Physiotherapy and exercise interventions for People with Multiple Sclerosis with minimal gait impairment

A thesis in fulfilment of the requirements for the degree of Doctor of Philosophy

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Submitted to the University of Limerick, June 2011
ABSTRACT

Title: Physiotherapy and exercise interventions for people with Multiple Sclerosis with minimal gait impairment

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Multiple Sclerosis (MS) is a demyelinating, degenerative disease of the central nervous system. It is the leading cause of disability in young adults for which there is no cure. In a disease that has no cure, minimising its impact is arguably the main goal of intervention.

The literature review demonstrated that exercise results in many important outcomes for People with MS (PwMS) with minimal gait impairment. However no community-based interventions have been evaluated.

A large (N = 372), multi-centred, block-randomised, waiting list controlled trial was conducted with the primary objective of establishing the efficacy of three community-based exercise interventions. These were Physiotherapy (PT)-led exercise, Yoga and Fitness Instructor (FI)-led exercise delivered over an hour a week for ten weeks. The second objective was to establish if there was a difference between interventions. The third objective was to investigate the results at 3-month follow-up. The final objective was to establish predictors of outcome after the intervention period. Outcomes used were the Multiple Sclerosis Impact Scale-29, v 2 (MSIS-29, v2), the Modified Fatigue Impact Scale (MFIS) and the Six Minute Walk Test (6MWT).

This study found that there was a significant improvement in the MSIS-29, v2 and the MFIS due to all interventions (p<0.05) and no change in the control. There was a significant improvement in the 6MWT due to PT-led and FI-led exercise interventions. There was no change in 6MWT in the Yoga group (p>0.05) and a trend towards worsening in the control. There were significant differences between the PT-led group and yoga (p<0.05) and FI-led exercise and yoga (p<0.05). At 3 month follow-up there was a statistically significant worsening of all of the positive findings. However outcomes remained significantly improved from baseline for the MSIS-29, v 2 (psychological component) and for the MFIS (p<0.05). Fifty-seven per cent of the variance in outcome was accounted for through five predictor variables.

This study demonstrated important outcomes for PwMS. These findings suggest that some of the needs for PwMS with minimal gait impairment can be met in community settings which may ease the burden of health service delivery. This challenges the current model of one to one physiotherapy in a medical setting. Future research should attend to developing interventions to increase long term exercise participation and explore other variables that may influence outcome.
DECLARATION

I declare that this thesis is entirely my own work and that it has not been submitted as an exercise for a degree at this or any other University.

I hereby give my permission for this thesis to be lent or copied on request, with the consent of the librarian, and with due acknowledgement of the author.

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ACKNOWLEDGEMENTS

This PhD Thesis was examined by Professor Alan Thompson and Dr Ciarán Mac Donncha. I would like to thank them both for bringing their wealth of knowledge and stimulating discussion to the Viva Voce and for taking the time and care in reading and examining this work.

This programme was made possible through 1.) Multiple Sclerosis Ireland by the financial support of Tesco Ireland, through their Charity of the Year Programme and Pobal, through administration of the Dormant accounts funding and 2.) Through The Irish Research Council for Science Engineering and Technology through the Embark postgraduate initiative.

There are many people I would like to extend my sincere thanks to:

- My supervisor Dr Susan Coote, without whose guidance “The Getting the Balance Right” project would ever have a materialised. I want to thank her for her time, encouragement and inspiration in many ways throughout the life of this project and for always pointing me in the right direction.

- My second supervisor Prof Phil Jakeman, for his fresh perspective, willingness to spend time exploring ideas, reading drafts and asking challenging questions.

- Dr Jean Saunders, director of the Statistical Consulting Unit at the University of Limerick, for her input into the statistical analysis of the data.

- Aidan Larkin (Multiple Sclerosis Ireland), who co-ordinated the “Getting the Balance Right” project and contributed to the methodology of the main trial.
• Neasa Hogan - fellow PhD candidate, who assisted with the moderating of the pilot study, who contributed to the methodology of “Getting the Balance Right” and for her help in collecting data.

• The staff of Multiple Sclerosis Ireland regional offices, who co-ordinated delivery aspects of this study locally.

• The many people with Multiple Sclerosis, who participated in the assessments and interventions during the study in this thesis.

• The fitness instructors and yoga teachers who agreed to be part of delivering this project.

• The physiotherapists who attended training days and delivered the physiotherapy intervention for this project.

• Fellow postgraduate students Neasa Hogan, Catriona O’Dwyer, Lonan Hughes, and Elaine Toomey who all enhanced the PhD experience.

• Elaine Toomey for modelling for pictures and demonstrating a perfect squat and my Dad (John Garrett) for taking pictures.

• In addition to my supervisors, all those who willingly contributed to proofreading drafts of this thesis - Dr Norelee Kennedy, Dr Amanda Clifford, Catriona O’Dwyer, Marie O’ Donnell, Anne Garrett and Albert Kehoe.

• My Head of Department, Dr Amanda Connell and all my colleagues at the University of Limerick who have been very supportive in many ways since starting my new role.

• My family, Albert and all my friends for their patience, kindness and support most especially during the last three and a half years.
Finally and most importantly, I would especially like to thank my parents, Anne and John, who have always supported and encouraged me in every way possible. I will never be able to aptly express my gratitude in words.
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CHAPTER 1: INTRODUCTION

1.0 SETTING THE SCENE

The aim of this chapter is to set the scene for the thesis. It briefly summarises the neurological condition that is Multiple Sclerosis (MS), its known pathophysiology, epidemiology, consequences and the current management of the disease. The aims and objectives of this thesis are outlined and the foundations to each chapter are laid down.

1.1 MULTIPLE SCLEROSIS

MS is a chronic neurological condition characterised by an interruption of action potentials in the brain and spinal cord due to areas of inflammation, demyelination and axonal degeneration (Compston and Coles 2008). This disease activity can lead to a countless number of impairments such as visual disturbances, sensory loss, weakness, reduced co-ordination, increased tone, bladder and bowel difficulties, cognitive and speech impairments. Most people with MS (PwMS) also complain of fatigue limitations (Debouverie 2009, Tintoré and Arrambide 2009, Forbes et al. 2006). Fatigue is poorly understood and can be very disabling even in isolation. These symptoms can come and go with relapses and recovery, relapses may stop and impairments may progress over time or they may progressively get worse from the onset depending on the type of MS. Activities such as walking and balance can be affected. Additionally, participation in social activities and work can be limited and every person with MS has individual personal and environmental factors that contribute to their experience of their health condition. The expression of the disease is unique for each patient, in terms of the pattern of impairment and disability that occurs (Langdon and Thompson 1999). There are four main types of MS: Relapsing-Remitting MS (RRMS), Secondary progressive MS (SPMS), Primary progressive MS (PPMS) and Progressive-relapsing MS (PRMS). These are described in Table 1.
TABLE 1 DESCRIPTION OF DIFFERENT TYPES OF MS (LUBLIN AND REINGOLD. 1996)

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapsing/remitting multiple sclerosis</strong></td>
</tr>
<tr>
<td>Clearly defined disease relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterized by a lack of disease progression.</td>
</tr>
<tr>
<td><strong>Secondary progressive multiple sclerosis</strong></td>
</tr>
<tr>
<td>Initial relapsing/remitting disease course followed by progression with or without occasional relapses, minor remissions or plateaus.</td>
</tr>
<tr>
<td><strong>Primary progressive multiple sclerosis</strong></td>
</tr>
<tr>
<td>Disease progression from onset with occasional plateaus and temporary minor improvements allowed.</td>
</tr>
<tr>
<td><strong>Progressive-relapsing multiple sclerosis</strong></td>
</tr>
<tr>
<td>Progressive disease from onset, with clear acute relapses, with or without full recovery.</td>
</tr>
</tbody>
</table>

The cause of MS remains unknown. However, it is thought that immune, environmental and genetic factors interact, resulting in a pathophysiology that is known to be increasingly complex. Two processes occur simultaneously: inflammation leading to demyelination and degeneration of the axon (Compston and Coles 2008).

1.2 Epidemiology

MS is the leading cause of disability in young adults. Globally, the median estimated prevalence of MS is 20 people per 100,000. Europe has the highest estimated prevalence of MS in the world at 80 per 100,000 (Dua et al. 2008). A high prevalence has been estimated at between 120.7 in the south east of the Republic of Ireland to 184.6 per 100,000 in the north west of the Republic of Ireland (McGuigan et al. 2004).
MS affects women more than men (Dua et al. 2008). In the Republic of Ireland there is an estimated female: male ratio at 1.7:1 in Wexford and 3.4:1 in Donegal (McGuigan et al. 2004). There is recent evidence of a world-wide increasing ratio estimated to be approximately 5:1 (Graziano et al. 2010). The average age at onset is 33 (Dua et al. 2008).

1.3 CONSEQUENCES OF MS

There are many consequences of MS including a negative physiological profile, reduced physical components of Quality of Life (QoL) and a large cost of the disease. These have substantial implications both for the PwMS and for the health service that provides their care.

The negative physiological profile of people with MS has been summarised as an increased risk of cardiovascular disease, increased depression and fatigue, decreased bone mineral density, VO\textsubscript{2} max and muscle strength (Dalgas et al. 2008) – all of which are associated with inactivity.

MS can dramatically affect the Health Related Quality of Life (HRQoL) of people for many years without causing death. The literature consistently demonstrates that PwMS have lower physical components of QoL than healthy people and people with other chronic conditions (Rudick and Miller 2008, Trisolini et al. 2010, Riazi et al. 2003a). The impact on physical components of QoL is more affected than psychological, social or mental components ((Riazi et al. 2003a, Turpin et al. 2010). Benito-Leon et al (2003) discuss the many features that may contribute to low QoL in PwMS. Firstly, MS affects physiological functioning in a diverse number of areas. Secondly, the disease is diagnosed primarily in young adults, which maximally influences productivity and personal development.
Thirdly MS has an unpredictable course and there is at present no possibility of cure. Finally, there are problems accessing health care (Benito-León et al. 2003).

The Multiple Sclerosis International Federation conducted a review of the literature to evaluate the global economic impact of MS (Trisolini et al. 2010). They found that the total costs of MS vary substantially in all countries with an estimated mean (weighted by prevalence of MS) cost of $13,198 (2007 International Dollars) per person per annum for total direct medical costs, $11,383 for total direct non-medical costs and $16,755 for total indirect cost.

1.4 MANAGEMENT OF MS

As there is currently no cure for MS, current management of MS is aimed at reducing relapse rates, preventing disability directly due to relapse, providing management of fixed neurological deficits, preventing disability acquired through progression and treating established progression (Compston and Coles 2002). Thus, it is important to find an intervention that optimally addresses change at many levels.

Exercise is one strategy that can ameliorate the condition at the levels of “Body structure and function”, “Activity” and “Participation”. Previously exercise was thought to be harmful for PwMS, due to the temporary worsening of symptoms observed by a German Neurologist, Wilhelm Uhtoff late in the 19th century (Uhtoff’s phenomenon) (Stutzer and Kesselring 2008). However, early indications in the 1980s and 90s suggested that exercise was well tolerated in PwMS and did not exacerbate the disease (Gehlsen, 1984).

Today, exercise is being increasingly acknowledged as important in the management of the aforementioned consequences of MS. Exercise is a multi-faceted intervention
that may address many issues including reduced brain volume, grey matter degeneration, inflammation by promoting inflammatory regulation, neural protection, neural repair and plasticity (Prakash et al. 2007, Prakash et al. 2010, White and Castellano 2008b, White and Castellano 2008a, Schulz et al. 2004, Golzari et al. 2010).

Exercise can be used to address the negative physiological profile associated with MS and contributing to minimising cardiovascular co-morbidities associated with a sedentary lifestyle (Dalgas et al. 2008). Additionally, it has been shown that PwMS use more energy for ADLs than healthy controls (O'Dwyer and Coote 2010) thus it could be argued that PwMS need to be fitter to cope with the demands of daily life.

With the advent of primary care and its emphasis on prevention and rehabilitation, exercise is an appropriate multi-dimensional intervention that should be considered as a primary intervention strategy for PwMS in minimising the impact of the disease. However, no study to date has looked at exercise in the community context.

1.5 The background to this thesis

This work took place in the context of the “Getting the Balance Right” project. This was a nationwide programme for the delivery of physiotherapy and exercise-based interventions for PwMS in the community. It resulted from collaboration between the Department of Physiotherapy at the University of Limerick and Multiple Sclerosis Ireland.

Multiple Sclerosis Ireland (MSI) received funding from Tesco Ireland as part of their Charity of the Year programme in 2008. The Tesco funding was augmented by the Pobal Dormant Accounts fund giving a total of €1.6 million for the project.
Previous market research by MSI identified that people with MS wanted physiotherapy. Subsequently, MSI set about delivering physiotherapy and exercise interventions for PwMS. Thus the collaboration with the Department of Physiotherapy at the University of Limerick began. The question MSI posed was “What physiotherapy and exercise programmes should be provided for PwMS”.

The programme was stratified into three strands, Strand A which concerns PwMS who use at most one stick to walk outdoors, Strand B which concerns those who use bilateral aid to mobilise or may use a wheelchair for longer distances and Strand C, a pilot study concerning those who are non-ambulatory. This thesis concerns the development and evaluation of the Strand A component – those with minimal gait impairment who use at most one stick to walk outdoors.

1.6 AIM OF THIS THESIS

The overarching aim of this thesis was to inform MSI regarding the community-based exercise programme(s) that should be provided for PwMS with minimal gait impairment.

1.7 THE MAIN OBJECTIVES

The main objectives of this thesis were as follows:

- To review the current literature regarding exercise for PwMS with minimal gait impairment and factors that might influence outcome in response to exercise-based interventions.
- To describe the methodology for a multi-centred, community-based, block-randomised, controlled, single blind trial evaluating and comparing an
Aerobic Training and Progressive Resistance Exercise intervention led by a Physiotherapist, Yoga and a Fitness-Instructor led class.

- To establish the efficacy of the three community-based exercise interventions
- To establish if there was a difference between groups due to intervention
- To investigate the results three months after the intervention
- To investigate the predictors of outcome after the intervention period

1.8 Thesis Summary

Chapter 2 reviews the current literature regarding exercise for PwMS with minimal gait impairment. Outcomes were largely positive for Aerobic Training (AT), Progressive Resistance Exercise (PRE), “Combined” (AT+PRE) exercise and Yoga. However, there was a moderate to high risk of bias for most studies to date. Outcomes were largely variable, a finding that other reviews of the literature has not addressed, indicating that outcomes are not equal for all participants. Additionally participants have been described superficially in terms of their clinical characteristics to date; this limits the extent to which findings can be applied to other settings (generalisability) and makes sub-group analysis impossible. Long term follow-up has been conducted in only three small studies to date.

Chapter 3 further examines the literature for variables that may influence the response to intervention (particularly exercise) in PwMS. To date no known study has explored such factors when evaluating the effects of exercise.

A pilot study and a main study were conducted. Chapter 4 describes the aspects of the methodology that are common to both the pilot study and the main study methodology which includes the participant selection criteria and the outcome measure. The pilot study which informed the main study methodology is described in Chapter 5. The main study methodology is described in Chapter 6.
Chapters 7 to 10 focus on the results of this study. Chapter 7 describes the main study results addressing the first two objectives of the present study regarding the efficacy of the interventions and the differences between groups. Chapter 8 describes the follow-up results for the three community-based exercise interventions. Chapter 9 describes a post-hoc exploration of data to describe the participant characteristics that predict outcome after the intervention period. Chapter 10 summarises all of these results.

Chapter 11 discusses this novel work in the context of the literature to date and what it means for research, practice and health service delivery. The conclusions and recommendations from this research are revealed in Chapter 12. Chapter 13 describes the publications arising from this work and the publication plan.

The study in this thesis is novel in many ways. It is the largest trial evaluating exercise interventions in PwMS to date. It is the first study to address community-based exercise interventions. As modern health services move towards a community-based delivery of interventions, this is a timely piece of work to inform health service delivery. It is the first study to evaluate a “Combined” (AT+PRE) exercise programme while minimising selection and detection bias. It is the first known study to use the psychometrically sound Multiple Sclerosis Impact Scale-29, version 2 (Hobart and Cano 2009). Furthermore, this study adds to the literature regarding follow-up of interventions. This is crucial in the management of any chronic disease. Finally, the research in this thesis addresses the heterogeneous presentation of PwMS in the interpretation of the findings and identifies the participant characteristics that best predict outcome after the intervention period.

This work has informed Health Service delivery nationally and recognised internationally. At the closing remarks of “European Committee for Treatment and Research in Multiple Sclerosis”, this study was acknowledged as “Methodologically sound from which real conclusions can be drawn” (Cohen 2010).
CHAPTER 2: EXERCISE FOR PEOPLE WITH MULTIPLE SCLEROSIS WITH MINIMAL GAIT IMPAIRMENT – A REVIEW OF THE LITERATURE

2.0 INTRODUCTION

In recent years the positive role of exercise has been acknowledged in people with mild to moderate Multiple Sclerosis (MS). However, some current research evaluates exercise interventions for PwMS of many levels of walking ability together, making it difficult to inform clinical practice. Individuals who walk with bilateral assistance are included in the same interventions as individuals who ambulate independently and have no gait abnormalities even though there is a marked difference in their salient presentation. The aim of this thesis is to inform the delivery of community-based exercise interventions for PwMS with minimal gait impairment to lead to more targeted effective interventions for PwMS. Thus, this review will focus on studies evaluating exercise interventions with participants with an Expanded disability Status Scale (EDSS:scale range 0 – 10, higher score indicates more disability) of up to 6.0. Having an EDSS of 6.0 indicates that a person with MS uses intermittent or constant unilateral assistance (cane/ crutch/brace).

This review is novel in that outcomes are carefully evaluated in terms of body function and structure, activities and participation following the WHO-ICF framework. Additionally, the parameters used in the studies are described using the FITT principle (Frequency, Intensity, Type and Time). All exercise interventions are considered including Aerobic Training (AT), Progressive Resistance Exercise (PRE), combined exercise (AT+PRE), yoga comparative studies and “other interventions”. Quality is evaluated using the Cochrane tool for evaluating bias.
2.1 METHODOLOGY

2.1.0 INTRODUCTION

The paragraphs in this section describe the search strategy, selection criteria and quality assessment that were used in this review of the literature.

2.1.1 SEARCH STRATEGY

Trials published in English were retrieved from electronic sources of MEDLINE, CINAHL, EMBASE, AMED and the Cochrane Collaboration. The search words used were “Multiple Sclerosis” or “MS” and “exercise” and related words aerobic, strength*, progressive resistance exercise*, sport*, fitness, physical*, physiotherapy, PT, rehab* Reference lists of reviews and potentially relevant studies were hand searched. Potential studies that were returned were assessed against the selection criteria.

2.1.2 INCLUSION CRITERIA

- Trials that have included only people with an EDSS of less than or equal to 6
- Quantitative studies

2.1.3 EXCLUSION CRITERIA

- Studies in languages other than English
- Unpublished studies
- Studies that have only looked at the acute response to exercise
- Animal studies
2.1.4 Quality Assessment

Trials were not excluded based on an evaluation of their quality. There is no valid cut-off point in any scale or checklist to determine whether a study is of “good” or “bad” quality, thus it is difficult to justify exclusion of particular studies based on quality, as other studies have done such as the Cochrane review by Rietberg et al 2004 (Rietberg et al. 2004). Including all studies has the potential to address some gaps in knowledge such as identifying effective components of interventions and components of feasible protocols that can be brought forward into a definitive RCT. Thus, this review systematically reports the findings and risk of bias of all available studies matching the selection criteria.

There are four criteria of systematic errors in trials evaluating the effects of healthcare (Higgins and Green 2009) – selection bias, detection bias, performance bias and attrition bias. Selection bias refers to the concealment of treatment allocation and sequence generation. Detection bias refers to blinding of outcome assessors. It is not possible to blind participants or deliverers of the interventions in exercise interventions. Thus in this context, it is the blinding of the outcome assessor that is considered. Performance bias refers to the equal treatment of groups apart from the treatment being evaluated. Attrition bias refers to adequate reporting of losses of participants. These biases are serious threats to the validity of studies. The approach in this review involves rating these four criteria as “met”, “partly met”, “unmet” or “unclear”. When all of the criteria are met, there is a low risk of bias that is unlikely to alter the results. When one or more of the criteria are partly met there is a moderate risk of bias and there is some doubt about the results. Finally when one or more criteria are not met then there is a high risk of bias that seriously weakens confidence in the results (Higgins and Green 2009). Using this method it allows all trials to be included and the reviewer to make a judgement on the strength of all available studies, rather than only including a selected number of trials based on their scores on rating scales. This approach is advocated by the Cochrane Reviewer’s Handbook (Higgins and Green 2009).
2.2 RESULTS

2.2.0 INTRODUCTION

Thirty-two studies matching the selection criteria were identified. These are described in detail in terms of exercise parameters, outcome measures and results in Table 2 to Table 11. Results in the tables are described in terms of means ± SD (standard deviation) unless otherwise stated. Studies were categorised into one of five categories based on the type of exercise used. These are Aerobic Training (AT), Progressive Resistance Exercise (PRE), Combined Exercise (AT and PRE combined), Yoga and “Other” Interventions (core stability training). For each category the participants are described and the outcomes of each of these groups are divided into three different sections based on the World Health Organisation’s International Classification of Functioning (WHO-ICF 2001) i.e. Body Structure and Function, Activity and Participation. For each mode of exercise there is a comment on the quality of the trials and a summary of parameters used i.e. the Frequency, Intensity, Type and Duration. Not all studies described estimates of variability within the results and there are differences in the index used (e.g. standard deviations, standard error of the mean, interquartile ranges, 95% confidence intervals), thus for ease of comparison between studies, mean % changes are used to explore the results.

2.2.1 AEROBIC TRAINING

Thirteen studies evaluating aerobic training (AT) in PwMS with a maximum EDSS score of 6 were identified. These are summarised in Table 2. Overall results suggest a positive effect on outcomes with no increase in relapse rate due to the interventions. Large variability is seen in most outcomes as indicated by large standard deviations, ranges or interquartile ranges and wide confidence intervals that cross zero indicating that not all participants benefit equally from intervention and that those participants start at different baseline points. Studies were small with a mean number of 12 participants (range 2 – 20) in the exercise groups.
**Participant characteristics**

In all thirteen studies, most participants were women (at least 3:1) and were aged between 25 and 65 years. PwMS were excluded if they had significant co-morbidities that limited the ability to participate in exercise such as lower limb osteoarthritis or cardiac disease. Participants were also excluded if they had an exacerbation in the last one to three months or had steroid therapy in the last one or two months. Frequent participant characteristics reported were age, height, type of MS, disease duration, EDSS score and use of an aid. In one study (Pariser et al. 2006) evaluating aquatic exercise in two people with MS, participants were described more fully in terms of their most disabling symptoms, medications, sensory, visual and motor function and participation level.

**Effect on Body Structure and Function**

At the level of body structure and function, studies of aerobic exercise have evaluated its effect on fitness, strength, cytokines and Brain Derived Neurotrophic Factor (BDNF) and spasticity.

The cumulative evidence suggests that AT improves fitness. In three trials, maximal oxygen consumption (VO$_2$ max) improved between 10 and 21% which was statistically significant (p<0.05) in two of the three trials when participants trained for 30 minutes 2-3 times a week (Petajan et al. 1996, Castellano and White 2008, Newman et al. 2007) In one trial there was a reduction in VO$_2$ max (Newman et al. 2007). However, the associated workload with the graded exercise test was not reported and the intervention was 4 weeks in duration. The interventions in which there were consistent and similar improvements were at least 8 weeks. This may contribute to explaining this unexpected result. Aquatics exercise improved VO$_2$ max
in two (out of two) participants (Pariser et al. 2006). Additionally, training with both treadmills and cycle ergometers yielded positive results on VO$_{2\text{max}}$.

Preliminary studies have evaluated the effect of exercise on neurotrophic factors and immune endocrine parameters (Castellano and White 2008, Schulz et al. 2004). The results of these can be seen in Table 2. BDNF is a protein responsible for enhancing neuroprotection, neurogenesis and neuroregeneration, thus it may influence disease progression and symptomology (Castellano et al. 2008). Additionally, it is postulated that some immune endocrine parameters (IL-6R and sIL-6R) regulate inflammation and have neurotrophic potential. These studies provide a rationale that AT may potentially modify disease activity in MS. However, no conclusions can yet be drawn on the effect of exercise on these proteins or their neuroprotective roles in people with MS. Of note, large variability can be seen in pre and post intervention scores.

One study found no significant change in “spasticity” as measured by the Modified Ashworth Scale (Sosnoff et al. 2009). These participants had low stiffness scores at baseline (1.9±0.3).

**Effect on Activity**

At the level of activity, studies of AT have evaluated its effect on walking speed, walking distance, maximal walking distance and gait parameters.

Cumulatively, the results suggest that AT results in small (6-17%) improvements walking speed and distance which were statistically significant using the 10-m walk test, Two Minute Walk Test (2MWT), and Six Minute Walk Test (6MWT), (Rampello et al. 2007, Kileff and Ashburn 2005, Van den Berg et al. 2006). Maximal
walking distance was extended by 650m ± 474m in a treadmill training group compared to 96±70 in a control group (Dettmers et al. 2009). Gait parameters (duty factor and stride length) improved significantly in the only study that evaluated them (Newman et al. 2007). Large variability can be seen around all point estimates in all walking outcomes in Table 2.

**Effect on Participation**

At the level of participation, studies of AT have evaluated outcomes of fatigue and health-related quality of life (HRQoL).

The effect on fatigue seems to vary between a small (8%), trend for improvement, which did not reach significance (Newman et al. 2007, Schulz et al. 2004, Van den Berg et al. 2006) and a larger (15%), statistically significant improvement on fatigue (McCullagh et al. 2008, Kileff and Ashburn 2005). The studies that showed small, non-significant effects had low mean fatigue scores at baseline: mean MFIS = 23.0 (Schulz et al. 2004) or used the FSS to evaluate outcome (Van den Berg et al. 2006, Newman et al. 2007). This might suggest that the MFIS is more sensitive to change following an intervention, when there is a change to be achieved. There appears to be no relationship between exercise parameters and a change in fatigue (i.e. no dose-response). The cumulative evidence of this review suggests that AT improves fatigue and no harmful effects were noted. In the only study that examined follow-up to an AT intervention, improvement remained significantly better than baseline three months after a 12 week intervention. However, there was a reduction in the magnitude of improvement (McCullagh et al. 2008).

AT consistently improved Quality of Life (QoL). Mean improvements of approximately 10% were found when measured by the Multiple Sclerosis Quality of Life-54 (MSQoL-54) and the Hamburg QoL Questionnaire for MS (Rampello et al.
There were improvements of at least a small effect (ES = 0.15) for pain, sexual functions and energy subscales of the MSQoL (Sutherland and Andersen 2001). A trend towards improvement was seen using the Multiple Sclerosis Impact Scale-29. The MSIS-29 was not separated into its physical and psychological components which may explain why the improvement seen did not reach statistical significance.

**Differences between groups**

In trials where there was a control group (n = 8/13), 6/8 trials compared the differences between group (Sutherland et al. 2001, Schulz et al. 2004, Van den Berg et al. 2006, Rampello et al. 2007, McCullagh et al. 2008, Sosnoff et al. 2009, Dettmers et al. 2009) There were significant differences between exercise groups and a control group in at least one outcome. These include the MSQoL and the Profile of Mood States (POMS) (Sutherland et al. 2001), Hamburg Quality of Life Questionnaire in MS (HAQUAMS) (Schulz et al. 2004), the 10-m walk (Van den Berg et al. 2006), VO\textsubscript{2} max, work load measured in Watts, and in the Functional Assessment of MS (FAMS) and Modified Fatigue Impact Scale (MFIS) (McCullagh et al. 2008). Lack of statistical power, large variability, lack of a control group and not testing the difference between groups may explain that out of all the outcomes listed in Table 2 only 8 outcomes were statistically different from a control group.
<table>
<thead>
<tr>
<th>Author, year Design</th>
<th>Intervention - Frequency, Intensity, Type Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gehlsen et al. 1984</td>
<td>F: 3/ week I: 60 – 75% MHR T: Aquatic exercise T: 60 minutes Duration: 10 weeks</td>
<td>Force Work Muscular fatigue Torque</td>
<td>Force (N) 129 ±57.9 to 148.5±57.6 to 189.5±65.3* Work (Nm) 89.3 ±43.3 to 105±8.8* midtrial to 126.3±46.3* Muscular fatigue (% of decline in peak torque) was 55.15% ±11.0 to 42.3 ±12.6 to 41.01 ±15) Torque (Nm) values at predetermined angular velocities increased from pretrial to mid trial. Values reduced in magnitude from mid trial to post trial * for extension</td>
</tr>
<tr>
<td>Petajan et al. 1999</td>
<td>F: 3 / week I: 60% VO₂ max T: combined arm and leg ergometers T:30 minutes</td>
<td>EDSS and ISS No. of exacerbations GXT (VO₂ max) Maximum voluntary isometric contractions Skinfold thickness Blood lipid profile SIP FSS – Raw scores not reported</td>
<td>EDSS EG: 3.8±0.3 to 3.7±0.3, CG: 2.9±0.3 to 2.8±0.3. ISS EG: 9.0±0.9 to 6.8±1.1, CG: 8.1±0.9 to 8.3±0.9. Exacerbations EG: 4/21 CG: 3/25. VO₂ max (ml.kg/min) EG 24.2±1.4 to 29.4±1.3* CG 26.0±1.3 to 26.4±1.4 UL Strength (N) EG: 1309±68 to 1532±92, CG: 1562±88 to 1532±92* LL Strength (N) EG: 1309±136 to 2362±140, CG: 2644±169 to 2716±167*. Skinfold thickness (mm) EG: 70mm± to 64±4*, CG: 79±6 to 81±7 Serum triglyceride (mg/dl) EG: 114mg/dl±11 to 95±9*, CG: 116±7 to 115±9. SIP EG: 94.4±29.6 to 68.5±24.7* at week 10 (55.5±24.0), CG: 65.9 to 65.7±18.1 POMS (fatigue) reduced from 48.7±2.0 to 46.0±2.1 * at week 10 (44.4±1.8). All other subscales reduced in magnitude, * for depression and anger at week 5 and 10. Mean scores for CG did not change or increased NS</td>
</tr>
</tbody>
</table>

All values in table 2a presented as mean ±SD, EG = Exercise Group, CG = Control group, MHR = Maximal Heart Rate, minutes = minutes, EDSS = Expanded Disability Status Scale, GXT = Graded Exercise Test, VO₂ max = Maximal oxygen uptake, UL = Upper Limb, LL = Lower Limb, SIP = Sickness Impact Profile, POMS = Profile of Mood States, Nm = Nanometers, N = Neutons, mg/dL Milligrams per Deciliter, mm = millimetres, * = statistically significant p <0.05, NS = Not statistically significant
<table>
<thead>
<tr>
<th>Author. year Design n = number of participants</th>
<th>Intervention - Frequency, Intensity, Type Time (FITT)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sutherland et al (2001) RCT EG (n = 11) CG (n = 11)</td>
<td>F: 3/ week I: unknown T: water aerobics (jogging and deep water running) T: 45 minutes Duration: 10 weeks</td>
<td>MSQoL-54 POMS MSPSS Bicycle ergometer exercise test</td>
<td>MSQoL EG: 9/11 MSQoL subscales improved (at least a medium effect (ES 0.15, p-values &lt;0.09). Largest ES was for pain (0.29)* and sexual functions subscale (0.21)* and energy (ES 0.51)* POMS all aspects better than control except confusion with ES &gt;0.15 in favour of the exercise group. Vigor ES 0.55* MSPSS EG 59.3 ±18.9 to 63±14.2. CG 61.6±17.8 to 60.6±15.8. Time to voluntary termination of cycling EG: 5.2±1.4 to 6.0±2.0. Not measured in CG</td>
</tr>
<tr>
<td>Schulz et al (2004) RCT EG (n = 15) CG (n = 10)</td>
<td>F: 2 / week, I: 60% VO₂ max, T: Bicycle Ergometers, T: 30 minutes, Duration: 8 weeks</td>
<td>GXT (Max performance, VO₂ max) IL – 6, sIL – 6R BDNF NGF HAQUAMS MFIS Coordinative function – walking test and figure of 8 (1=not able, 4=completely accurate) and KAT2000 SF-36: result not reported Self-efficacy: result not reported POMS: result not reported</td>
<td>GXT (W) EG: 176.0±47.4 to 187.4±51.9 / CG: 161.5±33.6 to 174.7±36.8. (VO₂ max ml/kg/min⁻¹) EG: 33.1±7.1 to 36.5±7.6 / CG: 28.9±7.8 to 31.3±6.9 IL-6 (pg/ml) EG:1.9±2.1 to 1.6±2.5 / CG:1.3±0.7 to 1.9±2.0 sIL-6R (ng/ml) EG:32.9±8.3 to 36.9±10.7 / CG :36.7±8.8 to 37.0±12.1. BDNF (pg/ml) EG: 4353±3217 to 5930±5178 / CG: 5081±2312 to 4200±2073. NGF (pg/ml) EG:31.6±22.3 to 25.6±26.0 / CG:18.6±6.4 to 16.0±6.0, p = 0.09 HAQUAMS EG:1.8±0.4 to 1.6±0.3 / CG:1.9±0.5 to 2.0±0.5* MFIS (0-84) EG:23.0±15.4 to 21.1±15.0 / CG:37.0±15.7 to 30.3±13.3 Coordinative function displayed graphically. Figure 8 score* mean difference between groups&lt;1. KAT mean difference between groups post intervention approx. 100*. Mean difference in walking at both time points &lt;0.5. Large variability in for all point estimates pre and post intervention.</td>
</tr>
</tbody>
</table>

EG = Exercise Group CG = Control Group, RCT = Randomised Controlled Trial, MSQoL-54 = Multiple Sclerosis Quality of Life-54, POMS = Profile of Mood States, MSPSS = Multiple Sclerosis Perceived Social Support, GXT = Graded Exercise Test, IL – 6 = Interleukin-6, sIL – 6R = soluble Interleukin-6 receptor, BDNF = Brain Derived Neurotrophic Factor, NGF = Nerve Growth Factor, HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis, SF-36 = Short Form-36, ES = Effect Size, p = probability. *statistically significant
<table>
<thead>
<tr>
<th>Author, year Design</th>
<th>Intervention - Frequency, Intensity, Type Time (FITT)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Kileff and Ashburn (2005) Pre/Post intervention study Exercise group (n = 8)</td>
<td>F: 2 / week I: MHR – RHR T: Bicycle Ergometers T: 30 minutes Duration: 12 weeks</td>
<td>FR 10-m walk (steps / s) 6MWT FSS GNDS The Gulick Scale MAS: result not reported</td>
<td>FR (L) 25.1cm±4.0 to 26.7±4.4 2 (R) 27.1cm±3.6 to 28.4±3.65 10-m walk 19.3steps±2.4 to 17.4±3.6, p=0.07 / 12.4±2.6 to 12.9±2.8 6MWT 204.2m±84.4 to 236±99.3 9 FSS 50.3±6.4 to 40.6±8.92, p = 0.06 The Gulick 298.7±27.5 to 290.4±36.1, p = 0.08 GNDS 16.0±5.7 to 9.9±6.4*</td>
</tr>
<tr>
<td>Van den Berg (2006) RCT crossover EG (n = 10) DG (n = 9) Tested at baseline (week2), post (week 7) and follow-up (week 12)</td>
<td>F: 3 / week I: 60% APHRM T: Treadmill training T: 30 minutes Duration: 4 weeks</td>
<td>10-m walk 2MWT FSS RMI - result not reported GNDS</td>
<td>10-m walk EG: baseline 17.8±5.4 Δ -3.1±2.5* Score at week 12: 17.2±6.2. DG: 14.0 ±5.5 Δ -0.6 ±1.4. Score at week 12: 13.1 ±6.5 2MWT timed walk EG: baseline 71.0±22.8* Δ 10.8±6.7* Score at week 12: 74.5±33.9. DG: 99.5±30.0 Δ 5.8±7.8*. Score at week 12: 106.8 ±36.7 FSS timed walk EG: baseline 30.6±9.2 Δ -4.5±7.7. Score at week 12: 26.1±14.1. DG: 32.1±9.1 Δ -4.4±7.8. Score at week 12: 26.1±14.1. GNDS timed walk EG: baseline 12.1±3.8 Δ 0.75±1.8. Score at week 8: 11.8±5.9. DG: 12.9±4.9 Δ 0.13±2.0. Score at week 8: 9.0±4.1</td>
</tr>
<tr>
<td>Pariser et al (2006) Case studies (pre and post intervention) EG (n = 2)</td>
<td>F: 2 / week I: Unknown T: Aqua-aerobics T: 1 hour Duration: 8 weeks</td>
<td>GXT Lactate threshold FSS</td>
<td>VO2 max Participant A: 23.4 ml/kg/min to 26.10 (but reached higher workload on GXT from 80W to 100W). Participant B: 17.6ml/kg/min to 20.6 (GXT from 60W to 80W) Lactate threshold Participant A: 3.34 METS to 4.5. Participant B: 2.09 METS to 3.18 FSS Participant A: 5.4 to 3.6. Participant B: 5.6 to 5.6</td>
</tr>
</tbody>
</table>

RCT = Randomised Controlled Trial, EG = Exercise Group, CG = Control Group, DG = Delayed Group, APHRM = Age Predicted Heart Rate Max, FR = Functional Reach, m = metre, s = seconds, 6MWT = Six Minute Walk Test, FSS = Fatigue Severity Scale, GNDS = Guys Neurological Disability Scale, MAS = Modified Ashworth Scale, GXT = Graded Exercise Test
<table>
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</thead>
<tbody>
<tr>
<td>Newman et al (2007) Pre/Post intervention study EG (n = 16)</td>
<td>F: 3 / week I: 55 - 85% APHRM T: Treadmill training T: 30 minutes Duration 4 weeks</td>
<td>VO₂ max Gait rite mat 10-m walk 2WT distance FSS</td>
<td>VO₂ max (mL/kg per minute) at rest from 2.10 ± 0.58 to 1.54 ± 0.85* and while walking from 6.30 ± 2.01 to 4.97 ±2.17* Stride length (cm) on strong side from 98.7±21 to 104.0±21 <em>, Stride length on weak side from 98.6±21.9 to 103.2±21.5 10-m (s) 15.6 ±5.6 to 13.9s ±5.3</em> 2MWT (m) 88.2 ±32.2 to 94.3±32.2* Median FSS 30 (IQR 22, 37) to 27.5 (12, 32)</td>
</tr>
<tr>
<td>Rampello et al (2007) RCT crossover EG (n = 13) NR (n = 16)</td>
<td>F: 3 / week I: 60% VO₂ max T: Bicycle ergometers T: 30 minutes &amp; 15 minutes stretches Duration – 8 weeks</td>
<td>Lung function tests (FEV₁/VC) 6 MWT MFIS MSQoL – 54</td>
<td>FEV₁/VC EG: 84±6 to 83±8, NR from 82±8 to 84±7 6MWT (m) EG: 308±98 to 332±108*, NR from 298±114 to 308±110 MFIS EG: 36 (range 3, 57) to 29 (4, 56), NR from 30 (6, 53) to 26 (3, 67) MSQoL-54 (PCS) EG: baseline median 60 (IQR 10, 86) to 66 (24, 90). NR: 63 (18, 85) to 66 (32, 87)*</td>
</tr>
<tr>
<td>Castellano and White (2008) Experimental study Group with MS (n = 11) Healthy group (n =11) tested pre (week 1), mid (week 4) and post (week 8) intervention</td>
<td>F: 3 / week I: 60% VO₂ max T: Bicycle ergometry T: 30 minutes Duration – 8 weeks</td>
<td>VO₂ max Serum BDNF IGF – 1</td>
<td>VO₂ max ↑10% in MS group and 14% in Healthy CG* Resting BDNF (pg/mL) elevated in PwMS weeks 0-4 but not in the CG. They started significantly lower than the CG (by approx. 10,000), p&lt;0.05*. BDNF post exercise disappeared faster in MS patients at week 4 (86%) than week 8 (59%)*. CG was 73% throughout. Resting IGF-1 (ng/mL) MS: 191±19 pres intervention did not change significantly at 4 weeks (206±154) or post intervention (161±199). The response was similar in both groups</td>
</tr>
</tbody>
</table>

EG = Exercise Group, CG = Control Group, VO₂ max = Maximal oxygen uptake, 2MWT = 2 Minute Walk Test, FSS = Fatigue Severity Scale, FEV₁/VC = Forced Expired Volume in 1 second/Vital Capacity, 6 MWT = Six Minute Walk Test, MFIS = Modified Fatigue Impact Scale, MSQoL – 54 = Multiple Sclerosis Quality of Life, BDNF = Brain Derived Neurotrophic Factor, IGF-1 = Insulin-like Growth Factor, pg/mL = pictograms per millilitre, ng/mL = nanograms per millilitre
TABLE 2 CONTINUED

<table>
<thead>
<tr>
<th>Author, year Design n = number of participants</th>
<th>Intervention - Frequency, Intensity, Type Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCullagh et al (2008) RCT EG (n = 12) CG (n = 11) tested at baseline, post intervention (3/12) and follow-up (6/12)</td>
<td>F: 3 / week I: RPE 11 – 13 T: Circuit class x 2, HEP x 1 T: 60 minutes Duration – 12 weeks</td>
<td>FAMS MSIS-29 MFIS GXT</td>
<td>FAMS EG: median 169 (IQR150, 200) Δ₁ 23 (9.5, 42.5) at 3/12, Δ₁9 (4, 31) at 6/12. CG median 191 (IQR170.5, 208) Δ² -3.5 (-16, 5) at 3/12 Δ-4.5 (-25, 8) at 6/12. P&lt;0.05* MSIS-29 EG: 43 (IQR40, 61) median Δ₁ -6.5 (10, 1) at 3/12, Δ-6 (-9, 0.5) at 6/12. CG median 44.5 (IQR38.5, 57) Δ² -1 (-4.5, 4.5) at 3/12 Δ 0 (-1, 1) at 6/12 MFIS EG: median 26. (IQR17, 40.5) Δ₁ -13 (-20.5, -3) at 3/12, Δ² -8.5 (-19.5, -1). CG median 26.5 (IQR21.5, 33.5) Δ² 1(-4, 4.5) at 3/12 Δ 0.5 (-2.5, 6.5) at) at 6/12. P&lt;0.05* Values for workload (W) not presented for 3/12 or 6/12</td>
</tr>
<tr>
<td>Sosnoff et al (2009) Pilot – comparative study EG (n = 12) CG (n = 10)</td>
<td>F: 3 / week I: Unloaded T: Bicycle ergometers T: 30 minutes Duration – 4 weeks</td>
<td>H/M Ratio MAS MSSS-88</td>
<td>Magnitude displayed graphically Significant reduction in H/M Ratio in the CG immediately after intervention period. Significant reduction in EG 4 weeks after the exercise intervention period. No mean change &gt; 0.1 observed in this outcome* No significant change in the MAS. (No mean change &gt;0.5 observed on the scale) Significant reduction in MSSS-88 in exercise condition which persisted for 4 weeks*. No mean change &gt;1 on the scale</td>
</tr>
</tbody>
</table>

FAMS = Functional Assessment in Multiple Sclerosis, MSIS-29 = Multiple Sclerosis Impact Scale, MFIS = Modified Fatigue Impact Scale, GXT = Graded Exercise Test, MAS = Modified Fatigue Impact Scale, MSSS-88 = Multiple Sclerosis Spasticity Scale, RPE = Rate of Perceived Exertion
TABLE 2 CONTINUED

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<thead>
<tr>
<th>Author, year (design)</th>
<th>Intervention Frequency, Intensity, Type Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
</table>
| Dettmers et al (2009) | EG n = 15  
               CG n = 15  
 F: 3 / week  
 I: unknown  
 T: Treadmill walking with intermittent games that included walking games  
 T: 45 minutes  
 Duration – 3 weeks | Maximal walking distance (treadmill)  
 Walking speed  
 MFIS  
 FSMC  
 BDI  
 HAQUAMS | Maximal walking distance increased 650m±474m in the EG compared with 96 ± 70m in the CG. P<0.01  
 EG improved 66%  
 improved  
 CG improved 12%. P<0.01 |

<table>
<thead>
<tr>
<th>Measure</th>
<th>EG</th>
<th>CG</th>
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<tbody>
<tr>
<td>MFIS</td>
<td></td>
<td></td>
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<tr>
<td>Improvement</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Worsening</td>
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<td>1</td>
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<tr>
<td>Motor MFIS</td>
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<tr>
<td>Improvement</td>
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<td>9</td>
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<tr>
<td>Worsening</td>
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<td>1</td>
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<tr>
<td>BDI</td>
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</tr>
<tr>
<td>Worsening</td>
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<td>3</td>
</tr>
</tbody>
</table>

CG = Control Group, EG = Exercise Group, MAS = Modified Ashworth Scale, MSSS-88 = Multiple Sclerosis Spasticity Scale, MFIS = Modified Fatigue Impact Scale, FSMC = Fatigue Scale for Motor and Cognition, BDI = Beck Depression Inventory, HAQUAMS = Hamburg Quality of Life Questionnaire in Multiple Sclerosis
Quality of studies

The methodological quality of the trials is shown in Table 3. Studies evaluating AT have a high risk of bias. No study met the criterion for detection bias. Three out of the nine studies met the criterion for selection bias. Three studies missed out on being categorised as a “low” risk of bias due to not having a blind outcome assessor (McCullagh et al. 2008, Van den Berg et al. 2006, Rampello et al. 2007).

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection bias</th>
<th>Detection bias</th>
<th>Performance bias</th>
<th>Attrition bias</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sutherland et al (2001)</td>
<td>Unclear</td>
<td>Not met</td>
<td>Unclear</td>
<td>Met</td>
<td>High</td>
</tr>
<tr>
<td>Kileff and Ashburn (2005)</td>
<td>Not met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>High</td>
</tr>
<tr>
<td>Castellano and White (2008)</td>
<td>Not met</td>
<td>Not met</td>
<td>Met</td>
<td>Met</td>
<td>High</td>
</tr>
</tbody>
</table>
Intervention parameters

Table 2 demonstrates that all AT trials use an intensity ranging from 55-85% Heart Rate Max (HRM) for 30 to 60 minutes, two to three times a week using aquatic exercise, cycle ergometers or treadmill training. Age Predicted Heart Rate Max (APHRM) was used to calculate intensity in two studies (Newman et al. 2007, Van den Berg et al. 2006). A trial of four weeks did not sustain any of the positive results after a four week break (Van den Berg et al. 2006). However, a twelve week intervention retained some positive outcomes three months after the intervention finished (McCullagh et al. 2008). Thus, longer interventions may result in maintenance of positive outcome for longer.

Summary

In summary, the cumulative evidence suggests that AT positively influenced fitness, walking speed, gait parameters, fatigue and quality of life. There were no harmful effects but all trials had a high risk of bias. The main reasons for a high risk of bias were due to selection and detection bias.

2.2.2 Progressive Resistance Exercise

Nine publications evaluating progressive resistance exercise (PRE) in PwMS were identified. No harmful effects were noted. A detailed description of these can be found in Table 4. White et al (2004) and Guttierrez et al (2005) are data from the same trial. Dalgas et al (2009), (2010a) and (2010b) are different data from the same trial, thus six studies were conducted.
Participant characteristics

There were a mean number of 13.5 participants in trials evaluating PRE (range: 2, 22).

The selection criteria were similar to that of AT. However baseline activity levels were also accounted for. Baseline activity levels were very different between studies. For example participants were excluded if they participated in systematic resistance training within the last three months (Dalgas et al. 2010b), if they participated in any PRE programmes in the 4 weeks before the start of the study (Taylor et al. 2006), if they participated in light physical activity in the three months prior to the study (White et al. 2004), or if they were considered “physically inactive before the trial” (White et al. 2006b, Dalgas et al. 2009, Dalgas et al. 2010b).

Effect on Body Structure and Function

Studies of PRE measured outcomes of body structure and function using measures of strength and some physiological outcomes.

Mean improvements in strength were between 7% and 52% and were statistically significant in all studies that measured it (Dalgas et al. 2009, White et al. 2004, Gutierrez et al. 2005, Taylor et al. 2006, Dalgas et al. 2010b, Dalgas et al. 2010a).

There is a paucity of information regarding body structure and function in response to a PRE. One study found triglyceride levels improved significantly (White et al. 2006b). There was a trend towards improved blood glucose levels. The magnitude of change can be seen in Table 4. The number of coronary artery disease risk factors (17 less risk factors in 12 participants) reduced significantly (White et al. 2006b).
Effect on Activity

Walking, stepping and gait parameters were outcomes of activity in the studies evaluating PRE.

The cumulative results of PRE on walking are positive for small (3.6-15.8%) improvements in walking (Dalgas et al. 2009, Taylor et al. 2006, White et al. 2004). There were statistically significant improvements in speed over 10m (Taylor et al. 2006, Dalgas et al. 2009) and distance as measured by the 6MWT (Dalgas et al. 2009) but not for the 25ft (White et al. 2004) walk or the 2MWT (Taylor et al. 2006). Similar to the trials of AT, large variability was seen for all walking outcomes.

Three minute stepping (Gutierrez et al. 2005) and a timed stairs test (Taylor et al. 2006) both improved (by a mean of 8.7% and 3.3% respectively). EDSS showed a statistically significant trend for improvement (↓0.5 EDSS unit) (White et al. 2004). However, this is not valid as a subjective measure. There was preliminary evidence for significant improvements in gait parameters – changes that are indicative of normal stride patterns (Gutierrez et al. 2005).

Effect on Participation

Fatigue, HRQoL and QoL were measured as participation outcomes in PRE trials.

Fatigue reduced significantly when measured by the Modified Fatigue Impact Scale (White et al. 2004, Gutierrez et al. 2005) and the Fatigue Severity Scale (Dalgas et al. 2010b). The mean magnitude of change was 19% and 10.3% respectively.
The physical components of both the MSIS – 29 and SF-36 improved significantly by a mean of 33% and 8.4% respectively with similar interventions (Dalgas et al. 2010b, Taylor et al. 2006). The psychological component of the MSIS-29 improved by a mean of 7.1% in Taylor et al (2006) and by a mean of 15% in Sabapathy et al (2010).

**Differences between groups**

Three out of seven studies compared PRE to another group. Dalgas et al (2009, 2010a and 2010b) showed a statistically significant difference in change scores after a PRE intervention compared to a control in maximum voluntary contraction for knee extension and knee flexion, SF-36 (PCS), the Major Depression Inventory, and the Multidimensional Fatigue Index-20 (General Fatigue section), type IIa and type IIx muscle fibres and muscle fibre cross sectional area. Çakit et al (2010) found a statistically significant difference between a cycling PRE intervention and a control for all outcomes and between the cycling programme and another exercise intervention for all outcomes except the 10-m walk test (Cakit et al. 2010). Additionally, no significant differences were found for any outcomes comparing PRE and AT (Sabapathy et al. 2010).
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al (2004) Pre/Post intervention study EG (n = 8)</td>
<td>F: 2 / week I: 50-70% MVC x 10-15 repetitions T: Conventional weight machines, knee extension, knee flexion, plantar flexion and spinal flexion/extension T: 30 minutes Duration: 8 weeks</td>
<td>Isokinetically strength Burst superimposed technique Muscle Contractile Area (Quadriceps CSA) 25-ft walking test 3 minute step test MFIS EDSS Subcutaneous fat - post intervention result not presented</td>
<td>Strength ↑7.4% Knee extension*, ↑52% plantarflexion*, ↑43% knee flexion, ↑9% dorsiflexion Central activation area 0.9±5 0.05 to 0.86±1.0 Quadriceps CSA 43.1±3.9cm² to 43.4±4.7, Hamstring CSA 28.6 ±7.7 to 31.3± 6.6. 25-ft walk 6.1 2.1s to 6.2 2.5s 3 minute step test 64.5±13 to 70.1±19* MFIS 32±18 to 25.8±17* Self-reported EDSS 3.7± 0.8 to 3.2±1.4</td>
</tr>
<tr>
<td>Guttierrez et al (2005) Pre/Post intervention study EG (n = 8)</td>
<td>F: 2/ week I: 50% 1RM T: Conventional weight machines, knee extension, knee flexion, trunk flexion, plantarflexion T: 30 minutes Duration: 8 weeks</td>
<td>Kinematic gait parameters Isometric strength 3 minute stepping MFIS EDSS</td>
<td>Gait ↑double support time from 0.23 ± 0.07 to 0.21 ±0.05*, ↑support from 18.3± 2.8 to 16.8 ±2.8 <em>, ↑ stride length from 1.06±0.16 to 1.14±0.12</em> Strength ↑ 7.2% knee extension*, ↑55% plantar flexion*, ↑14.5% knee flexors, 0% dorsiflexors (were not trained) 3 minute stepping ↑ stepping by 8.7% MFIS 32 to 26* (variability not described) EDSS 3.7 to 3.2 (variability not described)</td>
</tr>
</tbody>
</table>

EG = Exercise Group, MVC = Maximum Voluntary Contraction, CSA = Cross Sectional Area, MFIS = Modified Fatigue Impact Scale, EDSS = Expanded Disability Status Scale
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taylor et al (2006)</td>
<td>Pre/Post intervention study EG (n = 9)</td>
<td>F: 2 / week I: Approx. 60 – 80% 1RM T: Gym based, lat pull down, seated arm press, seated row, seated leg press, knee extn, seated calf raise T: 60 minutes Duration: 10 weeks</td>
<td>Strength (1RM), Endurance (Repetitions 50% 1RM) 2MWT 10-m walk MSIS – 29</td>
</tr>
<tr>
<td>White et al (2006)</td>
<td>Pre/Post intervention study EG (n = 12)</td>
<td>F: 2 / week I: Weight increased by 2-5% when 15 repetitions achieved T: Conventional weight machines, knee extension and flexion, trunk extension and flexion, plantar flexion T: 30 minutes Duration: 8 weeks</td>
<td>Skinfold measurements Resting BP Total cholesterol and HDL - C Plasma triglycerides, Glucose MFIS-results not presented</td>
</tr>
</tbody>
</table>

1RM = 1 Repetition Maximum, 2MWT = 2 minute walk test, m = metres, SBP = systolic blood pressure, DBP = diastolic blood pressure, TC = total cholesterol, HDL-C = High density lipoprotein, TG = triglycerides, CAD = coronary artery disease, mmol/L = millimoles/litre
**TABLE 4 CONTINUED**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
</table>
I: Unknown  
T: Calisthenic (body weight), squats, sit-ups, trunk rotation, flexion and extension, Throwing 2 – 5kg ball, static balance exercises  
T: 60 minutes  
Duration : 6 weeks | MB (unknown)  
CT (repetitions)  
K-W (repetitions)  
Z-Z (distance)  
DF (repetitions)  
L-L (repetitions)  
FB (s)  
VJ (cm)  
BM (repetitions)  
AT (repetitions) | MB 3.3 to 3.5 (All median values reported)  
CT 16 to 23  
K-W 22 to 24.5  
Z-Z 19 to 16  
DF 16 to 19.5  
L-L 6.5 to 13  
FB 0 2.0  
VJ 14.6 to 14.8  
BM 0 to 17.5*  
AT 1.5 to 8.5* |
I: Week 1 – 2, 3 x 10 x 15 RM  
Week 3 – 4, 3 x 12 x 12 RM  
Week 5 – 6, 4 x 12 x 12RM  
Week 7 – 8, 4 x 10 x 10RM  
Week 9 – 10m 4 x 8 x 8RM  
T: Lower extremities – Leg press, knee extension, hip flexion, hamstring curl and hip extension  
T: unknown  
Duration : 12 weeks | Maximum Voluntary Contraction (Biodex dynamometer)  
1RM leg press  
Functional capacity score (FS) = chair stand test (CST) + ascending stair climbing test(SCT) + 10-m walk test + 6MWT | KE MVC EG: Δ↑ 15.7% (95% CI 4.3 – 27.0)*, CG: 1.3% (95% CI -7.3, 10.0).  
KF MVC EG: Δ↑ 21.3% (95% CI 10.7, 43.3)*, CG: -0.4% (95% CI-6.1, 5.2).  
Strength (follow-up)  
In the EG results were not significantly different at follow-up for KE ↓ 2.3 (95% CI - 6.3, 1.7) or KF ↓ 3.9% (95% CI-10.2, 2.5). At follow-up after participating in the same intervention CG KE ↑ 10.0 (95% CI 5.3, 14.7)*, KF ↑6.3 (95% CI0.3, 13.6)  
1RM EG: ↑ 37.1% (95% CI 26.6, 47.6)*. Not reported in CG. At follow-up (after PRE) CG ↑37.9 (95% CI 23.4, 52.5)*  
FS EG: ↑ 21.5% (95%CI 17, 26.1), at follow-up EG ↓0.3 (95%CI -3.3, 2.7)  
CG: -3.3 (95%CI -8.1, 1.5)*  
CG ↑12.8 (95% CI 9.0, 16.6)* |

MB =thowing a medicine ball overhead, CT = clapping test,  K-W = Kraus Weber test, Z-Z = zig zag run of 9m, DF = dynamic flexibility test,  L-L = leg lifts, FB = flamingo balance test,  VJ = vertical jump,  BM= back muscle test,  AT = abdominal test, cm = centimetres, s = seconds. Unit of measurement in parentheses ().  * = statistically significant, KE = Knee Extension, KF = Knee Flexion.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalgas et al. (2010b)</td>
<td><strong>As above</strong></td>
<td>FSS</td>
<td>FSS (EG) 5.8 (95% CI 5.4, 6.1) to 5.2 (95% CI 4.4, 6.0) to 4.9 (95% CI 4.3, 5.5) compared to (CG) 5.5 (95% CI 5.0, 6.0) to 5.6 (95% CI 4.9, 6.3) to 5.1 (95% CI 4.2, 6.0)</td>
</tr>
<tr>
<td>RCT trial including follow-up 12 weeks after the intervention and CG crossed over to EG.</td>
<td></td>
<td>MFI-20</td>
<td>MFI-20, general fatigue (EG) 12.9 (95% CI 10.9, 13.8) to 12.1 (95% CI 10.2, 13.8) to 12.7 (95% CI 10.1, 14.0) compared to (CG) 11.6 (95% CI 9.7, 13.4) to 13.7 (95% CI 11.7, 15.7) to 11.8 (95% CI 9.4, 14.0)</td>
</tr>
<tr>
<td>EG (n = 15)</td>
<td></td>
<td>MDI</td>
<td>MDI (EG) 10.3 (95% CI 7.0, 13.5) to 7.9 (95% CI 5.2, 10.6) compared to (CG) 8.8 (95% CI 6.4, 11.3) to 9.9 (95% CI 7.4, 12.5) to 8.9 (95% CI 6.5, 11.2)</td>
</tr>
<tr>
<td>CG (n = 16)</td>
<td></td>
<td>SF-36</td>
<td>SF-36, PCS (EG) 41.4 (95% CI 37.5, 45.3) to 44.9 (95% CI 40.9, 48.9) compared to (CG) 42.6 (95% CI 37.8, 46.6) to 41.6 (95% CI 37.8, 45.4) to 41.5 (95% CI 38.2, 44.8)</td>
</tr>
<tr>
<td>Dalgas et al. (2010a)</td>
<td><strong>As above</strong></td>
<td>Muscle biopsies (CSA and fiber type -VL)</td>
<td>Muscle fiber CSA EG: 3278±1399µm² to 3893±1403µm², CG: 3391±1002µm² to 3278±1032µm². No changes in the proportion of fiber types in EG. Power would require 99 participants in each group to see a difference</td>
</tr>
<tr>
<td>RCT as above</td>
<td></td>
<td>Thigh volume</td>
<td>Thigh volume (l) EG: 7.4±1.4 to 7.7±1.5, CG: 6.8±1.7 to 6.9±1.8</td>
</tr>
<tr>
<td>EG (n = 15)</td>
<td></td>
<td>Isokinetic strength at slow (90°/s) and fast (180°/s)</td>
<td>KE180 (Nm) EG: 89.1±34.1 to 95.3±31.0, CG: 87.2±28.8 to 86.7±31.8†</td>
</tr>
<tr>
<td>CG (n = 16)</td>
<td></td>
<td></td>
<td>KE90 (Nm) EG: 63.8±25.7 to 73.2±23.9, CG 56.3±17.8 to 54.2±24.3 †</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KE180 (Nm) EG: 52.1±21.8 to 59.9±22.3*, CG: 42.8±16.5 to 39.5±16.2 †</td>
</tr>
</tbody>
</table>

FSS = Fatigue Severity Scale, EG = Exercise Group, CG = Control Group, MFI-20 = Multidimensional Fatigue Inventory, MDI = Major Depression Inventory, SF-36 = Short Form -36
<table>
<thead>
<tr>
<th>Author. year</th>
<th>Design</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cakit et al (2010)</td>
<td>EG1 (n =15) EG2 (n = 15) CG (n = 15)</td>
<td><strong>EG1</strong>&lt;br&gt; F: 2 / week 15 sets of a particular workload&lt;br&gt;I: High resistance pedalling (40% of tolerated maximum workload), and low resistance pedalling (30 – 40W). Load increased in 10 W increments when &gt; 12 successful sets at particular workload.&lt;br&gt;T: PRE on a static bike - followed by supervised warm up exercises, 20 – 25 minutes of balance exercise, and stretching&lt;br&gt;T: 90 minutes&lt;br&gt;Duration: 8 weeks</td>
<td>TUG  DGI  FR  FES  10-m walk  FSS  BDI  SF-36</td>
<td>Adherence was better in EG1 compared to EG2 (93% vs 60% out of 224 prescribed session)&lt;br&gt;TUG(s) EG1: 10.7±1.4 Δ 0.1±1.2*, EG2: 17.0±8.8Δ 0.2±0.5, CG: 14.6±9.1Δ -0.2±0.8†&lt;br&gt;DGI EG1: 17.4±4.4Δ 2.7 ±0.5*, EG2: 14.8±4.6Δ 0.2±0.4, CG: 16.4±4.9Δ 0.4±0.4†&lt;br&gt;FR (cm) EG1: 24.7±6.3 Δ 2.7 ±0.5*, EG2: 21.2±10.2 Δ 0.2±0.4, CG: 25.8±7.3Δ 0.4±0.4†&lt;br&gt;FES EG1: 19.7±11.7 Δ -11.3 ±7.8*, EG2: 44.1±20.3 Δ -2.1±1.3*, CG: 32.4±24.1Δ -2.6±3.1†&lt;br&gt;-10-m walk (s) EG1: 12.0±2.4 Δ-1.9±1.2, EG2:14.7±2.8 Δ -0.8±0.07, CG:12.2±3.1 Δ0.1±0.8&lt;br&gt;FSS EG1: 39.8±9.5 Δ -9.5 ±2.9*, EG2: 50.0±69.9 Δ -0.4±2.1, CG: 44.2±2.8 Δ -5.8±5.3†&lt;br&gt;BDI EG1: 22.8±12.7 Δ -5.5±5.3*, EG2: 40.2±15.8 Δ 1.6±3.6, CG: 27±17.6Δ -1.6±6.0.&lt;br&gt;SF-36, Physical functioning: EG1: 43.3±16.6 Δ 21.2 ±14.4*, EG2: 32.1±16.8 Δ12.1±5.0*, CG: 43.2±17.7Δ 7.7±7.4.</td>
</tr>
<tr>
<td>EG2</td>
<td>F: A/A I:A/A</td>
<td>T: HEP delivery of balance and LL strengthening&lt;br&gt;T: A/A&lt;br&gt;Duration : 8 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3 – Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Quality of studies

The methodological quality of PRE studies can be seen in Table 5. Most (4/6) studies had a high risk of bias with the exception of the recent work of Dalgas et al (2010b) and Çakıt et al (2010). Selection bias was only met by these two groups.

Table 5: Methodological quality of studies evaluating progressive resistance exercise

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection bias</th>
<th>Detection bias</th>
<th>Performance bias</th>
<th>Attrition bias</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gutierrez et al (2005)</td>
<td>Not met</td>
<td>Unclear</td>
<td>Not met</td>
<td>Met</td>
<td>High</td>
</tr>
<tr>
<td>Dalgas et al (2009), (2010a)</td>
<td>Met</td>
<td>Not met</td>
<td>Partly met</td>
<td>Met</td>
<td>High</td>
</tr>
<tr>
<td>Dalgas et al (2010b)</td>
<td>Met</td>
<td>Met</td>
<td>Partly met</td>
<td>Met</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Intervention parameters

The PRE programmes in this review generally followed the American College of Sports Medicine Guidelines for progressive resistance exercise (ACSM 1995). Table 4 demonstrates the parameters of progressive resistance exercise. Studies used the following parameters; twice a week at 50 – 80% of Maximum Voluntary Contraction (MVC) or that the weight is increased by 2 – 5 % when 12 repetitions have been achieved. Two to three sets of 12 repetitions were repeated for at least all major lower limb muscle groups, for 30 - 60 minutes. Conventional weight machines were used and interventions took place for 6 - 12 weeks.

Summary

In summary, studies had small numbers of participants, usually did not use a control group or have blinded assessments. Due to the moderate or high risk of bias in all of these studies, no firm conclusions can be made regarding the effectiveness of this type of intervention. The cumulative results suggest that there is no harm caused by PRE and that there may be positive effects.

Comparing AT and PRE

One study to date has compared the effects of AT and PRE (Sabapathy et al. 2010). This study had a high risk of bias due to lack of clarity regarding the concealment allocation of participants to a group and two out of the four outcome assessors were aware of the group allocation. This study is described in Table 6. The author was contacted for the total MFIS for each group. In the AT group, there was a mean score of 38.44±16.7 pre intervention reducing to 32.07±14.11 after intervention, and 36.19±16.53 pre-PRE to 29.29 ±14.9 post-PRE. Both improvements were statistically significant but not significantly different from each other.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabapathy et al. (2010)</td>
<td>Cross-over design with 8 week washout period AT and PRE groups (n = 16 per group)</td>
<td>Grip strength</td>
<td>Grip strength (kg) AT: 32.4±13.3 to 33.0±13.0, Δ 0.6±2.7, PRE: 30.3±14.2 to 31.6±12.8, Δ 1.3±7.8</td>
</tr>
<tr>
<td></td>
<td>F: 2 / week I: Based Borg Category Ratio Scale 3-5 (moderate to hard) T: Aerobic (step –ups, arm cranking, upright cycling, arm cranking, recumbent cycling, cross trainer, treadmill walking, arm cranking) T: 5 minutes at each station, 2 minutes rest after every 2 stations F: 2 / week I: 2-3 sets of 6 – 10 repetitions. 30-60s rest between each set T: PRE (3 Upper body, 3 lower body and 1 core exercise) T: Unknown Duration: 8 weeks</td>
<td>FR</td>
<td>FR (cm) AT 38.6±5.9 to 40.0±5.3*, Δ -0.6±9.6, PRE: 35.8±6.7 to 41.3±5.2*, Δ 7.4 13.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Four step square test</td>
<td>Four step square test (s) AT: 8.8±1.8 to 8.1±1.9*, Δ -0.7 ±0.9, PRE 9.5±2.4 to 8.3±2.1*, Δ -1.21.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TUG</td>
<td>TUG (s) AT: 7.2±1.7 to 6.7±1.4*, Δ-0.5±0.7, PRE: 7.5 ±2.2 to 6.8±1.8*, Δ-0.7±0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6MWT</td>
<td>6MWT AT: 484±96 to 503±100*, Δ18.6±40.1, PRE: 447±111 to 486±107*, Δ38.1± 70.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSIS-29 (physical component)</td>
<td>MSIS-29-29 (physical component) AT: 43.5±12.4 to 39.1±12.9*, Δ-4.1±9.6, PRE: 43.8±15.3 to 39.3±13.1*, Δ -6.3±12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSIS-29 (psychological component)</td>
<td>MSIS-29 (psychological component) AT: 19.6±8.0 to 16.9±6.1, Δ – 2.7 PRE: 20.0±9.3 to 17.1±7.2, Δ -2.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BDI</td>
<td>BDI AT: 9.7±11.6 to 10.3±11.6, Δ 0.6±3.9, PRE: 9.8±9.0 to 8.7±7.7, Δ -2.3±5.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MFIS</td>
<td>MFIS (summative score-calculated from subscales)AT: 39.7 to 32.8, Δ5.2PRE: 36.3 to 31.2, Δ5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SF-36</td>
<td>SF-36, MCS AT: 37.8±6.8 to 37.7±7.7, Δ-0.2±6.8 PRE: 36.1±9.1 to 39.8±7.3, Δ3.7±7.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SF-36, MCS</td>
<td>SF-36, MCS AT: 48.1±13.3 to 53.2±11.2, Δ2.3±10.6 PRE: 53.2±11.2 to 51.3±12.9, Δ -1.9±9.7</td>
</tr>
</tbody>
</table>

AT = Aerobic Training, PRE = Progressive Resistance Exercise, FR = Functional Reach, TUG = Timed Up and Go, 6MWT = Six Minute Walk Test, MSIS-29 = Multiple Sclerosis Impact Scale, BDI = Beck Depression Inventory, MFIS = Modified Fatigue Impact Scale, SF-36 = Short Form (MCS = Mental Composite score, PCS = Physical Composite score)
2.2.3 Combined Exercise

Six publications evaluating combined exercise in people with MS were identified and are summarised in Table 7. Due to the methodological limitations, varying parameters of interventions, and questionable outcomes measures used in these studies, it is difficult to draw any conclusions from these studies.

Participants

There were a mean number of 18 participants in studies evaluating combined exercise (range: 6, 47).

Similar to the selection criteria of other trials most participants were women, were aged between 25 and 65 years, were excluded if they had significant co-morbidities that limited the ability to participate in exercise. Participants were also excluded if they had an exacerbation in the last one to three months or had steroid therapy in the last one or two months. Romberg et al (2004) reported social history (including marital status, employment status and time spent in education).

Participants had been excluded from combined exercise programmes if they participated in intensive exercise at least 5 times a week for at least 30 minutes during the preceding 3 months before admission (Romberg et al. 2005, Romberg et al. 2004b, Surakka et al. 2004) or active engagement in an exercise programme during one month prior to study onset (Bjarnadottir et al. 2007).
Effect on Body Structure and Function

Outcomes of strength and fitness were frequently measured at the level of body structure and function in studies of combined exercise.

Strength improved significantly in both studies in which it was measured (Romberg et al. 2005, Golzari et al. 2010). However, the control group also improved significantly in one study (Romberg et al. 2004b). This may be explained by practice effects or other issues with the measure, as this is not an effect one would expect in a control group of PwMS. Strength improved by 85.6 % in a recent study (Golzari et al. 2010). It was not clear how strength was measured in either study.

There was a trend towards improved fitness (14.6%) in a group that took part in a programme for 5 weeks (measured as Graded Exercise Test) (Bjarnadottir et al. 2007). This was not statistically significant. Similarly, there was no statistically significant change in fitness in the studies with a 3 week intervention and a 23 week HEP using VO
\(_{2}\) max. These raw scores were not presented (Romberg et al. 2004b). There was a small (5%) reduction in VO
\(_{2}\) max in Golzari et al (2010). The above studies lack clarity in terms of what participants actually did during the trial and both lack clarity regarding how strength and fitness were measured. Thus, it is not possible to draw a conclusion regarding the effect of combined exercise on strength and fitness.

Effect on Activity

There is very little information regarding the effect of a combined exercise programme on activity. A measure of activity was used in two studies (Romberg et al. 2004a, Romberg et al. 2005, Romberg et al. 2004b). The Multiple Sclerosis Functional Composite (MSFC), which is compiled of a timed 25 ft walk, nine hole peg test and
paced auditory serial addition test, improved significantly (Romberg et al. 2005). The z-
scores presented (a combination score of the three subcomponents of the test) are
difficult to interpret clinically. There was no statistically significant change in balance.
However, the raw scores were not presented (Romberg et al. 2004b).

**Effect on Participation**

Similar to the AT and PRE studies, the effect of a combined exercise intervention on
fatigue and QoL were measured.

Minimal improvement (3.6%, p =0.07) was reported on fatigue severity as measured by
the Fatigue Severity Scale (Surakka et al. 2004). Larger (15%) improvement was seen
using the Chalder Fatigue Scale in a progressive programme over 20 weeks (Fragoso et
al. 2008).

A mean reduction of 2.1% on the MS-QoL – 54 (PCS) and a mean reduction of 2%
using the SF-36 (PCS) were seen. Neither of these was statistically significant.
Participants had a high (good) score to begin in both of these trials with a mean of 61.7
±18.2 (Romberg et al. 2005) and 81.7 (no variability given) (Bjarnadottir et al. 2007)
This suggests that the lower physical aspect of QoL usually seen in PwMS (Turpin et al.
2010) did not apply in these cohorts.
<table>
<thead>
<tr>
<th>Author, year (design)</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surakka et al (2004)</td>
<td>F: Unknown I: Aerobic (65 -70%HRM) PRE 50-60%1RM T: Aerobic (aquatic / bicycle ergometers) PRE (Circuit and HEP) T: Aerobic (30 – 35minutes) PRE (unknown) Duration: 3 weeks supervised, 23 weeks HEP</td>
<td>Fatigue Index FSS AFI Diary for adherence</td>
<td>Fatigue index for leg extension: Females (EG, n = 30) 27.3 (SEM2.6) Δ -3.3 (95% CI -8.2, 1.6), (CG, n = 31) 22.4 (SEM2.6) Δ4.3 (95% CI -0.7, 9.4). Males (EG, n = 17) 24.9 (SEM3.7) Δ2.0 (95% CI -5.1, 9.1), (CG, n = 17) 25.3 (SEM3.5) Δ 1.8 (-4.8, 8.4). A second table presented this result. A different CI was presented for the female exercises (-6.0, -0.6) and it was also indicated that this improvement between baseline and 26 weeks was statistically significant. The time effect was statistically significant for the AFI in both the exercise and the control groups 2.44 (95% CI 0.67, 4.21)* and approaching significance for the FSS 0.17 (95% CI -0.02, 0.36), p = 0.07. Adherence Women completed 62% (29h) and men completed 53% (23h) of the strength sessions when aerobic and strength sessions were combined. The targeted amount of exercise sessions was 98% (63h) of women and 85% (53h) of men completed the targeted amount of exercise sessions.</td>
</tr>
<tr>
<td>Romberg et al (2004)</td>
<td>F: 10 classes over 3 weeks I: Unknown T: Aerobic (Aquatic / preferred type), PRE (circuit) T: Unknown Duration: 3 weeks supervised, 26 weeks HEP</td>
<td>7.62m WT 500m walk, Strength (dynamometer) – KE and KF (Nm) UEE (weight lifting) Gross manual dexterity VO₂ max – raw scores not presented Static balance (Equiscale) 0 – 16 – raw scores not presented</td>
<td>7.62m WT EG: 12% (95% CI 16, 7)<em>, CG: 6% (95% CI 11, 2)</em> 500m walk EG: 6% (95% CI 10, 2)<em>, CG: 0% (95% CI -3, 4) Strength (Nm) (R) KE EG: Δ 7.2 (-2.7, 17.2), CG Δ 5 (-4.8, 14.8), (L) KE EG: Δ 5.9 (-1.7, 13.5), CG: Δ 0.1 (-7.4, 7.6), (R) KF EG: Δ 9.6 (3.7 to 15.5)</em>, CG: Δ 7.0 (1.2, 12.8)* (L) KF EG: Δ 10.1 (3.6, 16.6)*, CG: Δ 4.4 (-1.9, 10.8). No differences between groups for any strength outcomes UEE: (R) EG: 2.9 (95% CI 0.7, 5.1), CG: 0.2 (95% CI -2.0, 2.4), (L) EG: 3.1 (95% CI 1.1 to 5.0) , CG: 0.3 (-1.7, 2.3) * between groups for (R)&amp;(L) Gross manual dexterity Both groups increased in box and blocks test mean increase was 2.4 (95% CI 1.1, 3.7) in the dominant hand and 1.3 (95% CI 0.1, 2.5) in the non-dominant hand. No statistically significant change over time was seen for VO₂ max or balance</td>
</tr>
</tbody>
</table>

EG: Exercise Group, CG= Control Group, HEP = Home Exercise Programme, FSS = Fatigue Severity Scale, AFI = Ambulatory Fatigue Index, WT = Walk Test, UEE = Upper Extremity Endurance, SEM = Standard Error of the Mean
<table>
<thead>
<tr>
<th>Author, year (design)</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romberg et al (2005)</td>
<td>RCT EG (n = 47) CG (n = 48)</td>
<td>MSFC</td>
<td>MSFC (EG) mean Δ 0.114 (95% CI 0.01, 0.218), ES 0.16* (CG) -0.0128 (95% CI -0.232, 0.025), ES -0.18*.</td>
</tr>
<tr>
<td></td>
<td>F: 3 / 4 week I: Unknown T: 5 aerobic classes, 5 PRE classes, theraband for 23 weeks T: Unknown Duration: 3 weeks supervised, 23 weeks HEP</td>
<td>EDSS, FIM, MSQoL-54 CES – D</td>
<td>EDSS (EG) mean increase of 1, ES = -0.09, (CG) mean decrease of 0.1 ES 0.09 FIM mean increase of 0.3 in both groups. ES for EG = 0.15, ES for CG = 0.04. 63% of participants scored at least 124 at baseline. MSQoL-54 PCS (EG) 61.7 ±18.2 to 63.0 ±17.8, ES 0.07, (CG) 62.1±14.7 to 63.3±16.6, ES = 0.09 CES-D – no group x time interaction (p = 0.47), no follow-up or change scores presented.</td>
</tr>
<tr>
<td>Bjarnadottir et al (2007)</td>
<td>RCT EG (n = 6 ) CG ((n = 10)</td>
<td>GXT (VO₂ max)</td>
<td>VO₂ max EG: 27.3 to 31.3, (CG) from 23.4 to 22.9. Difference between groups 4.54 (95% CI 1.65, 7.44)</td>
</tr>
<tr>
<td></td>
<td>F: 3 / week I: Aerobic (55-70% HRM), PRE not described T: Aerobic (ergometer), PRE (UL and LL exercises) T: 60 minutes in total, Aerobic (30 minutes), resistance (20 minutes), stretching (5 minutes) Duration: 5 weeks</td>
<td>SF – 36, EDSS</td>
<td>SF-36 – PCS EG: 81.7 to 80, CG: 72 to 71.5. Difference between groups -1.17 (95% CI -16.13, 13.8) SF-36 – MCS EG: 68.0 to 67.3, CG: 75 to 80.4. Difference between groups -5.47 (95% CI -27.69, 16.76) EDSS EG 2.1 to 1.9, CG: from 1.8 to 1.7 Difference between groups -0.07 (95% CI -0.74 to 0.61) No estimates of variability given for pre and post mean scores.</td>
</tr>
</tbody>
</table>

MSFC = Multiple Sclerosis Functional Composite, FIM = Functional Independence Measure, MSQoL-54 = Multiple Sclerosis Quality of Life, CES-D = Centre for Epidemiologic Studies Depression Scale, GXT = Graded Exercise Test
### TABLE 7 CONTINUED

<table>
<thead>
<tr>
<th>Author, year (design)</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragoso et al (2008)</td>
<td>Pre/post design EG (n = 9) F: 3 / week I: Unknown T: Weeks 1- 4 Stretching (60minutes), weeks 4-14 stretching + light weights (60 minutes), weeks 14 – 20 stretching, resistance and walking/running (90 minutes) T: up to 90 minutes Duration: 20 weeks</td>
<td>Chalder Fatigue Scale</td>
<td>46±6.3 to ±39.4±3.4*</td>
</tr>
<tr>
<td>Golzari et al (2010)</td>
<td>RCT EG (n = 10) CG (n = 10) F: 2 / week I: unknown T: Aerobic and Resistance (includes warm up, stretch, AT, endurance and resistance training and relaxation) T: 60 minutes Duration: 8 weeks</td>
<td>EDSS VO₂ max - method of measurement not clear Muscle strength – method of measurement not clear Balance – method of measurement not clear IFN-γ IL-4 IL-17</td>
<td>EDSS EG: 2.14±1.06 to 1.65±1.12*, CG: 1.95 ±1.06 to 2.12±1.24 VO₂ max(ml/kg/min) EG: 33.84±13.08 to 32.07±12.05, CG: 32.0±4.99 to 35.00±15.78 Muscle strength (kg) EG: 37.53±13.47 to 69.61±18.25*, CG: 37.50±20.29 to 49.75 ±13.79 Balance (s) EG: 76.69±36.98s to 120.87 121.6s, CG: 87.00±57.88s to 100.5± 77.96s IFN-γ (pg/mL) EG 597±128.26 to 426±74.60* CG: raw scores not reported IL-4 (pg/mL) EG:287.4± 67.88 to 299.5± 50 CG: raw scores not reported IL-17 (pg/mL) 519.5±108.94 to 232± 84.85 CG: raw scores not reported No significant* changes in the control in IFN-, IL-4 or IL-17 after 9 week intervention. Raw scores not given but graphs demonstrate raw scores of participants.</td>
</tr>
</tbody>
</table>

EG = Exercise Group, CG = Control Group, EDSS = Expanded Disability Status Scale, IFN = Interferon, IL = Interleukin, pg/ml = picograms per millilitre, kg = kilograms, s = seconds, pg/mL = pictogram per millilitre, *statistically significant
Quality of studies

Table 8 describes the methodological quality of studies evaluating combined exercise. It was mostly unclear whether the criteria for bias were met due to inadequate reporting. It is difficult to draw conclusions from these studies regarding outcomes. The results regarding combined exercise must be interpreted with caution. However, attrition is well accounted for in these studies and no harmful effects were reported suggesting a combined intervention is feasible PwMS.

**TABLE 8 METHODOLOGICAL QUALITY OF STUDIES EVALUATING COMBINED (AEROBIC AND PROGRESSIVE RESISTANCE) EXERCISE**

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection bias</th>
<th>Detection bias</th>
<th>Performance bias</th>
<th>Attrition bias</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romberg et al (2004a)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Met</td>
<td>High</td>
</tr>
<tr>
<td>Romberg et al (2005)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Met</td>
<td>High</td>
</tr>
<tr>
<td>Fragoso et al. (2008)</td>
<td>Not met</td>
<td>Unclear</td>
<td>Not met</td>
<td>Met</td>
<td>High</td>
</tr>
</tbody>
</table>

**Intervention parameters**

Parameters are described in Table 7. Frequency ranges from unknown to 3 – 4 times a week. Intensity parameters are well defined in two studies with AT being at 55 -70% HRM and PRE being 50 – 70% 1RM (Surakka et al. 2004, Bjarnadottir et al. 2007). There were 10 classes over 3 weeks for three of the publications, followed by 23 weeks of a Home Exercise Programme (HEP) for these studies (Surakka et al. 2004, Romberg et al. 2004b, Romberg et al. 2005). Two interventions took a different approach and combined aerobic and PRE components in the one class.
Summary

In summary research into combined exercise is in its exploratory stages. There was a high risk of bias in the studies retrieved, so it is difficult to draw any firm conclusions on the effects of combined exercise for PwMS, but no deleterious effects were reported.

2.2.4 YOGA

Three studies evaluating yoga in PwMS were retrieved. No harmful effects were noted. A description of these can be found in Table 9. One study compared yoga, exercise and a control in an unknown setting (Oken et al. 2004), one study compared a sports climbing group to a yoga group in a rehabilitation setting (Velikonja et al. 2010) and one took place in a physiotherapy clinic and was supervised by a neurologist and physiotherapist (Ahmadi et al. 2010).

Participant characteristics

The mean number of participants in yoga groups was 14.3 (range 10, 22).

Participants with major medical problems were excluded in two of the three studies evaluating yoga (Oken et al. 2004, Ahmadi et al. 2010). Additionally those with visual acuity worse than 20/50 binocularly, those who had participated in yoga or tai chi in the last six months and people who reported taking part in regular AT of more than 30 minutes per day were excluded by Oken et al (2004). Most of the participants were women (20/22 in Oken et al. 2004 and all of the participants in Ahmadi et al. 2010).
Effect on Body structure and function

Cognitive function, depression and spasticity were evaluated at the level of body structure and function.

Changes in cognitive functions ranged from 6.4%-21.2% but these were similar in a control group (26.3%) (Oken et al. 2004, Velikonja et al. 2010). This may be explained by practice effects of the measures used. Attention improved after yoga but not sports climbing but participants in the sports climbing group started at a higher baseline score in attention (Velikonja et al. 2010). There was a trend towards a small reduction in depression scores in both studies that measured it that was not statistically significant. However, participants were not depressed to begin with (mean CES-D score <15) (Velikonja et al. 2010, Oken et al. 2004).

There were no statistically significant changes in spasticity as measured by a sum of scores from the Modified Ashworth Scale (Ahmadi et al. 2010).

Effect on Activities

Walking related activities and balance were evaluated in studies with a yoga intervention.

There was a small, statistically significant, improvement in a 10-m walk (9.26%) and in a 2MWT (4.6%) after participation in yoga with a frequency of three times per week (Ahmadi et al. 2010). There was a statistically significant worsening in gait speed (↓3.4%) using the 10-m walk and distance (↓2%) using the 2MWT in a control group (Ahmadi et al. 2010).
There was a statistically significant improvement (16.5%) in balance, using the Berg Balance Scale after yoga and statistically significant worsening in balance in the control group (↓ 6.3%) in the only study that measured it (Ahmadi et al. 2010).

**Effect on Participation**

Similar to all of the other categories of exercise, fatigue and QoL were the chosen measures of participation.

There was a reduction in the mean or median fatigue score from all three yoga interventions regardless of the measure used. This was statistically significant decrease in two of the three studies (Ahmadi et al. 2010, Oken et al. 2004) and approached this statistical significance (p=0.057) in Velikonja et al (2010).

There were statistically significant improvements in some components of the MSQoL-54 namely physical function, role limitations - emotional wellbeing, energy, cognitive function, overall quality of life, physical health composite and mental health composite which were also statistically significantly different from the control group (Ahmadi et al. 2010).
<table>
<thead>
<tr>
<th>Author, year (design)</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oken et al (2004)</td>
<td>YG F: 1 / week I: 10-30s hold, rest 30s-1min T: 19 Iyengar Yoga poses, 10 minutes deep relaxation. Daily home practice was encouraged and participants were given a booklet demonstrating poses T: 90 minutes</td>
<td>EEG Median Power Frequency Stroop Colour and Word Test (colour-word interference) SF-36 Health Survey MFI POMS CESD-10</td>
<td>EEG EG: 9.7±1.1 to 9.2±2, YG: 9.7±0.8 to 9.2 ±1.1, CG: 9.7±0.9 to 9.4±1.1 Stroop Colour-Word interference EG: 10.1±7 to 9.9±6.2, YG: 10.8±6.0 to 8.5±4.5, CG: 11.0±7.1 to 8.1±4.4 SF-36 (Energy and Fatigue) was the only baseline score&lt;50 at baseline. EG: 45.7±22.7 to 52.8±18.8*, YG: 43.1±17.7 to 51.2±16.7*, CG: 39.7±18.1 to 36.7 ±18.1 MFI-general fatigue EG: 13.2±4.0 to 12.1±2.8*, YG: 14.7 ±3.3 to 13.0 ±2.9*, CG: 15.1±3.4 to 14.9±3.0 POMS Sections for tension-anxiety, depression-dejection, anger-hostility, confusion had a trend towards reduced mean scores with large variability for all groups. There was a trend towards and increased mean score for all groups for vigour and an increased score for fatigue in the EG. Variability was again large for pre and post scores. CESD-10 EG: 6.8 ±5.0 to 6.4 ±5.8, YG: 9.1±4.3 to 7.5±4.7, CG: 11.3±5.5 to 11.2 ±5.8.</td>
</tr>
<tr>
<td>Istvan &amp; Velikonja et al (2010)</td>
<td>F: 1 / week I: Unknown T: Hatha Yoga (YG) T: 60 minutes Duration - 10 weeks</td>
<td>MAS (summative score) NAB ToL CESD-10 MFIS</td>
<td>MAS SCG: median of 10 (IQR 8.5, 18.3) to 12.5 (IQR10.0, 17.3), YG: median 9.3 (3.5, 3.5, 18.4) 8.8 (5.5, 17.1) NAB SCG: median 14.0 (SIQR7.5, 19.5) to 16.0 (11.0, 20.5), YG: 20.3 (12.5, 22.5) to 19.0 (12.8, 21.5) ToL SCG: median of 14 (IQR7.5, 19.5) to 16.0 (11.0, 20.5), YG: 210.0 (176.0, 296.3) to 276.5 (148.3, 237.8) CESD-10 SCG:10.0 (6.5, 22.5) to 5.0 (3.0, 22.5), YG: 9.5 (3.8, 20.3) to 3.0 (1.8, 13.0) MFIS SCG:40.0 (36.5, 53.0) to 27.0 (21.5, 45.5)* YG: 32.0 (22.0) to 23.0 (20.5, 36.), p = 0.057</td>
</tr>
</tbody>
</table>

EG = Exercise Group, YG = Yoga Group, CG = Control Group, SCG = Sports Climbing Group, EEG = Electroencephalogram, MFI = Multi-dimensional Fatigue Inventory, POMS = Profile of Mood States, CESD-10 = Centre for Epidemiology Studies Depression Scale, MAS = Modified Ashworth Scale, NAB = Maizes subset of Executive module from Neuropsychological Assessment Battery, ToL = Tower of London Test total time, MFIS = Modified Fatigue Impact Scale (total score)
<table>
<thead>
<tr>
<th>Author, year (design)</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmadi et al (2010)</td>
<td>F: 3 / week I: Each pose was held for 10 – 30s with rest between poses 30 – 60s T: Hatha yoga T: 60 – 70 minutes Duration – 8 weeks</td>
<td>FSS MSQoL-54 BBS 10-m walk 2MWT</td>
<td>FSS YG: 4.07 (1.11, 5.78) ±1.11 to 2.44 (1.44-6.66)±1.5*, CG: 4.17 (1.11, 5.78)±1.28 to 4.23 (1.78, 5.33)±1.04 MSQoL-54 YG: ↑ PCS from 58.9 (35.4, 74.7) to 65.7 (46.2, 86.9)<em>. ↑MCS from 56.12 (38.6, 68.7)±9.7</em>, CG: 67.24 (39.4, 81.7)±2.9 to 66.6 (41.6, 84.1)±12.3*. MCS 60.5 (33.4, 83.6)±15.5 to 65.5 (41, 84.6) ±14.9 BBS YG: 46.19 (28, 54)±8.1 to 53.81 (45, 56)±3.4. CG:44.50 (28, 54)±9.43 to 41.70 (28, 54) ±8.48 10-m walk (s) 8.96 (6.62, 12.24) ±1.8 to 8.13 (6.12, 11.25)±1.87, CG: 9.16 (6.62, 12.01)±1.88 to 9.47 (7, 12.75) ±1.92 2MWT (m) YG: 115 (71, 172) ±23.15 to 120.36 (86-162.5)* ±20.6, CG: 121.5 (71, 172)±20.6 to 119.05 (73, 165)±27.12. The YG statistically significantly different from the CG for all outcomes*</td>
</tr>
</tbody>
</table>

YG = Yoga Group, CG = Control Group, FSS = Fatigue Severity Scale, MSQoL = MS Quality of Life, BBS = Berg Balance Scale, 2MWT = Two Minute Walk Test
**Quality of studies**

The methodological quality of the trials is shown in Table 10. In two of the three studies, conclusions could not be made regarding the quality of the study (Ahmadi et al. 2010, Velikonja et al. 2010). After completion of baseline assessments, randomisation took place in Ahmadi et al (2010). It is not clear how and by whom this took place, or if the clinical findings had an influence on the allocation process. Additionally, it was not reported if the assessor was blind to group allocation. Similarly in Velikonja et al (2010), the randomisation process is not clearly described. Additionally, while the neurologist assessing EDSS was blind to group allocation, it is not clear if the physiotherapist or psychologist who conducted all other outcome measures was blind.

<table>
<thead>
<tr>
<th>Study Selection bias</th>
<th>Detection bias</th>
<th>Performance bias</th>
<th>Attrition bias</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmadi et al (2010)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Met</td>
<td>Met</td>
</tr>
</tbody>
</table>

**Intervention parameters**

All three studies used a “Hatha” yoga intervention. In both studies that described their interventions in more detail, participants conducted 19 poses and held poses from 10 to 30 seconds - but could be shortened if necessary depending on the person’s ability – with rest for 30 – 60 seconds between poses. Poses were adapted and modified to individual needs using props such as a chair/wall or Swiss ball. Both classes finished with deep relaxation. In Ahmadi et al (2010) participants began with stretching and calmative music and the participants in Oken et al (2004) finished with visualisation during their relaxation.
In summary, the cumulative evidence for “Hatha” yoga for PwMS suggests that there may be small, statistically significant improvements in short walking distances and balance. Studies consistently found improvements in fatigue and improvement in some aspects of QoL. However, firm conclusions cannot be drawn due to unclear reporting of some methods in these studies.

2.2.5 “Other” Exercise Interventions

One last intervention was identified using the search criteria for this review. The intervention was a core-stability training programme (Freeman et al. 2010). This was a multi-centred physiotherapist-led intervention. A single case study (ABA) design was used. Due to the variability of outcomes found in all other exercise interventions and small numbers of participants, this was an appropriate method of exploring outcomes in this pilot study. Parameters of the intervention and outcomes at group level are described in Table 11 below.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Design (n)</th>
<th>Intervention Frequency, Intensity Type, Time (FITT)</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman et al (2010)</td>
<td>8 Single case studies: ABA design (n = 8)</td>
<td>F: 2/week I: Progressed according to the ability of the patient T: Core stability training (Table top, 4-point kneeling, forward bend, bridge, 1-leg stretch, backward lunge, bent leg side lifts, single leg drop out, horizontal hold, straight leg side lifts, T: 30 minutes + 15 minutes daily HEP of the same exercises Duration: 8 weeks</td>
<td>10-m walk MSWS, TUG, FR, LR, SLS, VAS1(difficulty carrying a drink), VAS2 - difficulty with an identified functional task ABC Scale</td>
<td>10-m walk 10.8±2.9 to 9.1±2.7 to 9.4±3.2* MSWS-12 66.4±17.8 to 51.5±16.2 to 58.9±15.0* TUG(s) 11.9±4.1 to 10.2±4.9 to 10.4±4.4* FR (cm)24.5±6.6 to 32.5 ±5.5 to 30.4±7.0* LR(cm) 24.9 ±9.6 to 31.4±11.3 to 31.7±14.5 SLS (s) 17.3±29.5 to 24.7±39.1 to 29.6±45.8 VAS1 6.4±2.6 to 4.9±2.7 to 5.5±2.5 VAS2 7.5±2.3 to 6.2±2.6 to 6.6±2.3 ABC Scale 51.6±13.2 to 67.7±25.8 to 63.5±25.2</td>
</tr>
</tbody>
</table>

MSWS = MS Walking Scale, TUG = Timed Up and Go, FR = Functional Reach, LR = Lateral Reach, SLS = Single Leg Stance, VAS = Visual Analogue Scale, ABC = Activities and Balance Confidence
Quality

There was a high risk of bias as not one of the criteria for a low risk of bias was met in this exploratory study.

2.3 DISCUSSION

2.3.0 INTRODUCTION

The aim of this review was to evaluate all studies evaluating an exercise intervention for PwMS who have an EDSS ≤ 6.0. This review supports other reviews findings that AT, PRE and combined exercise are well tolerated in an ambulatory population of people with MS (Rietberg et al. 2004, Dalgas et al. 2008). In the following paragraphs, content and outcome of interventions, participants of studies and the methodological quality of studies to date will be discussed. Implications for the study in this thesis going forward will be addressed in each section.

2.3.1 THE CONTENT AND OUTCOME OF INTERVENTIONS

In participants with an EDSS of up to 6, the cumulative results from studies in this review suggests that AT positively influences fitness and endurance related outcomes. Additionally, PRE improves strength related outcomes and both have been shown to improve fatigue and health related quality of life. Dealing with the physical demands of modern life requires a combination of aerobic fitness and strength for example walking briskly for a bus, lifting a heavy box up on to a shelf, carrying a toddler up stairs. Thus, a combination of aerobic and strength training would seem a logical way of maximising activities and participation by addressing the impairments noted in PwMS which have been summarised as reduced aerobic capacity and reduced muscle strength (Dalgas et al. 2008).
To date, evaluation of combined exercise has relied on Home Exercise Programmes (HEPs) as the mode of delivery, bringing in the issue of compliance. While this seems representative of community-based interventions it is not yet known how to optimise adherence to programmes over the duration used in studies in this review (23 weeks). This questions the effect of compliance on the outcome of the intervention. A programme where a HEP is monitored and progressed weekly by a therapist may be more appropriate in order to maximise adherence and reflect changes due to the intervention as opposed to compliance to the programme. This was successfully carried out in a study of aerobic intervention (McCullagh et al. 2008). As combined exercise could be a more aggressive form of exercise, it is important to know that this can be done safely without excessively exacerbating symptoms or the disease. This review found no negative effects of this type of intervention. However, combined exercise programmes need to be evaluated in a methodologically sound study (i.e. reducing selection and detection bias in particular).

The parameters used in AT ranged between 55 – 85% HRM, 30 – 60 minutes, 2 – 3 times a week and studies used either a treadmill, cycle ergometers or aquatic training. The PRE programmes in this review generally followed the American College of Sports Medicine Guidelines (ACSM 1995). Results of papers in this review suggest positive results when participating in a strengthening programme twice a week ranging from 50 – 80% of Maximum Voluntary Contraction (MVC) or that the weight is increased by 2 – 5 % when 12 repetitions have been achieved. The findings of this review suggest that two to three sets of 12 repetitions for each exercise could be repeated over 30 - 60 minute duration. Conventional weight machines were used and three out of five interventions took place for 8 weeks (White et al. 2004, White et al. 2006b, Gutierrez et al. 2005). These parameters are considered when designing a combined exercise programme for people with MS who use, at most, one stick for walking.

Thus, the study in this thesis will evaluate a combined exercise programme, keeping in mind the effective parameters of exercise used for AT and PRE studies to date.
Yoga has been shown to be feasible in this population. At the beginning of this thesis only one small scale study had evaluated Yoga in PwMS (Oken et al. 2004). Subsequently, two more trials have been published in 2010 (Ahmadi et al. 2010, Velikonja et al. 2010). The cumulative evidence suggests that “Hatha” yoga can improve short walking distance when delivered three times per week, balance in PwMS with little balance impairment, fatigue and some aspects of QoL. Trials to date have been set in supervised health care settings. MS Ireland reports that many of its members participate in yoga in the community. However, the content and effectiveness of these interventions is not known for PwMS.

Internationally, primary care is becoming the cornerstone of modern health services with its emphasis on prevention and rehabilitation. However, health budgets are being restricted internationally due to the global recession. Exercise professionals in the community (such as a fitness instructor in a gym) may address some of the physical needs of PwMS, which may take some of the strain off the health service that currently provides services for PwMs, stimulate the economy locally and contribute to the good health of people with chronic conditions such as MS. However, no study has evaluated the content and effectiveness of such a community-based programme. Interventions to date have been generally supervised by a Physiotherapist (Rampello et al. 2007, Sutherland and Andersen 2001, McCullagh et al. 2008, Bjarnadottir et al. 2007, Taylor et al. 2006) and where it is documented, set in a hospital (Pariser et al. 2006, Kileff and Ashburn 2005, McCullagh et al. 2008, Freeman et al. 2010), a research laboratory (Schulz et al. 2004) or a rehabilitation centre (Romberg et al. 2004b, Romberg et al. 2005, Surakka et al. 2004, Velikonja et al. 2010). Thus, this thesis will establish the content and effectiveness of community-based yoga and fitness instructor-led gym-based classes for PwMS.
2.3.2 Follow-up

MS is a chronic condition from young adulthood until death, thus addressing problems related with the disease is required over a long time. There are only three (out of thirty) intervention studies followed up at three months (McCullagh et al. 2008, Dalgas et al. 2010b, Dalgas et al. 2009, Van den Berg et al. 2006). In studies of AT, the magnitude of improvement gained during the intervention was not maintained (Van den Berg et al. 2006, McCullagh et al. 2008). In the studies of PRE, improvements gained were better maintained even though only 3 of the 15 participants reported continuing with systematic exercise training (Dalgas et al. 2010b, Dalgas et al. 2009). The study in this thesis will include follow-up to intervention to inform the delivery of exercise programmes over time.

2.3.3 Measures

It appears from the results of the studies in this review that MS specific quality of life measures are more sensitive to change than generic measures and that more specific effects are demonstrated when they are analysed in their sub sections. Motl and Gosney (2008) found a similar result whereby there was a larger effect size after exercise interventions when a MS specific measure was used.

The 6MWT test consistently demonstrated statistically significant change indicating that it may be a more sensitive test that other measures of walking (2MWT and 25ft-walk) to use when evaluating walking in PwMS. The FSS only showed statistically significant improvement (p<0.05) in one of the six studies that used it (Dalgas et al. 2010b). However there were statistically significant (p<0.05) improvements in four out of the six studies that used the MFIS (McCullagh et al. 2008, White et al. 2004, Gutierrez et al. 2005, Sabapathy et al. 2010). This suggests that the MFIS may be more sensitive to change than the FSS. This apparent sensitivity to change will be considered when choosing outcome measures to evaluate interventions.
2.3.4 Participants

There was large variability for point estimates of pre-intervention, post intervention and change score indicating that an effective intervention is not equally effective for all participants thus, this review supports the Cochrane Review findings that the effectiveness of interventions for different types of MS remains indistinct (Rietberg et al. 2004).

Numbers of participants in trials to date have been small. Additionally, participants have been described in terms of type of MS, disease duration, age, height, gender, EDSS score, use of an aid and baseline outcome measures have been reported. In one study (Pariser et al. 2006) evaluating aquatic exercise in two people with MS, participants were described more fully in terms of their most disabling symptoms, medications, sensory, visual and motor function and participation level. Dalgas et al (2009 and 2010) reported use of immunomodulatory drugs and Romberg et al (2004) reported social history (including marital status, employment status and time spent in education). Small numbers of participants and a superficial description of participants make subgroup analysis impossible.

Snook and Motl (2009) concluded that considering the heterogeneity of people with MS and its disease course, a more complete reporting of participants’ characteristics should be a priority for future research examining outcomes of exercise training interventions among PwMS. Thus a large sample size and complete reporting of participants’ baseline characteristics is essential for generalisability of findings and subgroup analysis to establish what variables influence outcome. This will lead to more effective, targeted interventions for PwMS.
2.3.5 Quality

Studies in each category of exercise have a moderate to high risk of bias – mainly due to selection and detection bias. While this would cast some doubt on the validity of the findings, the cumulative evidence of all of the studies provides some important information when making clinical decisions of exercise interventions for people with MS. Despite the methodological limitations of the studies included, it can be seen that all results are pointing in the same direction suggesting that aerobic exercise, progressive resistance exercise, combined exercise, yoga and core stability training have positive outcomes for people with MS with minimal gait impairment.

Detection bias was the most obvious criterion that was not met as assessors were not blinded to participant allocation. Perhaps this is as a result of conducting preliminary research in a clinical setting. With careful planning, it is possible to have a blind assessor in this setting. It was not clear if selection bias was met in many studies due to inadequate reporting of the method of randomisation. Thus the resulting study in this thesis will carefully address the issues of selection and detection bias in order to minimise the overall risk of bias.

2.3.6 Limitations

Firstly, it is possible that papers were not found as only one reviewer searched the literature. However, the literature was searched many times and the reference lists of retrieved papers were also hand searched in order to capture as many papers as possible. Email alerts with any new papers with the search criteria were received. Secondly, qualitative studies, which may have given us more information, were excluded.
2.4 Conclusion

The results of the studies in this review suggest that aerobic, PRE, combined exercise and yoga have positive effects for PWMS with an EDSS ≤ 6.0. No harmful effects were seen in any intervention. However, studies had small numbers of participants and due to inadequate reporting of participants’ clinical characteristics, effectiveness of interventions for patients with different types of impairments remains unclear.

A combination of AT and PRE is feasible and theoretically appears to offer favourable results in terms of the negative symptomology and physiological profile of MS but it’s effects on walking, fatigue and HRQoL in PwMS are unknown. Both AT and PRE are delivered in very defined and reproducible parameters. However, combined programmes still need to be evaluated without the confounding variable of compliance.

“Hatha Yoga” also appears to offer favourable outcomes for PwMS and is delivered frequently by MS Ireland in the community. Additionally, other exercise professionals may meet some of the needs of PwMS with minimal gait impairment which may take the strain of providing long term management of PwMS off health services. The content and efficacy of community-based exercise programmes is unknown.

Future research should focus on eliminating selection and detection by describing adequately the randomisation process and having an assessor blind to intervention.
CHAPTER 3: VARIABLES THAT MAY INFLUENCE OUTCOME IN PEOPLE WITH MULTIPLE SCLEROSIS

3.0 INTRODUCTION

In Chapter 2, several studies indicated that exercise is effective for People with MS (PwMS). However, large variability for point estimates of pre-intervention, post intervention and change scores reflect the variability of the disease and indicate that an effective intervention is not equally effective for all participants.

Establishing variables predictive of outcome and identifying participants that best respond to interventions can lead to targeted delivery of effective programmes and prompt the development of better interventions for those who did not respond favourably. Thus, the aim of this chapter is to explore variables that may influence the response to exercise based interventions so that a post-hoc exploration of results may be conducted.

Variables such as lesion load, brain volume and grey matter degeneration (Fisniku et al. 2008) may influence disease progression in PwMS. However, this information is usually not readily available in community care. There are other variables that may influence outcome of the disease over time due to the natural history of the disease. These variables may also influence the response to an exercise intervention. These are type of MS, gender and age at onset of MS. Other variables that may specifically influence the response to exercise interventions include body function and structure variables of somatosensation (tactile and proprioceptive sensation), co-ordination dysfunction (ataxia), tone (resistance to passive movement), strength and baseline exercise participation and adherence to interventions.
The variables explored in this chapter are those commonly assessed in clinical practice by a Chartered Physiotherapist as part of a routine neurological assessment in PwMS. These are type of MS, gender, age at onset, somatosensation, tone, co-ordination, strength, adherence and baseline exercise participation.

3.1 VARIABLES IDENTIFIED BY NATURAL HISTORY STUDIES

3.1.0 INTRODUCTION

While a single reliable prognostic marker is not yet available, a series of indicators have been identified from natural history and epidemiological studies. These include type of MS, age at onset and gender. These natural history studies were conducted using the Kaplan Meier method. The end point was the time to assignment of irreversible disability landmarks as indicated by a score of 4, 6 or 7 on the Kurtzke Disability Status Scale. As this thesis concerns PwMS who use at most one stick to walk, the following paragraphs will focus on time to EDSS 6. Subjects in these studies were recruited using geographically defined populations rather than hospital based patients thus, representing the most accurate information.

3.1.1 TYPE OF MS

It has been consistently shown that assignment of irreversible disability landmarks occurs sooner in people with primary progressive MS (PPMS) than those with RRMS, thus people with different types of MS may achieve different outcomes as a result of exercise interventions depending on the natural history of the subtype.

Confavreux et al (2000) found that the median time to an EDSS of 6 in RRMS (n = 1562) was 23.1 years (95% CI 20.1, 26.1) with 73 (5%) of participants not meeting the end point. In PPMS (n = 282), time to an EDSS of 6 was a median of 7.1 (95% CI 6.3,
In another study, over half of the people with PPMS \( (n = 216) \) reached Disability Status Scale (DSS) 6.0 at median of 8.7 years (Cottrell et al. 1999).

In a recent study, out of 5779 patients with definite MS, 553 \( (10\%) \) had PPMS. Of these 109 \( (19.7\%) \) were ineligible as they had already reached an EDSS of 6.0. This may explain why the median time to EDSS 6.0 was 14 years \( (95\% \text{ CI } 11.3, 16.7) \) (Koch et al. 2009). The cumulative evidence suggests that people with RRMS have a more favourable disease course than those with PPMS, thus in the context of the disease course and pathophysiology, it is feasible that people with RRMS would appear to fare better from an exercise intervention.

Most studies use types of MS as defined by a panel of international experts in MS (Lublin and Reingold 1996). These were RRMS, Secondary Progressive MS (SPMS), PPMS and Relapsing Progressive MS (RPMS). It is difficult to compare SPMS in this context, as participants may reach EDSS 6.0 before progression is identified. Additionally, due to the initial relapsing-remitting course and occasional minor, remissions, categorisation is even more arbitrary. Thus the effect of intervention studies should be compared separately for RRMS and PPMS as they are more distinct clinical entities.

**3.1.2 AGE AT ONSET**

Younger age at onset has consistently been associated with a longer time to assignment of irreversible disability landmarks. Conversely, an older age at onset has consistently been associated with a shorter time to accumulation of irreversible disability.

In a population based cohort, “age at onset” was categorised into decades \( (<20, 20-29, 30-39, 40-49, \geq 50) \) and found progressively shorter times to EDSS 6 with increasing age of onset from a median of 33.3 years when onset began under the age of 20 compared to progression in a median of 10.2 years in those whose onset was at age 50 or more,
p <0.0001 (Debouverie 2009). Similar findings were reported in another study where late-onset MS (LOMS) was defined as patients who were > 50 years at diagnosis. Young-onset MS (YOMS) was defined as < 40 years at diagnosis. The progression index (EDSS score/disease duration) was calculated for each group. The progression index for each group was 0.60 for the LOMS group and 0.35 for the YOMS group. A relapsing remitting course was more frequent in the YOMS group (49/52, 94%) than the LOMS group (43/52, 8%), p = 0.001 (Kis et al. 2008). Another group also divided up “age at onset” by decade. Patients in the < 30 years category at onset had the longest time to EDSS 6.0, p = 0.004 (Koch et al. 2009). For comparability, age at onset should be examined as a potential predictor of outcome by decades, as well as in continuous form.

While age at onset may influence progression of the disease over time, there may be a different response to exercise intervention in the context of age.

3.1.3 GENDER

Gender differences are frequently reported in PwMS. Firstly, the disease is more common in women than in men and secondly women appear to have a more favourable outcome than men. These gender differences have been found in people with RRMS and SPMS. Due to the differing hormonal composition of males and females and hormonal responses to exercise, there may also be different response to exercise-based interventions in males and females.

It has been demonstrated that male gender is associated with an earlier age at assignment of irreversible disability landmarks and female gender is independently associated with an older age at assignment of irreversible disability landmarks (Confavereux and Vukusic 2006). Debouverie et al (2009) echoed that time to EDSS 6 scores was significantly longer in females (median 24.3 years 25th and 75th percentiles: 14.5 – 36) than in males (median 19.2 25th and 75th percentiles: 11.6 – 31.7), p < 0.0001.
Additionally, Tremlett and colleagues showed that males reached SPMS more rapidly from onset than females (p<0.0005) and at a younger age (P<0.0005), the difference in both cases averaged 3-5 years (Tremlett et al. 2008).

Pozzilli et al (2003) provides additional support for a gender difference in the MRI characteristics occurring in the brain as a result of MS. Participants had mostly RRMS (n = 266) or SPMS (n = 147). Men (n = 132) had a median of 0 Gadolinium (Gd) enhancing lesions (indicating inflammation) and women (n = 281) had a median of 1. There was a higher proportion of T1-hypointense lesions (indicating axonal loss and disease progression) in men compared to women (Men had a median 11 lesions, n = 132; Women had a median 10 lesions, n = 281, p = 0.09). While this is a cross-sectional study, this study is suggestive of a gender difference in PwMS whereby men develop less inflammatory and more degenerative lesions than females (Pozzilli et al. 2003). Furthermore, a tendency for more pronounced remyelination has been identified in women compared with men (Goldschmidt et al. 2009).

In one exercise intervention to date that examined gender differences - women, but not men showed reduced motor fatigue after a six month exercise period (Surakka et al. 2004). Although there were methodological limitations to this study (discussed in Chapter 2), this is the only study to date that examined gender differences in response to an exercise intervention. It was also found that adherence was slightly lower in men compared to women, which may have accounted for some of the differences.
3.2 IMPAIRMENT

3.2.0 INTRODUCTION

Current clinical status according to presence or absence of sensory impairments, proprioception, co-ordination, tone and strength and acknowledging other variables such as baseline exercise activity and adherence to programmes may have a significant impact on the outcome of the interventions. Langdon and Thompson (1999) suggested that any or all of the physical, cognitive and emotional attributes of person with MS may have an impact on the progress that they are able to make in rehabilitation. This applies to any type of intervention. There is some evidence suggesting that current clinical signs may influence the outcome in response to exercise interventions. These include somatosensation, ataxia, tone and strength which will be described in the following sections.

3.2.1 SOMATOSENSATION

Altered somatosensation (tactile and proprioceptive sensation) may be a potential confounder for response to an exercise intervention. A potential mechanism for this is that sensory input modulates muscle contractions (Shumway-Cook and Woollacott 2001). Additionally, the responses of neurons to sensory stimuli may be affected by their context. Thus, the lack of sensation may confound the ability to improve at participation level.

The true incidence of sensory impairments in people with MS is unknown as most of the literature to date focuses on objective measures of physical and motor performance rather than sensory impairments. Two small scale studies have attempted to assess the occurrence of these symptoms. In a postal survey that assessed the frequency and character of a variety of symptoms in multiple sclerosis, half of the respondents (n = 106/213) reported having transient neurological events lasting seconds to minutes not
compatible with an acute exacerbation, 40% (47/106) of whom reported having altered sensation as this transient episode. Furthermore, 10% (n = 24) of all respondents reported paresthesias as their worst symptom (Rae-Grant et al. 1999). In another study, 78% (61/78) of toes tested had abnormal vibration sensation (Zackowski et al. 2009).

In the stroke literature the incidence of sensory dysfunction varies between 11% to as high as 85% (Sullivan and Hedman 2008). Stroke and MS share lesions in the somatosensory cortex in the brain and sensory impairments in their clinical presentation, and due to the lack of specific information regarding sensory impairment in PwMS, it is logical to look to the wealth of stroke literature for information regarding sensory impairments. However, caution needs to be taken when extrapolating evidence from an acute vascular lesion to that of a chronic progressive inflammatory and degenerative disease.

The stroke literature has consistently demonstrated that normal somatosensory function 10 days post stroke, predicts positive outcomes and that somatosensory impairment is not strongly related to negative outcome. One well conducted study (n = 77) demonstrated that participants with normal somatosensory function (identified using pinprick, light touch and thumb localising test) had significantly (p <0.001) better activity scores (median Barthel Index (BI) = 85, quartiles (Q): 55-95, median Rivermead Mobility Index (RMI): 8.5, Q: 5 – 12) and length of stay than patients with overall impaired somatosensory function (median BI: 40, Q: 20 -60, median RMI: 2, Q: 0 – 3). Using Keplan-Meier curves, it was evident that a large proportion (0.9) of people with normal somatosensation was discharged home within 3 months. However, 0.7 of the impaired group remained in hospital. Using a Cox proportional hazard regression model, the relative risk of discharge home within 3 months was 1.0 for those with impaired somatosensory dysfunction and 15.3 for those with normal somatosensory function (Sommerfeld and Von Arbin 2004). Similarly, in 115 participants over the age of 65, using multivariate logistic regression, normal proprioception (thumb localising test) was significantly associated with better mobility according to the RMI (Odds Ratio 3.4, 95% CI = 1.1, 10.6) (Welmer et al. 2007, Tyson et al. 2008).
A more recent study (n = 102) reported moderate and statistically significant relationships between somatosensation (tested using the Rivermead Assessment of Somatosensory Performance 20) and independence in ADL and mobility (measured using the BI and RMI) in the acute stages (r = 0.416, p < 0.005 to r = 0.515, p < 0.005) and low to moderate, statistically significant relationship at follow-up 3 months after stroke (r = 0.287, p <0.01 to r = 0.533, p <.005) (Tyson et al. 2008). In another study (n = 26), tactile extinction (measured using a “Face-Hand Test”) at one month post stroke accounted for 23% (P<0.05) of the variability in Functional Independence Measure (FIM) score at six months post stroke and 20% (P<0.005) when measured 3.5 months post stroke (Rose et al. 1994).

Based on the stroke literature, it is plausible that people with normal somatosensation may present as a subgroup of responders to exercise interventions.

3.2.2 CO-ORDINATION

Ataxia is the general term used to describe the abnormal co-ordination of movements (Carr and Shepherd 2004). It is demonstrated by deficits in speed, amplitude of displacement, directional accuracy and force of movement (Brown et al. 1990). There are many clues that ataxia maybe due to dysfunction of the cerebellum. However, in MS lesions in isolation are rare thus ataxia may be cerebellar of origin, sensory or both (Koch et al. 2007).

The incidence of cerebellar type symptoms of ataxia and tremor in PwMS is high, with about 25.5-80% reporting symptoms (Pittock et al. 2004, Swingler and Compston 1992). A Cochrane review for treatment of ataxia in MS found that due to poor methodological quality of studies, small numbers of participants, problems with measurement and poor results of trials to date, there is not enough evidence to suggest that any treatment (drugs, physiotherapy or neurosurgery) provides sustained improvement in ataxia or tremor (Mills et al. 2007).
Ataxia appears to be a resistant symptom that is difficult to treat. This may be because cerebellar lesions may have reduced capacity to remyelinate in PwMS. In 18 chronic cerebellar lesions, the majority of plaques (72%) were characterised by complete demyelination (Goldschmidt et al. 2009). However, this may also be explained by the chronicity of the lesions rather than the location. Evidence also suggests complex roles for the cerebellum in motor learning (Saywell and Taylor 2008) thus potentially reducing the capacity of people with cerebellar lesions to achieve an autonomous stage of skill acquisition.

In a study of 38 consecutive patients admitted to a rehabilitation unit of mostly “chronic progressive MS” (Langdon and Thompson 1999), a Kurzke Cerebellar function (along with baseline FIM and WAIS-R vocabulary) accounted for a significant proportion of the variance ($R^2 = 0.57$, $p <0.001$) to the change in the Functional Independence Measure. It is not reported if this was a positive or negative association. Participants in this study had a mean EDSS of 7.5 (range 5.0 – 9.0), thus results may not be comparable to a population with an EDSS $\leq 6.0$.

In a study evaluating an AT intervention of cycle ergometers, the training group showed improvements in two out of three co-ordinative tasks and the control group showed deterioration. Large variability was displayed as illustrated by large standard deviations in both groups pre and post intervention (Schulz et al. 2004). All participants had an EDSS <4.0 but nothing is known about their clinical characteristics.

No study to date has evaluated how people with co-ordination difficulties respond to an exercise-based intervention.

### 3.2.3 Tone
Increased tone is an abnormal resistance to passive movement. It may be as a result of central factors affecting motor output such as spasticity and peripheral mechanical
factors. Spasticity is a velocity-dependent increase in tonic stretch reflexes, which results from abnormal spinal processing of proprioceptive input (Sheean 2002). Mechanical factors may include compliance of the muscle, tendon and connective tissue.

Recent evidence from the Patient Registry of North American Research Committee on MS (NARCOMS) indicated that 84% of the total sample (n = 20,380) reported spasticity. Spasticity was described for the patients as “unusual tightening of muscles that feels like leg stiffness, jumping of legs, a repetitive bouncing of the foot, muscle cramping in legs or arms, legs going out tight and straight or drawing up”. Of those who reported spasticity 31% reported that spasticity was minimal. 19% reported mild (occasional), 17% moderate (frequently affects activities), 13% severe (need to modify daily activities) and 4% total (prevents daily activities). Those who reported minimal or mild spasticity had a mean Patient determined Disease Steps Score (PDSS) of 3.45 (SD, 2.2), those who had moderate spasticity had a PDSS of 4.75 (SD 1.7). This means that those who had minimal to moderate spasticity also reported being able to walk with at most one stick (Rizzo et al. 2004). A smaller study in Britain found that 97% of the whole sample (n = 68) demonstrated lower limb spasticity in either leg as demonstrated by a Modified Ashworth Scale (MAS) score of 1 or more. Fifty per cent of the sample had detectable upper limb spasticity as judged by the same criterion (Barnes et al. 2003).

Repetitive exercise has consistently demonstrated decreases in tone in people with moderate increases in tone. A crossover study examined the changes in spastic tone in five people with a complete spinal cord injury, using functional electrical stimulation (FES) to induce cycling movements and passive leg movements (Krause et al. 2008). As people with complete spinal cord lesions have no active movement below the level of the lesion, FES is the only way to simulate repetitive active exercise. Using FES for between 60 to 90 minutes always resulted in a significant reduction of spastic muscle tone when measured by the MAS and pendulum testing using an electrical goniometer (31% -207% improvement in peak velocity). Only in one participant did the passive
training session result in improved scores in the pendulum test. Both groups resulted in statistically significant reductions in the MAS but these were not different from each other. In six PwMS, with minimal gait impairment, Motl et al (2007) showed that tone, as measured by the H-reflex and MAS, was reduced in response to a single bout of unloaded leg cycling. The group at the University of Illinois at Urbana-Champaign also showed that although there were no reductions in the H-reflex and MAS after 4-weeks on unloaded leg cycling, 3 times a week for 30 minutes (n = 12), Multiple Sclerosis Spasticity Scale-88 scores were reduced (Sosnoff et al. 2009). This may be because acute cycling may result in short term reductions in spasticity. In the acute cycling bout, measurements were taken 10, 30 and 60 minutes post exercise but the chronic exercise condition was measured 1 day, 1 and 4 weeks after the 4-week period, which may explain why the objective measures did not detect change in the chronic exercise condition but the subjective measure did. It was reported in all studies that there were no adverse effects or increases in tone due to the active interventions.

Using the MAS, no distinction is made between resistance to passive movement due to reflex hyperactivity or increased mechanical stiffness. Both seem likely to improve using active repetitive exercise by improving neural control of the muscle and by improving the extensibility of the muscle. Thus, participants with moderately increased tone may be likely to do well from exercise-based interventions. Due to the apparent short lasting effects, improvements may be confounded by the frequency of exercise participation.
3.2.4 Strength

Reduced or lack of strength is a primary impairment in PwMS. Community-based cohort reported “weakness” as a main impairment and PwMS have reduced strength compared to normative values (Reich et al. 2008, Coote et al. 2010, Khan et al. 2006). This can be due to the disease itself with lesions along central motor pathways (Reich et al. 2008), inactivity reported in PwMS (Motl et al. 2005) or a combination of both (Dalgas et al. 2008). Weakness is the third largest barrier to employment cited by 56% of PwMS (N = 2134) after fatigue and mobility related problems.

It had been noted that PwMS demonstrate a reduced number and size of Type IIa muscle fibres (Dalgas et al. 2010a). For such a primary impairment, there is a paucity of literature examining different aspects of strength and appropriate interventions in PwMS. In PwMS, studies that have shown improvements in strength have also shown improvements in function (Dalgas et al. 2009). Level 1a evidence has shown that normal aging populations also demonstrate a consistent reduction in Type IIa muscle fibre size (Brunner et al. 2007). Thus, extrapolation from the aging population might help to inform the relationship between strength and function.

In an older population (aged 70±7.9 years), strength accounts for some (3 – 38%) of the variance seen in functional tasks (Knutzen et al. 2002).

PwMS with strength impairments are likely to demonstrate improvements in strength from an intervention that includes a strengthening component. This improvement may be associated with a moderate and statistically significant improvement in functioning or participation levels. Thus baseline strength should be considered as a predictor of outcome in these types of interventions.
3.3 Baseline exercise participation level

The variety in baseline activity of participants in the PRE studies identified in Chapter 2 means that comparison of the magnitude of effect of the differing interventions is difficult. Studies of exercise training should consider baseline measures of participants’ exercise levels to allow comparison between previously active and inactive participants.

3.4 Adherence

Studies to date have not consistently accounted for adherence to exercise programmes. Less than half of all quantitative exercise studies conducted since 2004 reported adherence to programmes (Dalgas et al. 2009, Taylor et al. 2006, Gutierrez et al. 2005, White et al. 2006b, Newman et al. 2007, McCullagh et al. 2008, McAuley et al. 2007, Oken et al. 2004). As participation in interventions may influence outcome, future studies should examine if there is a relationship between adherence and outcome.
3.5 Conclusion

To date, studies evaluating exercise programmes have not adequately described the clinical characteristics of their participants. In a heterogeneous population, this is fundamental in order for effective programmes to be applied appropriately in the clinical setting. Additionally, adequate description of participants’ characteristics can allow identification of factors that predict outcome.

In this chapter, variables that may influence the response to exercise-based interventions have been described. These were type of MS, age at onset and gender were identified in natural history studies and any intervention should be analysed in the context of the natural history of the disease. Sensation, proprioception, co-ordination, tone and strength are aspects of body structure and functions that are commonly impaired in PwMS. These are assessed in practice by Chartered Physiotherapists. Additionally, baseline exercise participation level and adherence are logical contributors to outcome.

Potential favourable predictors of outcome are having RRMS, a young age at onset, being female, having normal somatosensory function, no more than a moderate increase in tone, and adhering to the programme. Other variables including PPMS, older age at onset, being male and co-ordination impairment are associated with negative outcomes. These variables will be considered going forward when describing the cohort in order to inform generalisability of the findings and in order to conduct a post-hoc exploration of results to identify the participant characteristics that that best predict outcome after the intervention period in the present study.
CHAPTER 4: METHODOLOGY COMMON TO THE PILOT AND THE MAIN STUDY

4.0 INTRODUCTION

The overarching aim of this thesis was to inform Multiple Sclerosis Ireland regarding what exercise programmes should be provided for PwMS with minimal gait impairment.

The objectives of the present study were as follows:

- To establish the efficacy of the three community-based exercise interventions
- To establish if there was a difference between groups due to intervention
- To investigate the results three months after the intervention
- To investigate the predictors of outcome after the intervention period

Two studies were conducted. A small pilot study was completed as a logistical exercise and to assess the feasibility and the suitability of the measures. A main study was carried out to meet the aforementioned objectives. In this Chapter the participant selection criteria and the outcome measures which were common to both will be described. This will be followed by the methodology for and learning from the pilot study and the methodology for main study in the two following chapters separately.
4.1 Participant Selection Criteria

4.1.1 Inclusion Criteria

Participants who fulfilled the following criteria were eligible for inclusion in both the pilot study and the main study:

1. A diagnosis of MS confirmed by a Neurologist to the participant.

2. A Guys Neurological Disability Scale (lower limb disability section) score of 0, 1 or 2. This means that participants usually use unilateral support (single stick, crutch, one arm) to walk outdoors, but walk independently indoors (Sharrack and Hughes 1999). This simple classification was extrapolated from a larger tool to provide a simple screen so that administrators could ensure participants would be allocated to the correct strand of the project over the phone.

3. Over the age of eighteen years.

4. Participants with any type of MS were included as this reflects the presentation of PwMS in the community. People with PPMS tend to be more impaired than people with RRMS. Therefore, people with PPMS could have as much, if not more to gain from participating in an exercise intervention as participants with RRMS. Thus, the type of MS was be documented and put into the prediction of outcome model to account for the different disease subtypes.

4.1.2 Exclusion Criteria

Participants were excluded if they were under any of the following conditions at the time of assessment:

1. Currently experiencing an exacerbation of symptoms due to relapse.

2. Had steroid treatment or a relapse within 3 months prior to baseline measurement.
3. Had any co-morbidity that severely impacted on the ability to safely participate in exercise as assessed by a Chartered Physiotherapist.

4. Were pregnant at the time of referral.

5. Aged less than 18 years of age were excluded.

4.2 **OUTCOME MEASURES**

This section describes the rationale, description, development, validity, reliability and sensitivity to change of the measures chosen to evaluate outcome in the pilot study and the main study.

4.2.1 **JUSTIFICATION FOR BATTERY OF MEASURES CHOSEN**

The Multiple Sclerosis Impact Scale-29 (MSIS-29, v 2), the Modified Fatigue Impact Scale (MFIS), the Six Minute Walk test (6MWT) and Hand-held dynamometry (HHD) were chosen to evaluate outcome. These tools measure important outcomes for PwMS. Emphasis is on the Multiple Sclerosis Impact Scale-29. In a chronic condition, where there is no cure, the aim of intervention is to minimise the impact of the disease. The World Health Organisation-International Classification of Functioning (WHO-ICF) framework supports measuring outcome at the level of participation. Additionally, a primary outcome should have strong psychometric properties so that it truly contributes to knowledge. The MSIS-29, v2 (physical component) adequately addresses these issues, thus it is appropriate to use this as the primary outcome.

**Participation: Multiple Sclerosis Impact Scale-29, version 2**

Evidence suggests that there is a difference in what major issues are for PwMS and health professionals (Dua et al. 2008). In the modern view of multidisciplinary teams,
the PwMS is at the centre of the teams, thus robust patient reported outcomes should be chosen to reflect their priorities.

The review of the literature in Chapter 2 showed that the following participation scales have been used to evaluate HRQoL or QoL after an exercise intervention in PwMS: Multiple Sclerosis Quality of life-54, Short Form-36, Hamburg Quality of Life Questionnaire in Multiple Sclerosis, Medical Outcomes Study Short Form-12, Multiple Sclerosis Quality of Life Inventory, Multiple Sclerosis Impact Scale-29 (MSIS-29), Satisfaction with Life Scale and the Sickness Impact Profile.

Studies have consistently found that the MS specific measures had more sensitivity to change than generic measures. Additionally, when comparing the different MS specific instruments, the MSIS-29 consistently showed the strongest psychometric properties (Riazi et al. 2003b, Riazi 2006, Motl and Gosney 2008, Hobart et al. 2005).

The developers of the MSIS-29 used interviews with PwMS in developing all of the questions, thus all items are of importance to PwMS (Hobart et al. 2001). Psychometric evaluation yielded the best results for use in PwMS, and so this scale was chosen as the primary outcome of interest to measure the impact of the disease at the level of participation.

### Participation: Modified Fatigue Impact Scale

Fatigue is a main problem for PwMS with many personal and social implications. Compared to the general population, PwMS report fatigue as one of their worst problems (68% vs 21%). It causes significantly more impact in daily activities among individuals in PwMS (Md = 71, Q₁ = 45, Q₃ = 95 vs Md = 13, Q₁ = 2, Q₃ = 43.25, p = <0.001) and PwMS experience more hours of fatigue per day (6-12 hours per day vs <
hours per day) and days of fatigue per month (Md = 20-29 days vs Md = 1-4 days, p <0.001) (Flensner et al. 2008).

In a recent study conducted by the Multiple Sclerosis International Federation of nearly 8,700 people with MS in 125 countries, 85%, of those who were unemployed due to MS (N = 2,957), reported that fatigue was the biggest barrier to employment (Chandraratna 2010). Another study commissioned by the MSIF into the global economic impact of MS highlighted that loss of employment / early retirement as the single largest cost factor in the total cost of MS (Trisolini et al. 2010). From a large population based study – it was estimated that workers with fatigue cost employers $136.4 billion USD annually in health related Lost Productive Time (LTP), an excess of $101.0 billion compared to workers without fatigue. When fatigue exists with conditions such as pain, cold or flu, feeling sad or blue, allergies, asthma, cancer and heart disease, there is a threefold increase with the proportion of workers with LPT. Fatigue has also been associated qualitatively and quantitatively with falls in PwMS (Hogan et al. 2010, Nilsagård et al. 2009). Additionally, fatigue has been implicated with approximately 10% of serious road crashes (Philip et al. 2005).

There is no universally accepted definition or cause of fatigue in PwMS. What is acknowledged is the multifactorial and subjective nature of fatigue. The review of the literature in Chapter 2 identified that primarily two scales have been used to assess the impact of fatigue in PwMS in interventions studies. These are the Fatigue Severity Scale (Kileff and Ashburn 2005, Van den Berg et al. 2006, Pariser et al. 2006, Newman et al. 2007, Surakka et al. 2004) and the Modified Fatigue Impact Scale (Rampello et al. 2007, McCullagh et al. 2008, White et al. 2006b, Dalgas et al. 2010b, Sabapathy et al. 2010, Dettmers et al. 2009). The review also found that the MFIS appeared more sensitive to change than the FSS. Thus, the MFIS was chosen to evaluate outcome.
Activities: Six Minute Walk Test (Walking distance)

Walking is a major limitation in MS with between 50 and 90% of PWMS reporting problems (Sutliff 2010). PwMS perceive gait function as the most important domain (Heesen et al. 2008a) Walking ability is predictive of independence in ADLs (Paltamaa et al. 2007), community ambulation (Gijbels et al. 2010) and participation in Physical Activity (Motl et al. 2008). After fatigue, mobility related problems (difficulty walking/moving) are the second largest barrier to maintaining employment (Chandraratna 2010).

The review of the literature suggested that the 6MWT is more sensitive to change with statistical significance consistently reached after an intervention. This is the most logical test to measure walking ability in PwMS with minimal gait impairment as sometimes shorter measures such as the 2MWT or 10-m walk do not pick up impairment such as dropped foot or fatigue which is often seen clinically in these types of PwMS.

Impairment: Handheld dynamometry (Strength)

Strength is a primary impairment in PwMS as described in Chapter 2. Measurements of strength can be taken using an isokinetic dynamometer (IKD) which is the gold standard of strength measurement (Miller and Dishon 2006). However, IKD is expensive and not portable for use in a community based trial. Alternatives are handheld dynamometry (HHD) or manual muscle testing (MMT). MMT is based on an ordinal system of grading movement against gravity or examiner resistance (Giesser 2002). Manual muscle testing has long been reported as inadequately precise as a measure of strength. Thus, HHD was chosen as the measure of strength outcome.
4.2.2 Multiple Sclerosis Impact Scale – 29, Version 2: Description, Development and Psychometric Properties

Description

The MSIS-29 is a 29 item questionnaire which aims to measure the physical and psychological impact of MS from the patient’s perspective. It has two subscales: a 20-item physical impact scale and a 9-item psychological impact scale. Increasing scores on the questionnaire indicate a greater impact of MS. All items in the original scale have five response categories (not at all, a little, moderately, quite a bit and extremely) that are assigned sequential integers (1, 2, 3, 4 and 5). Total scores for the two scales are achieved by summing the item scores for the 20 physical items (items 1-20) and the psychological items (21-29). Thus, possible scores on the physical scales are 20-100. Scores on the psychological component are 9-45.

Version 2 of the scale has the “quite a bit” response category removed (Appendix A), and the subsequent assignment of integers was 1-4 to the four item response categories. Thus, scoring of Version 2 is from 20-80 for the physical component and 9-36 for the psychological component (Hobart and Cano 2009).

Scores are converted separately for both components, to a 0 - 100 scale using the following formula:

\[
100 \times \frac{(\text{Observed score} - \text{minimum score})}{(\text{Maximum score} - \text{minimum score})}
\]

Development

The original MSIS-29 was the first MS specific instrument developed using a robust psychometric approach and involved PwMS in its generation. It was developed in three stages – item generation, item reduction and an evaluation of its psychometric properties (Hobart et al. 2001). Questionnaire items were generated from 30 patient interviews on the impact of MS on their lives.
Data were transcribed and content was grouped into themes. Data reached saturation after 20 interviews. These statements generated 91 questionnaire items. Interviews were also conducted with health professionals who were involved in the care of PwMS. These interviews generated a further 38 items. The preliminary 129-item questionnaire was reviewed for content, wording and clinical appropriateness by patients and clinicians who were involved in its development. It was then administered by postal survey to 1530 randomly selected members of the MS Society. Standard item reduction techniques were used to develop the 29 item scale. Standard item reduction involved using descriptive statistics and reliability estimates to identify redundant items. In a second part to this study, the authors evaluated its psychometric properties which are described below. Most of the participants in this study (n = 766) could walk (79%), thus, this scale is relevant for participants selected for inclusion in the present study.

In all trials, psychometric analysis of the MSIS-29 was performed separately for the physical and psychological components. The following paragraphs describe the validity, reliability and sensitivity to change for the original MSIS-29.

**Validity**

By reading the questionnaire and taking into account the manner in which it was developed – it is evident that this measure has face and content validity, thus being fit for purpose. It also had good construct validity. The MSIS-29 was validated in a large (n = 200) outpatient clinic-based sample of people with MS (Hoogervorst et al. 2004). The main hypothesis of this study was that the correlation between the MSIS-29 and Guys Neurological Disability Scale (GNDS), Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) would be the strongest with the GNDS followed by the EDSS and lowest with the MSFC. As expected, Hoogervorst and colleagues (2004) found the MSIS-29 physical component is strongly correlated with the GNDS (r = 0.79). It was moderately correlated with EDSS (r = 0.68) and the MSFC (r = 0.53). The psychological component had moderate correlation with the GNDS (r = 0.58) and low correlation with the EDSS (r = 0.22) and MSFC (r = -0.30).
The GNDS, EDSS and MSFC are measures of physical impairments. They were not appropriate constructs against which to measure the psychological impact of MS. Construct validity was further examined by McGuigan and Hutchinson (2004). The physical component of the MSIS-29 was tested against the EDSS, MSFC and London Handicap Scale (LHS) in a community population and against the EDSS in an outpatient population. The psychological component was assessed against the Beck’s Depression Inventory (BDI-II), a generic measure of depression, which is more appropriate scale on which to assess construct validity for the psychological component of the MSIS-29 (McGuigan and Hutchinson 2004). In 172 community-based patients with a mean EDSS of 4.4 (SD 2.3) there was a correlation of 0.704 with the EDSS, 0.843 with the LHS – also a measure of participation and a moderate correlation of 0.577 with the MSFC. These results are similar to those of Hoogervorst et al (2004). The psychological component correlated highly with the BDI-I1 (r = 0.799). Similarly to Hoogervorst et al (2004), the psychological component correlated poorly against the EDSS and the MSFC (r = 0.095 and 0.020 respectively). These findings indicate that the physical and psychological components measure different constructs.

**Reliability**

The original authors of the scale reported test re-test reproducibility (ICC) of 0.94 (Hobart et al. 2001). Two questionnaires (separated by a ten day interval) were completed by 32 people who could walk unaided, 40 people who walked with an aid and 28 participants who use a wheelchair. The authors did not report a measure of absolute reliability. Table 12 summarizes the studies that have independently examined the relative and absolute reliability of the MSIS-29.
<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Setting</th>
<th>Mobility level</th>
<th>Reliability Physical component (Cronbach’s alpha)</th>
<th>SEM Physical component</th>
<th>Reliability Psychological component (Cronbach’s alpha)</th>
<th>SEM Psychological component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riazi et al (2002)</td>
<td>53</td>
<td>Rehabilitation</td>
<td>EDSS 7.1 (SD .8)</td>
<td>0.88</td>
<td>6</td>
<td>0.87</td>
<td>8.8</td>
</tr>
<tr>
<td>Riazi et al (2002)</td>
<td>76</td>
<td>Corticosteroid</td>
<td>EDSS 5.6 (SD 1.1)</td>
<td>0.94</td>
<td>5.7</td>
<td>0.91</td>
<td>7.8</td>
</tr>
<tr>
<td>Riazi et al (2002)</td>
<td>104</td>
<td>PPMS</td>
<td>19 walk unaided, 54 walk with an aid, 28 use a wheelchair</td>
<td>0.95</td>
<td>5.2</td>
<td>0.92</td>
<td>6.9</td>
</tr>
<tr>
<td>Riazi et al (2002)</td>
<td>703</td>
<td>Community</td>
<td>32 walk unaided, 40 walk with an aid, 28 use a wheelchair</td>
<td>0.96</td>
<td>5.3</td>
<td>0.91</td>
<td>7.6</td>
</tr>
<tr>
<td>Riazi et al (2003)</td>
<td>121</td>
<td>Rehabilitation</td>
<td>EDSS 6.4 (SD 1.2)</td>
<td>0.91</td>
<td>6</td>
<td>0.89</td>
<td>8.4</td>
</tr>
<tr>
<td>Mc Guigan and Hutchinson (2004)</td>
<td>36</td>
<td>Community</td>
<td>EDSS 4.4 (SD 2.3)</td>
<td>0.96</td>
<td>5</td>
<td>0.89</td>
<td>9.2</td>
</tr>
</tbody>
</table>

N = Number of participants, Rehab = Rehabilitation, PPMS = Primary Progressive Multiple Sclerosis, EDSS = Expanded Disability Severity Scale, SD = Standard deviation, SEM = Standard error of the measure
Responsiveness

Several studies suggest that the MSIS-29 is more responsive than other measures of participation. These are outlined below.

The original authors of the scale reported a good effect size of 0.82 for the physical component of the MSIS-29 and a moderate effect size (ES) for the psychological component (Hobart et al. 2001). They had 55 participants who had participated in inpatient rehabilitation or intravenous steroid treatment. As treatment of intravenous steroids may clinically have a larger effect than rehabilitation it would be useful to calculate an ES for both groups separately which is what the group did next in a sample of 245 participants (Hobart et al. 2005). In a rehabilitation group of PwMS the MSIS-29 (physical component) had an effect size of 0.64, the ES for the Short Form 36 Health Survey (SF-36PF) was 0.45 and in the 59-item Functional Assessment of MS (FAMS), it was 0.61. In a steroid intervention group, the MSIS-29 also had the largest ES compared to the other measures (ES: 1.11). Responsiveness was independently examined by McGuigan and Hutchinson (2004) who found a high ES of 1.25 in 17 hospital attendees who were defined as having changed by one point or more on the EDSS between the two time points (6 months). On the same criteria for change, in another study there was an ES of 0.93 in 71 patients, for 2 points of the EDSS they found an ES of 1.4 and for 3 points the ES was 2.2 (Costelloe et al. 2007). Costelloe et al (2007) further divided up participants into EDSS range 0-5 and EDSS range 5.5-8.5. In the participants with an EDSS 0 – 5 there was a moderate ES of 0.57 in those who changed 1 EDSS step. However, they found that change in MSIS-29 and change in EDSS had a low correlation (SCC = 0.33). Thus, using EDSS as a construct for change is probably not suitable. This means that factors other than walking ability affect the impact of MS in people with a low EDSS score. Thus the minimally important MSIS-29 physical change score is most likely redundant as it is depending on change in EDSS to predict a change in the impact of MS.
Hobart et al (2005) reported an ES of 0.64 and 0.44 for the psychological component of the MSIS-29 after a rehabilitation intervention. In consultation with the Statistical Consulting Unit at the University of Limerick, it was deemed necessary to have 57 participants per group to have sufficient power to detect an ES of 0.44 with 90% power using a paired t-test with a 0.05 two-sided significance level.

**MSIS-29, v2**

In the pilot study the original version of the MSIS-29 as described above was used. However, the author of the MSIS-29 recommended version 2 of this scale for future studies.

A Rasch analysis of the MSIS-29 detected important limitations of the MSIS-29 which were not identified by traditional psychometric methods and converted it to an interval level scale rather than an ordinal outcome. The five-category item scoring function did not work as intended for nine items in the physical subscale and one item in the psychological subscale (Hobart and Cano 2009). Participants were less likely to distinguish reliably between “moderately”, “quite a bit” and “extremely”. Thus, the category of “quite a bit” was removed. This change should, in theory, make the scale more reliable and more balanced.

In conclusion, the MSIS-29 is a valid, reliable measure that is responsive following an intervention and has stronger psychometric properties than other participation scales that have been evaluated in PwMS with minimal gait impairments. This was used in the pilot study. During this time the original authors conducted Rasch analysis on the scale. This converted the scale to interval level data. By removing one response category, the resulting Version 2 of the scale should be more reliable and balanced. This was used in the main study going forward from the main study and chosen as the primary outcome.
4.2.3 Modified Fatigue Impact Scale: Description, Development and Psychometric Properties

Description

The MFIS is a 21 item scale which aims to measure the impact of fatigue from the patient’s perspective (Appendix B). All items have five response categories (never, rarely, sometimes, often and almost always) that are assigned sequential integers (0, 1, 2, 3 and 4). The total score can range from 0-84. Increasing scores on the questionnaire indicate greater impact of fatigue.

Development

The MFIS was developed from the Fatigue Impact Scale (Fisk et al. 1994a) by the group who developed the Multiple Sclerosis Quality of Life Inventory. There is no empirical evidence to the rationale on modifying the scale or why some items were omitted. Originally, questionnaire items were generated based on 30 interviews with patients with MS in which participants were asked to describe the ways in which fatigue impacts their lives. These interviews were audio-taped, transcribed and sorted thematically into groupings.

Validity

The developers of the Fatigue Impact Scale conducted an initial validation study (Fisk et al. 1994). The sample was 145 patients with Chronic Fatigue (ChF), 34 patients with mild hypertension and 105 patients with MS. As expected, the ChF group had the highest scores followed by the MS and hypertension groups respectively, giving the scale construct validity (Fisk et al. 1994b).
Furthermore, the authors also established high internal consistency with a Cronbach’s alpha of 0.98. The internal consistency of the subscales of the FIS was also examined and yielded a Cronbach’s alpha >0.87 for all three. Good convergent validity was shown between MFIS and Fatigue Severity Scale (FSS). Correlation was strong (r = 0.68, p <.0001) in 231 people with MS with a median EDSS of 2 (range 0 – 8.5) (Téllez et al. 2005). The physical subscale had the highest correlation with the FSS (r = 0.75) compared to the cognitive (r = 0.44) and the psychosocial (r = 0.63) subscales.

In one study, in the absence of a gold standard to measure fatigue, participants were classified into a “MS-related fatigue group” (MS-F) if they reported that fatigue was one of their three most disabling symptoms, occurs daily or most days and limits their activities at home or work. Patients fulfilling none of these criteria were classified as “MS-related non-fatigued group”. Those with one or two criteria were classified as “borderline” (Flachenecker et al. 2002). In 151 people with MS (114 females, 37 males with a median EDSS 3.5), the MFIS was useful in discriminating patients with and without fatigue with cut off values of 38 as there was no overlap of the 10th and 90th percentile for the fatigued and non-fatigued groups. This is indicative that the MFIS has discriminative validity in distinguishing PwMS with and without clinically significant MS-related fatigue.

**Reliability**

The MFIS has ICC values from 0.68 to 0.85 (Kos et al. 2007, Mathiowetz 2003). This indicates a moderate agreement. However, ICC measures the strength of a relation between two variables, not agreement between them. The ICC is required in a reliability study but it should not be employed as the sole statistic (Atkinson and Nevill 1998). A measure of absolute reliability was not established in either of these studies quoted above.
Responsiveness

No study has examined responsiveness in the MFIS. However, when used in studies evaluating exercise in PwMS, the MFIS detected change when other scales did not.

Rasch analysis

In the pilot study, the original MFIS as described above was used in the analysis. However, recently, further analysis of the MFIS that found that the original MFIS did not fit the Rasch model (Mills et al. 2010). The scale was found to have a physical subscale and a cognitive subscale. New subscales were identified as follows:

- The physical subscale 6+7+8+9+10+13+20+21, thus scores are from a minimum of 0 to a maximum of 32.

- The cognitive subscale 12+15+16+18+19, thus scores are from a minimum of 0 to a maximum of 20.

Thus, this new way of analysing the MFIS was also used in the main study analysis.

4.2.4 Six Minute Walk Test: Description, Development and Psychometric Properties

Description

The primary variable measured by the Six Minute walk Test (6MWT) is distance. The American Thoracic Society Guidelines (Enright 2003) suggested not using a treadmill or a bike in which the patient adjusts the speed or slope, not to use a circular or oval track and to standardise the phrases of encouragement and enthusiasm given as this can account for a difference of up to 30%.
With these guidelines in mind, it was decided to use a 10-m walkway separated by a chair at either end. Ten metres would be feasible in community settings and secondly participants would not need to pivot at the end of the 10-m and a chair was available if rest was required – thus potentially reducing the risk of falling. The instructions outlined in Goldman et al. (2008) specifically eliminated instructions for permitted rest during testing, emphasized speed and excluded encouragement phrases. However, three out of twenty MS subjects fell during a 6MWT. Thus, we chose the instructions from Fry and Pfalzer, (2006) that the participant was to walk “as fast and as safely as possible”.

Development

The 6MWT was developed as a measure in cardiac and respiratory disease studies. Evaluation of rehabilitation in stroke and Parkinson’s disease followed (Goldman et al. 2008). To date, two MS trials have used it to evaluate outcome in an AT intervention (Kileff and Ashburn 2005, Rampello et al. 2007). Dalgas et al (2009) used it to evaluate a PRE intervention.

Validity

In 40 PwMS with an EDSS of 0-6.5, the 6MWT has a moderate correlation with the MFIS physical subscale (Spearman’s Correlation Coefficient = 0.66) and a good correlation with the Multiple Sclerosis Walking Scale-12. It also correlated strongly with EDSS (SCC = -0.72).

This indicates that it has good construct validity as a measure of motor fatigue and walking ability (Goldman et al. 2008).

Reliability

The 6MWT can provide excellent intra-rater (ICC = 0.95) and inter-rater (ICC = 0.91) reliability values in people with MS (Goldman et al. 2008).
Using a repeated measures design to examine the test-retest and inter-rater reliability the 6MWT was found to have good inter-rater reliability (ICC = 0.93, Standard Error of the Measure (SEM) 35.85) (Paltamaa et al. 2005). An unpublished study (n = 4 participants, 5 raters), using some of the Chartered Physiotherapists that were involved in assessing the main trial in this thesis, found an ICC of 0.984 (95% CI of 0.939, 0.966) and a SEM of 13.26m in PwMS who use at most 1 stick to walk outdoors (Toomey and Coote 2009) using the instructions chosen for the present study. The ICC values for the 6MWT are excellent and the average difference between raters was low 8.48m (95% CI -14.8, 31.7). The SEM value found for 6MWT was lower than the Paltamaa study (n = 9 participants, 2 raters) suggesting greater agreement between the raters in the way the 6MWT was measured in the present study. This may be explained by the standardised training given to the raters prior to collection of data.

**Responsiveness**

From the review of the literature in Chapter 2, it could be seen that in studies evaluating exercise in people with MS, the 6MWT showed ability to change in an ambulatory population. However, outcome measures using shorter walking distances did not always show statistically significant change (Kileff and Ashburn 2005, Newman et al. 2007). This suggests that a 6MWT may be more sensitive to change than shorter walking distances in PwMS with minimal gait impairment.

**4.2.5 Handheld Dynamometry: Description and Development**

**Description**

A test using a gradual build-up of force to a maximal isometric contraction was performed. This is known as a “make” test which has been shown to be more reliable than a “break” test which involves the sudden interruption of a concentric muscle
contraction (Kurtzke 2000). Strength was assessed using standardised positions (Giesser 2002). The tester applied enough pressure to resist the participant’s ability to move away from the standardised position and the instruction “Don’t let me move you” was used.

Validity

An exhaustive review of the literature concluded that HHD has moderate – high criterion validity (Kolber and Cleland 2005).

This study showed high correlations to IKD in healthy populations ($r = 0.52 - 0.85$), patients with mental retardation ($r = 0.72 - 0.76$), knee dysfunction ($r = 0.57 - 0.80$), neuromuscular diseases ($r = 0.76 - 0.90$) and stroke patients ($0.94 - 0.97$). There are no validity studies in PwMS.

Reliability

Kolber and Cleland (2005) also reported high intra and inter-rater reliability for HHD as shown by consistently moderate to high levels of agreement as indicated by ICC values between 0.44 and 0.99. However, to date no absolute measure of reliability was reported. Recently, Toomey and Coote (2009) conducted a study to establish the inter-rater reliability of HHD in PwMS using raters from the present study. Inter-rater reliability was focused on due to the multi-centred nature of the present trial that used more than one rater. While relative measures of reliability were found to be high - similar to other studies - with ICCs of 0.852 for elbow flexion, and 0.824 for hip extension and 0.799 for ankle dorsiflexion and SCCs of 0.703 for knee extension and 0.787 for shoulder flexion. The associated absolute measures of reliability were high ranging from 19.5N (19.8% of the baseline mean) for shoulder flexion and 40.95N (31.7% of the baseline mean) for knee extension indicating that there was poor agreement between raters. Thus, data collected by different raters is not a reliable
estimate of strength. Based on studies published prior to commencement of this work in early 2008, HHD was used in the pilot study and was proposed for use in the main study. When data collection commenced for the main study, HHD was used. However, it emerged that it was not feasible for a multicentre trial due to more raters and centres than equipment available. Additionally, based on the results of Toomey and Coote 2009 results are not presented for the main trial as there was too much variability between rater to accurately describe change.

**Responsiveness**

No study has examined responsiveness in HHD.
CHAPTER 5: THE PILOT STUDY

5.0 INTRODUCTION

A pilot study was conducted as a logistical exercise, to inform the methodology of the main trial and to test the feasibility and suitability of the outcome measures for use in a multi-centred trial. This chapter describes the methodology, the main findings and the implications for the main study.

5.1 PILOT STUDY METHODOLOGY

A pre-post research design was used using both quantitative and qualitative evaluation. A convenience sample of 7 participants was recruited through the local MS regional office. The pilot study took place in the Clinical Therapies Lab at the University of Limerick in February 2008. The Mid West Regional Hospital Research Ethics Committee granted approval for this study. Informed consent was obtained from all participants (Appendix C and D).

Baseline and follow-up assessments were conducted by the deliverer of the intervention and author of this thesis. The content of the baseline assessment was decided by what factors might influence the results of an intervention as a result of a review of the literature from Chapter 3. The outcome measures used were the Multiple Sclerosis Impact Scale-29, The Modified Fatigue Impact Scale, the Six Minute Walk Test and Handheld dynamometry as described above. The six week intervention is described in detail in section 5.2.
A focus group took place after the intervention evaluating participants’ perception of the programme. This was done to further inform the methodology for a larger trial and to see if subjective reports reflected the objective findings. The questioning route (Figure 1) was used following the method outlined by Kreuger, 1998. Data were collected using a tape recorder. An assistant moderator took field notes and observed group dynamics to facilitate analysis. A summary of the focus groups was given at the end of the discussions by the assistant moderator to confirm interpretation of the findings. Immediately after the focus groups a debriefing session took place for approximately one hour and was recorded (Kreuger 1998).
Focus group questions

Introductory questions

1. What motivated you to participate in the programme?

2. Tell me about how you felt about exercising in a group of people with multiple sclerosis?

Key Questions

3. Tell me what you thought of the exercise programme

Probes:
   ○ Positive outcomes from attending the programme?
   ○ Problems you had from attending the programme?
   ○ Strength
   ○ Walking endurance
   ○ Fitness
   ○ Strength
   ○ QoL

4. How did you find the independent exercise?

5. What would you change about the programme to suit you better?

6. What strategies might encourage people with MS to participate in exercise or to stick to programmes?

7. If you could imagine the ideal exercise programme what would it look like?
   Probes:
   ○ What, who, where, when?

5.2 Intervention

This was a combined aerobic and progressive resistance exercise programme. Based on the review of the literature (Chapter 2), it was concluded that a combined exercise
programme may lead to positive outcomes for PwMS. However this type of intervention needs to be evaluated in a methodologically sound study.

Classes were held once a week for six weeks. They consisted of a 5 minute warm up and cool down and 40 minutes of PRE. This was a circuit style class. The class consisted of sit to stand or squatting, bridging, resisted shoulder flexion, resisted elbow flexion, lunges or resisted knee extension, hip extension, calf raises and a choice of walking or cycling for five minutes as these exercises reflect functional activities. These are shown in Figure 2.

Twelve repetitions of each exercise were completed. The aim was for the participant to be failing on the last repetition. The load was increased by 2-5% when twelve repetitions are easily achieved. Two to three sets of each exercise were completed (i.e. 12x2-3). If the next available load was higher than 2-5% (such as going from 1kg to 2kg in resisted shoulder flexion) the participant increased the repetitions so that they were still failing to achieve full range of motion on the last repetition. These parameters were identified as being effective in improving strength related outcomes from the review of the literature in Chapter 2.

A Home Exercise Programme (HEP) is common practice for Chartered Physiotherapists. Thus, at home, participants were required to complete two (20-30 minute) sessions of Aerobic Training (AT). In the first class, Uhtoff’s phenomenon (Stutzer and Kesselring 2008) and the evidence supporting aerobic activity was described to participants (Newman et al. 2007, JH. Petajan et al. 1996, Rampello et al. 2007, Schulz et al. 2004, McCullagh et al. 2008, Kileff and Ashburn 2005, Petajan et al. 1996).

Each participant was given a target heart rate in the first class. This was calculated using the Karvonen formula which is: Target Heart Rate = Heart Rate Resting + 65% (Heart
Rate_{\text{Max}} – \text{Heart Rate}_{\text{Resting}}). The participants were advised at the initial assessment how to get their resting heart rate, by feeling their carotid pulse for 30 seconds first thing on waking. The first beat they felt was to be zero. A maximal heart rate exercise test was not conducted as it was deemed not to be feasible in such a large trial. Thus, each participant’s age predicted maximum heart rate was used to calculate the maximal heart rate (i.e. 220 – age). If they are unable to detect a pulse, they were advised to use the Borg’s Rate of Perceived Exertion level of 11 – 14 which is valid to use for people with MS (Morrison et al. 2008).

Participants could choose the type of aerobic activity that they did (i.e. swimming / walking / running / cycling). They were asked take their pulse every ten minutes to ensure they are achieving the correct intensity.
FIGURE 2 CONTENT OF THE PHYSIOTHERAPIST-LED INTERVENTION

1. Sit to stand/squat

2. Bridging


5.3 Data Analysis

Quantitative data was analysed using SPSS 15.0 for Windows. Depending on the distribution of the data, means±SD and paired t-tests or medians and their semi-interquartile range (SIQR) and Wilcoxon Signed Ranks Test were used to describe the data.

The focus group data was transcribed verbatim and analysed using thematic content analysis (Kreuger 1998). Ideas in the transcripts were examined for frequency (number of times a theme emerged), extensiveness (number of participants mentioning a theme) and intensity (emotion).

5.4 Results of the Pilot Study

Quantitative findings

The physical component is scored from 20-80. A higher score indicates a higher impact of MS on participation. The mean MSIS-29 score reduced from 62.43±13.56 to 53.57 ± 14.66, p = 0.19. Sample size calculations conducted by the Statistical Consulting Unit at the University of Limerick indicated that a sample size of 60 in each group will have a 90% power to detect similar observation using a Wilcoxon rank-sum test with a 0.05 two-sided significance level.

The psychological component is scored from 9-45. A higher score indicates a higher impact of MS on participation. The median score on the MSIS-29 psychological component before treatment was 17.00 (SIQR =6.87). After treatment the median score was 21 (SIQR = 8.75), p = 0.461.
The MFIS ranges from 0 to 84 and a higher score indicates a greater impact of fatigue. The median score on the MFIS before treatment was 40 (SIQR = 6.88). After treatment the median score was 46 (SIQR = 14.25), $p = 0.588$. Two participants had missing values in their first assessment thus results were for 5 participants.

The median 6MW distance increased from 306m (SIQR = 128) to 345m (SIQR = 110), $p = 0.310$.

Pre and post scores for strength are shown in Figure 3 and Figure 4.

**FIGURE 3 UPPER LIMB STRENGTH VALUES PRE AND POST INTERVENTION IN THE PILOT STUDY**

<table>
<thead>
<tr>
<th>Movement resisted</th>
<th>Median Pre</th>
<th>SIQR Pre</th>
<th>Median Post</th>
<th>SIQR Post</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Elbow Flx</td>
<td>74.36</td>
<td>15.15</td>
<td>81.76</td>
<td>13.38</td>
<td>.018*</td>
</tr>
<tr>
<td>L. Elbow Flx</td>
<td>74.43</td>
<td>10.48</td>
<td>98.76</td>
<td>20.67</td>
<td>.028*</td>
</tr>
<tr>
<td>R. Shoulder Flx</td>
<td>70.39</td>
<td>16.41</td>
<td>69.3</td>
<td>8.62</td>
<td>.249</td>
</tr>
<tr>
<td>L. Shoulder Flx</td>
<td>68.93</td>
<td>11.02</td>
<td>71.50</td>
<td>11.19</td>
<td>.345</td>
</tr>
</tbody>
</table>

**FIGURE 4 LOWER LIMB STRENGTH VALUES PRE AND POST INTERVENTION IN THE PILOT STUDY**

<table>
<thead>
<tr>
<th>Movement Resisted</th>
<th>Median Pre</th>
<th>SIQR Pre</th>
<th>Median Post</th>
<th>SIQR Post</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. Knee Ext</td>
<td>101.97</td>
<td>30.29</td>
<td>99.23</td>
<td>27.01</td>
<td>.735</td>
</tr>
<tr>
<td>L. Knee Ext</td>
<td>90.10</td>
<td>7.66</td>
<td>87.53</td>
<td>11.82</td>
<td>.463</td>
</tr>
<tr>
<td>R. Hip Ext</td>
<td>100.40</td>
<td>27.62</td>
<td>97.47</td>
<td>24.5</td>
<td>.463</td>
</tr>
<tr>
<td>L. Hip Ext</td>
<td>99.8</td>
<td>49.9</td>
<td>112.56</td>
<td>28.4</td>
<td>.917</td>
</tr>
</tbody>
</table>
Qualitative findings

Three themes emerged from the focus group: 1.) The benefits of group exercise, 2.) Outcomes of the programme and 3.) The appropriateness of the intervention. The concepts identified within the theme of outcomes of the programme reflected the objective findings.

Group exercise

Group exercise was of great importance to the participants in this class. “The social aspect” and “motivation” were the two main concepts within this theme.

“The social aspect” of being in a group was one of the main drivers to participate in the class and this helped to maintain interest and participation in the intervention.

Participants agreed that the social aspect of the occasion was of great importance to their confidence in participating in exercise and

“It motivated me as well being in a group that we’re all in this together” (3)

“I found it nice to meet other people with the same condition and it was totally different to a gym situation in as far as we were all in the same boat and it was very comfortable doing the exercises” (6)
Additionally when asked directly about group exercise, six out of the seven participants agreed enthusiastically that it was a great motivator. Because it was a “group thing” (4), you wouldn’t want to let the side down” (2)

**Outcomes of the programme**

A greater sense of wellbeing was expressed with the greatest frequency, extensiveness and emotion. Participants reported “enjoyment” (5) from the exercise programme, “increased confidence” in daily living (6, 8), and “a greater feeling of wellbeing than when we started”. The participants also highlighted improved function and participation;

“I’m more confident coming down the stairs” (7),

“One thing I have noticed – I think I’m climbing the stairs better” (4),

“We’ve been doing things that we thought we could never do probably” (3).

Although one participant was adamant that she “certainly found an improvement in her arms”, other participants were not as forthcoming regarding any changes in strength.

There were mixed feelings about fatigue. One participant summed it up as

“You can’t just narrow it down to this class, other things in your life affect it (fatigue)” (3)
Similarly, there was mixed feeling regarding the change of walking endurance or fitness. These sentiments regarding the outcome of the intervention are reflective of the quantitative findings.

**Content of the Intervention**

The participants agreed that the parameters of the intervention were suitable for them. They felt that weekly class encouraged independent exercise. They also expressed curiosity about different types of exercise such as pilates or yoga. However, this triggered participants’ negative experiences of exercise. The ideal exercise programme would have the strengthening class on one day and something else on another day. There was collective agreement to;

>“This programme on one day, something else another day” (5)

Participants felt that the frequency and intensity was appropriate for them but would have liked to start doing more at week 6.

>“Better to get a taste for it first” (3)

>“Twice a week would have been fabulous” (6)
5.5 Informing Main Study Methodology

In the pilot study, the measures appeared suitable and feasible for a multi-centred trial. Participant’s reports broadly represented the objective findings. The main changes made to the main trial as a result of the pilot study were that the Physiotherapy-led intervention was increased to 10 weeks in duration to allow for sufficient time for neural and functional adaptation. At week 6, PRE was increased to twice a week AT was increased to three times per week so that the intervention was truly progressive over ten weeks. Additionally, recruitment aimed to minimise the risk of Type II error in the main study by recruiting more than 60 participants per group.
CHAPTER 6: MAIN STUDY METHODOLOGY

6.0 MAIN STUDY AIM AND OBJECTIVES

The overarching aim of this thesis was to inform Multiple Sclerosis Ireland regarding what exercise programmes should be provided for PwMS with minimal gait impairment.

The following sections describe the methods used in this thesis to address the main objectives.

6.1 TRIAL DESIGN

This was a multi-centre; block randomised, assessor blind, waiting list controlled study. Assessments were conducted pre (week 1) and post (week 12) intervention and at 3-month follow-up (week 24).

6.2 RECRUITMENT

The project was advertised through the print media, MSI’s network and through relevant health professional publications. Participants were referred to the project by themselves, their carer, through MSI, by Chartered Physiotherapists, Neurologists, GPs or Clinical nurse specialists. Referrals were made to MSI’s Regional Office. Participants were asked about their mobility level to ensure they were allocated to the correct strand of the 3 arm trial and screened for the selection criteria using an information collection sheet (Appendix E). Participants were then sent the information leaflet (Appendix F) and a consent form (Appendix G). The participants’ GP was sent a letter informing them of their participation (Appendix H) and a copy of the information leaflet.
6.3 Study Settings

This work took place in available community centres around Ireland. Local gyms and accessible venues were sourced by MS Ireland.

6.4 Ethics

Eleven Research Ethics Committees granted ethical approval for this research protocol. These are listed in Table 13.

<table>
<thead>
<tr>
<th>Research Ethics Committee</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cork University Hospital</td>
<td>Cork</td>
</tr>
<tr>
<td>HSE Dublin North East</td>
<td>Drogheda</td>
</tr>
<tr>
<td>Mater Misericordiae Hospital</td>
<td>Dublin</td>
</tr>
<tr>
<td>St Vincent’s Hospital</td>
<td>Dublin</td>
</tr>
<tr>
<td>Beaumont Hospital</td>
<td>Dublin</td>
</tr>
<tr>
<td>Adelaide and Meath Hospital / St James’ Hospital</td>
<td>Dublin</td>
</tr>
<tr>
<td>Galway Regional Hospitals</td>
<td>Galway</td>
</tr>
<tr>
<td>Mid West Regional Hospital</td>
<td>Limerick</td>
</tr>
<tr>
<td>Sligo General Hospital</td>
<td>Sligo</td>
</tr>
<tr>
<td>HSE – Dublin Mid Leinster</td>
<td>Tullamore</td>
</tr>
<tr>
<td>Waterford Regional Hospital</td>
<td>Waterford</td>
</tr>
</tbody>
</table>

6.5 Interventions

Participants were assigned to 1) Physiotherapy (PT) - led class - consisting of a combined PRE and AT, 2) Yoga, 3) a Fitness Instructor (FI) - led class or to 4) a waiting list control. All interventions were delivered over an hour a week for ten weeks. The PT-led intervention was pre-defined based on a review of the literature. However, the other community-based interventions were not defined a priori and were delivered as normal in the community by MSI, as the content or efficacy of such community-based programmes is not known. Detailed description of the content of these interventions was recorded during the study and are presented in the results section and
as an Appendix (X and Y). The following paragraphs describe the PT-led intervention in detail and how data was collected from the Yoga and FI-led classes.

**Physiotherapy led exercise class**

Three individual training days took place for the deliverers of the PT-led intervention. Deliverers also received a training handbook which can be found in Appendix K-T.

PwMS attended an hour long class as described in Section 5.2, once a week for ten weeks. The intervention type, intensity and duration was the same as the pilot study as described above.

To ensure that the programme was truly progressive over ten weeks, the intervention differed from the pilot in two ways. Firstly, after five weeks of attending the class, participants were advised to complete a second hour of strengthening themselves at home following the same principles. Secondly, from week 6, they were asked to participate in aerobic exercise three times a week.

So that adherence to the programme could be analysed, participants were asked to document all of the exercise that they do weekly and to return this to the physiotherapist at the end of each week (at the next class). All of the documentation for the PT-led intervention can be found in Appendix P-T.
Yoga

Yoga is an intervention frequently organised by Multiple Sclerosis Ireland (MSI) for PwMS, who anecdotally report positive outcomes from participation. However, at the start of this study, only one small scale study evaluated it in the literature (Oken et al. 2004). Thus, there was little to guide the content of interventions. This project was an ideal opportunity to evaluate community-based interventions.

Instructors used in this study had to be accredited by the Yoga Federation of Ireland. They were given standardised intervention packs in order to document the interventions. This was subsequently examined for frequency, intensity, type and duration of exercise, so that the content of interventions may be reported. All of the documentation given to the Yoga instructors to record the content of the classes can be found in Appendix U, V and W.

Fitness Instructor led exercise

Access to services, such as physiotherapy, is currently limited in Ireland. Other exercise professionals may be able to deliver safe, effective, enjoyable, evidence-based interventions to PwMS with minimal gait impairments. Fitness instructors have access to equipment that has been used in trials to date and may be a cost effective way of delivering exercise interventions in this lifelong disease.

Where possible, the fitness instructors used in this study had to have a level 2 National Certificate in Exercise and Fitness. This was initially a barrier to randomisation as there were insufficient numbers of this type of fitness instructor. Thus, an amended ethical approval was granted that the fitness instructor led classes were delivered by anyone with an appropriate qualification to be employed at a gym. The fitness instructors were
also given a standardized intervention pack in order to document the interventions (pro-
forma reporting as for Yoga). This was subsequently examined for frequency, intensity,
type and duration of exercise, so that the content of interventions may be reported. All
of the documentation given to the FI-led instructors to record the content of the classes
can be found in Appendix U, V and W.

Control

The control group were asked not to change their exercise habits between week 1 and
week 12 of the study period. As services in Ireland are extremely limited and most
PwMS are waiting for significant time periods for physiotherapy intervention the 3
month control period was not significantly disadvantageous. The individuals in the
control group received the treatment of their choice once the control period was over
but the outcome of this was not measured for the trial.

6.6 Assessments

Assessments were carried out by research assistants who were unaware of the treatment
allocation at baseline, twelve weeks and at three month follow up (Appendix I and J).
Initial assessments took between 1.5 to 2 hours. The author was directly involved in the
collection of data for 72 participants. To maximise the number of participants in the
study other Chartered Physiotherapists were trained in the assessment of the participants
at three national study days. This was deemed appropriate as the measures chosen and
described above had excellent inter-rater reliability.

The review of the literature in Chapter 2 concluded that large variability was evident in
studies evaluating exercise in PwMS to date indicating interventions with a positive
effect are not equally effective for all participants.
Chapter 3 identified variables that might influence outcome to an exercise intervention. These variables were measured at baseline. How they were measured and coded are described in Table 14.

Measures were chosen to reflect what is used in current clinical practice by Chartered Physiotherapists when conducting a standard neurological assessment. These have face and content validity and were deemed feasible in a community setting. This information was aimed at informing generalisability of results and to facilitate a post-hoc exploration of the results to further inform targeted intervention for PwMS.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Method of measurement</th>
<th>Coding used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of MS</td>
<td>Subjective examination (self-report)</td>
<td>Dummy variables: RRMS = 1, other types of MS = 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPMS = 1, other types of MS = 0</td>
</tr>
<tr>
<td>Gender</td>
<td>Observation (M/F)</td>
<td>Female = 1, Male = 0</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>Current age – age at onset of symptoms (self-report)</td>
<td>AOMS – continuous</td>
</tr>
<tr>
<td></td>
<td>LOMS &gt; 50</td>
<td>AOMS by category LOMS = 1, YOMS = 0</td>
</tr>
<tr>
<td></td>
<td>YOMS &lt; 30</td>
<td></td>
</tr>
<tr>
<td>Light touch sensation</td>
<td>Tissue paper (VNRS)</td>
<td>VNRS: 0-60</td>
</tr>
<tr>
<td>(UL/LL)</td>
<td>UL – middle fibres of deltoid, lateral forearm, lateral posterior aspect of the hand</td>
<td>(3 bilateral sites, summative score for UL and LL separately)</td>
</tr>
<tr>
<td></td>
<td>LL – dorsum of the foot, lateral aspect of the calf, medial aspect of the knee</td>
<td>1 = Normal, Abnormal = 0</td>
</tr>
<tr>
<td>Proprioception</td>
<td>UL – Physiotherapist passively flexed or extended the 1st phalanx of the UL or LL.</td>
<td>1 = Normal, 0 = Abnormal</td>
</tr>
<tr>
<td>(UL/LL)</td>
<td>Participant with his/her eyes closed had to describe the position of the phalanx</td>
<td></td>
</tr>
<tr>
<td>Tone</td>
<td>Modified Ashworth Scale</td>
<td>0 = No increase in Muscle Tone</td>
</tr>
<tr>
<td></td>
<td>1 = Slight increase in muscle tone, manifested by a catch and release or by minimal</td>
<td>1 = Slight increase in muscle tone, manifested by a catch, followed by minimal</td>
</tr>
<tr>
<td></td>
<td>resistance at the end of the range of motion when the affected part(s) is moved in</td>
<td>resistance throughout the reminder (less than half) of the ROM (range of</td>
</tr>
<tr>
<td></td>
<td>flexion or extension</td>
<td>movement).</td>
</tr>
<tr>
<td></td>
<td>2 = Slight increase in muscle tone, manifested by a catch, followed by minimal</td>
<td>3 = Slight increase in muscle tone, manifested by a catch, followed by minimal</td>
</tr>
<tr>
<td></td>
<td>resistance throughout the reminder (less than half) of the ROM (range of movement).</td>
<td>resistance throughout the reminder (less than half) of the ROM (range of</td>
</tr>
<tr>
<td></td>
<td>4 = Considerable increase in muscle tone passive, movement difficult.</td>
<td>movement).</td>
</tr>
<tr>
<td></td>
<td>5 = Affected part(s) rigid in flexion or extension.</td>
<td></td>
</tr>
<tr>
<td>Co-ordination</td>
<td>Finger to nose test - checking for speed, accuracy and tremor (affected side, if</td>
<td>1 = Normal, 0 = Abnormal</td>
</tr>
<tr>
<td></td>
<td>relevant)</td>
<td></td>
</tr>
<tr>
<td>Strength</td>
<td>Handheld dynamometer</td>
<td>N/A</td>
</tr>
<tr>
<td>Adherence</td>
<td>Number of classes attended</td>
<td>Continuous (0-10)</td>
</tr>
<tr>
<td>Current levels of exercise</td>
<td>Participant report of Frequency, Intensity, Type and Duration of exercise</td>
<td>1 = Meeting current ASCM guidelines for exercise, 2 = Meeting ‘95 guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for exercise, 3 = Reports being active but not meeting any guidelines, 4 =</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inactive</td>
</tr>
</tbody>
</table>

RRMS = Relapsing Remitting MS, PPMS = Primary Progressive MS, F = Female, M= Male, AOMS = Age and onset of MS, LOMS = Late Onset MS, YOMS = Young Onset MS, UL = Upper Limb, LL = Lower limb, VNRS = Verbal Numeric Rating Scale, N/A = Not applicable
6.7 INTERIM ANALYSIS AND STOPPING GUIDELINES

No interim analyses were conducted and data collection stopped when in excess of 60 participants per group had an initial assessment.

6.8 RANDOMISATION AND SEQUENCE GENERATION

Once 8 participants were recruited in a geographical area, the regional office contacted the national coordinator, who was independent from the clinical aspects (i.e. assessment and delivery) of the trial. The national co-ordinator block randomised that group of participants, to a control or an intervention, using a sealed envelope with 4 pieces of paper with the 1 of the 4 groups written on them. The paper chosen was emitted each time until four groups were chosen to ensure even numbers per group. When the fifth group was ready to go, all the pieces of paper were returned to the envelope, and so on.

Group allocation sequence was disclosed by the national co-ordinator to the regional office prior to assessment. Participants were told to which group they were allocated after assessment by the regional office.

6.9 BLINDING

Due to the nature of the trial, it was not possible to blind the participants or deliverers of the interventions from the allocated arm. Outcome assessors were blinded from the allocation.
6.10 Similarity of Interventions

All interventions were delivered over an hour a week for ten weeks. The physiotherapist led programme was defined a priori based on a review of the literature. The content of the other community-based interventions was not defined a priori to the trial but standardised data collection forms were used to gather this information.

6.11 Analysis Plan

All statistical analyses were conducted using Predictive Analytics Software (PASW) Statistics 17 (formerly SPSS Statistics 17).

6.11.1 The Distribution of the Data

Firstly, the distribution of the data was analysed using histograms, Quantile-Quantile plots and the Kolmogorov-Smirnov statistic.

6.11.2 The Differences Between Groups at Baseline

Depending on the distribution and nature of the data, One-Way ANOVA (normally distributed data) or Kruskall Wallis (skewed data) were used to analyse the differences between groups, for each measure, at baseline. Chi-square for independence was used to compare categorical data at baseline. Participants who dropped out during or after the exercise intervention were also analysed at baseline to ensure that there was no major difference in baseline characteristics that might explain why participants might not have continued with the programme.
6.11.3 The main effects

For data that was normally distributed, means, standard deviations, and repeated measures ANOVA were used to analyse the effect of group over time. A post-hoc Bonferroni adjustment was made to account for the number of statistical tests being conducted. Where there was a statistically significant effect, paired-samples t-tests (including mean change and confidence intervals) were used to identify where the statistically significant change over time occurred. Effect sizes were calculated using the formula: Mean difference/SD pooled baseline. The guidelines (proposed by Cohen 1988) for interpreting the effect size are 0.2 = small effect, 0.5 = moderate effect and 0.8 = large effect.

For data that was not normally distributed, medians, semi-interquartile ranges and Wilcoxon Signed Rank Tests were used to describe the differences within groups. Effect Sizes were calculated by dividing Z by the $\sqrt{N}$, where N is the number of observations. The guidelines (proposed by Cohen 1988) for interpreting the effect size are 0.2 = small effect, 0.5 = moderate effect and 0.8 = large effect. To establish the differences between groups, a change score (from pre to post intervention) was calculated for each group. Kruskal Wallis and Mann Whitney U tests were used to describe the differences between groups.

6.11.4 Annualised relapse rate

Some participants dropped out of the trial due to self-reported relapses. Thus the annualised relapse rate was calculated for each group. Annualised Relapse Rate (ARR) has been computed by dividing the total number of relapses reported during the study by the total number of patient years at follow-up (Inusah et al. 2010). Only participants with RRMS were included. Thus ARR was calculated in the four groups during the intervention period as follows: $(R/N)$

0.25
Where \( R \) is the number of relapses that occurred, \( N \) is the number of participants with RRMS and 0.25 is the duration of the trial in years. While this is interesting information, it must be treated as circumspect as it is not known what the ARR for the year prior to study entry was not known.

### 6.11.5 Post-hoc exploration of data

To address the objective to investigate the predictors of outcome after the intervention period, a standard Multiple Linear Regression analysis was conducted. The MSIS-29, v.2 post intervention was the outcome variable. Predictor variables were clinical variables explored in Chapter 2 and assessed at baseline as described above in section 6.6. Group allocation was also entered into the model. Dummy variables were created for each group separately (i.e. \{1 = PT-led intervention, 0 = all other groups\}, \{1 = Yoga, 0 = all other groups\}, \{1 = FI-led intervention, 0 = all other groups\}, \{1 = control, 0 = all other groups\}). Finally baseline values of measures of the outcome measures (MSIS-29, v.2, MFIS, 6MWT) and GNDS score were also entered into the model, as it was felt that where a participant starts on these important variables might influence outcome.

Combinations of variables were entered until the highest \( R^2 \) was achieved with the lowest number of variables. Each variable had to be statistically significant (\( p < 0.05 \)) in order to contribute to the line.
CHAPTER 7: MAIN STUDY RESULTS

7.0 INTRODUCTION

The main objectives of this study were

- To establish the efficacy of the three community-based exercise interventions
- To establish if there was a difference between groups due to intervention
- To investigate the results three months after the intervention
- To investigate the predictors of outcome after the intervention period

To date, participants have been minimally described in terms of their clinical presentations thus limiting generalisability of results. Combined exercise has not yet been fully evaluated and in terms of specificity of exercise training, this may offer favourable outcomes by minimising the impact of MS for the person with MS. Few perspective comparative studies have been conducted and no known study has evaluated community based interventions in terms of the content and effectiveness of the interventions.

In this chapter the flow of the participants are described from entry into the trial to 12 week follow-up. Baseline characteristics of participant to inform the generalisability of the findings are reported in section 7.2. Adherence to the intervention is reported in section 7.3. The content of the interventions in this pragmatic trial is reported in section 7.4. The main results addressing the first two aims of this study are detailed in sections 7.6 to 7.8 inclusive. Finally there is a summary of the main findings in section 7.9. The follow-up results are described in Chapter 8 and the predictors of outcome can be found in Chapter 9.
7.1 Attrition

Three hundred and seventy-two participants were assessed for eligibility. The flow of participants through the trial from week 1 to week 12 is described in Figure 5.

Seventy-nine (25.1%) of 323 participants were lost at week 12. This can be explained by a number of factors as detailed in Figure 5. These factors were categorised using the WHO-ICF framework as a guide. The most serious were relating to Health Condition. The most notable result here was the increased frequency of relapses in the control group. This was converted to an Annualised Relapse Rate (ARR) for each group. The ARR for the control group was 0.60, PT-led exercise was 0.18, yoga was also 0.18 and FI-led exercise was 0.26.

Other reasons why people could not attend for follow-up assessment were due to personal and environmental reasons. Personal reasons included work commitments, holidays, family bereavement and other appointments on the day. One participant in the control group pulled out of the research and 1 participant in the yoga group dropped out as she did not like the randomisation. Environmental factors were related to travel. For some participants the reasons for dropping out were unknown (n = 18). Analysis was conducted on the baseline characteristics of all of the dropouts at week 12 to ensure that there was no major difference in baseline characteristics that might explain why participants might not have continued with the programme.
FIGURE 5 FLOW OF PARTICIPANTS THROUGH THE TRIAL FROM WEEK 1 TO WEEK 12

Assessed for eligibility
n = (381)

Excluded (n = 58)
Did not meet selection criteria

Randomized (n = 323)

Allocated to control
(n = 73)

Allocated to PT-led exercise
(n = 83)

Allocated to yoga
(n = 78)

Allocated to FI-led exercise
(n = 89)

Lost to follow up at week 12
(n = 24)

Health Condition (n = 12)
Relapse (n = 6)
Unwell on the day (n = 3)
Sprained ankle
(n = 1)
Fall and # - unable to assess (n = 1)

Personal Factors (n = 6)
Environmental Factors (n = 1)
Unknown (n = 5)
Analysed (n = 49)

Lost to follow up at week 12
(n = 20)

Health Condition (n = 8)
Relapse (n = 2)
Unwell on the day (n = 3)
Steroids (n = 1)
Metatarsal # (n = 1)

Personal Factors (n = 1)
Environmental Factors (n = 2)
Unknown (n = 9)
Analysed (n = 63)

Lost to follow up at week 12
(n = 15)

Health Condition (n = 6)
Relapse (n = 3)
Unwell on the day (n = 2)
RA flare-up (n = 1)

Personal Factors (n = 3)
Environmental Factors (n = 1)
Unknown (n = 5)
Analysed (n = 63)

Lost to follow up at week 12
(n = 22)

Health Condition (n = 9)
Relapse (n = 3)
Unwell on the day (n = 1)
Upper limb # 2+ fall (n = 1)
Severe LBP (n = 1)
Hiatus hernia (n = 1)
Pregnancy (n = 1)
Personal Factors (n = 4)
Environmental Factors (n = 2)
Unknown (n = 7)
Analysed (n = 67)
7.2 Baseline characteristics

Table 15 demonstrates the most commonly reported main problems in this cohort (n = 314). Other problems reported were vertigo/dizziness (n = 8), lack of fitness (n = 7), depression/anxiety (n = 6), speech/swallow difficulties (n = 5), problems with sleep (n = 4), hearing impairments (n = 3), falling (n = 3), bowel problems (n = 2), hangover feeling (n = 1), erectile dysfunction (n = 1), difficulty in cold weather (n = 1), lack of motivation (n = 1) and restlessness (n = 1). Some participants mentioned difficulties with activity and participation. These were difficulty in using the upper limb (n = 4), difficulty getting up from a bent position (n = 1), difficulty in Activities of Daily Living (n = 1), dependence on a stick (n = 1) and temporary employment due to MS (n = 1).

<table>
<thead>
<tr>
<th>Reported in first 3 problems</th>
<th>Number of participants who reported problem (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/Tiredness</td>
<td>153 (48.7)</td>
</tr>
<tr>
<td>Weakness</td>
<td>99 (31.5)</td>
</tr>
<tr>
<td>Pain including headaches</td>
<td>84 (26.7)</td>
</tr>
<tr>
<td>Balance/Unsteadiness</td>
<td>77 (24.5)</td>
</tr>
<tr>
<td>Walking/Mobility/Gait</td>
<td>56 (17.8)</td>
</tr>
<tr>
<td>Sensory disturbance</td>
<td>55 (17.5)</td>
</tr>
<tr>
<td>Stiffness/Spasms</td>
<td>43 (13.6)</td>
</tr>
<tr>
<td>Bladder</td>
<td>36 (11.5)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>34 (10.8)</td>
</tr>
<tr>
<td>Tremor/Co-ordination</td>
<td>20 (6.4)</td>
</tr>
<tr>
<td>Memory</td>
<td>19 (6.1)</td>
</tr>
<tr>
<td>No problems</td>
<td>17 (5.4)</td>
</tr>
</tbody>
</table>

Table 16 details the participant characteristics relating to health condition including MS specific variables and use of disease modifying medication. There was no statistically significant difference between groups for any of these variables (p > 0.05). Variability was not reported for categorical variables where frequencies were reported. However, large variability was seen around all point estimates when means and medians were reported. Most participants reported having RRMS.
<table>
<thead>
<tr>
<th></th>
<th>Control (N = 49)</th>
<th>PT-led (N = 63)</th>
<th>Yoga (N = 63)</th>
<th>FI-led (N = 67)</th>
<th>Dropouts at week 12 (N = 72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guys Neurological Disability Scale (Mobility Section)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.372c</td>
</tr>
<tr>
<td>0 – Gait unaffected (N)</td>
<td>21 (42.9%)</td>
<td>19 (30.2%)</td>
<td>26 (41.3%)</td>
<td>15 (22.3%)</td>
<td>20 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>1 – Unsteady but doesn’t use aid (N)</td>
<td>12 (27.9%)</td>
<td>21 (33.3%)</td>
<td>14 (22.2%)</td>
<td>28 (41.8%)</td>
<td>26 (36.1%)</td>
<td></td>
</tr>
<tr>
<td>2 – Uses unilateral aid for outdoors (N)</td>
<td>16 (32.7%)</td>
<td>21 (33.3%)</td>
<td>22 (34.9%)</td>
<td>23 (34.3%)</td>
<td>21 (29.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of MS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>RRMS (N)</td>
<td>27 (55.1%)</td>
<td>35 (55.6%)</td>
<td>38 (60.1%)</td>
<td>33 (49.3%)</td>
<td>43 (59.7%)</td>
<td></td>
</tr>
<tr>
<td>SPMS (N)</td>
<td>10 (20.4%)</td>
<td>9 (14.3%)</td>
<td>7 (11.1%)</td>
<td>13 (19.4%)</td>
<td>5 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>PPMS (N)</td>
<td>3 (6.1%)</td>
<td>5 (7.9%)</td>
<td>8 (12.7%)</td>
<td>9 (13.4%)</td>
<td>5 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>Benign (N)</td>
<td>1 (2.0%)</td>
<td>0 (0%)</td>
<td>1 (1.6%)</td>
<td>3 (4.5%)</td>
<td>5 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>Unknown (N)</td>
<td>8 (16.3%)</td>
<td>14 (22.2%)</td>
<td>9 (14.3%)</td>
<td>9 (13.4%)</td>
<td>12 (16.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Length of time since onset of symptoms (years)</strong></td>
<td>14.1a (8.9)b</td>
<td>15.5b (9.4)b</td>
<td>13.8c (8.5)b</td>
<td>13.8c (8.5)b</td>
<td>13.3c (9.0)b</td>
<td>0.700b</td>
</tr>
<tr>
<td><strong>Length of time since diagnosis (years)</strong></td>
<td>10.6a (8.2)b</td>
<td>9.8a (7.1)b</td>
<td>11.6b (8.3)b</td>
<td>10.5b (6.9)b</td>
<td>10.5b (7.4)b</td>
<td>0.779d</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease modifying meds (N)</td>
<td>24 (48.9%)</td>
<td>33 (52.3%)</td>
<td>36 (57.1%)</td>
<td>38 (56.7%)</td>
<td>36 (50%)</td>
<td>0.933e</td>
</tr>
</tbody>
</table>

N = number of participants, a Mean, b Standard deviation, c Chi-square test for independence, d One-Way ANOVA
Table 17 demonstrates baseline characteristics at impairment level, the participants’ demographic details and information regarding activity and participation of the participants at baseline.

Most of the participants were female and participated in some physical activity but did not meet any of the recommended guidelines for exercise. There were no statistically significant differences in any of the variables. Large variability was seen around all of the point estimates. Although not statistically significant, the control group had a higher MSIS-29, v 2 score, higher fatigue and longer 6MWT distance than the three intervention groups.

The dropouts had a higher MSIS-29, v 2 (psychological component) score than the participants who remained in the trial. This difference approached significance (p= 0.093).
TABLE 17 VARIABLES MEASURED AT BASELINE

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 49)</th>
<th>PT-led (N = 63)</th>
<th>Yoga (N = 63)</th>
<th>FI-led (N = 67)</th>
<th>Dropouts at week 12 (N = 72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Limb Sensation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60(^a) (2.63)(^b)</td>
<td>60(^a) (1.00)(^b)</td>
<td>60(^a) (0.75)(^b)</td>
<td>60(^a) (1.25)(^b)</td>
<td>60(^a) (1.25)(^b)</td>
<td>0.412(^c)</td>
</tr>
<tr>
<td>Upper Limb Sensation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>60(^a) (0)(^b)</td>
<td>60(^a) (1.00)(^b)</td>
<td>60(^a) (0)(^b)</td>
<td>60(^a) (1.00)(^b)</td>
<td>60(^a) (1.13)(^b)</td>
<td>0.804(^c)</td>
</tr>
<tr>
<td>Lower Limb Proprioception</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (N)</td>
<td>43 (87.8%)</td>
<td>53 (84.1%)</td>
<td>49 (77.8%)</td>
<td>54 (80.6%)</td>
<td>55 (76.3%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Impaired (N)</td>
<td>5 (10.2%)</td>
<td>10 (15.9%)</td>
<td>9 (14.3%)</td>
<td>11 (16.4%)</td>
<td>14 (19.4%)</td>
<td></td>
</tr>
<tr>
<td>Upper Limb Proprioception</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (N)</td>
<td>49 (100%)</td>
<td>63 (100%)</td>
<td>57 (90.5%)</td>
<td>61 (91.0%)</td>
<td>64 (88.9%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Impaired (N)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (5.9%)</td>
<td>5 (6.95%)</td>
<td></td>
</tr>
<tr>
<td>Co-ordination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (N)</td>
<td>30 (61.2%)</td>
<td>37 (58.7%)</td>
<td>24 (38.1%)</td>
<td>41 (61.2%)</td>
<td>36 (50%)</td>
<td>0.362(^d)</td>
</tr>
<tr>
<td>Impaired (N)</td>
<td>19 (38.8%)</td>
<td>26 (41.3%)</td>
<td>37 (58.7%)</td>
<td>26 (38.8%)</td>
<td>34 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>Lower limb Tone</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MAS: Elbow flexion (N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35 (71.4%)</td>
<td>42 (66.7%)</td>
<td>37 (58.7%)</td>
<td>36 (53.7%)</td>
<td>36 (50.0%)</td>
<td>N/A</td>
</tr>
<tr>
<td>1</td>
<td>6 (12.2%)</td>
<td>15 (23.8%)</td>
<td>10 (15.9%)</td>
<td>16 (23.9%)</td>
<td>13 (18.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (4.1%)</td>
<td>3 (4.8%)</td>
<td>1 (1.6%)</td>
<td>4 (6.0%)</td>
<td>5 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (4.08%)</td>
<td>1 (1.6%)</td>
<td>1 (1.6%)</td>
<td>2 (3.0%)</td>
<td>6 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (2.0%)</td>
<td>0 (0%)</td>
<td>1 (1.6%)</td>
<td>0 (0%)</td>
<td>3 (4.2%)</td>
<td></td>
</tr>
<tr>
<td>Upper limb Tone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAS: Elbow flexion (N)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41 (83.6%)</td>
<td>54 (85.7%)</td>
<td>40 (63.5%)</td>
<td>45 (67.2%)</td>
<td>48 (66.7%)</td>
<td>N/A</td>
</tr>
<tr>
<td>1</td>
<td>4 (8.2%)</td>
<td>8 (12.7%)</td>
<td>11 (17.5%)</td>
<td>8 (11.9%)</td>
<td>14 (19.4%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (2.0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (4.5%)</td>
<td>1 (1.4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1.5%)</td>
<td>1 (1.5%)</td>
<td>2 (2.8%)</td>
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<tr>
<td>4</td>
<td>1 (2.0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1.5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

N = number of participants, \(^a\) Median, \(^b\) Semi-interquartile range, \(^c\) Kruskal Wallis Test, \(^d\) Chi-square test for independence, MAS = Modified Ashworth Scale, N/A = not applicable: assumptions for Chi-square test for independence not met.
<table>
<thead>
<tr>
<th></th>
<th>Control (N = 49)</th>
<th>PT-led (N = 63)</th>
<th>Yoga (N = 63)</th>
<th>FI-led (N = 67)</th>
<th>Dropouts at week 12 (N = 72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>48.8&lt;sup&gt;a&lt;/sup&gt; (11.9)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51.7&lt;sup&gt;a&lt;/sup&gt; (10.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>49.6&lt;sup&gt;a&lt;/sup&gt; (10.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50.3&lt;sup&gt;a&lt;/sup&gt; (10.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>46.5&lt;sup&gt;a&lt;/sup&gt; (12.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.206&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (12.2%)</td>
<td>13 (20.6%)</td>
<td>19 (30.2%)</td>
<td>22 (32.8%)</td>
<td>18 (25%)</td>
<td>0.092&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>Female</td>
<td>43 (87.8%)</td>
<td>50 (79.4%)</td>
<td>44 (69.8%)</td>
<td>45 (67.2%)</td>
<td>53 (73.6%)</td>
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<tr>
<td><strong>Exercise Activity Level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – Active and meeting ASCM Guidelines</td>
<td>5 (10.2%)</td>
<td>7 (11.1%)</td>
<td>3 (4.8%)</td>
<td>4 (5.9%)</td>
<td>4 (5.5%)</td>
<td>0.536&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 – Meeting 1995 Guidelines</td>
<td>9 (18.4%)</td>
<td>14 (22.2%)</td>
<td>16 (35.4%)</td>
<td>17 (25.4%)</td>
<td>11 (15.3%)</td>
<td></td>
</tr>
<tr>
<td>3 – Active but don’t meet any guidelines</td>
<td>26 (53.1%)</td>
<td>27 (42.9%)</td>
<td>31 (49.2%)</td>
<td>27 (40.3%)</td>
<td>32 (44.4%)</td>
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<tr>
<td>4 - Inactive</td>
<td>8 (16.3%)</td>
<td>14 (22.2%)</td>
<td>12 (19.0%)</td>
<td>19 (28.4%)</td>
<td>23 (31.9%)</td>
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<tr>
<td><strong>Baseline Outcome Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MSIS-29, v2 (physical component)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 0 – 100</td>
<td>29.6&lt;sup&gt;a&lt;/sup&gt; (23.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.0&lt;sup&gt;a&lt;/sup&gt; (18.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33.1&lt;sup&gt;a&lt;/sup&gt; (20.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>35.2&lt;sup&gt;a&lt;/sup&gt; (20.4)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>35.4&lt;sup&gt;a&lt;/sup&gt; (24.0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.491&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>MSIS-29, v2 (psychological component)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range 0 – 100</td>
<td>22.2&lt;sup&gt;d&lt;/sup&gt; (12.04)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>33.3&lt;sup&gt;d&lt;/sup&gt; (14.8)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>33.3&lt;sup&gt;d&lt;/sup&gt; (16.7)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>29.6&lt;sup&gt;d&lt;/sup&gt; (13.0)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>35.2&lt;sup&gt;d&lt;/sup&gt; (16.2)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>0.093&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>MFIS</td>
<td>36.2&lt;sup&gt;a&lt;/sup&gt; (18.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39.2&lt;sup&gt;a&lt;/sup&gt; (14.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40.1&lt;sup&gt;a&lt;/sup&gt; (16.2)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39.25 (17.6)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39.8 (19.9)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.794&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Range 0 – 84</td>
<td>4.81&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4.71&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.79&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>6MWT (metres)</td>
<td>350&lt;sup&gt;a&lt;/sup&gt; (103.2)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>287.5&lt;sup&gt;a&lt;/sup&gt; (94.4)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>268.0&lt;sup&gt;a&lt;/sup&gt; (80.0)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>290.0&lt;sup&gt;a&lt;/sup&gt; (111.0)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>312.6&lt;sup&gt;a&lt;/sup&gt; (89.3)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.427&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>(82, 620)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>(128, 555)</td>
<td>(30, 595)</td>
<td>(100, 600)</td>
<td>(66, 605)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean, <sup>b</sup> Standard deviation, <sup>c</sup> Range, <sup>d</sup> Median, <sup>e</sup> Semi-interquartile range, <sup>f</sup> One-Way ANOVA, <sup>g</sup> Kruskal Wallis Test, <sup>h</sup> Chi squared, MSIS-29 = Multiple Sclerosis Impact Scale – 29, version 2, MFIS = Modified Fatigue Impact Scale, 6MWT = Six Minute Walk Test
7.3 Adherence

Of the 10 classes in the programme, participants allocated to PT-led exercise attended a mean of 8.05 classes (95% CI 7.5, 8.5). Participants allocated to Yoga attended a mean of 7.8 classes (95% CI 7.2, 8.3) and participants allocated to FI-led exercise attended a mean of 7.3 classes (95% CI 6.7, 7.9).

In the PT-led programme there was a home exercise component consisting of 10 aerobic sessions in weeks 1 – 5 (i.e. a frequency of 2 per week). Data was returned for 47 (73%) participants. There was a mean reported adherence of 9.58 (95% CI 8.3, 10.8) sessions in total.

So that the programme was progressive, in weeks 6 – 10 it was advised that participants complete 15 sessions of AT (i.e. 3 per week). However, participants did not hand in their week 10 data to the deliverers of the interventions as the classes had finished thus a maximum of 12 sessions were advised between weeks 6 and 9 inclusive. Data were returned for 45 (71.4%) participants. There was a mean reported adherence of 10.2 (95% CI 8.9, 11.5) out of 12 sessions.

In weeks 6 – 10 participants were also asked to participate in a second session of progressive resisted exercise independently at home (i.e. a total of 5) but again participants did not return week 10 participation details as above thus there was a maximum of 4 sessions advised between weeks 6 and 9 inclusive. Data was returned for 44 (69.8%) participants. In these participants, there was a mean reported adherence to the recommended frequency of exercise of 3.5 (95% CI 3.1, 3.6).
7.4 CONTENT OF THE INTERVENTIONS

Little is known about the content and efficacy of community-based interventions. The content of yoga and fitness-instructor led exercise in this pragmatic trial are described below.

Yoga

Eleven community-based yoga classes took place throughout Ireland. Nine yoga instructors returned details regarding the content of the intervention. These are summarised in detail in Appendix X.

Seven out of the nine instructors that returned details on the intervention commenced the class with breathing exercise, relaxation or “body centring”. Most (8/9) classes followed these exercises with a “joint freeing series”, range of motion exercises or stretching exercises. In 7 of the yoga classes, deliverers of interventions reported dynamic weight-bearing poses (Asanas) such as Palm Tree Vinyasa, Forward Bends, Trinkonasana (triangle pose) and Warrior Pose. Eight classes concluded with relaxation, breathing exercises or Yoga Nidra. The types of exercises were described more specifically in 6 of the classes. Duration of hold of the different asanas was described in two of the classes as from 30 – 90 seconds. The duration of the different sections of the classes was described by 3 deliverers of yoga.

The Fitness Instructor led classes

Thirteen FI-led classes took place across 11 regions across the country. Details from 11 classes were obtained. The interventions are described in detail in Appendix Y. The majority (n = 8/11) of the interventions were a combined exercise intervention (i.e. aerobic and progressive resistance exercise). The others were a PRE (n = 1) and an AT intervention (n = 2). MSI reported that one of the groups in the west was very upset that
they were not doing physiotherapy and may have contributed to the high dropout rate in that region (West, class 1: N = 3). Number of repetitions or duration of exercise was reported in 8/11 classes. Five classes were reported as being progressive in nature. How exercises were progressed is not clear.

7.5 Primary Outcome Measure: Multiple Sclerosis Impact Scale – 29, Version 2 (Physical Component)

The physical component of the Multiple Sclerosis Impact Scale-29, v2 (MSIS-29, v2) is measured from 20-80 and converted to a scale of 0-100. A higher score indicates a greater physical impact of MS. Thus a reduction in score indicates an improvement. As data were reasonably normally distributed, parametric statistics were used. A repeated measures Analysis of Variance (ANOVA) with a Bonferroni correction for the number of tests was performed to assess the impact of the four different group allocations (PT-led exercise, Yoga, FI-led exercise and the control) on participants scores on the MSIS-29, v2 (physical component) across two time points (pre intervention and post intervention).

The main interaction effect (time x group) approached significance, Wilks Lambda = 0.970, F (3, 237) = 2.479, p = 0.062. The group x time, time and group effects are presented in Table 18.

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>P</th>
<th>Partial Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x Time</td>
<td>2.479</td>
<td>0.062</td>
<td>0.030</td>
</tr>
<tr>
<td>Time</td>
<td>18.394</td>
<td>&lt;0.0001</td>
<td>0.072</td>
</tr>
<tr>
<td>Group</td>
<td>0.327</td>
<td>0.806</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Time was the within-subjects factor. Independent of group, there was a mean score of 38.6±16.6 pre intervention which reduced to 33.3±18.0 post intervention, p <0.001.
Figure 6 and Table 19 demonstrate the within group effects for the MSIS-29, v 2 (physical component). The effect size was between small and moderate for all three exercise-based interventions with the smallest being for yoga and largest being the PT-led group. There was a probability of $\leq 0.05$ for all three interventions as indicated by paired-samples t-tests. There was no mean change in the control group over time.

**FIGURE 6 MEAN MSIS-29, V 2 (PHYSICAL COMPONENT) PRE AND POST INTERVENTION**

**TABLE 19 RESULTS WITHIN GROUPS USING THE MULTIPLE SCLEROSIS IMPACT SCALE-29, V 2 (PHYSICAL COMPONENT)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre Mean (SD)</th>
<th>Post Mean (SD)</th>
<th>Mean change (CI)</th>
<th>% Change</th>
<th>Effect size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>29.6 (23.0)</td>
<td>29.9 (20.7)</td>
<td>0.3 (-4.0, 4.6)</td>
<td>1.1</td>
<td>0.01</td>
<td>0.90</td>
</tr>
<tr>
<td>PT-led</td>
<td>33.0 (18.3)</td>
<td>26.2 (17.2)</td>
<td>-6.9 (-10.8, -2.9)</td>
<td>-20.9</td>
<td>-0.38</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Yoga</td>
<td>33.4 (20.0)</td>
<td>29.4 (19.4)</td>
<td>-4.0 (-7.5, -.5)</td>
<td>-12.0</td>
<td>-0.20</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>FI-led</td>
<td>35.2 (20.4)</td>
<td>29.5 (19.9)</td>
<td>-5.7 (-9.1, -2.4)</td>
<td>-16.2</td>
<td>-0.28</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Effect size = mean change/SD baseline. Values interpreted using Cohen’s criteria (0.2 = small change, 0.5 = moderate change, 0.8 = large change). * = statistically significant using Paired T tests
Independent of time, the main effect for group, to which participants were randomised, was not significant $p = 0.806$.

In summary, these results show that there is a time effect for the PT-led intervention, Yoga and the FI-led group. By order of magnitude the PT-led intervention showed the largest improvement but the differences between interventions were not significant. There was no change in the control group.

### 7.6 Multiple Sclerosis Impact Scale – 29, Version 2 (Psychological Component)

The psychological component of the Multiple Sclerosis Impact Scale-29, v2 (MSIS-29, v2) is measured from 9-36 and converted to 0 – 100. A higher score indicates a greater psychological impact of MS. Thus a lower score after interventions indicates an improvement. Although repeated measures ANOVA is the preferred method of analysing randomised controlled trials with baseline and post-intervention measures, the data failed to meet the key assumptions for this technique (normality, sphericity and equality of variances). Thus, non-parametric statistics were used. Box plots are used to describe the data. The dark line represents the median value. The boxes represent the 25th and 75th percentile and the whiskers represent the range. Wilcoxon Signed Rank Tests were used to establish the within-group effects for each intervention. Change scores were calculated and Mann-Whitney U tests were performed to identify if there was a difference in change scores between groups.

Figure 7 demonstrates the group MSIS-29, v2 (psychological component) values pre and post intervention. Using Cohen’s (1998) criteria (0.2 = small effect, 0.5 = medium effect, 0.8 = large effect), Table 20 shows that there was an effect between small and medium effect size. The improvement due to intervention was statistically significant for all three intervention groups. There was no change in the control group.
Similar to the MSIS-29, v 2 (physical component), the PT-led group demonstrated the largest change.

**FIGURE 7 GROUP VALUES USING THE MSIS-29, V 2 (PSYCHOLOGICAL COMPONENT) PRE AND POST INTERVENTION**

![Graph showing changes in MSIS-29, v 2 (psychological component) pre and post intervention for different groups.](image)

**TABLE 20 RESULTS WITHIN GROUPS USING THE MSIS-29, V 2 (PSYCHOLOGICAL COMPONENT)**

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>Median change week 1 – 12</th>
<th>Treatment effect size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (N = 49)</td>
<td>0.00</td>
<td>0.008</td>
<td>.937</td>
</tr>
<tr>
<td>PT-led (N = 63)</td>
<td>-11.11</td>
<td>0.36</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Yoga (N = 62)</td>
<td>-3.7</td>
<td>0.25</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FI-led (N = 67)</td>
<td>-3.7</td>
<td>0.30</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Effect size = \( \sqrt{Z/N} \). Values interpreted using Cohen’s criteria (0.2 = small change, 0.5 = moderate change, 0.8 = large change). * = statistically significant using Wilcoxon Signed Rank tests

A Kruskal-Wallis (equivalent of one-way between groups ANOVA) test on the change scores (post-pre intervention) indicated that there was a statistically significant difference (p = 0.013) between groups. The median change and the results of Mann Whitney U tests are described in Table 21.
There was a statistically significant difference between all three exercise-based interventions and the control group but no differences between the intervention groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control v PT-led</td>
<td>0.002*</td>
</tr>
<tr>
<td>Control v Yoga</td>
<td>0.043*</td>
</tr>
<tr>
<td>Control v FI-led</td>
<td>0.019*</td>
</tr>
<tr>
<td>PT-led v Yoga</td>
<td>0.228</td>
</tr>
<tr>
<td>PT-led v FI-led</td>
<td>0.208</td>
</tr>
<tr>
<td>Yoga v FI-led</td>
<td>0.974</td>
</tr>
</tbody>
</table>

* Statistically significant using Mann Whitney U tests

7.7 The Modified Fatigue Impact Scale

7.7.0 Introduction

In most studies to date, the Modified Fatigue Impact Scale (MFIS) has been presented as a summative score thus, in order to make comparisons with other studies, this is presented below. Recently Mills et al (2010) suggested that this scale is valid as physical and cognitive subscales after deletion of some items subsequent to Rasch analysis. Thus, results are presented in these two subscales in addition to the total score.

Data were normally distributed thus a repeated measures ANOVA was conducted.

7.7.1 The MFIS (Total Score)

The Modified Fatigue Impact Scale (MFIS) is measured from 0 – 84. A higher score indicates a greater impact of fatigue. Thus a lower score after intervention indicates an improvement. The main interaction effect suggests that there is a difference between groups over time Wilks Lambda= 0.969 (3, 237) =2.501, p =0.060. The group x time, time and group effects are presented in Table 22.
<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>P</th>
<th>Partial Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x Time</td>
<td>2.501</td>
<td>0.060</td>
<td>0.031</td>
</tr>
<tr>
<td>Time</td>
<td>38.050</td>
<td>&lt;0.0001</td>
<td>0.138</td>
</tr>
<tr>
<td>Group</td>
<td>0.131</td>
<td>0.942</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Time (from pre to post intervention) was the within-subjects factor. There was a substantial main effect for time with a pre intervention mean of 38.9±16.7 and a post intervention mean of 33.3±18.04, p <0.001.

Figure 8 indicates the pre and post scores on the MFIS.

Table 23 shows that there was moderate effect for the PT-led group and an effect part way between small and moderate for yoga and the FI-led groups. The effect reached statistical significance for all three interventions. There was no change in the control group.

FIGURE 8 MEAN MFIS (TOTAL SCORE) PRE AND POST INTERVENTION
### TABLE 23 RESULTS WITHIN GROUPS USING THE MFIS (TOTAL SCORE)

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre Mean (SD)</th>
<th>Post Mean (SD)</th>
<th>Mean change (CI)</th>
<th>% Change</th>
<th>Effect size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (N = 49)</td>
<td>36.2 (18.3)</td>
<td>35.1 (20.1)</td>
<td>-1.1 (-4.45, 2.25)</td>
<td>-3.04</td>
<td>-0.06</td>
<td>0.512</td>
</tr>
<tr>
<td>PT-led (N = 63)</td>
<td>39.3 (14.8)</td>
<td>31.8 (16.5)</td>
<td>-7.54 (-11.12, -3.89)</td>
<td>-19.18</td>
<td>-0.51</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Yoga (N = 63)</td>
<td>40.0 (16.2)</td>
<td>34.2 (17.9)</td>
<td>-5.82 (-9.21, -2.42)</td>
<td>-14.53</td>
<td>-0.35</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>FI-led (N = 67)</td>
<td>39.3 (17.5)</td>
<td>33.3 (18.0)</td>
<td>-6.69 (-9.82, -3.55)</td>
<td>-17.03</td>
<td>-0.38</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Effect size = mean change/SD baseline. Values interpreted using Cohen's criteria (0.2 = small change, 0.5 = moderate change, 0.8 = large change). * = statistically significant using Paired T tests.

The main effect for group was not significant, p = 0.942. These results show that there is a time effect for the PT-led intervention, Yoga and the Fitness instructor led group. Identical to the MSIS-29 results, by order of magnitude the PT-led intervention showed the largest improvement but the differences between interventions were not significant. There was no change in the control group.

### 7.7.2 THE MFIS (PHYSICAL SUBSCALE)

The physical subscale is measured from 0 to 32, with higher scores indicating a greater impact of fatigue on physical domains. The main interaction effect was statistically significant, Wilks Lambda = 0.949, F (3, 235) = 4.23, p = 0.006, partial eta squared 0.051. The main effects for group x time, time and group are presented in Table 24.

### TABLE 24 RESULTS OF ANOVA EVALUATING THE EFFECT OF GROUP ALLOCATION AND TIME ON THE MODIFIED FATIGUE IMPACT SCALE (PHYSICAL SUBSCALE)

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>P</th>
<th>Partial Squared</th>
<th>Eta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x Time</td>
<td>4.232</td>
<td>0.006</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>33.512</td>
<td>&lt;0.0001</td>
<td>0.125</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.673</td>
<td>0.570</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>
There was a main effect for time with the MFIS (physical subscale) reducing from 17.2±7.1 to 14.8±7.7 p < 0.001. Figure 9 and Table 25 demonstrate the MFIS (physical subscale) results for each group. A moderate effect was seen for the PT-led group, an effect part way between small and moderate for yoga and the FI-led groups and no real effect for the control group. The change seen in all three exercise-based interventions was statistically significant and there was no change in the control group.

FIGURE 9 MEAN MFIS (PHYSICAL SUBSCALE) PRE AND POST INTERVENTION
The between-subjects effect was the group to which participants were allocated to. This was not statistically significant, p = 0.57.

### 7.7.3 The MFIS (Cognitive Subscale)

The cognitive subscale is measured from 0 to 20, with higher scores indicating a higher impact of fatigue on cognitive domains. The main effects for group x time, time and group are presented in Table 26. The main interaction effect was not statistically significant Wilks Lambda = 0.977, F (3, 233) = 1.85, p = 0.139, partial eta squared = 0.023

#### Table 26 Results of ANOVA Evaluating the Effect of Group Allocation and Time on the Modified Fatigue Impact Scale (The Cognitive Subscale)

<table>
<thead>
<tr>
<th>Group</th>
<th>F</th>
<th>P</th>
<th>Partial Squared</th>
<th>Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x Time</td>
<td>1.850</td>
<td>0.139</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>21.292</td>
<td>&lt;0.0001</td>
<td>0.084</td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>0.209</td>
<td>0.890</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

There was a main effect for time with the MFIS (cognitive subscale) reducing from 7.6±5.3 to 6.5±5.3, p <0.0001. Figure 10 and Table 27 demonstrate results for the MFIS...
(cognitive subscale) for each group. There was a moderate effect for the PT-led group and a small effect for the yoga and FI-led groups. The control group had a small effect. Using paired-samples t-tests, there was a p-value of <0.05 for all three exercise-based interventions. The main effect comparing the four groups was not significant F (3, 233) = 49.487, p = 0.890.

FIGURE 10 MEAN MFIS (COGNITIVE SUBSCALE) PRE AND POST INTERVENTION

![Graph showing mean MFIS (cognitive subscale) pre and post intervention for control, PT-led exercise, yoga, and FI-led exercise groups.](image)

TABLE 27 RESULTS WITHIN GROUPS USING THE MFIS (COGNITIVE SUBSCALE)

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre Mean (SD)</th>
<th>Post Mean (SD)</th>
<th>Mean Change (95% CI)</th>
<th>% Change</th>
<th>Effect Size</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.36 (5.6)</td>
<td>6.9 (5.8)</td>
<td>-0.51 (0.7, -1.7)</td>
<td>6.9</td>
<td>0.09</td>
<td>0.38</td>
</tr>
<tr>
<td>PT-led exercise</td>
<td>7.75 (4.9)</td>
<td>5.6 (4.4)</td>
<td>-2.1 (-1.0, -3.1)</td>
<td>27.1</td>
<td>0.43</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Yoga</td>
<td>7.87 (5.3)</td>
<td>6.9 (5.5)</td>
<td>-0.96 (-0.1, 1.7)</td>
<td>12.2</td>
<td>0.18</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>FI-led exercise</td>
<td>7.38 (5.4)</td>
<td>6.4 (5.5)</td>
<td>-0.94 (-0.9, -1.8)</td>
<td>12.7</td>
<td>0.17</td>
<td>&lt;0.05*</td>
</tr>
</tbody>
</table>

SRM = standardised response mean: mean change/SD change. Values interpreted using Cohen’s criteria (0.2 = small change, 0.5 = moderate change, 0.8 = large change) * = statistically significant using paired-samples t-tests.
7.8 THE SIX MINUTE WALK

The Six Minute Walk Test (6MWT) is measured in distance (m). Thus a higher score after intervention indicates an improvement. Data were reasonably normally distributed with the exception of the Yoga group post intervention which was borderline (Kolmogorov Smirnov p = 0.054). Additionally, when both parametric and non-parametric statistics were used, the yoga group demonstrated results in opposite directions (i.e. mean reduction from 294m to 280m or median improvement from 268m to 285m. Thus, to err on the side of caution, non-parametric statistics were used to analyse 6MWT data.

Figure 11 demonstrates the pre and post intervention scores for each group using the 6MWT. The dark line represents the median value. The boxes represent the 25th and 75th percentile and the whiskers represent the range. Table 28 shows the median change. It can be seen that using Cohen (1998) criteria (0.2 = small effect, 0.5 = medium effect, 0.8 = large effect), an effect between small and moderate was seen for PT-led exercise, FI-led exercise and the control. This change was in the direction of improvement and statistically significant for the PT-led and FI-led groups. No change was seen in the yoga group. There was a trend towards worsening in the control. Large variability was seen around all point estimates.
FIGURE 11 GROUP 6MWT VALUES PRE AND POST INTERVENTION

TABLE 28 RESULTS WITHIN GROUPS USING THE 6MWT

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>Median change week 1 – 12 (m) (CI)</th>
<th>Effect size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (N = 40)</td>
<td>-10 (-0.21 0.17)</td>
<td>-0.21</td>
<td>0.17</td>
</tr>
<tr>
<td>PT-led (N = 55)</td>
<td>10 (0.28 &lt;0.05*)</td>
<td>0.28</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Yoga (N = 62)</td>
<td>0 (-0.14 0.26)</td>
<td>-0.14</td>
<td>0.26</td>
</tr>
<tr>
<td>FI-led (N = 59)</td>
<td>20 (0.35 &lt;0.01*)</td>
<td>0.35</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Effect Size = Z / \sqrt{N}. Values interpreted using Cohen (1998) criteria (0.2 = small effect, 0.5 = medium effect, 0.8 = large effect) * = statistically significant using Wilcoxon Signed Rank Tests

A Kruskal Wallis Test indicated that there was a statistically significant difference between the change scores calculated for each group p < 0.01. Results of Mann Whitney U tests comparing where are these differences are described in Table 29. These results suggest that the change achieved by the PT-led and FI-led groups were both significantly different to both the control group and yoga (p<0.05) but were not different from each other (p>0.05).
<table>
<thead>
<tr>
<th>Groups</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control v PT-led</td>
<td>&lt;0.02*</td>
</tr>
<tr>
<td>Control v Yoga</td>
<td>0.73</td>
</tr>
<tr>
<td>Control v FI-led</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>PT-led v Yoga</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>PT-led v FI-led</td>
<td>0.38</td>
</tr>
<tr>
<td>Yoga v FI-led</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

* = Statistically significant using Mann Whitney U tests

### 7.9 Summary of Findings

A large number of participants were recruited for this trial (n = 372). There were no statistically significant differences between groups at baseline. However, large variability was seen for all point estimates indicating that there was heterogeneity in the baseline presentation of participants.

The participants who dropped out of the trial had a greater psychological impact of MS than participants who returned for assessment after the intervention period. This difference approached statistical significance (p = 0.09). All other characteristics were similar to those who remained in the trial. There was a higher rate of dropping out due to relapse in the control group compared to the three exercise-based interventions.

There were improvements between 12 and 22% in reducing the physical impact of MS and reducing the impact of fatigue for all three exercise interventions. By order of magnitude, the PT-led group led to the largest improvements, followed by the FI-led group and Yoga. These improvements were statistically significant. There was no change in the control group for patient reported outcomes.
The PT-led group improved by a median of 10m using the 6MWT. The FI-led group improved by a median of 20m. These improvements were statistically significant (p<0.05). The yoga group did not change and the control group worsened by 10m. These changes were not statistically significant (p>0.05).

There was no change in the control group for any of the patient reported outcomes. However, there was a trend towards worsening for the 6MWT.
CHAPTER 8: FOLLOW-UP

8.0 INTRODUCTION

To date, three trials have explored follow-up data after an aerobic or PRE exercise intervention (Kileff and Ashburn 2005, McCullagh et al. 2008, Dalgas et al. 2010a, Dalgas et al. 2010b, Dalgas et al. 2009). This is the first study to explore follow-up to a combined AT and PRE intervention and community-based interventions.

8.1 PARTICIPANTS

Figure 12 describes the flow of participants through the trial from week 12 to week 24. Control group data were not collected after week 12 to allow participants to embark on the treatment of their choice. In this instance the comparison was the intervention period, thus a control was not required.

In the PT-led intervention 42 participants attended for follow-up. Of these, 9 (21.4%) reported increased exercise participation since the programme finished, 13 (30.9%) reported decreased exercise and 18 (42.8%) reported maintaining their exercise participation level since the intervention. In the Yoga intervention 38 participants attended for follow-up. Of these, 12 (31.6%) reported increased exercise participation since the programme finished, 9 (23.7%) reported decreased exercise and 14 (34.1%) reported maintaining their exercise participation level since the intervention. In the FI-led intervention 41 participants attended for follow-up. Of these, 10 (24.4%) reported increased exercise participation since the programme finished, 14 (34.1%) reported decreased exercise and 15 (36.6%) reported maintaining their exercise participation level since the intervention.
In all groups, some participants embarked on a second “Getting the Balance Right” intervention immediately after taking part in the research arm of the programme – as these participants may confound the follow-up results, they were not included in the analyses.
*Not conducted: One regional office forgot that there was a 24 week follow-up component to the study, thus follow-up was not conducted for participants in this region.
Participants who dropped out at 24 weeks were a mean of 47 years old ±10.4. They had a mean time since onset of symptoms 12.6±8 years and were diagnosed for a mean of 10.6±6.8 years. Participants had a median upper limb sensation score of 60 (SIQR 0) and a median lower limb sensation score of 60 (SIQR 0).

They had a mean MSIS-29, v 2 (physical component) of 32.9±19.8, a median MSIS-29, v 2 (psychological component) of 20 (SIQR 18.8), mean MFIS of 39.9 (16.8) and a 6MWT of 372.5 (SIQR 146.1). Gait was unaffected (GNDS, lower limb disability section = 0) in 14 (37.8%) participants, unsteady gait in 12 (32.4%) participants and 11 (29.7%) participants use at most one stick for outdoors. 18 (48.6%) participants reported having RRMS, 9 (24.3%) reported having SPMS, 7 (18.9%) had PPMS and 1 (2.7%) had benign MS. Twenty-two (59.5%) were on disease modifying medications. Thirty-six (97.3 %) participants had normal upper limb proprioception, 33 (89.2%) had normal lower limb proprioception, 25 (81.1%) had no increase in upper limb tone, 25 (67.7%) had normal lower limb tone. Twenty-three participants (62.2%) had normal co-ordination.

These participants were largely similar to participants who remained in the trial in terms of their baseline characteristics.

8.2 Results

8.2.0 Introduction

The main aim in analysing the follow-up data was to investigate the results 3 months after the intervention period. Trials with follow-up to date have been small, non-blinded, supervised programmes, where attrition has been minimal. However, there were many dropouts in this trial as outlined above. Thus, to maximise the data, all participants who attended after intervention were analysed so that the treatment effect may be established with adequate power (i.e. 49 participants in the control,
63 in PT-led exercise, 63 in yoga and 67 in FI-led exercise). However, to establish the follow-up effect, participants who attended for follow-up were analysed at the three time points (i.e. approx. 40 participants per group pre intervention, post-intervention and at follow-up)

8.2.1 MSIS-29 (PHYSICAL COMPONENT)

The main effects for group x time, and for time and group individually are presented in Table 30. The main interaction effect (time x group) was not statistically significant, Wilks Lambda = 0.970, F (4, 228) = 0.891 = 8.132, p = 0.470.

Figure 13 suggests that the three interventions changed in a similar magnitude and direction over time. Independent of group, there was a mean score of 34.6 ±20.0 pre interventions to 29.4±20.0 post intervention with scores returning to 33.0±21.1 at follow-up, p < 0.0001.

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>P</th>
<th>Partial Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x Time</td>
<td>0.891</td>
<td>0.470</td>
<td>.015</td>
</tr>
<tr>
<td>Time</td>
<td>8.132</td>
<td>&lt;0.001</td>
<td>0.124</td>
</tr>
<tr>
<td>Group</td>
<td>1.987</td>
<td>0.124</td>
<td>0.033</td>
</tr>
</tbody>
</table>

FIGURE 13 MEAN MSIS-29, V 2 (PHYSICAL COMPONENT) PRE-INTERVENTION, POST-INTERVENTION AND AT FOLLOW-UP
Paired-samples t-tests indicated that there was a significant improvement across the groups between pre and post intervention with a mean change of -5.21 (95% CI -7.82, -2.60), p < 0.0001 and a significant worsening of scores between post intervention and follow-up with a mean change of 3.60 (95% CI 1.22, 6.0), p =0.003. Follow-up scores did not differ significantly from baseline with a mean change of 1.61 (95% CI -0.81, 4.03), p = 0.189.

These results demonstrate that there is a similar time effect for the three interventions in terms of direction. This reflects the findings of the treatment results explored in Chapter 7. Positive results obtained due to intervention were not maintained. However, in terms of magnitude of change, values observed did not return to pre intervention levels.
8.2.2 MSIS-29 (PSYCHOLOGICAL COMPONENT)

As the distribution of data was skewed for the MSIS-29 (psychological component), non-parametric statistics were used. Figure 14 and Table 31 indicate that there was a trend towards returning to baseline scores for yoga and FI-led exercise. The median improvement made by the PT-led group was maintained. The overall difference between pre-intervention and follow-up was statistically significant (p=0.01).

FIGURE 14 GROUP MSIS-29, V2 (PSYCHOLOGICAL COMPONENT) PRE-INTERVENTION, POST-INTERVENTION AND FOLLOW-UP

TABLE 31 RESULTS WITHIN GROUPS USING THE MSIS-29, V 2 (PSYCHOLOGICAL COMPONENT) AT FOLLOW-UP

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>Median change (post-pre)</th>
<th>Median change (follow-up - post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT-led (N= 42)</td>
<td>-11.1†</td>
<td>0‡</td>
</tr>
<tr>
<td>Yoga (N = 36)</td>
<td>-3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>FI-led (N = 41)</td>
<td>-5.6‡</td>
<td>3.7</td>
</tr>
</tbody>
</table>

†p ≤0.01, ‡p ≤0.05 using Wilcoxon Signed Rank tests
8.2.3 MFIS

The MFIS (total score)

The main interaction effect, the time effect and the group effect are presented in Table 32. Figure 15 suggests that the three interventions changed in a similar magnitude and direction over time. Independent of group, the cohort had a mean of 39.45±15.77 pre intervention which improved to 32.70 ±17.68 post intervention and returned to 34.77±17.34 at follow-up. This time effect was statistically significant, p < 0.001. The mean change between pre and post intervention was -6.76 (95% CI -9.26, -4.26) p =<0.0001. The mean change between post intervention and follow-up was 2.07 (95% CI -0.27, 4.41), which approached significance (p = 0.082). The mean difference between pre intervention and follow up (-4.68 95% CI -6.91, -2.45) remained significant p <0.001. These results suggest that the intervention maintained a significant improvement from the start of intervention to follow-up. However, there was a trend towards returning to baseline scores.

<table>
<thead>
<tr>
<th>TABLE 32 RESULTS OF ANOVA EVALUATING THE EFFECT OF GROUP ALLOCATION AND TIME ON THE MODIFIED IMPACT SCALE (TOTAL SCORE) AT FOLLOW-UP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x Time</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Time</td>
</tr>
<tr>
<td>Group</td>
</tr>
</tbody>
</table>
The physical subscale

The MFIS (physical subscale) is measured from 0 to 32 with higher scores indicating a higher impact of fatigue on physical domains. The main effects are presented in Table 33. Independent of group, the cohort improved from 17.45 ±6.68 pre-intervention to 14.30 ± 7.81 post intervention and reduced to 15.73 ±7.58 at follow-up. Paired-samples t-tests showed a significant improvement of -3.15 (95%CI -4.33, -1.97) from pre to post-intervention and a significant (p = 0.009) worsening of 1.42 (95%CI 0.36, 2.49) from post intervention to follow-up. The difference between pre intervention and follow up (mean -1.72 95% CI -2.78, -0.67) remained significant p =0.002. These results are similar to the MFIS (total score) results and suggest that although positive results are not maintained, scores do not return to pre-intervention values.
TABLE 33 RESULTS OF ANOVA EVALUATING THE EFFECT OF GROUP ALLOCATION AND TIME ON THE MFIS (PHYSICAL SUBSCALE) AT FOLLOW-UP

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>P</th>
<th>Partial Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x Time</td>
<td>0.907</td>
<td>0.461</td>
<td>0.016</td>
</tr>
<tr>
<td>Time</td>
<td>13.630</td>
<td>&lt;0.0001</td>
<td>0.192</td>
</tr>
<tr>
<td>Group</td>
<td>1.237</td>
<td>0.294</td>
<td>0.021</td>
</tr>
</tbody>
</table>

FIGURE 16 MEAN MFIS (PHYSICAL SUBSCALE) VALUES PRE-INTERVENTION, POST-INTERVENTION AND FOLLOW-UP

The cognitive subscale

The MFIS (cognitive subscale) is measured from 0 to 20 with higher scores indicating a higher impact of fatigue on cognitive domains.
Table 34 demonstrates the main effects for group x time, time and for group independently. There was a significant main effect for time with the cohort demonstrating a mean MFIS (cognitive subscale) score of 7.82±.008 pre-intervention, 6.54±4.97 post-intervention and 6.57±4.92 at follow-up. However, Figure 17 suggests different time effects within the groups. The return towards baseline scores only occurred in the PT-led group where there was the greatest magnitude of change with the most precision as demonstrated in Table 35.

**TABLE 34 RESULTS OF ANOVA EVALUATING THE EFFECT OF GROUP ALLOCATION AND TIME ON THE MFIS (COGNITIVE SUBSCALE) AT FOLLOW-UP**

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>P</th>
<th>Partial Eta Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group x Time</td>
<td>1.794</td>
<td>0.131</td>
<td>0.031</td>
</tr>
<tr>
<td>Time</td>
<td>9.776</td>
<td>&lt;0.0001</td>
<td>0.146</td>
</tr>
<tr>
<td>Group</td>
<td>0.062</td>
<td>0.940</td>
<td>0.001</td>
</tr>
</tbody>
</table>
TABLE 35 RESULTS WITHIN GROUPS USING THE MFIS (COGNITIVE SUBSCALE) AT FOLLOW-UP

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre</th>
<th>Post</th>
<th>Follow-up</th>
<th>Mean change (post-pre) (95% CI)</th>
<th>Mean change (follow-up-post) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT-led</td>
<td>8.2 (4.6)</td>
<td>5.8 (4.0)</td>
<td>6.7 (4.4)</td>
<td>-2.4 (-3.8, -2.7)†</td>
<td>0.9 (-0.01, 1.9)‡</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)
† p ≤ 0.01 using Paired T tests, ‡p ≤ 0.05 using Paired T tests

8.2.4 SIX MINUTE WALK TEST

Figure 18 and
Table 36 show the changes over time for the three groups. The findings suggest that what was observed between pre and post intervention, was reversed at follow-up.

FIGURE 18 GROUP 6MWT VALUES PRE INTERVENTION, POST INTERVENTION AND FOLLOW-UP
TABLE 36 MEDIAN CHANGES FOR THE SIX MINUTE WALK TEST AT FOLLOW-UP

<table>
<thead>
<tr>
<th>Randomisation</th>
<th>Median change (post-pre)</th>
<th>Median change (follow-up-post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT-led (N= 34)</td>
<td>10m</td>
<td>-9.5m</td>
</tr>
<tr>
<td>Yoga (N = 37)</td>
<td>0m</td>
<td>10.0m</td>
</tr>
<tr>
<td>FI-led (N = 20)</td>
<td>25m†</td>
<td>-29.4m</td>
</tr>
</tbody>
</table>

† p≤ 0.01 using Wilcoxon Signed Rank test

The difference between pre intervention and follow-up described in Figure 18 was not statistically significant for the PT-led group (p=0.857), Yoga (p=0.325) or the FI-led group (0.513).

8.3 SUMMARY OF FINDINGS

The main objective of this chapter was to establish the efficacy of the three interventions 3 months after the intervention period.

Seventy-two participants were lost to follow-up after the intervention (37.3%). Forty three per cent of all participants (41/94) who attended for follow-up reported a reduction in their exercise participation levels during the follow-up period.

There was a statistically significant improvement in the MSIS-29, v 2 (physical component), the MFIS (total score) and the MFIS (physical subscale) as seen in the main effect in Chapter 7. There was a statistically significant reduction from post intervention to 3-month follow-up. In terms of magnitude of change, all of the statistically significant positive findings achieved during the intervention period were reversed (p<0.05).
Interestingly, in the MSIS-29, v 2 (physical component) and the Six Minute Walk, participants at follow-up did not remain statistically significantly improved from baseline. However the MSIS-29, v 2 (psychological component) and MFIS remained significantly improved from baseline. This may suggest that psychological variables may be better maintained that physical variables. Importantly, point estimates did not return to baseline values.
CHAPTER 9: A POST-HOC EXPLORATION OF DATA

9.0 INTRODUCTION

All three exercise-based interventions in this study led to an improvement in the primary outcome variable, the MSIS-29, v 2 (physical component) that was statistically significant. However, some participants did better than others as indicated by the variability around the mean scores. The relationship between clinical variables and HRQoL in PwMS is of considerable interest to clinicians to inform targeted treatment.

The aim of this chapter is to present a further exploration of data to identify the predictors of outcome after the intervention period.

Baseline characteristics associated with outcome are described using Multiple Linear Regression. This will inform what participant characteristics were associated with a low disease impact score after participating in the intervention period of the RCT described in this thesis.

By exploring this data further, clinicians will be more informed regarding what participant characteristics predict outcome after an intervention.

9.1 WHAT PREDICTS OUTCOME

Standard multiple linear regression was used to predict outcome in the full cohort. The outcome variable was the primary outcome measure – the post intervention score on the MSIS-29, v 2 (physical component).
Predictor variables were those identified from the literature as described in chapter 3. These were type of MS, age at onset (including age, length of time since onset of symptoms and age at onset), gender, somatosensation (sensation and proprioception), ataxia (co-ordination), tone, baseline exercise activity level and adherence. Other predictor variables were also used including the GNDS (lower limb disability section) score, MSIS-29, v 2 (physical component), the MSIS-29, v 2 (psychological component), the MFIS (total score), the MFIS (physical subscale), the MFIS (cognitive subscale) and the 6MWT as it was hypothesised that participants starting point on these measures might influence outcome. Finally, group allocation (which group participants were randomised to) was entered in to the model to try to further identify who does best from what.

The strongest predictive models were identified by entering these predefined variables in hundreds of combinations until each contributing variable was statistically significant (thus contributing to the regression line) and that the highest amount of variance was accounted for using the least number of variables.

Table 37 demonstrates the strongest model from the entire cohort and accounted for 57.4% of the variance. This model was statistically significant: F (5, 211) = 59.24, p <0.01.

<table>
<thead>
<tr>
<th>TABLE 37 PARTICIPANT CHARACTERISTICS PREDICTING OUTCOME MSIS-29, v 2 (PHYSICAL COMPONENT) AFTER INTERVENTION – THE STRONGEST MODEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1, R² = 57.4%</td>
</tr>
<tr>
<td>Constant</td>
</tr>
<tr>
<td>MSIS-29, v 2 (physical component)</td>
</tr>
<tr>
<td>MFIS (physical subscale)</td>
</tr>
<tr>
<td>Group (0 = Exercise, 1 = Control)</td>
</tr>
<tr>
<td>Distance (6MWT)</td>
</tr>
<tr>
<td>Gender (0 = Male, 1 = Female)</td>
</tr>
</tbody>
</table>
This model shows that the following variables predict a lower physical impact of MS score after the intervention period:

- A lower MSIS-29, v 2 (physical component) at baseline
- A lower MFIS (physical subscale) at baseline
- Randomisation to an exercise-based intervention
- A longer walking distance measured by the 6MWT at baseline and
- Female gender

There was a moderate correlation between the MSIS-29, v 2 (physical component) and the MFIS (physical subscale) ($r = 0.66$, $p<0.01$). Tabachnick and Fidell (2007) suggest a cut-off correlation between predictor variables as 0.7 for breach of the assumption of multicollinearity (Predictor variables in the model being correlated with each other).

As this cut-off is arbitrary, the strongest model without the MSIS-29, v 2 is also presented in Table 38. This model accounted for 48.4% of the variance and was statistically significant: $F (5, 210) = 41.34$, $p<0.01$.

**TABLE 38 PARTICIPANT CHARACTERISTICS PREDICTING OUTCOME MSIS-29, V 2 (PHYSICAL COMPONENT) AFTER INTERVENTION – MODEL 2**

<table>
<thead>
<tr>
<th>Model 2, $R^2 = 48.4%$</th>
<th>Unstandardised coefficient (95%CI)</th>
<th>Standardised coefficient</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>9.9 (0.51, 19.35)</td>
<td></td>
<td>0.039</td>
</tr>
<tr>
<td>MFIS (physical subscale)</td>
<td>1.10 (0.76, 1.4)</td>
<td>0.41</td>
<td>$\leq 0.01$</td>
</tr>
<tr>
<td>Distance (6MWT)</td>
<td>-0.04 (-0.05, -0.02)</td>
<td>-0.24</td>
<td>$\leq 0.01$</td>
</tr>
<tr>
<td>MSIS, 29 v 2 (psychological component)</td>
<td>0.20 (0.09, 0.31)</td>
<td>0.21</td>
<td>$\leq 0.01$</td>
</tr>
<tr>
<td>GNDS 0 = no gait impairment (0)/unsteady gait (1), 1 = uses unilateral aid to walk outdoors (2)</td>
<td>3.12 (0.20, 6.0)</td>
<td>0.14</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Group (0 = Exercise, 1 = Control)</td>
<td>6.13 (1.47, 10.78)</td>
<td>0.13</td>
<td>$\leq 0.01$</td>
</tr>
</tbody>
</table>
The MFIS (physical subscale), distance and group allocation remained significant in the model. This model added that a GNDS (lower limb disability) score of 2 (i.e. using one stick to walk outdoors) and the MSIS-29, v 2 (psychological component) at baseline contribute to the variance in outcome after intervention when the MSIS-29, v 2 (physical component) at baseline is removed.

This model suggests that the following variables predict a lower physical impact of MS score after the intervention period:

- A lower MFIS (physical subscale) at baseline
- A longer walking distance measured by the 6MWT at baseline
- A lower MSIS-29, v 2 (psychological component) at baseline
- Using no walking aid to walk (includes people who may be unsteady) and
- Randomisation to an exercise-based intervention

### 9.2 \textbf{Summary}

The aim of this chapter was to present a further exploration of data to identify the participant characteristics that predict outcome after the intervention period.

In summary, the MFIS (physical subscale) at baseline, 6MWT at baseline and participating in an exercise intervention were present in the two strongest models to predict outcome after the intervention. This suggests the MFIS (physical subscale) and 6MWT distance are important variables to measure. A particularly important finding is that participating in any one of the three exercise paradigms was significant contributor to minimising the physical impact of MS. Furthermore, male gender was significant in contributing to a poorer outcome.
Interestingly, not one of the impairment variables identified by the literature that are routinely collected during assessment by Chartered Physiotherapists in practice contributed significantly to the strongest predictors of outcome using the MSIS-29, v2 (physical component).
CHAPTER 10: SUMMARY OF RESULTS

10.0 INTRODUCTION

The following paragraphs summarise the main results of the present study in the context of the objectives defined from the onset.

10.1 THE TREATMENT EFFECT

Using the Multiple Sclerosis Impact Scale-29, v 2 (physical component), repeated measures ANOVA indicated that there was an almost significant group x time interaction (p=0.062). Independent of group there was a mean score of 38.6±16.6 pre-intervention which reduced to 33.3±18.0 post-intervention (p<0.0001). Post-hoc paired-samples t-tests demonstrated that there was a mean improvement of 20.9% (-6.9 points on the scale) in the PT-led group (p<0.01), 12.0% (-4.0 points on the scale) in the Yoga group (p<0.05) and 16.2% (-5.7 points on the scale) in the FI-led group (p<0.01). There was no change in the control group (p=0.90).

Using a non-parametric evaluation of the Multiple Sclerosis Impact Scale-29, v 2 (psychological component), there was a median improvement of 11.1 points for the PT-led group (p<0.01), 3.7 for the Yoga group (p<0.01) and 3.7 for the FI-led group (p<0.01). There was no change in the control group (p=0.94).

Using the Modified Fatigue Impact Scale, repeated measures ANOVA indicated that there was an almost significant group x time interaction (p=0.060). Independent of group there was a mean score of 38.9±16.7 pre-intervention which reduced to 33.3±18.4 post-intervention (p<0.0001). Post-hoc paired-samples t-tests demonstrated that there was a mean improvement of 19.18% (-7.54 points on the
scale) in the PT-led group (p<0.01), 14.53% (-5.82 points on the scale) in the Yoga group (p<0.01) and 17.03% (-6.69 points on the scale) in the FI-led group (p<0.01). There was no change in the control group (p=0.512).

Using non parametric analysis for the Six Minute Walk Test (m), there was a median improvement of 10m for the PT-led group (p<0.01) and a median improvement of 20m for the FI-led group (<0.01). There was no change in the Yoga group (p=0.26). There was a trend towards worsening in the control (-10m, p=0.17).

In conclusion, the three community-based exercise interventions were effective in improving all aspects of the patient reported outcomes. For the 6MWT only the PT-led intervention and the FI-led group improved their distance walked (p<0.05). The yoga group did not change; there was a trend towards worsening in the control.

10.2 THE DIFFERENCES BETWEEN INTERVENTIONS

This study found that there were no significant differences between interventions with the exception of the difference between PT-led exercise and yoga and FI-led exercise and yoga for the 6MWT. By order of magnitude the PT-led group demonstrated the largest improvements for all outcomes, with the exception of the 6MWT in which case the FI-led group showed a larger median improvement (a median of 10m vs. 20m respectively).

10.3 FOLLOW-UP

In terms of magnitude of change, all of the positive findings achieved during the intervention period were reversed (p<0.05). Interestingly, in the MSIS-29, v 2 (physical component) and the Six Minute Walk, participants did not remain statistically significantly improved from baseline. However the MSIS-29, v 2
(psychological component) and MFIS remained significantly improved from baseline. This may suggest that psychological variables were better maintained than physical variables. Point estimates of variables did not return to pre-intervention values.

10.4 Predictors of outcome

The post-hoc exploratory analyses show many important outcomes for exercise-based interventions for PwMS which were not evident from the preliminary examination of results. This study found that the MSIS-29, v 2 (physical component) post intervention was best predicted by the MSIS-29, v 2 (physical component), the MFIS (physical subscale), 6MWT distance at baseline, participation in any of the exercise interventions and gender. This, the strongest model accounted for 57.4% of the variance.
CHAPTER 11: DISCUSSION

11.0 INTRODUCTION

The main objectives of this study were:

- To establish the efficacy of the three community-based exercise interventions
- To establish if there was a difference between groups due to intervention
- To investigate the results three months after the intervention
- To investigate the predictors of outcome after the intervention period

This study was novel in many ways. This study developed and evaluated a combined (Aerobic Training and Progressive Resistance) exercise programme led by a Physiotherapist and identified the content and efficacy of community-based interventions provided by Yoga and fitness Instructors which resulted in clinically meaningful and statistically significant results. This was the first trial evaluating exercise in PwMS that has described participants’ clinically relevant, subjective and objective characteristics, thus informing generalisability of results.

As MS is a lifelong disease with no known cure, follow-up to intervention is important. At the start of this trial only two Aerobic Training (AT) studies had evaluated follow-up (McCullagh et al. 2008, Kileff and Ashburn 2005). Subsequently two PRE studies were published which included follow-up to a PRE programme (Dalgas et al. 2009, Dalgas et al. 2010b). This is the first study to evaluate the follow-up to a combined exercise intervention led by a physiotherapist, yoga and exercise intervention led by a fitness instructor.

This is the first study to explore post-hoc analyses to identify participant characteristics predictive of outcome to further inform targeted delivery of exercise-
based interventions. This was facilitated by the large numbers of participants in the trial.

The following discussion chapter is separated into its components to match the objectives of the present study. The effectiveness of the interventions is discussed in section 11.1. The participants are discussed in terms of their clinically relevant baseline subjective and objective characteristics in section 11.2 to inform the extent to which these findings can be applied in settings other than which they were tested. Attrition is discussed in section 11.3. The differences between groups are discussed in section 11.4. Follow-up results are discussed in section 11.5. A discussion of the predictors of outcome is detailed in section 11.6. Limitations to the methodology used in this thesis are reflected upon in section 11.7. Finally, implications for future research, practice and health service delivery are presented in from section 11.8 to 11.10 inclusive.

11.1 THE TREATMENT EFFECT

11.1.0 SUMMARY OF THE TREATMENT EFFECT

Chapter 10 concluded that there was a positive treatment effect for all three interventions for the primary outcome the MSIS-29, v 2 (physical component), MSIS-29, v 2 (psychological component), the MFIS (total score), the MFIS (physical subscale) and the MFIS (cognitive subscale). There was a positive treatment effect on walking as measured by the 6MWT for the PT-led and FI-led groups only. In the following sections, the treatment effect will be detailed for each measure, how this treatment effect compares to other interventions and the clinical relevance of these findings will be addressed.
11.1.1 MSIS-29 (PHYSICAL COMPONENT)

The MSIS-29, v 2 (physical component) is measured from 0 to 100 with higher scores indicating greater physical impact of MS. In the present study, there was a mean improvement of 20.9% (-6.9 points on the scale) in the PT-led group (p<0.01), 12.0% (-4.0 points on the scale) in the Yoga group (p<0.05) and 16.2% (-5.7 points on the scale) in the FI-led group (p<0.01). There was no change in the control group.

Three previous studies evaluating exercise in PwMS have used the MSIS-29 to evaluate outcome. It must be remembered they used the original version of the scale and version 2 was used in the present study, thus comparisons may not be directly applicable. Additionally, all of the psychometric testing to date has evaluated the two components of the scale separately, thus it is not valid as a summative score and it is advised that the two subcomponents are transformed to a score out of 100 (Hobart et al. 2001). McCullagh et al (2008) used the original version and summed the physical and psychological components together thus the minimum score was 29 and the maximum score was 145. There was a median reduction of 6.5 points on this scale in the AT group. It is not known if this improvement originated from the physical impact or the psychological impact.

Similarly, Taylor et al (2006) used the original MSIS-29. This was separated into its physical and psychological components as intended and transformed to a scale out of 100. There was mean reduction of 6.1 points indicating a relative reduction of 24% in the physical component in the Progressive Resistance Exercise (PRE) group. Participants in Taylor et al (2006) started with a lower mean physical impact of MS (25.3±9.8) than in the present study (32.9±20.3), thus increasing the relative improvement.

Sabapathy et al (2010) found a mean improvement of 10.3% (4.5 points), p <0.05 from a PRE and 10.1% (4.4 points), p <0.05 from and AT intervention delivered on...
two occasions per week. These participants started with a higher mean physical impact of MS score than the present study (43.4±12.4 for AT and 43.8±39.3 for PRE).

In terms of their absolute values, these studies show a reduction of 4.4 to 6.5 units on the scale. These are similar to the absolute values seen in the present study with reductions of 4 to 6.9 points. The relative values are dependent on where participants start on the scale at baseline.

When comparing the results of this study to others that used other HRQoL measures as an outcome, this study found similar effect sizes to studies evaluating the effect of exercise on HRQoL to date. Using meta-analytic procedures to establish the effect of exercise training on quality of life in MS, Motl and Gosney (2008) yielded a mean effect size of 0.23 from 13 studies with 484 MS participants. This thesis adds that a higher effect size is yielded by combined exercise (0.38) compared to aerobic (0.31) or non-aerobic (0.12) interventions (Motl and Gosney 2008). Due to the few examinations of non-AT, Motl and Gosney (2008) could not conclude that there were no effects on HRQoL from non-aerobic forms of exercise. The present prospective randomised controlled trial adds that yoga and FI-led exercise resulted in a small effect (0.20 and 0.28 respectively) on HRQoL.

In a systematic review of the literature prepared by Trisolini et al (2010) for the Multiple Sclerosis International Federation, 13 studies were identified that analyse the impact of MS on generic measures of QoL. It was reported in these studies that there is approximately a 30% decline in physical functioning for mild MS and 40% for moderate MS. In the present study, there was a 20.9%, 12% and 16.2% improvement in the MSIS-29, v 2 (physical component) for PT-led exercise, yoga and FI-led exercise. As the physical impact of MS on QoL is expected to increase as the disease progresses over time, the results from the exercise-based interventions in this study appear clinically meaningful.
In a focus group study (Clarke and Coote, 2007) of a small subgroup of PwMS who took part in the present study, participants agreed that they felt they were now able to participate in functional or leisure time activities that they were unable to do previously. Furthermore, in a 2 year follow-up study of participants in the present study (Condon et al. 2010), participants indicated overwhelmingly positive effects from the project including improved mobility, psychosocial benefits, increased activity, improved flexibility, improved fitness or strength and improved balance. Positive change was noted by family members in terms of psychosocial benefits, improved mobility, better appearance, increased activity and increased energy. One man wrote “My daughter said it’s great I can do things with the grandchildren that I couldn’t do before like playing a little football. My son said it was like having his dad back again because I have more interest in doing things”. These changes reported may have contributed to the increased HRQoL after the exercise interventions.

The SF-36 is a commonly used measure of HRQoL. Rudick et al (2007) found that the Physical Composite Score (PCS) of the SF-36 was found to correlate with 1) level of disability as measured by EDSS, sustained disability progression using EDSS ($r^2=0.24$, $p<0.0001$) or MSFC ($r^2=0.16$, $p<0.0001$), 2) occurrence of a relapse and 3) volume of T-2 hyperintense ($r^2=0.07$, $p<0.012$) and T-1 hyperintense MRI lesions ($r^2=0.01$, $p<0.016$). It was suggested that these findings confirm and quantify the importance of neurological disability, relapses and MRI findings from the perspective of the person with MS. In the same study, the effect of Natalizumab (Tysabri™) - a leading disease modifying drug for PwMS on HRQoL was investigated. The mean change of the SF-36 (PCS) from baseline was described visually. The largest mean change from baseline was seen at week 52 from initiation of treatment. This was less than 1 point on the scale ($p<0.05$). Additionally, using the mean change score (estimated as 0.9) and the SD at baseline, the effect size was 0.09 which is minimal. Thus exercise could be a more effective intervention than medical intervention at improving HRQoL.
In conclusion, the exercise-based interventions in the present study demonstrated a small to medium treatment effect in the primary outcome measure as indicated by their mean change scores, 95\% CIs, small to moderate effect sizes and were statistically significant (p <0.05) for each intervention. This concurs with findings of other studies evaluating the effect of different exercise programmes on HRQoL. These findings appear clinically meaningful as they were opposite to the decline in physical functioning expected over time, were important to patients and their families and of greater magnitude than that of one of the leading disease modifying drugs available.

11.1.2 MSIS (PSYCHOLOGICAL COMPONENT)

The MSIS-29, v 2 (psychological component) is measured from 0 – 100 with higher scores indicating greater psychological impact of MS. Data were skewed, thus data are presented using non-parametric statistics. There was a median improvement of 11.1 points for the PT-led group (p<0.01), 3.7 for the Yoga group (P<0.01) and 3.7 for the FI-led group (<0.01). The changes in all three exercise-based interventions were significantly better (p<0.05) than in the control which demonstrated a median change of 0.

In the literature, there is little with which to compare this finding as only two studies have analysed this component separately. Taylor et al. (2006) found a mean reduction of 1.8 points in the MSIS-29 (psychological component) following PRE, using the original scale. Sabapathy et al. (2010) found a mean improvement of 2.7 or 2.9 points following AT and following PRE respectively. However, these were both using the original version of the scale.

These physical interventions focus on outcomes of physical impairment and functioning. However exercise interventions including yoga have also been shown to improve psychological aspects of functioning including mood (Sutherland and
Andersen 2001, Oken et al. 2004, Petajan et al. 1996) or depression (Hoogervorst et al. 2004, Velikonja et al. 2010) which may have contributed to this positive finding.

One aspect of the interventions that may have brought about this improvement is the group element of the interventions or “peer support” available to participants during the interventions. In exploratory pilot work for this RCT, group exercise was the main theme of great importance noted by participants in the class. While some research suggests that peer support groups for PwMS are ineffective in improving QoL and depression (Uccelli et al. 2004), the interventions used were very structured and feign normal peer interactions in that the topics for discussion were pre-defined by the deliverers of the interventions.

11.1.3 MFIS:

The total MFIS score is measured from 0 to 84 with increasing scores indicating greater impact of fatigue. There was a mean improvement of 19.18% (-7.54 points on the scale) in the PT-led group (p<0.01), 14.53% (-5.82 points on the scale) in the Yoga group (p<0.01) and 17.03% (-6.69 points on the scale) in the FI-led group (p<0.01). There was no change in the control group.

Similarly, in an AT intervention with a Borg’s RPE of 11 – 13 of 17 PwMS, McCullagh et al (2008) showed a statistically significant improvement in the MFIS after a twice weekly intervention over twelve weeks (pre-intervention median: 26.5 {IQR21.5, 33.5}, median change: 13{IQR-20.5,-3}, p = 0.02). White et al. (2004) also found a similar statistically significant reduction in mean MFIS from 32±8 to 25.8±17 (p <0.05) as a result of a PRE after an eight week training programme (N = 8).
When data in Chapter 7 were analysed in more detail, 17 (27%) participants in the PT-led group, 11 (18%) participants in the yoga intervention, 15 (23%) participants in the FI-led intervention moved from a category of fatigued to non-fatigued (i.e. crossed the discriminatory threshold of 38 or more for clinically meaningful fatigue to less than 38) (Flachenecker et al. 2002). Thus, the results were both statistically significant and clinically meaningful.

Velikonja et al (2010) showed that the MFIS reduced, in a group who participated in Hatha yoga, from a median of 32.0 (22.0 – 42.0) to 23.0 (20.5 – 36.0), \( p = 0.057 \) in just one hour a week. Oken et al (2004) found a small but statistically significant reduction in fatigue using the Multi-Dimensional Fatigue Inventory in an exercise intervention, a yoga intervention but not in a waiting list control. Similarly fatigue (as measured by the FSS) reduced significantly in a yoga intervention that took place three times a week by 38.69\% (\( p = 0.01 \)) and a negligible increase in the control group by 1.41\% (\( p = 0.82 \)) (Ahmadi et al. 2010). The cumulative evidence is in favour of yoga - consisting of breathing or relaxation exercises, range of motion exercises, various asanas and Yoga Nidra or relaxation - to reduce fatigue in people with MS who use at most one stick to walk. Positive findings have been identified with three different measures of fatigue.

The MFIS reduced from 59.1±12.21 to 51.6±16.27 (\( p <0.0001 \)) in a study of 89 PwMS taking Natalizumab (Tysabri\textsuperscript{TM}) after 12 weeks. Thus the absolute magnitude of change in the exercise interventions was similar to those achieved by a leading monoclonal antibody used as a disease modifying drug.

Fatigue is an ill-defined concept in PwMS. It is multifactorial and many central and peripheral mechanisms have been implicated in fatigue in PwMS (Vucic et al. 2010, Braley and Chervin 2010, Kos et al. 2008). The cause remains unknown and it appears likely to be due to a combination of factors. While this study did not address the mechanism for the reduction in fatigue, it may have improved through many
pathways from interventions used in the present study. Central pathways may have been improved through plasticity, improved cortical and neural control over movement, pruning of functional pathways and axonal regeneration. Peripherally, there may have been improved strength, fitness and inflammatory modulation which may contribute to a lower impact of fatigue. Finally there may have been an element of peer learning within the groups where participants shared fatigue management strategies amongst each other.

In conclusion, fatigue is the most commonly reported symptom in people with MS. It is more common than the general population (Flensner et al. 2008). The impact of fatigue is improved by exercise-based interventions however the mechanisms indicated are multifactorial. To date, medical management, fatigue management strategies, complementary therapies and exercise have shown modest improvements in fatigue in PwMS in isolation. Multidisciplinary intervention may optimally address this multifaceted domain. Research needs to be conducted in this area to minimise the impact of fatigue in PwMS.

11.1.4 The Six Minute Walk Test

The Six Minute Walk Test (6MWT) was reported as distance in metres. Thus, a higher score indicated an improvement. Data were skewed, thus non-parametric statistics were used. There was a median improvement of 10m for the PT-led group (p<0.05) and 20m for the FI-led group (<0.01). The Yoga group did not change as seen by a median change of 0m (p = 0.17) and the control group demonstrated a median worsening of -10m (0.26). The differences between the PT-led group and the control and the FI-led group and the control were statistically significant (p<0.05). There was an effect size between small and moderate for both of these interventions.

In the PT-led group, there was an ES of 0.28, In the FI-led group; there was an ES of 0.35. These are a larger than the cumulative weighted mean effect size from 22
studies of 0.19 found by Snook and Motl (2009). Effect size increased if a cohort contained mixed samples of people with both RRMS and PPMS (ES 0.52), if a supervised setting (ES 0.32) was used and if the intervention was less than three months of duration (0.28). The present study met all of these criteria; this may have increased the effect slightly upwards of Snook and Motl’s mean ES. Yoga also fulfils these criteria but the ES was -0.14. This was similar to the ES reported from Oken’s 2004 study of yoga (-0.16). There was no aspect of walking trained in yoga, thus it is probable that walking did not improve due to the specificity principle of exercise training.

The above mentioned meta-analysis included all walking outcomes. However, some studies have also used the 6MWT. In 8 participants with an EDSS of 4-6, participants improved from a mean of 204.21m (SD 84.38) to 236.71m (SD 99.39) (Kileff and Ashburn 2005). Similarly, in 11 participants with an EDSS of 1-4 participants significantly improved from a mean of 308m (SD 98) to 332m (SD 108), p = 0.02 from an AT intervention (Rampello et al. 2007). In participants with an EDSS of 3.2 – 4.2, participants improved from 440.9m (range: 345.0 to 535.7) to 495.4 (range: 401.2 to 589.5) and positive results were maintained at follow-up: 494.6 (range: 397 to 591) after a PRE intervention (Dalgas et al. 2009). It is difficult to compare the magnitude of change in this study to these other studies due to the different ways of conducting a 6MWT. However, the method used in the present study has excellent reliability (ICC 0.98, 95% CI 0.94, 0.97, SEM = 13.26m) and very small measurement error between raters (mean 8.5m) which may explain smaller changes compared to other studies (Toomey and Coote 2009).

It is not feasible to use a 30m walkway for a 6MWT consistently in the community setting as recommended by the American Thoracic Society (Enright 2003). Thus, the international community of healthcare professionals should agree on a measure of walking performance in PwMS so that comparisons between sites and interventions may be easily performed. This will facilitate continuity of patient care between sites (such as inpatient setting, outpatient setting, rehabilitation and the community) and
enable identification of the most effective treatments on walking ability for PwMS in order to prevent or delay the secondary consequences with reduced walking ability including reduced participation in physical activity, employment and ADLs.

Walking is a significant impairment in people with MS. It is ranked as the highest priority compared to other bodily functions among PwMS (Heesen et al. 2008b). A change in walking ability is the most visible sign of MS and the classic clinical manifestation. Walking distance (as measured by the 6MWT) has been identified as a significant predictor of patient independence in self-care, mobility and domestic life in PwMS (Paltamaa et al. 2007). The study by Paltamaa and colleagues indicated that for every 1m longer participants walked during the 6MWT, they had a 1% increased likelihood of being independent in these domains. Thus improvements of 10m and 20m in the PT and FI-led interventions could be linked with a 10% and 20% increased likelihood of independence in these domains. Conversely, randomisation to the control group which saw a median reduction of 10m could be linked with a 10% reduced likelihood of independence in domains of self-care, mobility and domestic life. Thus, these findings in the present study are clinically meaningful and statistically significant.

In the MS International Federation survey on employment and MS, difficulty walking or moving was cited as the second highest primary symptomatic factor preventing PwMS maintaining employment (Chandraratna 2010). It is difficult to apply clinical application to the results found in this study regarding maintenance of employment. It is likely that this is a complex issue and includes personal and environmental factors for the individual with MS.
11.2 Generalisability of the Findings

In studies evaluating the effect of exercise to date, type of MS, disease duration, age, height, gender, EDSS score, use of an aid and baseline outcome measures have been reported. In one study (Pariser et al. 2006) evaluating aquatic exercise in two people with MS, participants were described more fully in terms of their most disabling symptoms, medications, sensory, visual and motor function and participation level. Dalgas et al. (2009 and 2010) reported use of immunomodulatory drugs and Romberg (2004) reported social history (including marital status, employment status and time spent in education). This is the first study to give a detailed description of baseline subjective and objective characteristics of its participants that are frequently collected by physiotherapists in practice. The following sections will discuss the baseline subjective and objective characteristics of the participants to inform the extent to which the present findings can be applied to other settings (generalisability).

Subjectively, the most commonly reported problem in the cohort was fatigue. One hundred and fifty three (48.9%) of participants said “fatigue” first, second or third when reporting what were their current problems due to MS. Other studies with MS have reported a prevalence of fatigue of between 40 - 100% (MS Atlas 2008, Lee 2008). Fatigue is a more prevalent problem in PwMS than in the general population. In studies of the general population, fatigue ranges from 20% (Flesner et al. 2009) to 25.6% (Ricci et al. 2007).

Followed by fatigue, weakness, pain, balance/unsteadiness and walking/mobility/gait were the main problems reported by the cohort. Similarly, in a separate Irish cohort (Coote et al. 2010) (n = 293) found that balance, fatigue, walking, mobility and strength/weakness were the top five main problems. Khan et al (2008) (n = 101) also reported fatigue (82.2%) and mobility (74.8%) as the top two main problems in their community based cohort followed by bladder/bowel problems (58.2%), depression (18.9%) and sexuality (18.9%) for participants with an EDSS \( \leq 6.0 \). The study in this
thesis added pain (including neuropathic pain, musculoskeletal pain, low back pain and headaches) as a main problem for PwMS with minimal gait impairment with 26.7% of the total cohort reporting some pain. Pain was also reported as a main problem elsewhere with 12.7% of the community based population (Khan et al. 2008).

The method of probing in the present study may have led to an under-reporting of some main problems. Both of the Irish studies asked about current/main problem(s) due to MS. This open method of questioning is beneficial in that it does not probe or bias the participants. However, it may not reveal problems of a sensitive nature. For example, in this study only one participant reported erectile dysfunction. Conversely, when a closed question (yes/no) asked by postal questionnaire to a similar community cohort, 88% (144/164) of participants reported sexual problems (Vazirinejad et al. 2008). In the present study, 36 (11.5%) of participants identified bladder problems as a current problem while prevalence studies of “urinary function” problems have been reported as up to 99% (de Sève et al. 2007). Other problems frequently reported by PwMS include depression with 67% of another community sample (n = 101) and 32% reported taking anti-depression medication when left an open ended questionnaire to return by post (Khan et al. 2008). Physiotherapy and exercise based interventions may have positive effects for these problems, thus future studies and practice should consider different methods of eliciting this sensitive information and if intervention is effective for these main problems in PwMS.

The majority of participants in all groups reported having RRMS (49.3% - 60.1%). Other profiling studies have found similar results with 43.3% - 57.5% of participants having RRMS (Jacobs et al. 1999, Coote et al. 2010, Minden et al. 2004). A minority of participants reported having PPMS in all groups being evaluated in this study (6.1 – 13.4%). This concurs with participants with PPMS of other profiling studies (9 - 15.5%), (Jacobs et al. 1999, Coote et al. 2010, Minden et al. 2004, Khan et al. 2008). The average age, age at onset of MS and disease duration in this cohort were similar.
to profiling studies set in the community (Jacobs et al. 1999, Coote et al. 2010, Minden et al. 2004, Khan et al. 2008, Vazirinejad et al. 2008, Dua et al. 2008) and similar to participants in studies evaluating the effect of exercise in PwMS to date (Van den Berg et al. 2006).

Objectively, participants in this study use at most one stick to walk outdoors. In a natural history cohort, the median time to using unilateral walking aid was 23.1 years (95% CI 20.1 – 26.1) with 5% of participants not reaching this endpoint. Cumulatively, this represents 40.7% of PwMS who access physiotherapy services in Ireland (Coote et al. 2010). With the average age at diagnosis being 33 (Dua et al. 2008), these results indicate that most PwMS will spend their most productive years in this category of mobility and are the participants most likely to access physiotherapy services in Ireland (compared to those who use bilateral aid to walk (32.5%) or those who are non-ambulatory (26.1%) (Coote et al. 2010).

It is well documented that MS is a disease that primarily affects females (Debouverie 2009, Dua et al. 2008, Confavereux and Vukusic 2006). There were a similar proportion of females in this study compared to the general MS population. For every male enrolled in this study, there was between 2.0 and 7.2 females, depending on the group allocation. Recent evidence suggests that there are an increasing proportion of females to males in people with MS with most recent estimates as high as 5 females for every male being reported (Wolfson 2010, Graziano et al. 2010).

The most common objective impairments were abnormal co-ordination as measured by the finger to nose test (108/240, 44.4%) followed by abnormal lower limb light touch sensation (81/242, 33.3%) and increased tone/stiffness as measured by the Modified Ashworth Scale (65/215, 28.8%). Large variability was seen in these impairments. This reflects the complex and heterogeneous nature of the MS disease process of inflammatory lesions and degenerative changes.
To summarise, the population used in this study makes up the largest category of PwMS who attend Physiotherapy clinics in Ireland (Coote et al. 2010) and PwMS will spend their most productive years in the mobility category used in this study (GNDS-lower limb disability score of 0, 1 or 2). Analyses of subjective and objective baseline variables suggest that participants in this study are broadly representative of PwMS who use at most one stick for outdoors. They are comparable to participants from profiling studies that have taken place in Europe (Vazirinejad et al. 2008, Coote et al. 2010)), the US (Minden et al. 2004, Jacobs et al. 1999), Australia (Khan et al. 2008) and worldwide (Dua et al. 2008). Thus the findings from the present study may be generalisable to international communities.

11.3 Attrition

11.3.1 Dropouts

Twenty-five per cent (n = 79/314) of participants dropped out between week 1 and week 12 of the trial. Kileff and Ashburn (2005) reported an attrition of 25% (n = 2/8). Rampello et al (2007) reported an attrition rate of 26.3% (n =5/19) from the aerobic training group. Attrition was generally lower in other exercise studies. These studies had smaller numbers of participants, were completed in one centre and often participants were assessed by the deliverer of the programme. These features may have affected attrition in trials to date.

To minimise attrition bias, most of the reasons for dropout were accounted for. Additionally, the baseline characteristics of dropouts were analysed. Participants who did not attend for post intervention assessment at week 12 demonstrated a higher median psychological impact of MS at baseline than participants who completed the intervention period. These other subjective and objective characteristics of participants who dropped out were similar to those who completed the trial indicating that they had the same characteristics that would benefit from intervention. This subgroup of PwMS should be explored further in modelling...
studies to establish why a high psychological impact of MS was a finding in participants who dropped out of the trial and to develop effective interventions that will maintain adherence. This finding highlights the importance of analysing dropout characteristics at baseline in future trials.

Attrition due to unknown reasons was well below that reported in other trials. In the present study, dropouts due to unknown reasons was 6.7% (n = 21/313). In a review of RCTs in two leading medical journals after adoption of the CONSORT statement, attrition due to unknown reasons declined from 68.7% pre-consort to 13% post consort (Kane et al. 2007).

11.3.1 Relapse rate

Relapse was one of the reasons for dropping out in each of the groups in this study. This was calculated into an Annualised Relapse Rate (ARR) for each group. This study confirms that of all others - that exercise does not increase the frequency of relapse in PwMS, in fact the converse may be true.

The ARR of participants with RRMS the control group in this study was 0.60 and the majority (n = 35/40, 87.5%) of participants with RRMS reported taking disease modifying drugs (DMD). This ARR is comparable to the mean ARR identified in a review of 32 studies evaluating Disease Modifying Drugs (DMDs) which was 0.68 (Inusah et al. 2010).

The ARR for PT-led exercise was 0.18 (with 43/45 {96%} of participants taking DMD), for yoga was 0.18 (with 38/44 {86.4%} of participants taking DMD) and for FI-led exercise was 0.26 (with 38/47 {80.9%} of participants taking DMD).
The ARR in the exercise-based interventions is considerably lower than the control group and lower than the mean ARR those taking DMDs in the RCTs reported by Inusah et al. (2010). This finding may be explained by the increasing evidence that exercise may have immunomodulatory effect through cytokine modulation (White et al. 2006a, Golzari et al. 2010).

Relapses contribute to the large costs of MS with estimates varying between $243 USD and $12,870 USD per person depending on the intensity of management required (usual care physician versus hospitalisation), how estimates were calculated (hospital reported versus patient reported) and in what continent (US versus Europe) (Kobelt et al. 2006a, Kobelt et al. 2006b, Naci et al. 2010, O’Brien et al. 2003). The average cost per person participating in supervised group exercise for ten weeks intervention during the trial was €81.25. This cost has reduced to the current price of €68.75 since the economic recession. Future research into exercise-based interventions should consider conducting a cost effectiveness analysis.

This study suggests that participating in supervised group exercise may contribute to the reduction in the ARR in PwMS with RRMS who take DMDs. This may also reduce the economic costs associated with RRMS by reducing the number of relapses. Further prospective and longitudinal research is warranted to establish if exercise has an effect on relapse number, frequency or intensity and the role of exercise in immunomodulation in MS.

11.4 The differences between groups

Few prospective comparative trials have been conducted comparing different parameters of exercise in PwMS. The second objective of the study was to compare the differences between groups. This study found that there were no significant differences between interventions with the exception of the difference between PT-led exercise and yoga and FI-led exercise and yoga on walking distance.
By order of magnitude the PT-led group demonstrated the largest improvements for all outcomes, with the exception of the 6MWT in which case the FI-led group showed a larger median improvement.

The PT-led group may have led to the largest magnitude of change for a number of reasons. Firstly, the type of exercise may have been more beneficial. By deductive reasoning AT and PRE in isolation have shown positive outcomes in PwMS, thus logically a combined programme may also have positive outcomes for PwMS. This is reinforced by the fact that the magnitude of change was closely followed by the FI-led group, where a similar intervention was delivered. Secondly, the frequency of exercise participation of exercise may have been in favour of the PT-led group. A home exercise programme was part of the intervention, which reflects regular PT-led interventions. Anecdotally, this transpired to be regular practice by other exercise professionals. However, it was not formally documented. Thus, it cannot be said with certainty the difference in magnitude of improvements in the three exercise programmes can be explained by frequency of exercise participation. A combination of frequency and type of intervention may have accounted for the differences between groups in terms of magnitude of change. Finally, patient preference and expectation may have contributed to these differences. Previous market research by MSI indicated that Physiotherapy was the greatest unmet need of PwMS. This may imply that PwMS already have preconceived bias regarding the efficacy of PT-led interventions over those delivered in the community.

Both the FI-led group and the PT-led group led to statistically significant and clinically meaningful improvements in walking. The yoga group did not change. This may be explained by the specificity principle of exercise training whereby improvements can be achieved in a particular outcome by training that outcome or components of it. Either FI-led and PT-led interventions had walking or subcomponents of walking as part of the intervention. Due to the setting in which FI-led classes took place, treadmills were readily available which might explain the slightly larger magnitude of change in walking in this group compared to the PT-led class.
11.5 Follow-up

At the start of this trial McCullagh et al (2004) was the only study that had completed a follow-up. Subsequently Dalgas et al. 2009 and 2010 included a follow-up in their work. One of the main aims of this thesis was to investigate outcome three months after the intervention period.

In terms of magnitude of change, all of the positive findings achieved during the intervention period were reversed. However, point estimates did not return to pre-intervention values. Similarly, McCullagh et al. (2004) found that while improvements made in function, HrQoL and fatigue remained statistically significantly improved compared to baseline values, they reduced in magnitude. Detraining effects on muscle physiology in healthy people have been seen in as little as two weeks (Mujika and Padilla 2000). These results suggest that improvements are transient and reversible and may explain why improvements were not maintained three months after the trial had finished. This is re-enforced by the fact that the physical variables measured did not remain statistically significant from baseline to follow-up.

Conversely, Dalgas et al (2010) found no significant deterioration in comparison with post trial values of scores of fatigue, mood, QoL, strength or functional scores in PwMS. However, it was reported that all participants maintained exercise participation levels. In this thesis 29.8% of participants (36/121) admitted to reducing their exercise levels during the follow-up period which may explain the reduction in magnitude of the positive results achieved during the intervention period.

A focus group study that reached data saturation found that environmental, psychological and disease specific barriers to participating in exercise for PwMS. These were access to facilities, time, temperature, cost, lack of motivation,
embarrassment, fatigue and continence issues (Garrett and Coote 2008). These are modifiable factors which should be considered in facilitating exercise in PwMS in practice. Perhaps these issues need to be addressed concurrently during exercise interventions so that PwMS have the tools to continue participating in exercise.

Group exercise is one tool to facilitate exercise which has been iterated time and time again by PwMS in Ireland both anecdotally and in the unpublished literature (Garrett and Coote, 2007, Clarke and Coote, 2009). Thus, regular groups could be established in order to maintain exercise participation.

Exercise is within the domain of physical activity (PA). In recent US studies, goal setting, exercise self-efficacy, efficacy for overcoming barriers, functional limitations, demographic variables including cane use, type of MS, employment status and age were identified as correlates of PA or accounted for some of the variance in physical activity (Motl et al. 2007, Morris et al. 2008, Motl et al. 2009, Motl et al. 2008). In an Irish setting, self-efficacy was not a correlate of PA (Bleuto and Coote 2009). There may be methodological or cultural differences that accounts for the differences from these studies. PA or exercise participation may be influenced by many personal or environmental factors or specifically in MS due to impairment or limitations in activity or participation. Due to the many primary and secondary benefits of exercise for PwMS described here and elsewhere, addressing barriers to exercise, identifying facilitators and developing maintenance programmes to maintain/continue to improve positive effects seen from these interventions is a key concern.

While this study evaluated the follow-up effect at three months, MS is a chronic progressive disease. Follow-up studies of longer duration are required to inform optimum exercise interventions and behaviours to increase or maintain exercise participation as necessary.
11.6 Predictors of outcome

The review of the literature identified large variability in results of studies to date, indicating that all participants do not respond equally to intervention. The interventions in this study showed similar variability. Chapter 3 identified participant characteristics that may influence response to intervention. Thus a primary aim of this thesis was to identify participant characteristics associated with a positive response to treatment.

The post-hoc exploratory analyses show many important outcomes for exercise-based interventions for PwMS which were not evident from the preliminary examination of results. This study found that the MSIS-29, v 2 (physical component) post intervention was best predicted by the MSIS-29, v 2 (physical component) the MFIS (physical subscale) and 6MWT distance at baseline, group allocation and gender.

Previous studies have shown that baseline measurement of the outcome variable contributes to the variance seen. Similarly, previous studies have found that that fatigue, walking ability and gender contribute to HRQoL in PwMS (Miller and Dishon 2006, Casetta et al. 2009). This study adds that in the two strongest models to predict outcome after a three month trial period, participating in the control group contributes to predicting a poorer outcome and conversely, participating in an exercise-based intervention contribute to predicting a more favourable outcome (i.e. a lower MSIS-29, v 2 - physical component) post intervention. No exercise intervention did more favourably than another in the prediction models.

Measures of impairment (i.e. tone, sensation, proprioception and co-ordination) did not feature in predicting outcome. Although psychometric properties of these nominal or ordinal variables are poor or have not been evaluated, they have face and content validity and what are used clinically by Chartered Physiotherapists in
practice. Chartered Physiotherapist’s traditionally focus on “impairment” (Dettmers et al. 2009) in their evaluation and treatment of PwMS. However, these results indicate that measures of Activity and Participation contribute significantly to the strongest models in predicting outcome, while measures of impairment did not. The World Health Organisation advocates addressing Activities and Participation. This study confirms that these are what influence HRQoL in PwMS thus; these should be the centre of our focus for assessment and intervention.

The best two prediction models accounted for 57.4% and 48.4% of the variance respectively. This suggests that other variables that were not measured were present influencing outcome.

After the baseline impact of MS, the physical impact of fatigue and distance during the 6MWT were the strongest predictors of outcome. Fatigue was the most commonly reported problem by participants in this study and the personal and social consequences of fatigue are well documented in the literature.

PwMS report fatigue as one of their worst problems (68%) compared to a reference group from the general population (21%). It causes significantly more impact in daily activities among individuals in PwMS compared to a reference group from the general population. Additionally, PwMS experience more hours of fatigue per day and days of fatigue per month than a reference group from the general population (Flensner et al. 2008). In PwMS, fatigue is perceived as the main barrier to employment with 80% of PwMS unemployed within ten years of diagnosis (Dua et al. 2008). Another study commissioned by the MSIF into the global economic impact of MS highlighted that loss of employment / early retirement as the single largest cost factor in the total cost of MS (Trisolini et al. 2010). Additionally, from a large population based study (Ricci et al. 2007) – it was estimated that workers with fatigue cost employers $136.4 billion USD annually in health related Lost Productive Time (LTP), an excess of $101.0 billion compared to workers without
fatigue. When fatigue exists with conditions such as pain, cold or flu, feeling sad or blue, allergies, asthma, cancer and heart disease, there is a threefold increase with the proportion of workers with LPT. Fatigue has associated qualitatively and quantitatively with falls in PwMS (Nilsagård et al. 2009, Hogan et al. 2010). Additionally, fatigue has been implicated with approximately 10% of serious road crashes (Philip et al. 2001). All three exercise-based interventions led to a statistically significant and clinically meaningful improvement in fatigue. Additionally, it was predictive of MSIS-29, v 2 (physical component) after the intervention thus there may have been important personal and social consequences from exercise-based interventions.

Walking consists of a complex interplay of many mechanisms including synchronised firing of muscles, strength and the sensory response to the interaction with the environment. Small changes in complex activities such as walking may occur due to degenerative changes in the CNS before obvious changes in symptomology or participation are noted by the person with MS or the clinician. The 6MWT has shown to be predictive of ADLs (Paltamaa et al. 2007), physical activity participation (Motl et al. 2008), habitual walking (Gijbels et al. 2010) and this study adds that it also contributes significantly to predicting HRQoL. Thus, it is an important clinical variable that should be measured and addressed by intervention in practice.

11.7 LIMITATIONS

Many of the methodological limitations of studies that have negatively influenced the internal and external validity of studies to date have been addressed. These were a meeting of the criteria for minimising selection and detection bias, recruiting large numbers of participants and describing more complete reporting of participants’ clinical characteristics. However, this study is not without its limitations.
These are mainly due to the complex nature of pragmatic, community-based, multi-centred interventions. Despite the following limitations, this trial reflects the reality of these types of interventions and has important implications for research, practice and health service delivery.

**Randomisation**

Block randomisation was conducted by geographical locality. Trials to date have had small numbers of participants thus limiting the generalisability of their findings. The method of randomisation used in the present study facilitated larger numbers of participants to be enrolled. This was an adequate method of randomisation as evidenced by the similar baseline characteristics in the groups at baseline. Differences have been noted in PwMS across different latitudes. Ireland is a small country. However, future studies using this method of randomisation across larger countries or between countries should ensure that participants in different geographical areas are similar.

**Blinding**

There are two issues pertaining to blinding in this study – concealment of group allocation to outcome assessors and to participants. In this study, the assessors of the interventions were independent of the delivery aspects of the interventions. The trial was set up in this way so that the assessors would remain blind to the intervention allocation. However, in practice, this was sometimes unintentionally revealed by the participant to the assessor during follow-up. The MSIS-29, v 2 and the MFIS are patient report measures, thus the blinding of an assessor would logically pose less assessor bias. However, the revelation of group allocation may have posed some element of bias in relation to the 6MWT. Khan et al (2010) reported in a recent RCT that “Patients were instructed to make no comments on whatever treatment they received”, however, in practice, this is not always successful due to the natural interaction between clinicians and patient populations. To address the issue of group allocation revelation to assessors who are meant to be blind, assessors can be asked
to which intervention arm they think participants were allocated so that by how much the treatment effect was influenced by blinding or non-blinding of the assessor may be established.

The original purpose of the “blinding” concept was to counteract the “placebo” effect. To take the possibility of a placebo effect in future trials evaluating non-pharmacological interventions, establishing patient preference of treatment arm prior to commencing a trial could help inform by how much the treatment effect was enhanced by patient preference. This has been recommended by the CONSORT guidelines for reporting of non-pharmacological treatments (Boutron et al. 2008). In 2010, Multiple Sclerosis Journal, a leading journal for MS related topics published 4 studies evaluating non pharmacological interventions (Dalgas et al. 2010b, Hugos et al. 2010, Dalgas et al. 2009, Freeman et al. 2010). None of these reported patient preference or expectations regarding the intervention under investigation.

The nature of a complex intervention

There were many variables in the study design that may have influenced outcome. The deliverers of the programmes may have had differences in their expertise, training, interest, enthusiasm, personality and encouragement of a home exercise programme. There may have been different interactions between participants within the classes, between participants and the deliverer of the programme and sharing of management tips amongst participants. The setting may have also influenced outcome. These varied between primary care settings, community halls, gyms and may have had different equipment available to the participants of the classes. The participants themselves may have had different intrinsic motivation, prior experience of exercise, preferences and interests in their allocated arm. Knowing that all of these variables may have contributed to the outcome, it was an achievement to account for more than half (57.4%) of the variance in a model with just 5 predictor variables.
**Inter-rater reliability**

Many raters were used in this study. The MSIS-29, v 2 and the MFIS are patient reported measures. Thus, inter-rater reliability is of little concern. The method used for the 6MWT in this study has excellent inter-rater reliability (Toomey and Coote 2009). The inter-rater reliability of baseline measures of impairment is questionable. However, they were measured as they are measured in clinical practice. These baseline measures of impairment were of limited value in predicting the outcome. This might be due to the lack of reliability between raters for these measures. How these clinical variables are measured and what they are used for needs to be considered carefully by clinicians and researchers alike going forward.

**Strength**

Handheld dynamometry was initially used to collect strength data. While it initially appeared reasonably reliable from a review of the literature and feasible for a multi-centred trial from the pilot study, it transpired not to be feasible or reliable (Toomey and Coote 2009) in this present multi-centred trial. Thus a measure of strength, a primary impairment in PwMS, which is usually addressed by Chartered Physiotherapists and exercise professionals, was missing from this trial. Future studies should carefully address this and perhaps consider more functional measures of strength.

**11.8 Major implications for future research**

Further directions for research were identified by the present study. These include questions around intervention, outcome evaluated, measurement, the participants, and follow-up.
Intervention

Reviews of the literature regarding exercise for PwMS have called to establish the optimum “dose” of exercise (Rietberg et al. 2004, Motl and Gosney 2008). However, based on the specificity principle of exercise training, it is probable that one particular prescription or “dose” does not exist for PwMS. General exercise in many forms has shown small to moderate improvements in various outcomes. The present study confirmed that all participants do not respond equally to any intervention and provides some preliminary evidence suggestive of matching interventions with specific limitations in activity, for example PT-led exercise and FI-led exercise with their subcomponents of walking and walking itself led to a small (median change 10m for PT-led exercise, 25m for FI-led exercise), statistically significant (p <0.05) improvement compared to a control (median change -10m) or a yoga intervention (median change 0m). Similarly, using exercises to challenge balance to address balance limitations in PwMS with limitations in balance would probably result in the best responses to exercise-based interventions. Research needs to carefully explore a more specific, targeted approach when choosing participant selection criteria, designing the intervention and choosing a relevant measure to assess outcome. This may be difficult in small geographical areas thus underpinning the value of multi-centred studies in this population.

Over half of the variance was accounted for in the post-hoc exploration of data. Future studies need to address other variables that may influence outcome. A multi-centred trial was one way to gain large numbers of participants for this trial. By having large numbers analysis of the variability in outcome was permitted. Future studies considering this method should account for the complex nature of these interventions and include variables such as setting, knowledge and experience of the deliverers of interventions, participants’ interest and enjoyment of the interventions in establishing the active components of interventions.

Due to the multifactorial nature of fatigue, multidisciplinary intervention may optimally address fatigue (i.e. to a greater magnitude than was seen in this study).
This may include disease modifying drugs, fatigue management strategies and exercise. Thus future research should explore multidisciplinary interventions.

**Outcomes evaluated**

There has long been speculation of exercise as a putative disease modifying agent. This study identified a greater Annualised Relapse Rate in the control compared to all three exercise interventions. The effect of exercise participation on relapse number, frequency, intensity and accumulation of disability should be established in a prospective, longitudinal study.

**Measurement**

Some issues regarding how outcome is evaluated needs to be addressed. An absolute measure of reliability for the MFIS, the new physical and cognitive subscales of the MFIS and the MSIS-29, v 2 should be established. This will facilitate interpreting outcomes as true change rather than due to error in the measure.

Consensus should be reached regarding a measure of walking ability. This will enable outcomes of interventions to be compared across studies. In the review of the literature the 10-m walk test and the 6MWT appeared more sensitive to change than the 25ft walk and the 2MWT in this population. However, prospective comparative studies of these measures are required.

Consideration should be given to a functional measure of strength, that is valid and reliable in settings other than formal research settings.
Participants

Participants who dropped out of the trial during the intervention period had a higher psychological impact of MS compared to the other participants. This highlights the importance of analysing the characteristics of participants who drop out of interventions and conducting exploratory and modelling studies to further inform successful intervention for this subgroup.

Follow-up

This study showed the effectiveness of three community-based interventions. However, positive outcomes were not maintained at follow-up. This can be explained by reduced exercise participation revealed by participants. Future studies should attend to developing interventions to improve independent exercise participation.

11.9 Implications for Practice

The present study has many implications for deliverers of exercise interventions in terms of the content of interventions and assessment of PwMS who use at most one stick for outdoors.

PwMS in this cohort reported fatigue as one of their main problems due to MS, the physical subscale of the MFIS was a significant predictor of outcome in this cohort. The three exercise interventions improved fatigue significantly. The present study demonstrated that, in PwMS who use at most one stick for outdoors, fatigue negatively affects the impact of MS. However, exercise can influence this relationship positively.
Another main problem due to MS reported by cohort was gait related problems. Participants in the present study have much shorter walking distances than a healthy reference population. Weakness may have contributed to these gait related problems as this was the second most commonly reported problem in this cohort. Walking distance at baseline was a significant predictor of outcome. Walking distance improved significantly due to the combined exercise programme – when led by a Physiotherapist or a Fitness Instructor. This is probably explained by the specificity principle of exercise training whereby walking, or components of walking (strength and endurance) were addressed in these interventions. This reinforces the specificity principle of exercise training which should be adhered to when prescribing exercise interventions for PwMS.

Participants in the present Irish cohort were not forthcoming regarding sensitive information such as continence, depression and sexual function. It is known from the international literature that these are common problems in PwMS. This information should be elicited from participants as these problems may have a serious impact on quality of life and may be effectively addressed during intervention. These issues are within the scope of Physiotherapy practice.

Some measures of impairment (tone, sensation, proprioception and co-ordination) did not significantly contribute to predicting the physical impact of MS after the intervention period nor were associated with participant characteristics who responded best from any intervention. Thus, clinicians should consider how and why they are assessing these variables in the context of delivering an exercise programme. This may be explained by the variability of the inter-rater reliability of the measures or may be that the importance of these is in other areas of practice such as in a rehabilitation setting or for people with more moderate/severe impairment.
11.10 Implications for Health Service Delivery

As modern health services move towards a community-based delivery of interventions, this is a timely piece of work to inform health service delivery. The present study has many implications for health service delivery - many of which have already been realised.

MS Ireland and other deliverers of health care now have an evidence base supporting their decision making in allocating funds to exercise-interventions. Three effective interventions were established for PwMS. The common components of the effective interventions were the following:

A) An exercise intervention
B) Peer group interaction in people with a similar mobility level
C) Supervision of exercise by a professional trained in the delivery of exercise programmes
D) Organisational effectiveness through the collaboration between MS Ireland (MSI), the deliverers of the exercise programmes and the participants

These parameters may be considered to be the effective components of the interventions delivered in the present study and should be considered going forward in community health service delivery in order to replicate the positive findings.

MS Ireland has established a good working relationship with Physiotherapists interested in MS and Community Physiotherapy Departments. A symbiotic relationship has been established using the strengths of MSI in administrative and logistical elements of organising classes and the expertise of Community Physiotherapists in the Health Service Executive which has resulted in the continued delivery of effective interventions for PwMS nationwide.
The results of the present study show that other exercise professionals can deliver safe and effective interventions that meet some of the needs for PwMS who use at most one stick for outdoors. Participation in exercise-based programmes is associated with a lower risk of many of the “lifestyle diseases”. Additionally, in the present study, those who participated in an exercise programme benefited from a reduced annualised relapse rate. Thus, delivery of these community-based exercise programmes may also ease the burden of health service delivery in the acute health care sector over time.
CHAPTER 12: CONCLUSIONS AND RECOMMENDATIONS

12.0 INTRODUCTION

This last chapter summarises the conclusions and recommendations arising from this thesis.

“If one of the advantages accruing from exercise were to be procur’d by any one Medicine, nothing in the World would be in more Esteem than that Medicine would be”

(Francis Fuller, 1718)

12.1 CONCLUSIONS

Multiple Sclerosis is a chronic progressive disease of the central nervous system of which there is yet no known cause or cure. In a disease that has no cure, minimising its impact is arguably the main goal of intervention. Thus the primary outcome was the Multiple Sclerosis Impact Scale-29, Version 2 which literature suggests is valid reliable and sensitive to change. In the present study, three community-based exercise interventions were effective in reducing the physical and psychological impact of MS in people with MS (PwMS) who use at most one stick for outdoors.

Fatigue is a main problem in PwMS. It is the largest barrier to maintaining employment and unemployment is the largest cost of the disease. In this cohort, fatigue was the most commonly reported problem due to MS. Three community-based interventions were effective in reducing the impact of fatigue for people with MS who use at most one stick for outdoors. There was no difference between the interventions groups for minimising the impact of MS or minimising the impact of fatigue.
Difficulty walking is a common problem in PwMS. Similarly, in this cohort, walking related problems were subjectively reported to be a current problem and participants were objectively measured to have shorter walking distances than a healthy reference population. Combined exercise led by a Physiotherapist or by a Fitness-Instructor was effective in improving walking distance. This meant that participants were 10-20% more likely to be independent in Activities of Daily Living. These interventions were significantly better than yoga and the control group.

The control group did not change significantly for any outcome measure. This reflects the nature of MS in a group consisting primarily of RRMS who have not had a relapse in the previous three months.

There were no significant differences between interventions but there was a trend towards improvements of larger magnitude in the PT-led intervention for patient reported measures.

Positive results were not maintained three months after the intervention period. Thus strategies to facilitate independent exercise participation need to be identified.

Baseline physical impact of MS, baseline impact of fatigue, baseline walking distance, participation in an exercise intervention and female gender explained 57.4% of the variance in the primary outcome - the physical impact of MS immediately after the intervention period. Type of MS, age at onset and impairment variables commonly measured by Chartered Physiotherapists (sensation, proprioception, tone, and co-ordination), baseline exercise participation or adherence did not contribute significantly to the model.
Exercise plays a key role in the management of MS. This study demonstrated important outcomes for PwMS. These results suggest that some of the needs for PwMS can be met in community settings when delivered by a professional trained in delivering exercise programmes to a group of PwMS with a similar level of mobility. Important implications for practice, future research and health service delivery were identified and discussed. These results are generalisable to the wider international communities of PwMS who use at most one stick for outdoors.

12.2 Recommendations for community-based service provision for people with multiple sclerosis with minimal gait impairment.

Exercise is a key component in the management of Multiple Sclerosis. With the shift of health service delivery towards Primary Care, it should comprise a critical aspect of this service delivery in people with minimal gait impairment.

On initial contact with the Health Service Executive at diagnosis, PwMS should be referred to the relevant Primary Care Team for an assessment with a Chartered Physiotherapist for a baseline assessment, education regarding exercise and referred as appropriate for inclusion in a ten week exercise intervention either as part of the Primary Care service, through MS Ireland or another exercise referral programme. The preference of the person regarding the nature of the intervention needs to be taken into consideration (such as type of exercise, location, group vs individual).

Multiple Sclerosis Ireland is currently providing exercise interventions nationally. However, the role of MSI in delivering these services needs to be defined. MSI have access to approximately 5,000 out of the estimated 8,000 PwMS in Ireland and from preliminary communications between MSI regional offices and primary care, it is estimated that many of these individuals do not appear on primary care teams’ lists. MSI are in a good position to collaborate with primary care teams in the delivery of
exercise interventions, however, funding is required to sustain such collaboration. Furthermore, there is a danger that PwMS will fall through the gaps of these two service providers and not receive any exercise intervention. Thus, an immediate priority is for each of these service providers is to define their role in the delivery of services. At the level of the regional office, it is important that statistics regarding implementation and maintenance are documented regarding what they are currently delivering so that appropriate amendments may be implemented over time. Further long term studies of surveillance of the emerging programme should be conducted.

The results of the research in this thesis suggest that participants reduce their exercise participation levels in the following 3-months after participation in a community-based exercise intervention. Additionally, there is worsening of all positive outcomes obtained during the trial. During a ten week intervention PwMS should be encouraged to keep active during the follow-up phase and future research should explore interventions to maintain appropriate exercise participation levels so that the benefits may be retained. At the six months stage participants should be reviewed for re-entry into an exercise intervention. For returning participants for exercise interventions, a full assessment by a Chartered Physiotherapist may not be necessary. However a screen might involve the Physical Activity Readiness Questionnaire for clearance to exercise, similar to that of the general population as well as an MS specific tool asking about the recent history of relapse, progression of the disease, and change in clinical presentation or levels of participation and, pregnancy to establish if the person with MS requires individual follow-up with their Primary Care Team. Currently, PwMS self-refer to MSI for participation in further exercise programmes or contact members on their list who have previously participated in similar programmes. The approach taken needs to be standardised and again in conjunction with the relevant primary care team to ensure PwMS receive appropriate intervention.
CHAPTER 13: PUBLICATIONS

13.0 INTRODUCTION

This chapter describes a list of the publication output of this thesis to date, including peer-reviewed publications, oral and poster presentations at conferences. It also describes the preliminary plan for future publications in peer-reviewed that are currently in preparation.

13.1 PEER-REVIEWED PUBLICATIONS


13.2 CONFERENCES


Garrett, M., Hogan, N., Larkin, A., Saunders, J., Coote, S. “Combined exercise led by a physiotherapist or fitness instructor significantly improves walking distance over six minutes”. Platform presentation and travel award, European Congress of Treatment and Research in Multiple Sclerosis, Sweden, October 2010.
Garrett, M., Hogan, N., Larkin, A., Saunders, J., Coote, S. “Physiotherapist-led exercise, yoga and fitness instructor-led exercise significantly improve the impact of MS”. Poster presentation (shortlisted for prize), European Congress of Treatment and Research in Multiple Sclerosis, Sweden, October 2010.


Invited speaker at ISCP (Midwestern branch) AGM 2010.

13.3 In preparation


Garrett, M. Hogan, N., Larkin, A., Saunders, J. Jakeman, P., Coote, S. Exercise in the community for people with Multiple Sclerosis – a follow-up to a randomised controlled trial.

Garrett, M. Hogan, N., Larkin, A., Saunders, J. Jakeman, P., Coote, S. Variables influencing Outcome in People with Multiple Sclerosis – a review.
Garrett, M. Hogan, N., Larkin, A., Saunders, J. Jakeman, P., Coote, S. *Predictors of Outcome following exercise interventions for people with Multiple Sclerosis.*

REFERENCES

ACSM (1995) [online], available:


Cohen, J. A. (2010) 'ECTRIMS 2010: Trials highlights', in *European Congress of Treatment and Research in Multiple Sclerose (ECTRIMS)*, Gothenburg, Sweden, 13th - 16th October,


Graziano, G., D'Onghia, M., Lucchese, G., Lepore, V. and Trojano, M. o. b. o. M. r. g. (2010) 'Sex ratio of multiple sclerosis: a comparison of distribution and trend over 60 year span among different countries', in *European Committee*

Heesen, C., Böhm, J., Reich, C., Kasper, J., Goebel, M. and Gold, S. M. (2008a) 'Patient perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable', *Multiple Sclerosis (Houndmills, Basingstoke, England)*, 14(7), 988-991.

Heesen, C., Bohm, J., Reich, C., Kasper, J., Goebel, M. and Goldman, S. M. (2008b) 'Patients perception of bodily functions in multiple sclerosis: gait and visual function are the most valuable', *Multiple Sclerosis*, 14(7), 988-971.


Turpin, K., Warren, S., Janzen, W., Warren, K. and Marrie, R. A. (2010) 'Health related quality of life over time: five-year longitudinal data from the North American Research Committee on Multiple Sclerosis', in European Congress of Treatment and Rehabilitation in Multiple Sclerosis, Gothenburg, Sweden, 13th-16th October,


Stroke: Importance of Somatosensory and Perceptual Functions', *Physical Therapy*, 87(12), 1633-1641.


WHO-ICF (2001) [online], available: [accessed

**APPENDIX A: MULTIPLE SCLEROSIS IMPACT SCALE VERSION 2 (MSIS-29, v2)**

- The following questions ask for your views about the impact of MS on your day-to-day life during **the past two weeks**.
- For each statement, please circle the one number that best describes your situation.
- Please answer all questions.

<table>
<thead>
<tr>
<th>In the <strong>past two weeks</strong>, how much has your MS limited your ability to ...</th>
<th>Not at all</th>
<th>A little</th>
<th>Moderately</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do physically demanding tasks?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2. Grip things tightly (e.g. turning on taps)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3. Carry things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4. Problems with your balance?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5. Difficulties moving about indoors?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6. Being clumsy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7. Stiffness?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8. Heavy arms and or/legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9. Tremor of your arms or legs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>10. Spasm in your limbs?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11. Your body not doing what you want it to do?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. Having to depend on others to do things for you?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>In the past two weeks, how much have you been bothered by ...</td>
<td>Not at all</td>
<td>A little</td>
<td>Moderately</td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------------------------------------</td>
<td>------------</td>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>13.</td>
<td>Limitations in your social and leisure activities at home?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14.</td>
<td>Being stuck at home more than you would like to be?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15.</td>
<td>Difficulties using your hands in everyday tasks?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>16.</td>
<td>Having to cut down the amount of time you spent on work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>17.</td>
<td>Problems using transport (e.g. car, bus, train, taxi etc.)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>18.</td>
<td>Taking longer to do things?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>19.</td>
<td>Difficulty doing things spontaneously (e.g. going out on the spur of the moment)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>20.</td>
<td>Needing to go to the toilet urgently?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>21.</td>
<td>Feeling unwell?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>22.</td>
<td>Problems sleeping?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>23.</td>
<td>Feeling mentally fatigued?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>24.</td>
<td>Worries related to your MS?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>25.</td>
<td>Feeling anxious or tense?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>26.</td>
<td>Feeling irritable, impatient, or short-tempered?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>27.</td>
<td>Problems concentrating?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>28.</td>
<td>Lack of confidence?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>29.</td>
<td>Feeling depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
**APPENDIX B: MODIFIED FATIGUE IMPACT SCALE (MFIS)**

Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. Below is a list of statements that describe the effects of fatigue. Please read each statement carefully, then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. Please answer every question. If you are not sure which to answer to select, chose the one answer that comes closest to describing you.

<table>
<thead>
<tr>
<th>Because of my fatigue during the past 4 weeks I have...</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Almost Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Been less alert</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>2 Had difficulty paying attention for long periods</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>3 Been unable to think clearly</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4 Been clumsy and uncoordinated</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5 Been forgetful</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6 Had to pace myself in my physical activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>7 Been less motivated to do anything that requires physical effort</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>8 Been less motivated to participate in social activities</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>9 Been limited in my ability to do things away from home</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Because of my fatigue during the past 4 weeks I have...</td>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Almost Always</td>
</tr>
<tr>
<td>10 Trouble maintaining physical effort for long periods</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>11 Had difficulty making decisions</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td>Score</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------------------------------------------------</td>
<td>-------</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>12</td>
<td>Been less motivated to do anything that requires thinking</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>Been feeling as though my muscles are weak</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>Been physically uncomfortable</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>15</td>
<td>Had trouble finishing tasks that require thinking</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>Had difficulty organizing my thoughts when doing things at home/work</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>Been less able to complete tasks that require physical effort</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>Been thinking more slowly</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>19</td>
<td>Had trouble concentrating</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>Limited my physical activities</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>21</td>
<td>Needed to rest more often or for longer periods</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
APPENDIX C: PARTICIPANT INFORMATION SHEET - PILOT STUDY

Physical activity programmes for mild to moderate MS – a pilot study

Introduction

Evidence has shown many benefits to exercise in people with MS. The aim of this study is to test the feasibility and suitability of outcome measures for use in a larger study.

Procedures

A weekly exercise programme/yoga class will take place in Limerick/Cork one hour per week for six weeks. A week before and a week after the programme fatigue and quality of life will be assessed by questionnaires, walking distance over six minutes and strength will also be assessed. There will also be a discussion about the benefits and disadvantages of the exercise programme for approximately 45 minutes after the last session.

Benefits

Trials do date have shown that a people with mild to moderate MS participating in an exercise programme can benefit from improvements in strength, fitness, body composition, disability, walking, fatigue, lung function, and participants can enjoy feeling confident, normal and experience improved mood and greater social support.

Risks

The risks of participating in this study are not over those in standard physiotherapy intervention or regular exercising in the community. Previously it was thought that exercise could exacerbate symptoms or relapses. However current research shows this is not the case.

Exclusion from participation

You need to have definite MS to participate in this study. If you use more than one stick for walking outdoors, or if your GP does not agree to your participation you will be excluded from this study.
Compensation

There will be no remuneration for participation in this study.

Permission

With your consent, permission will be sought from your GP regarding your eligibility to participate in this study.

Confidentiality

All information will be confidential within the research team. We will not disclose any information that can be identified with you nor connect your name to any information we present.

Voluntary participation and stopping the study

Your participation is completely voluntary and you may withdraw at any time.

Further information

If you have any questions regarding the study feel free to contact Dr Susan Coote 061 234278, email: susan.coote@ul.ie or Maria Garrett 087 2821128, email: maria.garrett@ul.ie

Complaints Procedure

The procedures in this study have been subject to review and approval by the Mid-Western Ethics Committee. If you have any concerns or complaints about this study and wish to contact someone independent, you may contact The Chairperson of the Mid-Western Ethics Committee.

The Chairperson

Scientific Research Ethics Committee
Limerick Regional Hospital,
Dooradoyle,
Limerick.
APPENDIX D: PARTICIPANT CONSENT FORM - PILOT STUDY

Physical Activity Programmes for Mild to Moderate - A Pilot Study.

Please read the following questions and tick the appropriate Yes or No box. Please sign the bottom of the page if you consent to participate in this study.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have read and understood the information sheet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I know that my participation is voluntary and that I can withdraw from</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the project at any stage without giving any reason.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I agree to permit contact with my GP regarding my participation in this</td>
<td></td>
<td></td>
</tr>
<tr>
<td>study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I agree to notify the Investigator of any side effects arising during</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I agree to participate in this study.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SIGNATURE BLOCK CAPITALS DATE

Participant: ____________________ ____________________ _______
Investigator: ____________________ ____________________ _______
Witness: ____________________ ____________________ _______
APPENDIX E: INFORMATION COLLECTION SHEET

Getting the Balance Right

REGION_________

Information collection sheet

NO ___________

STRAND_________

First I want to give you some information about the project which has 2 parts to it. The first part is that we are organising Physiotherapy classes and treatments; the second part is that we’re hoping to measure as many people as possible and use the results for a research study to show that these classes are beneficial and should be continued. Today we need to get some information from you and to check that you can take part, then we will send you out an information leaflet and consent form, then when you send that back and we have all the paperwork is in order we will be able to give you a date to be assessed by a Chartered Physiotherapist.

PART 1 – CONTACT INFORMATION

Name of participant______________________________________________________

Name of person giving information (where applicable)
__________________________

Address of participant:
___________________________________________________

Phone:_________________________________________________________________

We want to let your GP know that you’ll be taking part in the study, and have their contact details in case there is a problem at any time is that OK with you?  

YES □ NO □

What is your GP’s Name__________________________________________________

GP’s Address:
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

Do you see a neurologist? Who do you see and where?
__________________________

Are you a member of the MS Society?  

YES □ NO □
IF NO – You don’t need to be a member to be part of the project, but if you would like to join at any time just let us know

**PART 2 – MOBILITY LEVEL**

Do you have any problems walking?        YES ☐ NO ☐  
IF NO SCORE & MOVE ON TO PART 3

Do you use a walking aid?                YES ☐ NO ☐
IF NO SCORE & MOVE ON TO PART 3

How do you usually get around outdoors?  ____________________

IF USE A WHEELCHAIR ASK -

Can you stand and walk a few steps with help?  YES ☐ NO ☐

**MOBILITY SCORE**

Walking is not affected 0  
Walking is affected, but walks independently (without aid) 1  
Usually uses unilateral support (stick, single crutch, or one arm) to walk outdoors 2  
 Usually uses bilateral support (two sticks or crutches, frame, or two arms) to walk outdoors 3  
Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with or without help 4  
Restricted to wheelchair, unable to stand and walk a few steps even with help 5  
Unknown X

**SCORE** 0, 1, 2 – Strand A,  
**SCORE** 3, 4 – Strand B,  
**SCORE** 5 – Strand C

**PART 3 – EXCLUSION CRITERIA**

I need to ask you another few questions to check that it’s OK for you to take part:

Have you had steroid treatment in the last 3 months?        YES ☐ NO ☐

Are you currently having any worsening of symptoms or a relapse?        YES ☐ NO ☐

*WHERE APPLICABLE:

Are you pregnant?        YES ☐ NO ☐

IF YES TO ANY OF QUESTIONS ABOVE:  
Because you have been on steroids recently, we need you to wait until 3 months after that before you take part. We will get all of the paperwork sorted, then once the 3 months is up we will get back to you with a date

DATE FOR RE-CONTACTING  ____________________
Because you are having a worsening of symptoms at the moment you can’t take part in the research part of the project, but we can arrange for you to have Physio treatment, would you like us to do that?

YES ☐ NO ☐

Unfortunately if you’re pregnant you won’t be able to take part in the study and you should check with your GP to see if you should be having Physio or exercise classes at the moment.

IF NO TO ALL ABOVE QUESTIONS:
Great, it looks like you’ll be able to take part in the project. We’re going to send you an information leaflet to make sure that you have all the information you need about the project, and a consent form which I need you to fill out and send back to me. Then once we have those we’ll send you a date to be assessed. If you have any more questions after you get the information leaflet let us know and we can hopefully answer them for you.

Have you any specific transport needs, do we need to arrange transport for you to get to the classes?

YES ☐ NO ☐

Do you need us to arrange childcare or anything to allow you to attend?

YES ☐ NO ☐

NOTES
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
___________________________________
APPENDIX F: PARTICIPANT INFORMATION LEAFLET - MAIN STUDY

Getting the Balance Right – Strand A

The aim of the Getting the Balance Right project is to give people with MS physiotherapy and exercise programmes and to do research to see what the benefit is. The MS Society will organize the treatments and the Physiotherapy Department at University of Limerick will test the outcomes of these treatments.

Studies have shown many benefits to exercise for people with MS. Because we do not know which treatment is best, this study will put people into exercise groups and compare them. Which group they are in is chosen as if ‘by the toss of a coin’.

What will I have to do?

A weekly exercise class will take place for approximately one hour week for ten weeks.

The groups that you may be asked to take part in

1. Exercise led by a Physiotherapist
2. Group exercise led by a fitness instructor or
3. Group yoga.

The toss of the coin may mean you are allocated to a group that will not receive a class for the moment (a control group), but you will have the treatment in three months time.

A week before, a week after the class and twelve weeks after the classes, a Chartered Physiotherapist will assess you. S/he will ask you general questions about your health and look at your strength, walking and give you a questionnaire about fatigue and also one for quality of life. S/he will not know which group you were assigned to.
**Requirements to take part**

You have already been asked some questions regarding your suitability to take part. However, you will also be assessed by a Chartered Physiotherapist who will decide if there are any other reasons that you may not be suited to this exercise.

**Benefits and Risks**

You may have improvements in strength, fitness, disability, walking, fatigue, lung function, and some people can enjoy feeling confident and experience improved mood. The risks of participating in this study are not over those in standard physiotherapy intervention or regular exercising in the community. Your Doctor (GP) will be notified of your participation.

**Confidentiality**

All information will be confidential within the research team. We will not disclose any information that can be identified with you nor connect your name to any information we present.

**Voluntary participation**

Your participation is completely voluntary and you may withdraw at any time.

There will be no remuneration for participation in this study. If taking part in this research study harms you, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action.

If you have questions regarding the study please feel free to contact Susan, Neasa, Maria or Marie on 061 234278

**Thank you for considering taking part in this study**
**APPENDIX G: PARTICIPANT CONSENT FORM – MAIN STUDY**

Please read the following questions and tick the appropriate Yes or No box. Please sign the bottom of the page if you consent to participate in this study.

**Participant Name: ___________________________**

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have read and understand the information sheet.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Someone has read the information sheet to me and I understand about the study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am authorised to make decisions on behalf of the above person and I have read and understand the information leaflet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Please tick one of the above options*

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>I agree to be assessed by a chartered physiotherapist and for my data to be used for the research project</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I understand that I might have one of three treatments, or a three month wait before being treated, and I agree to this</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I know that my participation is voluntary and that I can withdraw from the project at any stage without giving any reason</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I agree that my GP will be notified of my participation in this study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I agree to notify the Investigator of any side effects arising during the study.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I agree to be treated as part of the Getting the Balance Right Project</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Please tick all of the above options*

| | | | | |
| | | | | |

Name of Participant (in block letters)  Date  Signature

| | | |
| | | |

Researcher  Date  Signature

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APPENDIX H: LETTER TO GENERAL PRACTITIONER

Physiotherapy Department,
University of Limerick,
Castletroy,
Limerick,
Date: _______________________

Dear Dr _____________________

The “Getting the Balance Right” project is collaboration between Multiple Sclerosis Ireland and the Physiotherapy Department at the University of Limerick, funded through Tesco Charity of the year and the Pobal, Dormant Accounts flagship projects fund.

The broad aim of the project is to deliver physiotherapy and exercise programmes for people with Multiple Sclerosis and to formally evaluate the outcome of these through a series of randomised controlled trials.

Your patient _________________________________ has expressed an interest in participating and has been stratified to strand __________, the information leaflet for that strand of the study is attached for your information.

All patients will be assessed by a chartered physiotherapist to establish their suitability for the programme. No adverse effects are anticipated as all interventions are either standard physiotherapy practice or currently in use by the MS Society.

If you have any questions or concerns please feel free to contact us at susan.coote@ul.ie or 061 234 278

Dr Susan Coote, MISCP
APPENDIX I: BASELINE PARTICIPANT ASSESSMENT SHEET
Participant Code:

GNDS score:

Date:

Section 1

Sex: __________
DOB: __________
Type of MS: __________
Length of time since first symptoms: __________
Length of time since diagnosis: __________
Number of hospital admissions for MS this year: __________
Number of steroid treatments this year: __________
Most recent Relapse: _________________
Medications: Dose and frequency
(e.g. anti spasmodic, disease modifying, analgesics, steroids)

Ask patient to bring in list if can’t remember)

Current problem(s) relating to MS?
(If pain reported get overall Verbal Numeric Rating Scale (VNRS) score)

Medical history (current and previous):
Have you been ill recently?

Probes
- Other medical conditions (Special questions, red flags)
- Previous Injury
- Any chest pain or breathlessness?
- Family Hx of heart problems
- Vision
- Continence
- Pain

History of falls? __________
If yes, frequency in the last three months __________
Dizziness? Unsteadiness?

**Section 2**

Activities in the last year?
Physiotherapy:
Details:

Exercise class (es):
Details of class (FITT):
Details:

**Current activities**
Details of exercise (Frequency, Intensity, Type, Duration):

Are you currently receiving any other treatment? (For example physiotherapy, exercise, complimentary and alternative treatment)

**Soc Hx**
Type of residence? Rural/urban? Assisted living? _____________
Employment status: _____________
Assistance at home (type):
Hours of help daily:

**Section 3**

**Co-ordination (affected arm)**

Finger to nose test
- Normal speed
- Normal accuracy
- Tremor yes/no
ROM

Ankle DF  R  L

Sensory Assessment

Describe:

Light touch VNRS  0 no sensation at all
   10 full sensation

Location 1. Dorsum of the foot
  2. Lateral Calf
  3. Medial Knee
  4. Middle fibres of Deltoid
  5. Lateral forearm
  6. Lateral Posterior aspect of the hand

Do you have any difficulties in feeling temperature with your hands or feet?

Proprioception

Normal/Abnormal

Big Toe  R)  L)

PIP Index Finger  R)  L)

Note: any impairment in ranger or strength
Section 4

Tone/Spasticity

Modified Ashworth Scale, Rate 0 to 5

Elbow and Knee

(most impaired side)

Note: any impairment of range

0 = No increase in Muscle Tone

1 = Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension

2 = Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM (range of movement).

3 = Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM (range of movement).

4 = Considerable increase in muscle tone passive, movement difficult.

5 = Affected part(s) rigid in flexion or extension.

Additional Notes:

____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________
____________________________________________________________________

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APPENDIX J: FOLLOW UP PARTICIPANT ASSESSMENT SHEET

Participant Code:

GNDS score:

Date:

In addition to repeating the outcome measures, the participant should be asked if there has been a change in any of the following:

- Medications: Dose and frequency
  (anti spasmodic, disease modifying, analgesics, steroids)

- Current problem(s) relating to MS?

(If pain reported get overall Verbal Numeric Rating Scale (VNRS) score)

- Have you been ill since entering into this programme?

(nb relapse / falls)

Describe details:
o Current exercise activities?
(Frequency, Intensity, Type, Duration)

o Hours of home help/ assistance?

o Have you had any change in employment status?

o Have you received any other physiotherapy since starting this programme?

o Additional notes (anything else the participant would like to report):
Dear Physiotherapist

Thank you for agreeing to participate in the “Getting the Balance Right” programme. The following Intervention pack includes some details in order for the research part of the project to be completed.

To get all the data needed for the outcome measures the Resting Heart Rate for each individual is required at **week 1 and week 10** of the intervention.

To reproduce this study and to write up the report, it is essential that we know what the participants are doing. In order to achieve this you must **document** as much as possible what the **intervention** involves for each participant every week. This means the Frequency, Intensity, Duration and Type of each exercise.

Forms for this are also included in the pack.

Finally, a sheet for attendance/ **adherence** is also provided. Please tick if the participant attended the class and also what percentage of the class was completed (approximately).

If you have any questions, please do not hesitate to contact the research team in the University of Limerick or the MS Society.

Kind Regards,

Maria Garrett, MISCP
Chartered Physiotherapist
Department of Physiotherapy
Health Sciences Building
University of Limerick
Limerick
Ireland

Phone: + 353 61 233768
APPENDIX L: STANDARD EDUCATION – WEEK 1

This needs to be presented orally to participants in week 1.

Previously it was thought that exercising make MS symptoms worse. However, it is now known this is definitely not the case. Evidence shows many benefits of exercise in people with Multiple Sclerosis (MS). Studies do date have shown that a people with mild to moderate MS participating in an exercise programme can benefit from improvements in fatigue, strength, fitness, body composition, disability, walking, lung function and participants can enjoy feeling confident, normal, experience improved mood and improvements in social support. Additionally there are the benefits that are well documented for example it’s good for your heart, muscles, bones and controlling weight.

There are two type of exercise – Aerobic Exercise and Resistance Training (Strengthening).

The American College of Sports Medicine (ACSM) defines aerobic exercise as "any activity that uses large muscle groups, can be maintained continuously, and is rhythmic in nature." It is a type of exercise that overloads the heart and lungs and causes them to work harder than at rest. The important idea behind aerobic exercise today, is to get up and get moving!! There are many activities to choose from, whether it is a new activity or an old one. Find something you enjoy doing that keeps your heart rate elevated for a continuous time period and get moving to a healthier life. Examples of aerobic activities include, walking, swimming or cycling. The intensity should be high enough to make you sweat a little! We will teach you how to achieve the appropriate intensity for exercise when you have MS. Everybody will be given a target heart rate to try and achieve during aerobic exercise. It is measured as you were shown in the assessment – at the pulse in your neck. Every ten minutes that you are exercising (aerobic) just stop and check that you are achieving the correct intensity. This is more accurate but if you find this difficult, please consult with the physiotherapist for an alternative.
Resistance training has been shown to be the most effective way of improving musculoskeletal strength. It takes approximately 6 weeks to see changes in strength. That’s why this programme is ten weeks long. To allow you to get the maximum benefit possible. There are many principles of resistance training – one of the most important is “overload” - this means that to get increase in strength you must work the muscle hard. This type of training has also been shown to be beneficial in people with MS. To do this correctly you must gradually build up to 12 - 15 repetitions of each exercise and repeat this 2 – 3 times. You get a break after each “set”. When you can do this easily, it’s time to increase the difficulty of the exercise.

Many of the effects of MS such as weakness and fatigue are made worse by the secondary effects of a sedentary lifestyle. These can be prevented by an active lifestyle. Research shows that almost all aspects of the physiological profile of people with MS improve after exercise programmes. However it must be done at the correct intensity to achieve this.

This intervention will focus on both aerobic exercise and resistance training. Don’t worry we’ll ease you in gradually and you won’t have to do anything that you are not able to do. Gradually week by week you will be able to do more and more. All exercises should be pain free. However, it is completely normal and even beneficial to be sore the day after exercise. This means that the muscles are adapting and it normally resolves within at most three days and it decreases with time. It is also normal for people with MS to experience some fatigue after exercise. This normally resolves within about 40 minutes of exercising.

We know there can be many things that can make exercise difficult for example fatigue, lack of motivation and fear of falling amongst many others. If anything proves to be getting in the way of a good work out please let me (Physio) know and together we’ll try and overcome it.
APPENDIX M: THE EXERCISE CLASS:

Demonstrate the exercises before the first class and reinforce and correct as necessary

Demonstrate Exercises

Warm up: 5 minutes – walking

Progressive Resistance Exercise

Duration - 40 minutes in total

Frequency – Weeks 1- 5 once a week, weeks 6-10 twice a week (one class and once at home). 2-3 sets

Intensity - ACSM guidelines for progressive resistance i.e.: 50 – 80% of 1RM or increase load by 2-5% when 12 – 15 reps achieved.

Type – Circuit style with each of the following:

1. STS/Squat – depending on ability and safety
2. Bridging (Encourage TrA activation)
3. Resisted shoulder flexion (Watch posture – nb “shoulders back and down”)
4. Walk/Treadmill/bike
5. Resisted elbow flexion (nb eccentric component)
6. Lunges or Resisted knee extension – depending on ability, safety and quality of movement
7. Hip extension in standing with support – nb = quality (no back extension)
8. Calf raises (nb eccentric component – instruct slowly down)

Ideas for progression –

1. Squat/STS – weights in hands, slow down speed, alter height of plinth
2. Bridging – lift alternate calves off the bed, weight across ASIS (if flat), one leg off plinth (if pelvis remains neutral, not rotated)
1., 3., 5., 6., 7., 8 = increase weight
4. – increase resistance/incline

Cool down: 5 minutes - walking
APPENDIX N: CALCULATING THE INTENSITY FOR AEROBIC EXERCISE

This can be done at the end of the first class as participants often need a physical break before they leave after the exercise

- Karvonen Formula: Target HR = Resting Heart Rate + % (Maximum Heart Rate - Resting Heart Rate)

- You will need to calculate this for each participant as they brought their RHR to the first class.

- We will use Age Predicted HR Max = 220 – Age in the above formula.

- If they forget their RHR – Ask them to bring it next week and use average HR (i.e. 72)

Example: Patient is 40 years old and has a resting HR of 70
THR = 70 + 65% (180 – 70)
THR = 141.5bpm
THR = 140bpm (Round it off to nearest multiple of 10)

Advice: Participant should feel 14 beats in 6 seconds in their Carotid Pulse, starting counting at zero.
If participants report having trouble with this the next available option is **Borg’s Rate of Perceived Exertion**. Borg’s Rating of Perceived Exertion (RPE) is based on a subjective feeling of exertion and fatigue during exercise, and it is used to assess and regulate exercise intensity. The theoretical premise of RPE is that a person will give a numerical value on a scale from 6 to 20, representing a verbal expression of effort during exercise. Advised RPE = 11 - 14

- 6 - 20% effort
- 7 - 30% effort - Very, very light (Rest)
- 8 - 40% effort
- 9 - 50% effort - Very light - gentle walking
- 10 - 55% effort - Fairly light
- 12 - 65% effort
- 13 - 70% effort - Somewhat hard - steady pace
- 14 - 75% effort
- 15 - 80% effort - Hard
- 16 - 85% effort
- 17 - 90% effort - Very hard
- 18 - 95% effort
- 19 - 100% effort - Very, very hard
- 20 - Exhaustion
**APPENDIX O: STANDARD EDUCATION - WEEK 4**

Hand out for participants to read in own time in week 4

**Exercise guidelines for People with MS**

**Aerobic Exercise:**

<table>
<thead>
<tr>
<th>Frequency:</th>
<th>2-3 times a week</th>
<th>Intensity:</th>
<th>65% - 75% of Maximal Heart Rate or a Rate of Perceived Exertion of 11-14.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Count beats of pulse after every 10 minutes of exercise as shown by physiotherapist</td>
<td>The original Borg scale of perceived exertion ranges from 6 to 20 (6 = no exertion at all and 20= maximal exertion). Ratings of 11-14 represent moderate intensity and the ideal target intensity zone in the absence of symptoms.</td>
</tr>
<tr>
<td>Type (self-selected):</td>
<td>Walking/Cycling/Swimming/Running</td>
<td>Duration:</td>
<td>20-30 mins</td>
</tr>
</tbody>
</table>

*Note: Aerobic exercise can bring on a temporary exacerbation of any sensory symptoms, this usually resolves within 40 mins*

**Strengthening:**

When you can perform 12-15 repetitions correctly in consecutive training sessions the weight can be increased by 2-5%.

Aerobic and resistance programmes should alternate on separate days of the week with 24 – 48 hours of recovery between training sessions. In this manner strength exercises will typically be performed on average of twice per week.

This class has included:

Sit To Stand/Squat, Bridging, Resisted shoulder flexion, Resisted elbow flexion, Lunges/Resisted knee extension, Hip extension and Calf raises, which can be repeated at home (use imagination for resistance e.g.: bottle of water/can of beans, bottle of sand etc…)

Ideally 15 repetitions should be repeated 3 times (3 sets), when this can be done without too much effort, it’s time to make it harder to get strength gains in the muscles.

If you would like advice on any other strengthening exercises. Please Ask!
APPENDIX P: WEEKLY CLASS EXERCISE SHEET – WEEK 1-5

Hand out this sheet to participants every week (i.e. 8 is required every week). This form should be handed back to physio at the end of each class. 8 every week required.

Weeks 1 – 10

Week number: __________

Name: __________________

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Weight (kg/N)</th>
<th>Repetitions</th>
<th>Sets</th>
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</tbody>
</table>

Any Other Exercise:

245
APPENDIX Q: DOCUMENTATION OF HOME EXERCISE PROGRAMME – WEEKS 1 – 5

Hand out weekly Home Exercise Sheet Weeks 1 – 5 (Bring back to Physio next week). 8 per week (1 – 5) required.

Week no: __________

Name: _____________________

Aerobic Exercise

<table>
<thead>
<tr>
<th>Type</th>
<th>Day 1</th>
<th>Day 2</th>
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<table>
<thead>
<tr>
<th>Duration</th>
<th>Day 1</th>
<th>Day 2</th>
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<table>
<thead>
<tr>
<th>Intensity</th>
<th>Day 1</th>
<th>Day 2</th>
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</table>

Any Other Exercise:
**APPENDIX R: DOCUMENTATION OF HOME EXERCISE PROGRAMME – WEEKS 6 – 10**

Week number: _____________

Name: ________________

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Weight (kg/N)</th>
<th>Repetitions</th>
<th>Sets</th>
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<tbody>
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### Aerobic Exercise

<table>
<thead>
<tr>
<th>Type</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
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</tbody>
</table>

Any Other Exercise:
APPENDIX S: WEEKLY ATTENDANCE SHEET/DEVIATIONS FROM NORMAL

Participant Name: __________________________

<table>
<thead>
<tr>
<th>Week</th>
<th>Attended (please tick)</th>
<th>Deviations from prescribed class (please comment)</th>
</tr>
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<tbody>
<tr>
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</table>
Please Document individual physiotherapy notes every week. 8 sheets required in total. Please keep a copy of these for the MS Society

Participant Name:

Week 1:

Week 2:

Week 3:

Week 4:

Week 5:
Week 6:

Week 7:

Week 8:

Week 9:

Week 10:
**APPENDIX T: DOCUMENTATION OF CLASS EXERCISE PRESCRIPTION**

Insert documentation of exercise prescription here.

*This is the most important sheet.* Fill out approximate % of exercise completion per participant per wee.

<table>
<thead>
<tr>
<th>Participant Name</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
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<tbody>
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<td>S1</td>
<td>A1</td>
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<th>Week 8</th>
<th>Week 9</th>
<th>Week 10</th>
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<tbody>
<tr>
<td>Participant Name</td>
<td>S1</td>
<td>S2</td>
<td>A1</td>
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<td>A2</td>
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</tbody>
</table>

251
APPENDIX U: LETTER TO YOGA INSTRUCTOR OR FITNESS-INSTRUCTOR

Dear Yoga Instructor/Fitness Instructor

Thank you for agreeing to participate in the “Getting the Balance Right” programme. The following Intervention pack includes some details in order for the research part of the project to be completed.

To get all the data needed for the outcome measures the Resting Heart Rate for each individual is required at week 1 and week 10 of the intervention.

The participants have been advised how to do this in a standard way during assessment and should have calculated this by the first week of the class. However, this must be documented by you at week 1 in the sheet provided. Remind the participants to get their new resting Heart Rate in week 9 and document it again when they come back in week 10.

Standardised instructions in how to get Resting Heart Rate and a sheet for documenting the same are included in this pack.

Additionally, in order to reproduce this study and to write up the report. It is essential that we know what the participants are doing. In order to achieve this you must document as much as possible what the intervention involves for each participant every week. This means the Frequency, Intensity, Duration and Type of each exercise (where applicable).

A form for this is also included in the pack.

Finally, a sheet for attendance/adherence is also provided. Please tick if the participant attended the class and also what percentage of the class was completed (approximately).

If you have any questions, please do not hesitate to contact the research team in the University of Limerick or the MS Society.

Kind Regards,

Maria Garrett, MISCP

Chartered Physiotherapist
Department of Physiotherapy
Health Sciences Building
University of Limerick
Limerick
Ireland

Phone: + 353 61 233768
APPENDIX V: DOCUMENTATION OF INTERVENTION (FOR YOGA/FITNESS INSTRUCTORS)

Please document as much as possible what the class involves for each participant each week. For this we would like the frequency, Intensity, Type and Duration, where relevant, of each activity that participants do. Please also ask participants to document any activity they are doing independently during the week. You need one of these sheets for every participant and it needs to be updated weekly.

Participant Name: _____________________

Week 1:

Week 2:

Week 3:

Week 4:

Week 5:

Week 6:
Week 7:

Week 8:

Week 9:

Week 10:
**APPENDIX W: WEEKLY ATTENDANCE SHEET/ADHERENCE TO PRESCRIBED PROGRAMME**

You need to keep one of these sheets for each participant and update it weekly.

Participant Name: __________________________

<table>
<thead>
<tr>
<th>Week</th>
<th>Attended (please tick)</th>
<th>Percentage of adherence to programme (approx.) i.e. 30%, 50%, 100% etc…</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
## Appendix X: Content of Yoga Interventions

<table>
<thead>
<tr>
<th>Region</th>
<th>Details of class</th>
<th>Asanas (postures)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Midwest</strong> (N = 5)</td>
<td>1. Breathing exercises to reduce stress</td>
<td>• Structural Yoga Therapy – (Joint freeing series – see Appendix) x3</td>
</tr>
<tr>
<td></td>
<td>2. Asanas performed</td>
<td>• Palm Tree Vinyasa (Tadasana), which involves standing with feet together and moving the trunk outside of Base of support – one to each side x 2</td>
</tr>
<tr>
<td></td>
<td>3. Yoga Nidra (visualisation, imagery and positive affirmation) took place at the end of each session to induce maximum relaxation (For example, “I am really enjoying my walk outside”)</td>
<td>• Bridging x 3</td>
</tr>
<tr>
<td></td>
<td>4. Home practice was encouraged – hand-out of Joint freeing series given to participants</td>
<td>• Spinal twist x 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Butterfly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Crossover</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Standing warrior</td>
</tr>
<tr>
<td><strong>Dublin-Northern Area</strong></td>
<td>1. Each class commenced with a joint freeing series</td>
<td>• Awakening the feet, rocking the feet, ankle rotation and flexion</td>
</tr>
<tr>
<td>(N = 5)</td>
<td>2. The classes were progressive, each week adding in a more complex exercise</td>
<td>• Knee rotations</td>
</tr>
<tr>
<td></td>
<td>3. Each class ended with relaxation</td>
<td>• Hip rotations, hip swinging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Easing out of lower back, legs curled to chest and gentle rocking from side to side, alternate knees curled to chest and stretching up leg lengthening hamstrings and calves, cat stretch</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stretching out of clavicle and breast bone, stretching out of shoulder blade and trapezius, shoulder rotations and shrugs, swinging of the arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Wrist flexions and rotations, awakening the hands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Neck rotations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The breath of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The squat</td>
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<tr>
<td></td>
<td></td>
<td>• The Ha Breath – knees slightly bent, swing arms over your head as you inhale, as you exhale make a “huh” sound, allow whole body to come forward into a forward bend as arms swinging down and repeat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Forward bends</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spinal twists</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• The 3 phase breath</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rocking back to centre – Lying on the floor with both knees held to the chest, cross ankles, hold the big toes, breathe in and on the out breath roll back to sitting.</td>
</tr>
</tbody>
</table>
CONTENT OF YOGA INTERVENTIONS CONTINUED…

<table>
<thead>
<tr>
<th>Region</th>
<th>Details of class</th>
<th>Asanas (postures)</th>
</tr>
</thead>
</table>
| North East | 1. Body “centring”.  
2. The classes were progressive, each week adding in a more complex asanas  
3. Each class ended with relaxation and Yoga Nidra | • Knees to chest  
• Ankle rotations  
• Standing tadasana (mountain pose)  
• Extended tadasana  
• Forward bend  
• Trikonasana (triangle pose)  
• Warrior  
• Dandasana  
• Sun salutation (chair version)  
• Anti-arthritis movements - neck, arms, hands, knees, hips, ankles  
• Supine tree  
• Supine cobbler  
• Table pose  
• Cat stretch – dip chest to floor – downward dog – camel pose -  
• Hare pose  
• Bridge pose  
• Warrior  
• Tree pose, child sequence |
| North West | 1. Each class commenced with relaxation (5 mins)  
2. Stretching (30 mins)  
3. Strengthening  
4. Standing work – use of a bar when needed  
5. Breathing  
6. Deep relaxation and visualisation (15 mins)  
7. Home practice encouraged | • Abdominal breathing  
• Stretching  
• Standing postures – squatting, strengthening thighs and legs  
• Eye, shoulder, neck and arm exercises encourages  
• Core strengthening |
CONTENT OF YOGA INTERVENTIONS CONTINUED…

<table>
<thead>
<tr>
<th>Region</th>
<th>Details of class</th>
<th>Asanas (postures)</th>
</tr>
</thead>
</table>
| **Dublin – South Western Area**  | 1. Abdominal breathing  
2. Stretching  
3. Core stability exercises (each conducted bilaterally)  
4. Stretching  
5. Yoga Nidra                                                                                       | Stretching  
  • Pull knee to chest x 5 bilaterally  
  • Nose to knee x 5 bilaterally  
Core stability exercises  
  • Bridge x 3  
  • Twist x 3  
  • Leg lifts x 5  
  • Adductor lift x 5  
  • Clam x 5  
Stretching  
  • cat stretch  
  • latissimus dorsi stretch x 3                                                                                                                            |
| (N = 3)                       |                                                                                                                                                                                                                  |                                                                                                       |
| **Tipperary South**           | 1. Every class started with Savasana (relaxation and deep breathing in the corpse pose) 15 minutes  
2. Asanas (posture) was balanced with a counter asana – for example if a posture was performed in a position of flexion, the following posture would encourage extension.  
3. After every asana, Savasana was performed. This was a deep breathing exercise to encourage relaxation which included inspiratory hold (Pranyama) and alternate nostril breathing (Anuloma Viloma).  
4. Asanas were maintained for 30 to 90 seconds and support was offered in the form of a chair /wall / belt / block depending on the person’s ability when required  
5. Yoga Nidra (15 minutes)  
6. Home practice was encouraged from 20 – 90 minutes                                                                                                    | Sukasana (seated position) eye and neck exercises  
  • Single leg raises x 5  
  • Double leg raises x 5  
  • Shoulderstand  
  • Fish pose  
  • Sitting forward bend  
  • Inclined plane  
  • Cobra  
  • Bow lying  
  • Childs pose  
  • Triangle  
  • Half spinal twist  
  • Butterfly  
  • Boat                                                                                                                                                |
| (N = 4)                       |                                                                                                                                                                                                                  |                                                                                                       |
CONTENT OF YOGA INTERVENTIONS CONTINUED…

<table>
<thead>
<tr>
<th>Region</th>
<th>Details of class</th>
<th>Asanas (postures)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southern Area</td>
<td>1. Relaxation</td>
<td>Range of motion exercises</td>
</tr>
<tr>
<td>(N = 21)</td>
<td>2. Yogic breathing (15 mins)</td>
<td>Strengthening postures.</td>
</tr>
<tr>
<td></td>
<td>3. Spinal mobilisation / posture</td>
<td>- Forward bend</td>
</tr>
<tr>
<td></td>
<td>4. To avoid injury, every asana (posture) was balanced with a counter asana – for example if a posture was performed in a position of flexion, the following posture would encourage extension.</td>
<td>- Inclined plane</td>
</tr>
<tr>
<td></td>
<td>5. Between every asana, Savasana was performed. This was a deep breathing exercise to encourage relaxation which included inspiratory hold (Pranayama) and alternate nostril breathing (Anuloma Viloma).</td>
<td>- Balance exercises such as the “Triangle”.</td>
</tr>
<tr>
<td></td>
<td>6. Asanas were maintained for 30 to 90 seconds and support was offered in the form of a chair /wall / belt / block depending on the person’s ability when required</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Home exercise practice was encouraged.</td>
<td></td>
</tr>
<tr>
<td>Western Area</td>
<td>Class 1:</td>
<td>Class 1: Stretching exercises – not described.</td>
</tr>
<tr>
<td>(N= 8)</td>
<td>1. Yoga Nidra</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Relaxation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Stretching exercises</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Yogic breathing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Class 2:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Yogic breathing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Alternate nostril breathing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Warm-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Rishikesh yoga</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Relaxation – gong meditation, emotional balance, for a calm heart</td>
<td></td>
</tr>
<tr>
<td>Midlands (N = 1)</td>
<td>No details returned</td>
<td></td>
</tr>
<tr>
<td>East Coast (N = 5)</td>
<td>No details returned</td>
<td></td>
</tr>
</tbody>
</table>
## Appendix Y: Content of Fitness-instructor Led Exercise

<table>
<thead>
<tr>
<th>Region</th>
<th>Details of class</th>
<th>Type of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southeast</td>
<td></td>
<td><strong>Combined</strong></td>
</tr>
</tbody>
</table>
| Kilkenny (N = 4)        | 1. Warm up  
2. Aerobic: 10 - 15 mins x 2 aerobic  
3. PRE: 6 reps x 3 sets or 12 x 2 progressed to 3 x 10  
4. Cool down bicycle 5 mins/stretching  
5. Progressed at week 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Aerobic:  
• Treadmil  
• Rower  
• Upright bicycle  
• Cross trainer  
PRE:  
• Dynaband  
• Shoulder press machine  
• Leg curl  
• Leg extension  
• Dorsal machines |
| Midwest                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | **PRE**                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Nenagh (N = 6)          | 1. Warm up  
2. Stretches (sitting) - 10s hold  
3. Rest  
4. PRE (sitting) x 8 reps  
5. Stretches (sitting) x 20s hold  
6. Progressed at week 5  
7. Were advised to do HEP on 2 more occasions during the week                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | PRE:  
• Lateral raise  
• Frontal raise  
• Biceps curls  
• Chest press  
• Shoulder press  
PRE (upper limb):  
• Leg abduction  
• Leg curl  
• Leg extension  
• Gluteals  
• Sit to stand  
• Ankle rolls |
| Dublin – Northern Area  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | **Aerobic**                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Coolock (N = 8)         | 1. Warm up  
2. Aerobic: 5 minutes on each of the machines  
3. Stretching x 5 mins  
4. Rest and repeat  
5. Operated in pairs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | • Stepper  
• Rowing machine  
• Exercise bike  
• Walking to and fro on a level |
## CONTENT OF FITNESS INSTRUCTOR LED EXERCISE CONTINUED…

<table>
<thead>
<tr>
<th>Region</th>
<th>Details of class</th>
<th>Type of exercise</th>
</tr>
</thead>
</table>
| **North East**  | *Warm up*  
*Combined Exercise Programme – increasing the intensity weekly*  
*Stretches*                                                                                                                                   | **Combined**  
**PRE**  
Aerobic  
Marching on the spot  
Walking  
**Stretches** |
| *(N = 2)*       |                                                                                                                                                                                                                  |                  |
| **North West**  | *Warm up*  
*Aerobic (5 – 20 minutes on each machine)*  
*PRE was only conducted once or twice by participants, main component of the class was aerobic*  
*Stretches of major muscle groups*                                                                                                       | **Aerobic (Mainly)**  
**PRE**  
Aerobic  
Recline bicycle  
Cross Trainer  
Treadmill  
Rower  
**Stretches** |
| *(N = 5)*       |                                                                                                                                                                                                                  |                  |
| **South**       | *Aerobic*  
*Week 1: tried Cardiovascular equipment*  
*Week 2 – week 10: Walking exercises, duration and intensity unknown*                                                                               | **Combined**  
**PRE**  
Aerobic  
Treadmill  
Cross Trainer  
Recline bicycle  
Walking forwards and backwards  
**Stretches** |
| *(N= 5)*        |                                                                                                                                                                                                                  |                  |
## CONTENT OF FITNESS-INSTRUCTOR LED EXERCISE...

<table>
<thead>
<tr>
<th>Region</th>
<th>Details of class</th>
<th>Type of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>West</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| (Class 1: N = 3) | Class 1: No details returned – had to ring deliverer of intervention Repetitive exercise. No incline and low resistance on the treadmill. Resistance used on bicycle as able. 5 – 10 repetitions of PRE depending on ability Intensity very low. | Class 1: Combined Aerobic (Class 1)  
Treadmill  
Bicycle (resisted where possible)  
PRE (Class 1 with dynaband)  
- Weight Machines  
- Chest press  
- Shoulder press  
- Lateral pull down  
- Rear row  
- Leg extension (depending on ROM and pain)  
- Abduction/Adduction |
| (Class 2: N = 6) | Class 2:  
Warm up  
Aerobic (10-15 minutes of each exercise)  
2 participants participated in PRE  
Cool down  
Stretches | Class 2: Combined Aerobic  
Treadmill  
Rower  
Cross trainer  
PRE (Class 2)  
- Bicep Curl  
- Front Raise  
- Leg press  
- Glutes  
- Ab machine |
| Wexford North   |                                                                                 |                                                                                 |
| (Class 1: N = 6) | Aerobic (5 – 25 minutes)  
PRE (15 reps x 2-3 sets) | Combined Aerobic  
Bicycle Treadmill  
Arm ergometry  
PRE  
- Lateral raises  
- Front raises  
- Biceps Curls  
- Triceps extensions  
- Leg abduction  
- Leg adduction  
- Chest press  
- Seated biceps curls  
- Abdominal machine |
<table>
<thead>
<tr>
<th>Region</th>
<th>Details of class</th>
<th>Type of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wexford South (N = 9)</td>
<td><strong>Aerobic</strong> (6 – 15 minutes) PRE (2x10x resistance)</td>
<td>Combined Aerobic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bike</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cross trainer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treadmill</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rower</td>
</tr>
<tr>
<td>Midlands</td>
<td><strong>Class 1: No details returned – retrieved via phone call</strong></td>
<td>PRE</td>
</tr>
<tr>
<td></td>
<td>Circuit style class – 30 seconds at each station doing as much as each participant could.</td>
<td>• Leg extension</td>
</tr>
<tr>
<td></td>
<td>Light resistance used for PRE (e.g. 1kg)</td>
<td>• Leg press</td>
</tr>
<tr>
<td></td>
<td>Home exercise component encouraged</td>
<td>• Ab crunch</td>
</tr>
<tr>
<td></td>
<td>FI had planned some floor exercises but participants reported not being happy to get up and down from the floor.</td>
<td>• Chest press</td>
</tr>
<tr>
<td></td>
<td>Exercises modified when required (e.g. holding on to a chair.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Class 2: No details returned</strong></td>
<td></td>
</tr>
<tr>
<td>East Coast Area (N = 5)</td>
<td>No details returned</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>PRE</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Leg extension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Leg press</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ab crunch</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Chest press</td>
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<tr>
<td></td>
<td><strong>Co-ordination</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Catching and clapping</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Basketball</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stretching</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Heal flicks</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>HEP: PRE – tins of beans/bottles of water</strong></td>
<td></td>
</tr>
</tbody>
</table>