance while trying/requires external support

9 PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION

INSTRUCTIONS: Pick up the shoe/slipper, which is in front of your feet.
( ) 4 able to pick up slipper safely and easily
( ) 3 able to pick up slipper but needs supervision
( ) 2 unable to pick up but reaches 2-5 cm(1-2 inches) from slipper and keeps balance independently
( ) 1 unable to pick up and needs supervision while trying
( ) 0 unable to try/needs assist to keep from losing balance or falling

10 TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE

STANDING

INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. (Examiner may pick an object
to look at directly behind the subject to encourage a better twist turn.)
( ) 4 looks behind from both sides and weight shifts well
( ) 3 looks behind one side only other side shows less weight shift
( ) 2 turns sideways only but maintains balance
( ) 1 needs supervision when turning
( ) 0 needs assist to keep from losing balance or falling

11 TURN 360 DEGREES

INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.
( ) 4 able to turn 360 degrees safely in 4 s or less
( ) 3 able to turn 360 degrees safely one side only 4 s or less
( ) 2 able to turn 360 degrees safely but slowly
( ) 1 needs close supervision or verbal cuing
( ) 0 needs assistance while turning

12 PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED

INSTRUCTIONS: Place each foot alternately on the step/stool. Continue until each foot has touched the step/stool four times.
( ) 4 able to stand independently and safely and complete 8 steps in 20 s
( ) 3 able to stand independently and complete 8 steps in > 20 s
( ) 2 able to complete 4 steps without aid with supervision
( ) 1 able to complete > 2 steps needs minimal assist
( ) 0 needs assistance to keep from falling/unable to try

13 STANDING UNSUPPORTED ONE FOOT IN FRONT

INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place
your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To
score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the
subject's normal stride width.)
( ) 4 able to place foot tandem independently and hold 30 s
( ) 3 able to place foot ahead independently and hold 30 s
( ) 2 able to take small step independently and hold 30 s
( ) 1 needs help to step but can hold 15 s
( ) 0 loses balance while stepping or standing

14 STANDING ON ONE LEG

INSTRUCTIONS: Stand on one leg as long as you can without holding on.
( ) 4 able to lift leg independently and hold > 10 s
( ) 3 able to lift leg independently and hold 5-10 s
( ) 2 able to lift leg independently and hold ≥ 3 s
( ) 1 tries to lift leg unable to hold 3 s but remains standing independently.
( ) 0 unable to try of needs assist to prevent fall
Mark these in the following table

( ) TOTAL SCORE (Maximum = 56)

PhoneFITT (Activity monitoring)

*"...Now I'd like to ask you about some physical activities and find out how often you do them, for how long, and how out of breath you feel. First, I'd like you to think about activities you did **around your home**, in a **typical week** in the **last month**."*

INTERVIEWER: ASK ABOUT EACH ACTIVITY LISTED IN THE FOLLOWING 2 CHARTS. IF RESPONDENT ANSWERS 'YES' TO ENGAGING IN ACTIVITY (Q1), ASK Q 2-4 FOR THAT ACTIVITY; OTHERWISE, SKIP TO THE NEXT ACTIVITY. RECORD ANSWERS IN CHARTS.

1. In a **typical week** in the **last month**, did you engage in _____?
2. How many times/week did you do this?
3. About how much **time** did you spend on each occasion? **(READ CATEGORIES)**
4. On average when doing this activity, how did you feel? Were you… **(READ CATEGORIES)**

Household activities

Activity	(Q1) Participated?	(Q2) Frequency (# x/wk)	(Q3) Duration MARK ONE ONLY.	(Q4) Intensity MARK ONE ONLY.
A. Light housework such as tidying, dusting, laundry or ironing.	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
B. Making meals, setting and clearing the table, and washing dishes.	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
C. Shopping (for groceries or clothes for example).	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
D. Heavy housework such as vacuuming, scrubbing floors, mopping, washing windows, or carrying trash bags.	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
E. Home Maintenance such as painting, raking leaves, or shoveling snow.	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
F. Caring for another person (such as pushing a wheelchair, or helping person in/out of a chair/bed).	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation

*Next, I'd like you to think about activities you did for **recreation or conditioning** in a **typical week** in the **last month**.*

Recreational & Conditioning Activities

Activity	(Q1) Participated?	(Q2) Frequency (# x/wk)	(Q3) Duration MARK ONE ONLY.	(Q4) Intensity MARK ONE ONLY.
G. Lifting weights to strengthen your legs.	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
H. Other exercises designed to strengthen your legs (such as standing up/sitting down several times in a chair or climbing stairs).	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
I. Lifting weights to strengthen your arms or other exercises to strengthen your arms (such as wall push-ups).	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
J. Other home exercises not already mentioned such as stretching or balance exercises.	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
K. Walking for exercise	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
L. Dancing	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
M. Swimming	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
N. Bicycling	☐ Yes ☐ No		☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation

Now I would like to ask you about 2 specific activities that are seasonal and about any other activities that you do.

INTERVIEWER: ASK ABOUT EACH ACTIVITY LISTED IN THE FOLLOWING CHART. IF THE RESPONDENT ANSWERS 'YES' TO ENGAGING IN ACTIVITY (Q5), ASK Q 6-8 FOR THAT ACTIVITY; OTHERWISE SKIP TO THE NEXT ACTIVITY. RECORD ANSWERS IN CHART.

5. Do you _____?
6. (a) When you do this activity, how many times in a **typical week** do you do it?
   (b) How many months in **this past year** did you do this activity?
7. About how much **time** did you spend on each occasion? **(READ CATEGORIES)**
8. On average when doing this activity, how did you feel? Were you… **(READ CATEGORIES)**

Seasonal Recreational Activities

Activity	(Q5) Participated?	(Q6) Frequency	(Q7) Duration READ CATEGORIES. MARK ONE ONLY.	(Q8) Intensity READ CATEGORIES. MARK ONE ONLY.
O. Golf Mark: ☐ use cart ☐ do not use cart	☐ Yes ☐ No	A. _____ (# x/wk) B. _____ (# mo./yr)	☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
P. Garden	☐ Yes ☐ No	A. _____ (# x/wk) B. _____ (# mo./yr)	☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation

9. Do you participate in any other regular physical activities that we haven't asked you about?
   ☐ Yes
   ☐ No **(GO TO CLOSING REMARKS)**

INTERVIEWER: IF RESPONDENT ANSWERS "YES" TO Q 9, ASK WHAT THE ACTIVITY IS, FOLLOWED BY Q. 6-8 (LISTED ABOVE). REPEAT THIS PROCESS FOR UP TO THREE 'OTHER' ACTIVITIES. RECORD ANSWERS IN CHART.

Other Physical Activities

Activity	(Q6) Frequency	(Q7) Duration READ CATEGORIES. MARK ONE ONLY.	(Q8) Intensity READ CATEGORIES. MARK ONE ONLY.
Q. Other #1: _____	A. _____ (# x/wk) B. _____ (# mo./yr)	☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
R. Other #2: _____	A. _____ (# x/wk) B. _____ (# mo./yr)	☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation
S. Other #3: _____	A. _____ (# x/wk) B. _____ (# mo./yr)	☐ 1 - 15 min ☐ 16 - 30 min ☐ 31 - 60 min ☐ 1 hour +	☐ Breathing NORMALLY and able to carry on a conversation ☐ SLIGHTLY out of breath BUT still able to carry on a conversation ☐ TOO out of breath to carry on a conversation

CLOSING REMARKS: Thank you very much for taking the time to complete this interview.

Gill, D.P., Jones G.R., Zou, G.Y., & Speechley M. (July 2008). The Phone-FITT: A brief physical activity interview for older adults. *Journal of Aging and Physical Activity, 16(3)*.

Timed Up & Go test (following Shumway-Cook, 2000 basic protocol)
Participants can use any assistive device they normally use.

Test number	Time	Comments
Test 1		
Test 2		
Test 3		

Assistive device used _____

Any other comments _____

Assessing lower limb (quadriceps) strength,

Distance (cm) Patella Apex to Mark (1), proximal to M malleoli	Left leg	Right leg

Test number	Left leg (kg)	Right leg (kg)	Comments
Test 1			
Test 2			
Test 3			

Any other comments _____

Six-minute walking test

Assistive device used _____

Test	Distance	Comments
1		

Borg pre-test _____

Borg post-test _____

The Goal Attainment Scale
Negotiate 3 of the following options.

Goal 1 [ ] Improve walking speed over 25ft
Goal 2 [ ] Improve distance walked over 6MWT
Goal 3 [ ] Improve functional strength (TUG)
Goal 4 [ ] Improve lower limb strength (HHD) weaker leg
Goal 5 [ ] Improve lower limb strength (HHD) stronger leg
Goal 6 [ ] Improve balance (overall stability)
Goal 7 [ ] Improve balance (BBS)
Goal 8 [ ] Improve balance (ABC)
Goal 9 [ ] Improve social interaction
Goal 10 [ ] Improve perceived quality of life (LMS QoL)
Goal 11 [ ] Improve perceived levels of anxiety and disability (HADS)
Goal 12 [ ] Attend the exercise programme
Goal 13 [ ] Improve perceived levels of fatigue
Goal 14 [ ] Other (but it is necessary to agree 5 outcomes, see accompanying instructions, and complete in second table below)

Each goal is weighted according to its importance to the patient (3-pt scale) either 1 (fairly important), 2 (very important), and 3 (extremely important)

Each goal is weighted according to the anticipated difficulty (according to the patient & the research team) (3-pt scale) 1 (probable), 2 (possible), or 3 (doubtful).

Chosen Goal	**Importance (1, 2, 3)**	**Perceived difficulty (1,2,3)**

		Goal option 14
Goal Attainment Level	Score	
Best anticipated outcome	+2	
More than expected outcome	+1	
Expected outcome	0	
Less than expected outcome	-1	
Unfavourable outcome	-2	

Appendix 4 Questionnaire Outcome Measures

Instructions for participants

Please complete the following four short questionnaires whilst you await the assessor. There are questions on both sides. **Please answer all questions.**

Leeds MS Quality of Life Scale Scoring Grid (LMSQoL)

Please read the following questions and circle a score which most describes how you have felt in the past month.

	Very much	Quite a lot	A little	Not at all
My health has affected my relationships with my family	3	2	1	0
I have felt lonely	3	2	1	0
I have felt good about my appearance	0	1	2	3
I have worried about my health	3	2	1	0
I have worried about other peoples attitudes about me	3	2	1	0
I have felt tired	3	2	1	0
I have had as much energy as usual	0	1	2	3
I have felt happy about the future	0	1	2	3

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

FOLD HERE

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		3
2		A lot of the time		2
1		From time to time, occasionally		1
0		Not at all		0
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much	0	
	2	Only a little	1	
	3	Hardly at all	2	
			3	
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		3
2		Yes, but not too badly		2
1		A little, but it doesn't worry me		1
0		Not at all		0
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now	0	
	2	Definitely not so much now	1	
	3	Not at all	2	
			3	
		Worrying thoughts go through my mind		
3		A great deal of the time		0
2		A lot of the time		1
1		Not too often		2
0		Very little		3
		I feel cheerful		
	3	Never	3	
	2	Not often	2	
	1	Sometimes	1	
	0	Most of the time	0	
		I can sit at ease and feel relaxed		
0		Definitely		0
1		Usually		1
2		Not often		2
3		Not at all		3

Now check that you have answered all the questions

A	D

TOTAL

Fatigue Severity Scale (FSS)

Read each statement and circle the number which best indicates how much you agree. Low numbers indicate you don't agree, higher numbers indicate stronger agreement.

During the past week, I have found that:	Score						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Activities-Specific Balance Confidence

Instructions: For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the scale of 1 (*Not at all confident*) to 10 (*Completely confident*).

How confident are you that you will not lose your balance or become unsteady when you ….

1. Walk around the house?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

2. Walk up and down stairs?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

3. Bend over and pick up a slipper from the front of a closet floor?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

4. Reach for a small can off a shelf at eye level?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

5. Stand on your tip toes and reach or something above your head?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

6. Stand on a chair and reach for something?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

7. Sweep the floor?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

How confident are you that you will not lose your balance or become unsteady when you…

8. Walk outside the house to a car parked in the driveway?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

9. Get into or out of a car?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

10. Walk across a parking lot to the mall?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

11. Walk up a ramp?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

12. Walk in a crowded mall where people rapidly walk past you?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

13. Walk through the mall and are bumped by other people?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

14. Step on or off on escalator while holding onto a railing?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

15. Stepping on or off an escalator, while holding onto parcels and are unable to hold onto the railing?

1	2	3	4	5	6	7	8	9	10
Not at all confident		Somewhat confident		Moderately confident		Quite confident			Completely confident

Appendix 5 Ethical approval

West of Scotland REC 3
Ground Floor, The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT

Telephone: 0141 211 2123
Facsimile: 0141 211 1847
21 December 2009

Miss Yvonne Learmonth
Division of Nursing & Healthcare
University of Glasgow
59 Oakfield Avenue
Glasgow G12 8LL

Dear Miss Learmonth

Study Title:	**The effectiveness of a 12 week community based group exercise class for people moderately affected with multiple sclerosis.**
REC reference number:	**09/S0701/104**
Protocol number:	**Version 1**

Thank you for your letter of responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered by a sub-committee of the REC at a meeting held on 17th December 2009. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation, as revised, to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. *Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		13 October 2009
REC application		14 October 2009
Protocol	Version 1	13 October 2009
Investigator CV		09 October 2009
GP/Consultant Information Sheets	Version 1	13 October 2009
Interview Schedules/Topic Guides	Version 1	13 October 2009
Questionnaire: Validated - Leeds MSQoL	Version 1	13 October 2009
CV - Student - Yvonne Learmonth		12 October 2009
Questionnaire: Validated - HADS	Version 1	13 October 2009
Questionnaire: Validated - FSS	Version 1	13 October 2009
Questionnaire: Validated - Phone FITT	Version 1	13 October 2009
Covering Letter		27 November 2009
Protocol	Version 1	13 October 2009
Participant Information Sheet	Version 2	27 November 2009
Participant Consent Form	Version 2	27 November 2009
Letter from Dr Mattison	Version 1	30 November 2009

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/S0701/104	Please quote this number on all correspondence

Yours sincerely

Liz Jamieson

Liz Jamieson
Committee Co-ordinator on behalf of Dr Robert McNeill, Acting Vice Chair

Email: Liz.Jamieson@ggc.scot.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting

"After ethical review – guidance for researchers

Copy to: Dr Debra Stuart

Appendix 6 Research and Development approval

Research and Development
58 Lister Street
Crosshouse Hospital
Kilmarnock
KA2 0BB

Tel: (01563) 825856
Fax: (01563) 825806

NHS Ayrshire & Arran

Miss Yvonne Learmonth
Division of Nursing and Healthcare
University of Glasgow
59 Oakfield Avenue
Glasgow
G12 8LL

Date: 14th January 2010
Your Ref:
Our Ref: CAW/KLB/MF 2009AA061

Enquiries to: Karen Bell
Extension: 25850
Direct Line: 01563 825850
Email: Karen.bell@aaaht.scot.nhs.uk

www.nhsayrshireandarran.com

Dear Miss Learmonth

The effectiveness of a 12 week community based group exercise class for people moderately affected with multiple sclerosis
R&D Ref: 2009AA61 Ethics Ref: 09/S0701/104

I confirm that NHS Ayrshire and Arran have reviewed the undernoted documents and approve the above study.

Approved documents:

Document	Version	Date
Protocol	1	13/10/09
IRAS R&D Form	2.5	15/10/09
Participant Information Sheet	2	27/11/09
Participant Consent Form	2	27/11/09
Questionnaire Validated – Leeds MSQoL	1	13/10/09
Questionnaire Validated – HADS	1	13/10/09
Questionnaire Validated – FSS	1	13/10/09
Questionnaire Validated Phone FITT	1	13/10/09
Interview schedule topic guide	1	13/10/09
GP Letter	1	13/10/09

Please note that prior to their involvement in the study we require a signed CV of the assessor and evidence that you have notified ethics of their involvement in the study. When this has been received we will issue R&D Management Approval for their involvement in the study. They must not participate in the study until this has been received.

The terms of approval state that the investigator authorised to undertake this study within NHS Ayrshire & Arran is: -

- Yvonne Learmonth, University of Glasgow

With additional investigator(s): -

- Dr Paul Mattison, NHS Ayrshire and Arran
- Ms Linda Miller, NHS Ayrshire and Arran

The sponsors for this study are University of Glasgow.

This approval letter is valid until 30th June 2012.

Regular reports of the study require to be submitted. Your first report should be submitted to Dr K Bell, Research & Development Manager in 12 months time and subsequently at yearly intervals until the work is completed.

Please note that as a requirement of this type of study your name, designation, work address, work telephone number, work e-mail address, work related qualifications and whole time equivalent will be held on the Scottish National Research Database so that NHS R&D staff in Scotland can access this information for purposes related to project management and report monitoring.

In addition approval is granted subject to the following conditions: -

- All research activity must comply with the standards detailed in the Research Governance Framework for Health and Community Care and appropriate statutory legislation.

- If any amendments are to be made to the study protocol and or the Research Team the Researcher must seek Ethical and Management Approval for the changes before they can be implemented.

- The Researcher and NHS Ayrshire and Arran must permit and assist with any monitoring, auditing or inspection of the project by the relevant authorities.

- The NHS Ayrshire and Arran Complaints Department should be informed if any complaints arise regarding the project and the R&D Department must be copied into this correspondence.

- The outcome and lessons learnt from complaints must be communicated to funders, sponsors and other partners associated with the project.

- As custodian of the information collated during this research project you are responsible for ensuring the security of all personal information collated in line with NHS Scotland IT Security Policies, until the destruction of these data. Under no circumstances should personal data be stored on any unencrypted removable media e.g. laptop, USB or mobile device (for further information and guidance please contact the Information Governance Team based at Ailsa Hospital 01292 513693 or 513694).

If I can be of any further assistance please do not hesitate to contact me. On behalf of the department, I wish you every success with the project.

Yours sincerely

Professor Craig A White
Assistant Director Healthcare Quality, Governance and Standards

Appendix 7 Invitation letter

The Douglas Grant
Rehabilitation Centre
Ayrshire Central Hospital
Kilwinning Road
IRVINE
Ayrshire KA12 8SS

Dear Sir/Madam

I am writing to inform you of a study taking place in association with the Douglas Grant Rehabilitation Centre and the University of Glasgow. Yvonne Learmonth, a Physiotherapist and PhD student under my supervision, is organising a study which will investigate the effects of a leisure centre based exercise programme on people mildly to moderately affected by MS.

Remaining as active as possible is particularly important for you and your MS symptoms. Past studies in those less severely affected by MS have found MS symptoms such as walking difficulty, reduced strength, poor balance and fatigue can be improved by exercise. Therefore, we would like to investigate if any similar benefits might occur in those more affected with MS-related problems. To do this we need participants to take part in a 12-week, twice-weekly exercise class at a local leisure centre. We will then monitor participants after 6 and 12 months to see the effects of the exercise class in the long term

Please note that as this is a research study we will have two groups of people; one group which undertakes the exercise programme and one group who doesn't and you could be allocated to either group. The group which is not exercising will continue to access any physiotherapy or other care they require. After the 12 weeks **all participants** will be informed of exercise options available to them, and will have access to the local authority exercise referral scheme, which offers expert advice in staying as healthy as possible and remaining active. Part of the scheme also offers discounts for leisure activities which may be of benefit.

If you feel you may benefit from participating in this study, then please take the time to read the participant information sheet enclosed. If you have questions and/or are interested in taking part then please contact:

Yvonne Learmonth who is the main researcher -
Telephone: **0141 330 xxxx** or Email: **xxxxxx@xxxxxx**

PLEASE CONTACT YVONNE BY THURSDAY 20TH May 2010

IF YOU ARE INTERESTED IN PARTICIPATING.

In addition should you have any further queries related to the study please do not hesitate to contact me.

Yours sincerely

Dr Paul G Mattison, Consultant Physician in Rehabilitation Medicine

Appendix 8 Participant Information Sheet

For the study entitled:

The effectiveness of a 12 week community based group exercise class for people moderately affected with Multiple Sclerosis.

The above study is the first part of a larger project being undertaken by Yvonne Learmonth a physiotherapist and PhD student at The University of Glasgow, under the supervision of Dr Lorna Paul, University of Glasgow and Dr Paul Mattison, Douglas Grant Rehabilitation Centre, Ayrshire Central Hospital.

You will also have received an invitation letter to take part from Dr Mattison, as stated the study is to assess the effects of a group exercise class for people with MS living in Ayrshire. The study is being undertaken in collaboration with NHS Ayrshire & Arran, the Division of Nursing and Healthcare at The University of Glasgow, East Ayrshire Leisure and North Ayrshire Leisure services.

Before you decide whether or not to take part it is important for you to understand why the research is being undertaken and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information.

It is important that you are aware that consenting to take part means that you may be randomly allocated to either the exercise group or the usual care group, however all participants will be offered referral into exercise referral schemes on completion of the study. Thank you in advance for taking the time to read this and to decide whether or not you wish to take part.

Part 1: Basic study information

What is the purpose of the study?

There is evidence to suggest that remaining active and exercising can help prevent many health problems and can help people improve their mood and encourage social interaction. This is as true for people with MS as for those without. From previous studies in those less severely affected with MS symptoms, we know that organised exercise classes can increase strength, mobility, exercise tolerance and can have an effect on mood and fatigue. However we don't know yet what the affects are in those more severely affected. This study will look at whether a 12 week, twice weekly exercise programme in a local leisure centre is effective in improving mobility, balance, strength, fatigue and mood. We will also gather patients' opinions of the exercise therapy classes, and follow-up patients progress after 6 and 12 months.

Why have I been chosen?

You have been identified by Dr Mattison as someone who has MS and who may benefit from this type of intervention and therefore suitable for inclusion in the study.

Do I have to take part?

Taking part in research is entirely voluntary; therefore it is up to you to decide. We will describe the study and then go through the information sheet with you, which you can then keep.

If you are interested in taking part you should phone Yvonne Learmonth (contact details are at the end of this sheet), who will explain the study in further detail.

An initial appointment will then be made for you to come to the Douglas Grant Rehabilitation Centre where we will explain the study further and you will then be asked to sign a consent form to show that you agree to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not have any effect on the standard of care you receive.

What will happen to me if I take part?

The study will aim to recruit 52 people with MS. You will initially be involved for 3 months. Because we need to find out whether or not the treatment is effective, or whether any benefits would have occurred anyway it is necessary to compare two groups and you may be allocated to either group. One group will be invited to attend a twice weekly group exercise class at a local leisure centre. The class will be supervised by 2 instructors specifically trained in exercise therapy for people with MS and will last approximately 60 minutes. It will take the form of a circuit class, where different levels of each exercise will be available to you, aerobic, strengthening and balance exercises will all be included. On completion of the 12 week class you will be invited to give your views during a recorded focus group. The second group will receive usual-care, and if you require any physiotherapy treatment during the study this will be available to you as normal. Group allocation will be randomly allocated by a computer

All participants (both groups) will be assessed at the beginning of the study, 8 weeks into the study, 12 weeks into the study (ie at the end of the exercise class), 6 months and 12 months after the classes. The assessments will involve measuring your walking ability, balance and lower limb strength. We will also measure your perceived levels of fatigue, mood and quality of life, and we will take the opportunity to set realistic goals for you to achieve during the study. These assessments will be carried out in the Douglas Grant Rehabilitation centre by a registered physiotherapist. Following the initial 12 weeks all participants will be given information on exercise and activity options available to them in their local leisure centres and will be offered inclusion into the exercise referral schemes, these offer advice on healthy living and discounts on local authority leisure facilities.

What do I have to do?

You will have to attend five appointments at the Douglas Grant Rehabilitation Centre. Patients in the exercise group will also have to attend the twice weekly exercise class for the 12 weeks of the study.

Disadvantages/risks of taking part

There are no expected risks, side effects or disadvantages expected from taking part in this study. However as with all exercise those taking part in the exercise group may notice some soreness or tiredness associated with the class.

What are the possible benefits of taking part.

We cannot promise that the study will help, however the information from this study will help improve treatment of other people with MS. It may be that leisure centres continue the exercise class on a long term basis.

Expenses and payment

The exercises classes will be free during the study, however you will be required to make your own travel arrangements to access the classes. There may be a possibility that patient transport (ambulances and volunteer drivers) may be organised if are unable to make your own way to the hospital for assessment purposes.

What happens when the research study stops?

On completion of the initial 12 week class, all participants will be given information on exercise and activity options available to them in their local leisure centres and will be offered inclusion into the exercise referral schemes; offering advice on healthy living and discounts on local authority leisure facilities. After the 12 months of access to the exercise referral scheme you will still be able to access local authority exercise facilities, however this may no longer be at a discounted rate.

Will my taking part in this study be kept confidential?

Yes, all information collected from you during the study will be kept strictly confidential and treated with normal ethical and legal practice for data collection. With your consent we will inform your own GP about your involvement in this study.

If the information in Part 1 interests you, and you are considering taking part please read the additional Part 2 information.

Part 2: Additional Information

What happens if new information becomes available?

Sometimes new treatment information becomes available. Although this is unlikely should this happen during the study the researcher will tell you and discuss whether you should stay in the study. If you decided not to continue the researcher will arrange for you to receive usual physiotherapy care. If you decide to continue you may be asked to sign an updated consent form. You may also be recommended by the researcher to withdraw from the study, we will explain the reasons and arrange for you to receive usual physiotherapy care. If the study is stopped for any other reason we will inform you, and arrange for you to receive usual physiotherapy care.

What will happen if I don't want to continue in the study?

You can withdraw at any time, however we would encourage you to keep in contact with us and let us know your progress. The information collected from you will still be used.

What if there is a problem?

Should you have a concern about any aspect of the study you should contact the main researcher (see contact details below) in the first instance, she will do her best to answer any questions. If this does not resolve the issue, and you would like to formally complain you can do this through the NHS Complaints Procedure details can be obtained from the Patients, Relations and Complaints Office tel: 01292 51xxxx. Independent advice about the study can be obtained from Dr Anna O'Neill tel: 0141 330 xxxx.

What happens to the results of the research study?

It is intended that the results of the study be used as part of a PhD student's thesis and will be published in smaller reports, all data will be anonymised before this. Should you wish to know the results of the study then we will send you a copy of the main findings once the research is complete.

Who is organising funding the research?

This study is funded by NHS Ayrshire and Arran

Who has reviewed this study?

All research in the NHS is looked at by the Research Ethics committee, an independent group of people who aim to protect patient safety, rights, well being and dignity. This study has been reviewed and given favourable opinion by the West of Scotland Research Ethics committee.

Participation, further information and contact details.
Should you wish to take part in this study or if you require any further information about this research study, want further advice as to whether you should participate or have any concerns during the study please do not hesitate to contact the main researcher on the number below

Yvonne Learmonth

PhD Student
School of Nursing & Healthcare
The University of Glasgow
59 Oakfield Avenue
Glasgow
G12 8LW

Tel: 0141 330 xxxx

Email xxx@xxx

Thank you for taking the time to read this information sheet.

Appendix 9 Assessor Instructions

Instructions for Assessor

Equipment required for every session;

Blank assessment sheets

Participant assessment folders

Stopwatch

Ruler (for Berg balance)

5 + Cones (for walking assessments/TUG)

2 x average height chairs (one with arms, one without arms, please use the same chairs in all assessments)

Small step/stool

Tape (to mark out 6MWT)

Pen with string

Card to cover biodex screen

3 x Clipboard (Borg on back)

Biodex system

Gaitrite System, including PC

Hand-held dynamometer

Large Borg scale

Wheel chair

Room for the walking assessments, 30m for the 6MWT

Felt Pen (for marking on skin)

Scales (seated)

Water

Stand and reach scale

Height measure

Order of testing

Protocol 1	**Protocol 2**	**Protocol 3**
Demographic data	Demographic data	Demographic data
Timed 25ft walk Gaitrite	6 MWT	Berg Balance
Balance plate	Berg Balance	Balance plate
Berg Balance	PhoneFITT questionnaire	Timed 25ft walk Gaitrite
Leg extensor strength	Balance Plate	PhoneFITT questionnaire
PhoneFITT questionnaire	Leg extensor strength	Timed Up and Go
Timed Up and Go	Timed Up and Go	Leg extensor strength
6 MWT	Timed 25ft walk Gaitrite	6 MWT

Timed 25ft walk test

- A 25 ft course (7.32m) course will be marked with cones.
    - Place a seat at either end if required
- The patient will start a few feet before the first cone
- They will be instructed to walk at their own pace to beyond the second cone.
    - The assessor can walk with the participant, but avoid dictating the pace.
- The time will be recorded from passing the first cone till passing the second cone.

This test will be repeated three times

During the test they will walk across the gaitrite carpet.

Temporal Spatial assessment

The participant will walk across the Gaitrite carpet with their shoes on **whilst they are performing the 25 ft walk test**. Measurements will be recorded on the computer.

6-minute walk test

- A set of cones will be placed 30m apart
  - Tape will be placed along the corridor every 3 m
- The participant will start in standing, in-line with the first cone (shoes on).
  - At this point they will be asked to rate their perceived dyspnea using the **Borg** Scale (show to participant)
- They will be asked to walk at their own speed using any walking aid of their choice, straight to the next cone, and around it, and then walk straight to the first cone. This pattern will be repeated for 6 minutes.
- Give instruction 1
- During test Give instructions 2

- The distance walked will be recorded.
- After the 6 minutes, ask and record their **Borg rating (RPE)**.
  - If they stopped say

  "What, if anything, kept you from walking farther?"

Borg 10 Point Scale

- 0 - Nothing at all
- 1 - Very light
- 2 - Fairly light
- 3 - Moderate
- 4 - Some what hard
- 5 - Hard
- 6
- 7 - Very hard
- 8
- 9
- 10 - Very, very hard

Instruction 1 (for 6MWT)

"**The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted.**

You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones.

You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line.

Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now, or whenever you are ready."

Instructions 2 (for 6MWT)

After the first minute, tell the patient the following (in even tones): **"You are doing well. You have 5 minutes to go."**

When the timer shows 4 minutes remaining, tell the patient the following: **"Keep up the good work. You have 4 minutes to go."**

When the timer shows 3 minutes remaining, tell the patient the following: **"You are doing well. You are halfway done."**

When the timer shows 2 minutes remaining, tell the patient the following: **"Keep up the good work. You have only 2 minutes left."**

When the timer shows only 1 minute remaining, tell the patient: **"You are doing well. You have only 1 minute to go."**

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: **"You can lean against the wall if you would like; then continue walking whenever you feel able."** Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this:

"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: **"Stop!"** Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

PhoneFITT

Ask the questions to each participant, recording the same for all participants and at each assessment.
For example:
For making meals, help them work out an average, if they say all meals, go with 21 in frequency (unless for example they are out every Saturday, or visit friends twice a week for dinner)
For shopping, note the total time out of the house, door-door, not just the time in the shop.
For Question H (…climbing stairs) if they have stairs in their house, record (on average) how many times they go up them in a typical week.

Timed Up & Go test

Participants can use any assistive device they normally use.

- A small cone is placed 3m away from the chair the participant is sitting on
- The participant starts in a seated position, with their back on the chair.
- The participant is asked to stand up, walk around the cone and sit back down, as quickly and safely as possible.
    - This is timed from initially (back leaving chair back) leaving the chair to sitting back down (back touching chair back).
- This test will be repeated three times

Leg strength

Assessing lower limb strength, using a Hand-held Dynamometer
Set the Machine to read KG output.

Baseline testing

- The participant starts in a seated position (with the knee bent at 90 degrees), feet not touching the floor, on a raised plinth, without back support.
- The Hand-held Dynamometer is placed just proximal to the medial malleoli on the anterior surface of leg, use the largest pad available.
    - Mark (1) on the leg the position of the top of the dynamometer pad (for replication).
    - Measure and record the distance from the Apex (most distal point) of the patella to Mark (1), with knees bent at 90 degrees.
- The participant is asked to cross their arms and straighten their leg against the dynamometer.
    - By saying “push as hard as you can after you hear the first beep, STOP pushing when you hear the second set of beeps”
- Repeat the process, by lining up with the above mark.
- Repeat three times in total, complete the same for the second leg..

Follow-up testing

- As above, however to ensure reliability and repeatability measure from the Apex of the patella to the distance used in previous testing. Mark (1)
- During testing line top of HHD pad with Mark (1)

Berg Balance Assessment

Complete as per protocol on data collection sheets

Overall Stability

Please set the Biodex balance plate machine as follows):

1. Turn on.
2. Test Duration: (20 s)
3. Weight Height (don't need to enter)
4. Stability Level (8)

Read the following

"I am now going to test your balance, in standing, this is a moving platform, when you first stand on, it will be stable, then when you are ready it will start moving.

Ask the participant to:
"stand on the plate please".
Participant to stand on biodex (holding on)
" Please assume a comfortable position, feet shoulder width apart. (patient can hold on at this point), look straight ahead,at the marked cross,when we begin testing I will ask you to and place arms across chest
(this is the standard position, assessor to note any deviation).

Patient position → [redacted]

5. Patient position → press [redacted] and get the participant to find centre, spend at least 30 s acclimatising participant. Press [redacted] once they are near the centre.
6. Patient position → look down at the platform, and add the co-ordinates of how the patient is standing..RECORD for follow-up assessments.

Remind them not to move their feet from now on, to try and maintain a stable position and to focus on the point marked on the wall in front of them (use your hand to cover the screen), to avoid biofeedback.

"Please now fold your arms across your chest"

7. Stability test → Press [redacted] to release the platform, allow 1 minute for participant to acclimatise → Press [redacted] to begin test
8. Perform test three times

Goal Attainment Scale

Goals will be set in collaboration with the participant/assessor.

You will have highlighted the Goal Attainment scale at the start of the assessment, and it is anticipated that through the assessment the participant and yourself will have found deficits, and areas which could be improved.

Use this knowledge to help the participant choose three realistic goals. Please see Goal options (if patient feels strongly about adding personal goal, do so, completing all 5 levels).

The participant is only expected to pick three goals, rate them in order of importance and anticipated difficulty.

Each goal is weighted according to its importance to the patient (3-pt scale) either 1 (fairly important), 2 (very important), and 3 (extremely important)

Each goal is weighted according to the anticipated difficulty (according to the patient & the research team) (3-pt scale) 1 (probable), 2 (possible), or 3 (doubtful).

The patient baseline scores for each goal should be allocated as -1 (unless they cannot be worse, in which case they would get a score of -2)

Example of potential Goals using the Goal Attainment Scale

Goal attainment is rated using a 5-point scale where 0 is the expected level of attainment

- Each goal is weighted according to its importance to the patient (3-pt scale) either 1 (fairly important), 2 (very important), and 3 (extremely important)
- Each goal is weighted according to the anticipated difficulty (according to the patient & the research team) (3-pt scale) 1 (probable), 2 (possible), or 3 (doubtful).
- The patient baseline scores for each goal should be allocated as -1 (unless they cannot be worse, in which case they would get a score of -2)
- Please pick three goals from the below options, if choosing Goal 14 it is necessary to agree 5 possible outcomes.

		Goal option 1	Goal option 2	Goal option 3
Goal Attainment Level	Score	Improve T25FW	Improve 6MWT	Improve TUG
Best anticipated outcome	+2	Reduction in time by >16%	Increase in distance by >4%	Reduction in time by >17%
More than expected outcome	+1	Reduction in time by 10-15%	Increase in distance by 2-4.9%	Reduction in time by 10-17%
Expected outcome	0	Reduction in time by 1-9%	Increase in distance by 0-2%	Reduction in time by 0-10%
Less than expected outcome	-1	No reduction in time	No increased distance	No increase in time for TUG
Unfavourable outcome	-2	Increase in time	Decreased distance	Reduction in time for TUG

	Goal option 4	Goal option 5	Goal option 6	Goal option 7
Score	Improve weaker leg strength	Improve stronger leg strength	Improve OS balance	Improve BBS
+2	Increase in Nm output by >5.35%	Increase in kg output by >5.35%	Decrease by 12.5%	Increase by >7 points
+1	Increase in Nm output 2-5.35%	Increase in kg output 2-5.35%	Decrease by 1-12.4%	Increase by 4-7 points
0	Increase in Nm output by 0-2.5%	Increase in kg output by 0-2.5%	Decrease by .1-6.9%	Increase by 1-3 point
-1	No change Nm output	No change kg output	No change in OB score	No change in score
-2	Decrease in Nm output	Decrease in kg output	Decrease in OB score	Reduction in score

	Goal option 8	Goal option 9	Goal option 10	Goal option 11
Score	Improve ABC	Improve **social interaction**	Improve LMS QoL	Improve HADS
+2	Increase in overall score by >5%	Has made positive external contact with more than one other class member (e.g phone call, meeting)	Reduction in score by > 2 points	Reduction in score by >10%
+1	Increase in overall score 2-5%	Has made positive external contact with other class member	Reduction in score by >1 point	Reduction in score by 5-10%
0	Increase in overall score 1-2%	Plans to make positive external contact with other class member (s)	Reduction in score by 0-1 points	Reduction in score by 0-5%
-1	No change in ABC score	No plans to make positive external contact with other class member (s)	No change in LMS QoL score	No reduction in score
-2	Reduction in ABC score	Not interacting in the class with others	Increase in LMS QoL score	Increase in score

	Goal option 12	Goal option 13	Goal 14
	Attend the exercise programme	Improve FSS	Participants own
+2	Attends > 90% of lasses	Improvement in score by >8%	
+1	Attends > 80% of classes	Improvement in score by 4-8%	
0	Attends > 70% of classes	Improvement in score by 0-4%	
-1	Attends > 60% of classes	No Improvement in score	
-2	Attends < 59% of classes	Deterioration in score	

Appendix 10 Study Consent Form

Patient Identification Number for this study: ☐

Title of Project: The effectiveness of a 12-week community based group exercise class for people moderately affected with Multiple Sclerosis.

Name of Researcher: Yvonne Learmonth

Please initial boxes

1. I confirm that I have read and understand the participant information sheet (version 2 dated 24/11/09) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

2. I understand that data collected during the study may be looked at by individuals from NHS Ayrshire & Arran and The University of Glasgow or from regulatory authorities, I give permission for these individuals to access my records. ☐

4. I agree to my GP being informed of my participation in this study ☐

1. I understand that this is a student project that will result in a PhD thesis that will be marked. ☐

2. I agree to take part in the above study. ☐

3. I understand that agreeing to take part in this study means that I will either be part of the exercise class (intervention) group or the usual care (control) group. ☐

_____ _____ _____

Name of Participant Date Signature

_____ _____ _____

Researcher Date Signature

*1 copy for participant; 1 copy for researcher and 1 (original) to be kept in medical notes.

Appendix 11 Effect size and Percentage (clinical) Change calculations

Effect sizes (ES) were calculated, using Cohen's *d*, analysis (Tyson and Connell 2009). A worked example using T25FW data at week 8 (Table 4.4) is shown below.

$$d = \frac{(BLI - Wk8I) - (BLC - Wk8C)}{(BLSDI + BLSDC)/2}$$

$$d = \frac{(22.1 - 16.7) - (16.1 - 15.4)}{(21.8 + 13)/2}$$

$$d = \frac{5.4 - 0.7}{17.4}$$

d= 0.30 for the T25FW at week 8.

Where BL – Mean baseline score, Wk8 – Mean week eight score, I -Intervention group, C-Control group, SD – Standard deviation.

Percentage change from baseline was calculated for all time-points. A worked example using T25FW data at week 8 (Table 4.4) is shown below.

$$\text{Percentage change} = \left(\frac{BL - Wk8}{BL}\right)x100$$

$$\text{Percentage change} = \left(\frac{22.1 - 16.7}{22.1}\right)x100$$

$$\text{Percentage change} = 0.24x100$$

Percentage change = 24% for T25FW in the intervention group at week eight.

Where BL – Mean baseline score, Wk8 – Mean week eight score

Appendix 12 Results of Temporal Spatial walking assessment, not shown in thesis

Group means (and standard deviations) for temporal special parameters

Temperal Spacial parameter (sec)	**Baseline**	**Week 8**	**Week 12**	**Month 6**	**Month 12**
Left Cycle Time					
Intervention	2.15 (2.5)	1.44 (0.9)	2.19 (2.7)	1.62 (1.1)	1.64 (1.4)
Control	1.11 (0.7)	1.75 (1.9)	1.29 (0.53)	1.24 (0.5)	1.52 (0.8)
Right Cycle Time					
Intervention	1.55 (1.1)	1.43 (0.9)	1.52 (1.1)	1.62 (1.1)	1.64 (1.4)
Control	1.21 (0.6)	1.73(1.8)	1.37 (0.44)	1.25 (0.5)	1.52 (0.8)
Left Swing Time					
Intervention	0.45 (0.2)	0.42 (0.2)	0.45 (0.1)	0.47 (0.2)	0.49 (0.2)
Control	0.4 (0.16)	0.4 (0.1)	0.51 (0.3)	0.42 (0.1)	0.48 (0.2)
Right Swing Time					
Intervention	0.45 (0.2)	0.44 (0.2)	0.43 (0.1)	0.46 (0.1)	0.48 (0.1)
Control	0.4 (0.2)	0.4 (0.1)	0.42 (0.1)	0.42 (0.1)	0.44 (0.1)
Left Single Support Time					
Intervention	0.45 (0.2)	0.44 (0.2)	0.44 (0.1)	0.45 (0.1)	0.48 (0.1)
Control	0.41 (0.2)	0.4 (0.1)	0.42 (0.1)	0.42 (0.1)	0.39 (0.1)
Right Single Support Time	0.44 (0.2)	0.42 (0.2)	0.45 (0.1)	0.48 (0.2)	0.49 (0.2)
Intervention	0.39 (0.16)	0.4 (0.1)	0.41 (0.1)	0.42 (0.1)	0.49 (0.2)
Control					
Left Double Support Time					
Intervention	0.67 (0.8)	0.58 (0.7)	0.64 (0.9)	0.68 (0.8)	0.68 (1.1)
Control	0.43 (0.3)	0.43 (0.2)	0.55 (0.3)	0.52 (0.4)	0.6 (0.6)
Right Double Support Time					
Intervention	0.69 (0.9)	0.1 (0.7)	0.64 (0.88)	0.46 (0.33)	0.66 (1.1)
Control	0.43 (0.3)	0.43 (0.2)	0.54 (0.35)	0.52 (0.4)	0.53 (0.7)

Gait cycle	From a first contact of first foot to the next first contact of same foot –lower number indicates improvement
Single support	From the last contact of the current footfall to the first contact of the next footfall of the same foot – lower number indicates improvement (this is relative to Double support time)
Double support	From the first contact of the current footfall and the last contact of the previous footfall, added to the time elapsed between the last contact of the current footfall and the first contact of the next footfall – lower number indicates improvement (this is relative to Single support time)

Appendix 13 T25FW scores at each time point for each level of disability

Means (SD) scores for the total T25WT scores, comparing EDSS level.

Outcome Measure and time-point	EDSS	Number of subjects	Mean	Standard Deviation
T25FW				
Baseline	5	3	8.74	1.95
	5.5	2	9.09	0.66
	6	17	12.82	2.27
	6.5	10	37.3	19.84
*Week 8**	5	3	8.45	1.85
	5.5	2	10.5	2.83
	6	13	10.96	3.54
	6.5	8	25.25	12.76
Week 12	5	3	8.4	0.55
	5.5	2	9.59	1.02
	6	13	10.21	2.25
	6.5	7	24.59	20.74
Month 6	5	2	8.93	0.23
	5.5	2	10.03	1.69
	6	14	12.43	5.23
	6.5	8	32.86	28.2
*Month 12**	5	2	7.58	1.8
	5.5	2	8.73	2.12
	6	12	10.74	3.21
	6.5	5	46.73	29.9

T25FW – Timed 25ft Walk, EDSS – Expanded Disability Status Score
*missing 25FWT for 2 participants (refer to section 4.4.2)

Glossary

ABC – Activities Balance Confidence scale

BBS - Berg Balance Scale

BMI- Body Mass Index

CNS – Central Nervous System

COP - Centre of Pressure

EDSS - Expanded Disability Status Scale

EMG - Electromyogram

FAP – Functional Ambulation Profile

FITT – Frequency, intensity, type and time

FSS – Fatigue Severity Scale

HADS - Hospital Anxiety and Depression Scale

HHD – Hand -held Dynamometer

ICC – Intraclass Correlation Coefficient

ICF – International Classification of Functioning

kg – kilogram

LMSQOL – Leeds Multiple Sclerosis Quality of Life scale

LSL – Left Step Length

LST – Left Step Time

m- metre

MCN – Managed Clinical Network

MDC - minimal detectable change

MMSE –Mini Mental Status Examination

MRI – Magnetic Resonance Imaging

MS – Multiple Sclerosis

MSFC - Multiple Sclerosis Functional Composite

MVC – Maximum Voluntary Contraction

NICE - National Institute for Health and Clinical Excellence

NHS – National Health Service

OS – Overall Stability

PAR-Q – Fitness Activity Readiness Questionnaire

PF - PhoneFITT

RCT – Randomised control Trial

RSL – Right Step Length

RST – Right Step Time

s - seconds

SEM - Standard Error of Measurement

SLS – Strongest Leg Strength

TUG - Timed Up and Go

T25FW – Timed 25 Foot Walk

VEP - Visual Evoked Potential

WCa - Walking Cadence

WLS – Weakest Leg Strength

WVel – Walking Velocity

6MWT - Six-minute Walk Test

Not all abbreviations in Section 2.4 appear in this glossary, they can be found in Table 2.4.

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