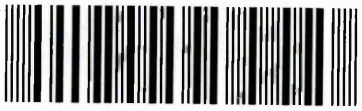

The Effects of a Pragmatic Exercise Intervention in People with Multiple Sclerosis

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ABSTRACT

Background: People with multiple sclerosis (PwMS) are less physically active than the general population. Moderate intensity exercise is likely to be safe and may provide an effective intervention for improving health outcomes for people with mild-to-moderate disability from MS. A robustly designed trial, using a pragmatic approach constructed to be cost-effective and elicit long-lasting behaviour change is required to influence health care practice.

Objectives:
To determine the feasibility of a pragmatic exercise intervention for PwMS and to determine if this type of intervention can provide a cost effective solution to improving health outcomes and increasing exercise and physical activity at up to nine months follow-up in PwMS compared with usual care alone.

Methods: We initially conducted a feasibility randomised controlled trial, recruiting a voluntary sample of 30 PwMS (male $n = 4$, female $n = 26$; mean age 40 years; range 24 to 49 years; Expanded Disability Status Scale (EDSS) 0.0 to 5.5). Results from which informed the design of a large-scale randomised controlled trial (RCT). A total of 120 PwMS (male $n = 34$, female $n = 86$; mean age 46 years; range 19 to 65 years; EDSS 1.0 to 6.5) were then recruited to a three month exercise intervention (two supervised and one home-based session for first six weeks; one supervised and two home-based session for the final six weeks) plus usual care or usual care alone. Cognitive behavioural strategies were used to promote long-term behaviour change. The primary outcome was self-reported exercise behaviour change (Godin Leisure Time Exercise Questionnaire (GLTEQ)). Secondary outcomes included clinical, functional and quality-of- life (MSQol-54) measures.

Results: The feasibility trial demonstrated that attrition was low (6.7% at immediate follow-up and 20% at three months follow-up) and compliance was high (>75% of all sessions). The main trial reported significant improvements in self-reported exercise behaviour ($p = 0.01$), fatigue ($p < 0.0001$) and many MSQol-54 domains ($p < 0.03$). Only the significant improvements in overall quality of life ($p = 0.001$), and the sub-domains of emotional wellbeing ($p = 0.01$) and social function ($p = 0.004$) were maintained at the nine months follow-up. The probability of the intervention being cost-effective was 0.75 at the threshold of £20,000 per quality adjusted life year (QALY).

Conclusion: This pragmatic intervention was not only feasible, but outcomes from the main trial suggest that it is highly likely to be cost effective, leading to improved self-reported exercise behaviour, fatigue and a sustained enhancement of health-related quality of life. This provides a strong evidence base to influence the prescription of exercise into the treatment pathway for PwMS within the NHS.

ACKNOWLEDGEMENTS

The production of this thesis has taken me on a challenging journey that I have thoroughly enjoyed, even if the time in which to indulge in the process has often been hard to find.

I would particularly like to thank all of the participants on the projects that made this thesis possible; they have been an absolute joy to work with offering me with many words of wisdom and laughs along the way.

I wish also to acknowledge the MS Society and the Sheffield Teaching Hospitals NHS Trust for funding and supporting these collaborative projects with Sheffield Hallam University.

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Finally I would like to dedicate this to my family. My husband, and my Mum and Dad, who have always supported and believed in me and my son Sebastian, who although having made this PhD a more challenging and lengthy process has provided me with laughs and perspective when I've needed it most. I hope I have done him proud.

RESEARCH OUTPUTS

Publications

McConnell (now Carter) AM, Daley AJ, Green SW, Saxton JM, Woodroofe N & Sharrack B. Impact of a pragmatic exercise intervention on quality of life and physical activity in people with mild to moderate multiple sclerosis: a feasibility study. *Mult Scler.* 2010; **16**(S7-S39).

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Crank H, Carter A, Humphreys L, Snowdon N, Daley A, Woodroofe MN, Sharrack B, Petty J and Saxton JM. New qualitative insights into the experience of exercise in people with mild to moderate multiple sclerosis. Multiple Sclerosis (in preparation).

Conference and Research Presentations

McConnell (now Carter) AM, Daley AJ, Green SW, Howell S, Saxton JM, Woodroofe MN and Sharrack B. Impact of a supervised exercise intervention on quality of life and functional capacity in people with mild to moderate multiple sclerosis (poster). MS Frontiers, Novotel London Euston, June 2007.

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McConnell (now Carter) AM, Daley AJ, Green SW, Saxton JM, Woodroofe N and Sharrack B. Impact of a pragmatic exercise intervention on quality of life and physical activity in people with mild to moderate multiple sclerosis: a feasibility study (poster). 26th Congress of the European committee for treatment and research in multiples sclerosis (ECTRIMS). October 2010.

McConnell (now Carter) AM. Conducting a pragmatic exercise therapy intervention for people with MS: the Sheffield ExIMS trial (symposium). The

Society for Research in Rehabilitation (SRR) Summer Meeting, Sheffield Hallam University, July 2010.

Saxton JM., Carter A., Daley A et al.. Pragmatic exercise for people with MS: a randomized controlled trial [CMSC abstract P10]. *Int J MS Care*. 2013; **15**(suppl 3):16.

Carter AM and Snowdon N. Exercise in MS: The EXIMS trial (Session). Physiotherapy UK Conference, Oct 2014.

Carter AM, Crank HC Humphreys L et al. Experiences of exercise in people with mild to moderate multiple sclerosis: a qualitative study. BASES Conference, Nov 2014.

IMPACT

Workshops and Presentations

McConnell (now Carter) AM and Sheridan A. Exercise and Multiple Sclerosis. Sheffield Multiple Sclerosis Conference (presentation). Sheffield. July 2009.

McConnell (now Carter) AM. Conducting a pragmatic exercise therapy intervention for people with multiple sclerosis (workshop). MS Frontiers, MS Society. Sofitel London Heathrow. May 2009.

Carter AM. Effects of a pragmatic exercise therapy intervention in people with multiple sclerosis: Sheffield ExIMS trial (presentation). Neuroinflammation Forum. Sheffield Teaching Hospitals Foundation Trust. September 2011.

Broadcast Events

McConnell (now Carter) AM. Can physical activity bring benefit to people with MS? The Sport and Exercise Scientist. BASES , 17 (12-13).

McConnell (now Carter) AM. Snowdon N and Holloway E. Exercise, MS and symptom management research (workshop). MS Society living with MS Sheffield, October 2009.

McConnell (now Carter) AM. MS and Exercise (presentation). Newly Diagnosed Course, Sheffield, September 2009

McConnell (now Carter) AM. Exercise for people with multiple Sclerosis (presentation). Neurological Enablement Service. Sheffield, May 2010.

McConnell (now Carter) AM, Humphreys L. and Petty J. Exercise and Multiple Sclerosis (workshop). MS Society: Living with MS day, Leeds, May 2010.

Carter AM and Humphrey, L. Sheffield exercise trial: research and practical tips (workshop). MS Society: MS Life event, Manchester, April 2012

Influencing Best Practice

The papers presented in chapters six and seven of this thesis are **referenced in the 2014 NICE guidelines** for the 'management of multiple sclerosis in primary and secondary care'.

Award Nominations

United Kingdom **MS Society 2014 Research Award Nominee** (shortlisted to final three for ExIMS Trial)

INDIVIDUAL CONTRIBUTION AND EXTENT OF COLLABORATION

This PhD comprises an initial feasibility study funded by the Sheffield Teaching Hospitals NHS Trust and a large randomised controlled trial (RCT) funded by a project grant from the MS Society (Grant reference 888/08). My role on the initial trial covered participant recruitment, study assessments and delivery of the intervention. With regards to the main study trial I was part of a larger project team of experts from different disciplines (neurology, physiotherapy, biomedical science, clinical exercise physiology, health economics, health statistics and exercise psychology). This enabled me to gain extensive knowledge and experience of working with these different disciplines and various health professionals. With regard to this project I was involved from the outset, assisting in writing the protocol, bid application and presenting to the MS Society to award the grant. Once the grant had been awarded my role was to manage the trial and its delivery. This involved applying for NHS ethics approval, recruiting participants, conducting the baseline assessments, delivering the intervention, collating data and being the main point of contact for all participants and members of the trial team. As the project was part of a large scale funded grant it involved team of individuals on the study from both trials. Table 1 outlines my role on each publication.

Table 1. Contribution to research publications.

Chapter	Article Title	Contribution
3	Pragmatic exercise intervention in people with mild-to-moderate multiple sclerosis: a randomised feasibility study.	I both ran and managed this trial on a day to day basis, acting as the primary point of contact for participants, consultants and other members of the research team. My role included: • Recruitment of participants, which involved attending MS clinics, explaining trial and conducting initial visits and screening for inclusion exclusion criteria. • Data collection, including booking in and conducting all assessments and exercise sessions and storing and collating results in excel. • Data analysis and statistics in SPSS. • Main author and contact for publication.
4	Pragmatic exercise intervention for people with multiple sclerosis (ExIMS Trial): study protocol for a randomised controlled trial.	Having conducted the pilot trial I was part of research team who designed the trial intervention and wrote the submission for funding for the ExIMS trial. I also provided information for and assisted with writing of the paper.
5	Participant recruitment into a randomised control trial for exercise therapy for people	Day to day management of recruitment process, involving attendance at clinics, conducting

	with multiple sclerosis.	familiarisation visits, presenting at relevant MS events and coordinating participant mail-outs. In addition I was responsible for all of the collection and collation of recruitment data and its analysis. I was also the main author of the paper.
6	Pragmatic intervention for increasing self-directed exercise behaviour and improving important health outcomes in people with multiple sclerosis: a randomised control trial.	I was involved in the trial from day one, helping in the writing, submission and defence of the bid. On receipt of the funding I became the primary point of contact for, consultants, participants and researchers involved in the project. My role included: • Obtaining NHS ethics • Day to day management of trial • Participant recruitment (see details for recruitment paper) • Data collection and storage (assessments and exercise sessions) • Provision of information for statistical analysis • Provision of information for MS Society and ethics reports • Contributing author and responsible for paper amendments

STRUCTURE OF THESIS

Content by Chapter

Chapter 1.0

Chapter one provides the background information on the area of exercise and Multiple Sclerosis, describing the history of MS and how it links with exercise as a treatment of the condition. A brief overview of the gaps in the literature and the purpose of this thesis are also provided.

Chapter 2.0

Chapter two provides a detailed literature review covering the epidemiology and aetiology of MS, the risk factors and pathogenesis of the disease. The current treatments available for the management of MS are also described.

Chapter 3.0

Chapter three contains the journal article published on the feasibility of a 'pragmatic' exercise intervention that included cognitive behavioural strategies to facilitate long-term behaviour change in people with MS. This article covers the recruitment to the intervention, acceptability of the intervention, compliance, attrition, safety and suitability of exercise dose and the appropriateness of outcome measures. In addition, preliminary results on the impact of the intervention on key health outcomes for PwMS are reported.

Chapter 4.0

Chapter four contains the published protocol paper for the main 'Exercise Interventions for Multiple Sclerosis' (ExIMS) study trial. This chapter provides a detailed description of the pragmatic design and theoretical underpinning used to facilitate physical activity behaviour change in the ExIMS intervention. In addition this chapter describes the randomisation procedures, inclusion and exclusion criteria, sample size calculation; primary and secondary study outcome measures and data analysis procedures.

Chapter 5.0

Chapter five contains a recruitment paper for the ExIMS study, reporting in detail the recruitment method used and comparing recruitment, response and accrual rates. The chapter also contains detail on reasons for ineligibility and declinations to participate in the trial and which methods were the most time and cost efficient.

Chapter 6.0

Chapter six contains the main study publication from the ExIMS trial, and primary and secondary outcome measures. Participant flow, recruitment, loss to follow-up and adherence are also reported.

Chapter 7.0

Using the evidence accrued from the five papers published or in press from the feasibility trial and the ExIMS RCT, chapter seven provides an overview of the findings and limitations of the study. In addition, this chapter outlines the practical implications of using exercise as a therapy for PwMS, alongside suggestions for future research and study conclusions.

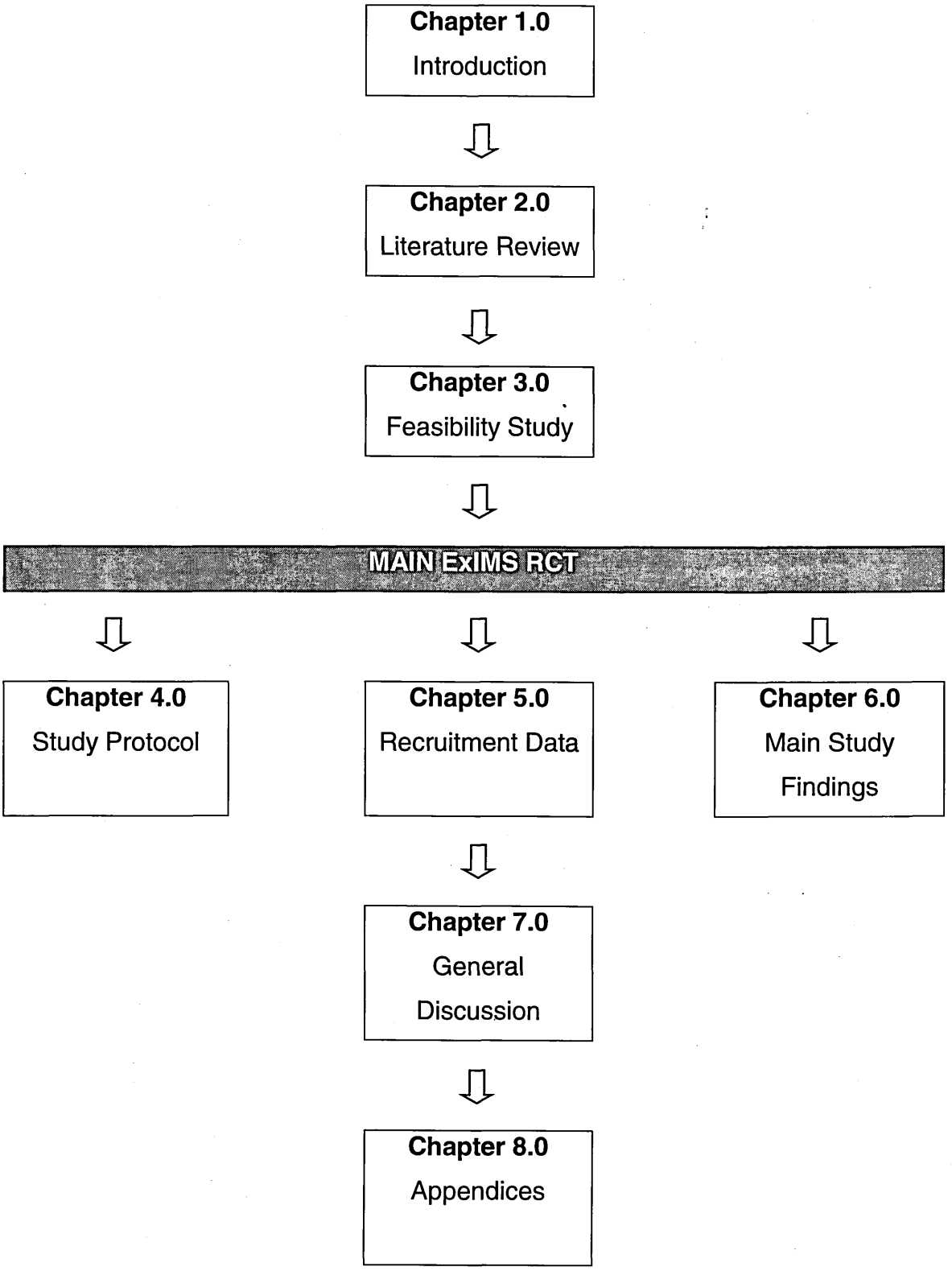
Chapter 8.0

Chapter eight contains Appendices for the ExIMS trial. Including additional information compiled for the studies ethics approval such as the patient information sheet and consent form, alongside data collections sheets and exercise advice booklets used during the trial.

References

Because of the publication nature of this thesis references are included at the end of each section, rather than at the end of the thesis. Referencing is kept in the format required for the chosen journal of publication.

FLOW DIAGRAM OF THESIS



ABBREVIATIONS

Includes those used in the main body of the text only, does not include additional abbreviations contained in figures and tables.

6MWT	Six Minute Walk Test
10MWT	Ten Metre Walk Test
BMI	Body Mass Index
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DMT	Disease Modifying Therapy
EBV	Epstein - Barr virus
EDSS	Expanded Disability Status Scale
ExIMS	Exercise Intervention for Multiple Sclerosis
FSMC	Fatigue Scale for Motor and Cognition
FSS	Fatigue Severity Scale
GLTEQ	Godin Leisure-Time Exercise Questionnaire
GNDS	Guy's Neurological Disability Scale
HAQUAMS	Hamburg Quality of Life in Multiple Sclerosis
HRQoL	Health Related Quality of Life
IPAQ	International Physical Activity Questionnaire
MFIS	Modified Fatigue Impact Scale
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis

MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
MSQol-54	Multiple Sclerosis Quality of Life-54
MSWT-12	Multiple Sclerosis Walking Test-12
NICE	National Institute of Clinical Excellence
PADS-R	Physical Activity and Disability Survey
PAR	Physical Activity Recall
PASAT	Paced Auditory Serial Addition Test
PeDro	Physiotherapy Evidence Database Scale
PPMS	Primary Progressive Multiple Sclerosis
PROMS	Patient Reported Outcome Measures
PwMS	People with Multiple Sclerosis
RCT	Randomised Control Trial
RRMS	Relapsing Remitting Multiple Sclerosis
SCT	Social Cognitive Theory
SDT	Self Determination Theory
SOC	Stages of Change
SPMS	Secondary Progressive Multiple Sclerosis
TPB	Theory of Planned Behaviour
TTM	Transtheoretical Model
TUG	Timed Up and Go
WH	Waist Hip Ratio

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8.0 APPENDICES

1.0 INTRODUCTION

1.1 History

1.1.1 General History

Multiple Sclerosis (MS) is an autoimmune disease that is typically progressive and involves damage to the sheaths of nerve cells (demyelination) in the central nervous system (CNS) (Dorland and Newman, 2000). MS symptoms can be categorised into eleven key areas; mobility, hand function, vision, fatigue, cognition, bowel/bladder function, sensory, spasticity, pain, depression, and tremor/coordination (Kister et al., 2013), with symptoms dependant on the CNS pathology (Döring et al., 2012). Symptoms present themselves either in acute attacks or slowly progressing over time (Lavery et al., 2014). The condition was first defined as a unique disease by neurology professor Jean-Martin Charcot in 1868 (Kumar et al., 2011). However, much of our early understanding of the disease, it's symptoms and pathogenesis, has come from the personal diary of Sir Augustus d'Este (1794-1848), which formed possibly the first case study of MS (Landtblom et al., 2010). In the last two decades our improved understanding of the disease, earlier diagnosis through technological advances and new disease modifying medications have assisted in modifying the course of MS, with the life expectancy of someone with the condition now near normal (Asano et al., 2009). MS is the most common cause of disability in young to middle aged adults in the developing world (Koch-Henrikson and Sorenson, 2010) and because of its progressive and unpredictable nature has a marked impact on the quality of life experienced for People with Multiple Sclerosis (PwMS) and their families (Benito-Leon et al., 2003; Mitchell et al., 2005). The high incidence rates and longitudinal nature of the condition has a substantial economic impact on both the health care system and PwMS and their families

(Naci et al., 2010). While treatments are now available to improve management of the condition, there is still no cure and the fundamental cause is still unknown, so symptom management and maintenance of function is crucial. In addition to drug treatments, therapeutic investigations such as exercise and rehabilitation are increasingly being recommended to better control the condition and assist PwMS to better self-manage their care (Jelinek and Hassed, 2009).

1.1.2 Exercise History

Historically, exercise has commonly been defined as "planned, structured and repetitive bodily movement" (Caspersen et al., 1985). However, this definition fails to recognise muscle activities of a static nature such as maintenance of posture and other activities of everyday living that expend energy. Therefore the following definition of exercise has been proposed by Winter and Fowler (2009) to encompass all types of activity, 'a potential disruption to homeostasis by muscle activity that is either exclusively, or in combination, concentric, eccentric or isometric'.

The beneficial effect of exercise on health is not a new concept and has been acknowledged since at least the time of Hippocrates, circa 400BC (Porter, 1999). Research into the use of exercise as a therapy for the treatment of MS in comparison is relatively new, with PwMS previously advised to avoid exercise to conserve energy and prevent increases in body temperature that could worsen symptoms (Uhthoffs syndrome) (Petajan and White, 1999).

Early research focused on rehabilitation-based physiotherapy treatments (Solari et al., 1999) and water-based exercise (Gehlsen et al., 1984); these studies

generally had small sample sizes and lacked the robust design of a randomised-control trial (RCT). An early review (Ponichtera-Mulcare, 1992), reported that exercise 'seems to improve cardio respiratory fitness and skeletal muscle function' in PwMS. The first RCT to explore the possible benefits of exercise for PwMS was conducted by Petajan et al. (1996) and reported increased aerobic capacity, strength and mobility, improved bowel and bladder function, decreased fatigue and depression, with no increase in the number of exacerbations. Research in the area has since gained momentum, with the Cochrane review on 'Exercise therapy for Multiple Sclerosis' (Rietburg, 2005) recognising nine RCT's of high technical quality, concluding that exercise is efficacious for improved outcomes in MS. However, it was recognised that further research of high technical quality is required. Further reviews by Heesen et al., (2006), Dalgas et al., (2008), Motl and Pilutti (2012), Latimer-Cheung et al., (2013) and Sá (2013) supported these findings and concluded that supervised exercise (aerobic and or strength) training is beneficial for people with mild-to-moderate MS. Moreover, a recent review on exercise safety for PwMS suggested that exercise causes no increase in relapse rate or the number of exercise-related adverse events reported in PwMS (Pilutti et al., 2014), indicating it is both a safe and effective treatment strategy for this patient group. Current evidence suggests that exercise does more than improve function and better manage symptoms in MS, but may slow down the disease process, with some evidence to indicate a possible disease modifying effect. This indicates that guidance for long-term prescription is required (Dalgas and Stenager, 2012).

Despite the suggested benefits of exercise, PwMS are often reported to be less physically active than the general population (Motl et al., 2008), with symptoms

being linked to physical activity levels and partially accounted for by low exercise self-efficacy (Motl et al., 2006). This low physical activity can lead to secondary complications such as obesity, cardiovascular disease and osteoporosis (Petajan and White, 1999; Heesen et al., 2006; Doring et al., 2012).

1.2 Brief overview of gaps in the literature

The current body of knowledge suggests that supervised one-to-one, facility-based exercise benefits people with mild to moderate disability from MS (Reitberg et al., 2011; Latimer-Cheung et al., 2013; Sá, 2013). However, long-term this approach is unlikely to be convenient or cost effective for both PwMS and healthcare systems. To date few trials are of sufficient quality (Döring et al., 2012) or have included: statistical power calculations to determine sample size (Sá, 2013), long-term follow-up (Döring et al., 2012; Latimer-Cheung et al., 2013) or cost effectiveness analysis (Reitberg et al., 2005). In addition, further information is required on optimal dose (Reitberg et al., 2005; Sá, 2013) of exercise required and the benefits of exercise for those with greater disability from MS (Döring et al., 2012; Latimer-Cheung et al., 2013).

In conclusion, there is a need for more high-quality RCT's that are statistically powered to show a clinically meaningful difference in outcome measures (Döring et al., 2012; Sá, 2013), with interventions that are MS-tailored and provide evidence to guide regular exercise prescription (Asano et al., 2009). There is also a need for more information on the exercise dose required to achieve optimal benefit (Reitberg et al., 2005; Sá, 2013) and a need to assess the efficacy of a pragmatic, tailored and cost-effective approach.

1.3 Purpose of Thesis

The purpose of this thesis was to determine if a pragmatically designed exercise intervention would lead to improvements in physical activity, function and health in a large population of PwMS, up to nine months of follow-up and whether this would be a cost-effective treatment strategy when compared with usual care. In addition, exercise preferences and dose-response relationships, between physical activity and health outcomes for people with mild and more severe disability will be explored.

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2.0 LITERATURE REVIEW

2.1 Background

2.1.1 Disease Epidemiology

Epidemiology is a study of the prevalence and distribution of a disease (Koutsouraki et al., 2010). MS is the most common cause of disability in young to middle aged adults in the developed world and has undergone extensive epidemiological research (Koch-Henrikson and Sorenson, 2010). The prevalence of MS across the globe is variable, with differences most commonly explained by exposure to environmental factors such as; sunlight, diet and infectious diseases, or ethnic differences in susceptibility (Milo and Kahana, 2010). European prevalence rates published by Puglialti et al., (2006) and Koutsouraki et al., (2010) suggested that 83 people per 100,000 have the disease, with an incidence rate of 4.3 cases per 100,000 per annum. Higher rates are reported in northern Europe and the female to male ratio is 2.0, with the highest prevalence rates occurring between the ages of 35 and 64 in both sexes and all countries. European figures show that there are nearly 700,000 people with MS across Europe (The European Multiple Sclerosis Platform, 2016), and in the UK approximately 100,000 people have the condition, with a lifetime risk from birth estimated at about 5/1000 in women and less than half this figure in men (Alonso et al., 2007). There has been an increased incidence in the condition over the last 10 years (Koch-Henrickson and Sorenson, 2010 and Koutsouraki et al., 2010), thought predominantly to be caused by increased incidence of relapsing remitting MS in women and an increased prevalence due to patients surviving with the condition for longer (Koch-Henrikson and Sorenson, 2010), with the women to men incidence rate reported to have increased from 1.4 in 1955 to 2.3 in 2000 (Aivaro and Hernàn, 2008).

2.1.2 Disease Aetiology, Risk Factors and Pathogenesis

Aetiology is the study of causes of disease (Kent, 2006). Extensive research has been conducted in an attempt to ascertain the exact causes of MS that would enable population based interventions to reduce the incidence of the condition. Despite these efforts, precise aetiology of the condition remains unknown. The majority of current data is based on epidemiological studies that have highlighted that both genetic and environmental factors are both associated with the incidence of MS (Milo and Kahana, 2010).

Genetic risk can be examined in terms of familial, gender and ethnic variations in disease prevalence. The familial risk of MS is low, with first degree relatives having an additional lifetime risk of 2.5%, above that of the general population irrespective of gender (Nielsen et al., 2005). Risk increases dependant on the amount of shared genetic information, with a first degree relative reported to have between 10 and 25 times greater risk than the general population (Willer et al., 2003), with monozygotic twins carrying the highest risk (Ramagopalan et al., 2010). This increase in risk is suggested to be genetic rather than environmental (Lindsey, 2005), with monozygotic twins having concordance rates of 30-40% compared to only 5% in dizygotic twins (Willer et al, 2003). In particular, certain patterns in the major histocompatibility complex genes, which control a large part of the immune system, such as HLA DR15 are reported to carry the highest genetic risk (Young, 2011). Ethnic origin is also thought to be important with some ethnic groups such as African Americans, Native Americans, Mexicans, Puerto Ricans and Japanese having much lower risk than Caucasians, with virtually no occurrence of the disease in people of Chinese and Filipino origin (Ramagopalan, 2010). It is well known that MS is more common in women than men, with the female to male ratio in Europe

reported to be 2:1 (Puglialti et al., 2006). It is suggested that this increased risk is related to female differences in physiology (Ramagopalan, 2010). In addition, the last 10 years have seen an increase in this ratio, with Canadian research indicating an increase to a ratio of almost 3:1 (Orton et al., 2006), leading to suggestions that changing environmental factors may influence women more than men (Koch-Henrikson and Sorenson, 2010).

Although research has reported that genetics play a part in the development of MS, environmental factors are thought to play an important role in determining overall risk. Viral infection, lifestyle, latitude and vitamin D exposure at present appear to have the strongest links (Ramagopalan et al., 2010). Epidemiological studies have often reported a link between different viruses and the occurrence of MS in particular Epstein-Barr virus (EBV) (Wingerchuk, 2011; Young, 2011; Ramagopalan et al., 2010 and Ascherio and Munger, 2007). The majority of PwMS (>99%) have been infected with EBV, compared with only around 94% of age-matched controls. Moreover, MS risk is about 10 times less in EBV negative individuals and 2-3 times greater in those who develop infection later in life (Ascherio and Munger, 2007). However, association based on epidemiological data, does not necessarily mean causation and further clarification is required as to the role of viral infection in the aetiology of MS (Brahic, 2010).

It is often reported in epidemiological studies that latitude (distance from the equator) plays an important role in MS risk, with incidence and prevalence increasing with increasing latitude in areas of temperate climate (-1 to 21 degrees Celsius) (Ramagopalan, et al. 2010; Ascherio and Munger, 2007). Duration and intensity of sunlight exposure has one of the strongest correlations with latitude and thus sunlight exposure and its links to vitamin D levels are the

most commonly sighted explanations for the latitudinal gradient in worldwide MS incidence rates (Young 2011; Ramagopalan etal., 2010; Ascherio and Munger, 2007). This link was noted in early studies with US war veterans which reported that average yearly sunlight exposure and winter solar radiation exposure at place of birth demonstrated a strong negative correlation with the incidence of MS (Acheson et al., 1960), indicating a protective effect of sunlight exposure. However, people living in the same area may share many other similar characteristics and thus, this explanation is not definitive. To overcome this bias further research has explored the risk amongst matched individuals, with different habitual levels of sunlight exposure, such as outdoor workers, reporting that working outdoors was significantly correlated with reduced MS mortality rates in areas of greater MS incidence (Freedman et al., 2000). For most people sunlight exposure is thought to be the main source of Vitamin D. However, dietary sources have also been reported to have an impact on the condition, with studies in Norway demonstrating decreased incidence rates in coastal communities that have greater fish consumption and hence Vitamin D in their diet, than inland farming communities (Kampman et al., 2008). It has even been hypothesised that Vitamin D may reduce the risk of EBV infection (Grant, 2010). This link has led to suggestions of possible supplementation at a population level in regions of high risk, in an attempt to reduce the risk of the condition in these areas (Ramagopalan et al., 2010; Ascherio and Mungar, 2007).

The increase in incidence of MS in recent decades, particularly in women (Sellner, et al 2011) has led to an increased focus on lifestyle related risk factors, such as smoking and obesity that have also increased in this population group over the same time period. Smoking has been consistently highlighted as

a potential modifiable risk factor for MS (Sellner et al., 2011; Romagopalan et al., 2010; Ascherio and Mungar 2007). Early studies have linked cigarette smoking to aggravation of symptoms after smoking (Perkin et al., 1975 and Emre et al., 1992), with further research linking smoking to both increased risk (Ascherio and Mungar 2007) and accelerated disease progression (Hernan et al., 2005). Mechanisms suggested for this increased risk include both the neurotoxic effect of tobacco smoking and its impact on respiratory infection rates which have been linked to increased relapse rates (Ascherio and Munger 2007). The obesity epidemic has also been linked to the increased incidence of MS in women (Sellner et al., 2011), with analysis of the Nurse's Health Study suggesting that obesity at the age of 18 (BMI > 30 kg/m2) more than doubles the risk of subsequent diagnosis of MS (Munger et al., 2009). The link between obesity and low levels of vitamin D are also currently being explored as potential mediating factors in increased MS risk (Sellner et al., 2011). Existing epidemiological data suggests that modifiable environmental factors such as vitamin D levels, smoking status and obesity may impact on MS risk; however the underlying mechanisms are still unclear.

Research has suggested that environmental factors in early years are particularly important in establishing risk in later life, as if an individual migrates after adolescence (aged 15) they are reported to maintain the risk of their country of origin, whereas before this age they adopt the risk of their new country (Koutsouraki et al., 2010). In addition, month of birth is also reported to be important, with babies born after a winter pregnancy reported to be at greater risk of developing MS in later life (Willer et al., 2005; Bayes et al., 2009; Salzer et al., 2010) This risk is hypothesised to be due to lack of sunlight exposure (vitamin D) during pregnancy, although further research is required to

further explore this link (Salzer et al., 2010). However, research now suggests that in North America and Europe latitudinal gradient may be of less importance, with studies needing to focus at a population level on western lifestyles that have changed (Koch-Henrickson and Sorenson, 2010).

Stress is often suspected to have a negative impact on the occurrence of MS relapses (Mohr et al., 2004), and has been proposed to provide an increased risk of onset of MS (Li et al., 2004). Although research to date cannot rule out the involvement of stress in the appearance of MS, there is no strong evidence to support this hypothesis (Riise et al., 2011).

The causal pathway for MS is complex and it appears that both a genetic susceptibility and exposure to various environmental factors, particularly in early life lead to the development of the abnormalities that lead to the incidence of MS. Further research is still required to enhance understanding of this pathway and thus advise public health strategies on the reduction of risk. However, research is still a long way from fully understanding the complex aetiology of MS and with incidence rates (women) still increasing, optimising strategies to better manage the condition are still of utmost importance.

2.1.3 Diagnosis, Symptoms and Prognosis

The diagnosis of MS is often complex and can take time to confirm as no one symptom is unique to MS, with other similar conditions such as neuromyelitis optica needing to be excluded before a definitive diagnosis can be made (Kelly et al., 2011). The UK National Institute for Health and Clinical Excellence (NICE) recommend that from the initial referral to a clinical diagnosis of MS should take no more than 12-weeks, six-weeks to see a consultant neurologist

and a further six-weeks for the diagnosis (NICE, 2014). MS usually presents with an acute occurrence of neurological symptoms. Diagnosis is clinical and is supported by a range of tests to look for evidence of MS, with the clinician looking for evidence of two or more lesions that have occurred at different times and on different parts of the Central Nervous System (CNS). Clinically the neurologist will be required to take a detailed medical history of symptoms and timing, alongside a neurological examination to help determine the cause of symptoms and what additional tests may be useful. This clinical assessment can suggest MS as a possible diagnosis, but this needs to be supported by additional tests which may include magnetic resonance imaging (MRI), analysis of cerebrospinal fluid (CSF) from lumbar puncture to provide evidence of chronic inflammation of the CNS and evoked potential assessments to indicate nerve damage (Tsang and MacDonell, 2011). The use of MRI has led to the currently accepted McDonald criteria for diagnosis (Polman et al 2011).

MS can be categorised into three main types; relapsing remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS). Despite this the effects can still vary greatly from person to person even in the same subcategory. The most common disease type at diagnosis is RRMS (85%), although after 10 years 40-45% of people with RRMS will have progressed to having SPMS (Tsang and MacDonell, 2011), whilst approximately 15% will experience PPMS from the outset (Wingerchuk, 2011).

People with RRMS will have periods of increased symptoms, called relapses or exacerbations that are suggestive of an acute inflammatory demyelinating episode in the CNS, lasting for at least 24-hours. This is followed by periods of remission, where the individual may recover completely, or retain a mild increase in symptoms (approximately 40% of people) (Tsang and MacDonell,

2011). Approximately 80% of people who start with RRMS will progress to having SPMS over there lifetime (Tsang and MacDonell, 2011), as this occurs the frequency of relapses decreases, whilst disability gradually gets worse. Those that have PPMS from the outset will experience a gradual increase in disability from the start.

The progression in disability experienced during the course of MS is monitored clinically to assess the extent of symptoms indicative of neurological impairment. The Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) is still the most commonly used assessment measure. Other tools used clinically include; Guy's Neurological Disability Scale (GNDS) (Sharrack and Hughes, 1999) and the MS Functional Composite (MSFC) (Cutter et al., 1999). There is considerable variation in the rate of disability progression in people with MS. However, it is reported that without treatment the median duration from diagnosis to requiring a cane is 20 years and to needing a wheelchair is 30 years (Brown and Kraft, 2005). The disability caused by MS also has a notable impact on employment, with two thirds of people with MS unemployed and 75% of these attributing it to their disability (Brown and Kraft, 2005).

The symptoms that an individual experiences will vary depending on the part of the CNS that has been damaged and can occur in many parts of the body. Fatigue is the most common symptom reported, affecting approximately 70% of PwMS (Brown and Kraft, 2005). Other symptoms include;

- Muscle symptoms such as poor balance, spasms, poor coordination, weakness, and tremors.
- Bowel and Bladder symptoms such as constipation, urgency and incontinence.

- Eye symptoms such as double vision, discomfort and vision loss.
- Sensation symptoms such as numbness, tingling and pain.
- Other brain and nerve symptoms such as cognitive difficulties, depression, dizziness and hearing loss.
- Other symptoms can include sexual problems, slurred speech and difficulty swallowing and chewing.

2.1.4 Current Management

There is no current cure for MS, treatment focuses on managing symptoms, reducing the number of relapses and maintaining the best possible quality of life. MS treatment has three main components; disease modifying therapy (DMT), relapse treatment and symptom management.

2.1.4.1 Disease Modifying Therapy

Current disease modifying medications work by reducing relapse rates, therefore they are only useful for people with RRMS and SPMS, no current disease modifying therapies are available for people with PPMS. It is currently recommended that patients with RRMS benefit from early intervention with disease modifying drugs to limit the effect of the disease on disability (Brown and Kraft, 2005). Commonly used approved drugs are outlined in Table 2.1.

Table 2.1. Common disease modifying drugs used for the treatment of people with RRMS and SPMS.

Medication	Brand Name	Mechanisms	Administration	Side Effects
Interferons Beta 1a Beta 1b	Avonex, Rebif Betaferon	Beta Interferon is a cytokine produced during viral infections and is suggested to work by healing the blood brain barrier, preventing cells of the immune system from entering the brain.	Regular (1-3x per week) self-injection	Flu like symptoms and skin reactions at injection sites
Glatiramer acetate	Copaxone	Synthetic peptides made of four amino acids, which are basic models of all proteins in the human body and is suggested to work by changing harmful inflammatory cells into the non-inflammatory healing cells of the immune system.	Daily injections	Injection site reactions
Natalizumab	Tysabri	Tysabri is a drug that blocks the passage of inflammatory cells of the immune system from entering the brain and the spinal cord.	Intravenous	Long-term effects unknown. Occasional infusion reactions. 3/3000 may suffer serious brain infection.
Fingolimod	Gilenya, Novartis	Causes lymphocytes to be retained in the lymph glands, dampening the immune response that causes nerve damage.	Daily tablet taken orally	Headaches, liver enzyme increase, flu, diarrhoea, back pain, cough, slowing heart rate, swelling in the eye.

Dimethyl fumerate	Tecfidera	Activates Nrf2, decreasing inflammation	Oral capsule taken twice a day	Flushing, Nausea, heartburn, abdominal pain and diarrhea.
Alemtuzimab	Lemtrada	Binds and kills white blood celles stopping them from entering the brain and attaching the myelin sheath	Two courses of infusion in hospital	Headaches, rash, nausea, fever and infections.

2.1.4.2 Relapse Treatment

The primary course of treatment during a relapse is a course of high dose corticosteroids, although there is no long-term evidence as to the effect of this treatment on prognosis (NICE, 2014).

2.1.4.3 Symptom Management

The goal of symptom management is to improve and maintain function and preserve quality of life (Crayton and Rossman, 2006). Symptoms are often interrelated and can be identified as primary, secondary or tertiary (Ben-Zacharia, 2011). Primary symptoms are those directly caused by demyelination and axonal loss, such as weakness and sensory loss; secondary symptoms are those occurring as a result of the primary symptoms, such as bladder infections; whilst tertiary symptoms are those related to the social and psychological consequences of the disease such as depression. MS symptoms are varied both between individuals and within the same individual across time, making the need for its management a complex process that needs to be individually tailored and multi-model using both pharmacological and non-pharmacological therapies to ensure the best patient care.

A variety of pharmacological therapies are used to treat the symptoms of MS such as, Baclofen and Tizanidine used for the treatment of spasticity and Gabapentine and Amitriptyline for the reduction of pain and tingling.

Non-pharmacological treatments include physiotherapy (balance, fatigue, walking), exercise (walking, balance, fatigue), cognitive behavioural therapy (depression, fatigue), functional electrical stimulation (foot drop), speech and language therapy (speech and swallowing problems) and occupational therapy (fatigue).

However, optimal treatment usually involves a combination of strategies, for example it is recommended that the management of fatigue may involve medication, exercise and the use of energy conservation techniques, whilst depression may be treated with a combination of psychotherapy and medication (Ben-Zacharia, 2011). The National institute of Clinical Excellence (NICE) is currently updating its guidelines for MS, with new recommendation for health care professionals including; 'considering supervised exercise programmes to give relief from fatigue and to increase mobility (NICE, 2014). This recommendation is supported by MS Charities (MS Society, MS Trust, 2015), providing information to PwMS about the benefits of exercise.

2.1.5 Economic Impact

The cost of MS places a meaningful burden on society, with the highest costs primarily associated with a decreased work capacity (Kobelt and Pugliatti, 2005). The introduction of DMT's over the last decade has also led to an increase in direct costs and more intensive management of PwMS (Rotstein et al., 2006). A review by Rotstein et al., (2006) concluded that, costs outside the

healthcare system surpass all other costs and that all costs increase as disease severity increase as measured by EDSS.

The economic impact of the condition is particularly significant as the majority of PwMS are of working age, costing the UK economy approximately £1.4 billion (McCrone et al, 2008). In a review of current literature, Adelman et al., (2013) reported that MS is the second most costly chronic condition after congestive heart failure. There is currently no cure for MS; however, disease modifying treatments exist that can reduce the number of relapses and slow disease progression (Brown and Kraft, 2005; Tsivgoulis et al., 2015). The cost effectiveness of these treatments in the current economic climate is being questioned, with some studies reporting DMT's to meet the current threshold and some reporting them to be well above the acceptable level (Manouchehrinia and Constantinescu, 2012; Phillips, 2004). Therefore if cost effective treatments (pharmacological or non-pharmacological) that help maintain function and reduce the number of relapse can be developed, this would be of notable importance in reducing the economic impact of MS on both the health care system and people with MS and their families.

2.1.6 Impact on Physical and Mental Health - Comorbidities

MS is a neurodegenerative disease and as such can lead to PwMS experiencing a wide variety of physical and mental symptoms that impact on health outcomes. Comorbidities are common, with an increased prevalence of many physical and mental health conditions when compared with the general population (Simpson et al., 2014).

Less than 20% of PwMS currently meet the recommended physical activity guidelines (Klaren et al., 2013), with more severe disability reported to be correlated with less physical activity (Kohn et al., 2014). Mobility and walking difficulties are common, with 40-50% of PwMS reported to have an EDSS score of 6.0 (requires a walking aid) within 15 years of disease onset (Myhr et al., 2001), rising to 60% by 20 years (Coenen et al., 2011). Comorbidities such as hyperlipidaemia, hypertension, arthritis, irritable bowel syndrome, osteoporosis and chronic lung disease are common in PwMS (Marrie and Hanwell, 2013). Simpson et al., (2014) conducted a large study into comorbidities in MS, looking at 39 different comorbidities in 3826 PwMS, compared with over one million controls. This research reported inconclusive evidence on the increased prevalence of cardiovascular disease in PwMS when compared with controls, sighting constipation as having the greatest increased prevalence, followed by visual impairment, chronic pain, migraine and epilepsy.

Mental health problems such as depression are reported to be one of the most significant predictors of patient quality of life in PwMS (Wynia et al., 2008; Göksel Karatepe et al., 2011). Depression is often cited as the most common mental health condition in PwMS, with a lifetime prevalence of 50%, followed by anxiety with a prevalence of 36% (Marrie and Hanwell, 2013; Simpson et al 2014). Moreover, problematic drug use has also been reported to be higher in PwMS (Simpson et al., 2014).

Physical inactivity is one of the leading causes of death from chronic diseases in the world (World Health Organisation, 2005), with physical activity having well documented benefits for improving mental and physical health in both the general population (Pedersen and Saltin, 2006), and PwMS (Giesser, 2015).

Therefore, exercise interventions that promote long-term improvements in exercise and physical activity participation are required in this population group.

2.1.7 Outcome Measures

Reliable and valid clinical outcome measures are essential when determining the effect of an intervention. The number of outcome measures used in the reporting of results from MS research is vast, leaving it difficult to compare studies and build a consistent evidence base. Recent reviews have stated the need for a more consistent approach in the reporting of outcome measures for both pharmacological and non-pharmacological clinical trials, if they are to provide robust data sets that can more successfully inform future clinical guidelines (Cohen et al., 2012; Noble et al., 2012; Paul et al., 2014). In addition outcome measures are required to cover a range of symptoms and disabilities (Cohen et al., 2012).

Historically, the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) has been used as the 'gold standard' measure for assessing the outcome of clinical trials (Brown and Kraft, 2005; Cohen et al., 2012; Uitdehaag, 2014, Bermel et al., 2014). The EDSS has long been popular with neurologists; however it is often reported to be of limited value as an outcome measure for clinical trials (Cohen et al., 2012; Potter et al., 2014; Uitdehaag, 2014; Bermel et al., 2014). The EDSS consists of a non-linear scale that is heavily reliant on walking ability (Bermel et al., 2014) and is not adequately responsive or sensitive to changes in disability from MS (Whitaker, 1995). A clinically meaningful change in EDSS is reported to have to be at least 2 levels (1 point) to be considered meaningful, this change can take time and most studies last less than a year, which will only

show subtle differences (Brown and Kraft, 2005). However, it is recommended that this popular measure should be upgraded rather than replaced as a measure of disability to ensure its continued acceptance (Cohen et al., 2012; Noble et al., 2012). More recently the Multiple Sclerosis Functional Composite Scale (MSFC) was developed by Cutter et al., (1999) as an alternative or secondary measure to the EDSS (Kurtzke, 1983) (Cohen et al., 2012). However, it is still unclear as to whether this is a suitable replacement (Cohen et al., 2012). Despite the limitations of the EDSS (Kurtzke, 1983) and MSFC (Cutter et al., 1999) there is an obvious link between scores for both assessments and patient relapse rates (Goldman, Motl and Rudick, 2010), with both of these measures frequently used in clinical studies and considered to be valid despite their methodological limitations (Meyer-Mooke et al., 2014). The research conducted as part of this thesis collected both of these measures to report impact on clinical outcomes.

Since the introduction of DMT's there has been much discussion over the most useful outcome measures for assessing their impact. This has led to numerous reviews being written looking at clinical outcomes (Amato and Portuccio, 2007; D'Souza et al., 2008), quality of life (Benito-Leon et al., 2003; Bandari et al., 2012), functional (Bethoux and Bennett, 2011; Learmonth et al., 2013) and cognitive measures (Scherer, 2007). However, studies have often focused on specific symptoms of MS and do not represent the wide range of disabilities experienced (Potter et al., 2013). Recent reviews have recommended that there is a need to investigate developing a comprehensive package of assessment measures to cover the wide range of symptoms and disability experienced in MS (Cohen et al, 2012, Noble et al., 2012).

The views outlined in clinical trials are mirrored in research on outcome measures for exercise and physical activity interventions, with reviews often highlighting poor quality outcome measures and the lack of consistency across trials as one of the major flaws preventing advanced statistics from being carried out (Rietberg et al., 2005; Asano et al 2009; Dalgas et al., 2008). At present research suggests that exercise is beneficial for PwMS, however the diversity of measures used makes it difficult to compare studies and build a consistent evidence base. Potter et al., (2014) reviewed 63 different outcome measures and looked at what measures were appropriate for different levels of disability from MS and in different practical settings, concluding that Patient Reported Outcomes (PROMS) such as the Multiple Sclerosis Quality of Life–54 (MSQoL-54) (Vickrey et al., 1995) and Multiple Sclerosis Impact Scale (MSIS-29) (Hobart et al., 2001) and Time based tests such as the MSFC (Cutter et al., 1999) (9-hole peg test, paced auditory serial addition test (PASAT) and the 25 foot walk), as being highly recommended for people with mild-to-moderate disability from MS. However, this review was aimed at determining what measures had clinical utility and were both reliable and valid for use in a practical setting. The review was not specifically aimed at clinical trials. Despite the recommendation by the Cochrane review in 2005 (Rietberg et al., 2005) for a consensus on outcome measure for exercise and MS trials, it wasn't until 2014 that a group of international experts met to discuss this issue. The resultant publication (Paul et al., 2014) recommended a range of measures covering MS Symptoms that are most likely to be influenced by exercise. These included PROMS, time based tests and objective measures to provide a triangulation of methods as recommended by Schäffler et al., (2013). The assessments suggested were all easy to deliver and were already in regular

use in exercise and MS research. The PROMS assessments recommended by Paul et al., (2014) included measures of Quality of life (MSIS-29 (Hobart et al., 2001) or MSQoL54 (Vickrey et al., 1993)) and fatigue (Modified Fatigue Impact Scale (MFIS) (Fisk et al., 1994ab) or Fatigue Severity Scale (FSS) (Krupp et al., 1989)), timed measures for exercise tolerance (6-Minute Walk Test (6MWT) (ATS Committee, 2002) and muscle function (Timed Up and Go (TUG) (Podsiadlo and Richardson, 1991) and objective measure of body measurement (Body Mass Index (BMI) or Waist Hip Ratio (WH)). It was also recommended that these be supported by qualitative measures and assessments of cost benefit where possible. The research reported in this thesis followed these guidelines utalising MSQoL54, MFIS, 6MWT, BMI and WH, supported by a cost effectiveness analysis and qualitaive report.

In summary, MS is a complex condition with varying degrees of disability and symptoms. There are a large number of tests that are used across the research literature, but the tests used to measure different symptoms are not consistent and often focus on individual symptoms. Moreover, measures such as the EDSS used to assess clinical disability are not sensitive or responsive enough, but at present we do not have a better alternative. A recommended battery of core tests now exists for exercise and MS Trials (Paul et al., 2014), however only time will tell if this is adopted by future research in the area, enabling provision of the data required to inform clinical guidelines such as those produced by the National Institute of Clinical Excellence (NICE). Moreover, with a condition as varied as MS it must not be forgotten that there can be large variability in results from day to day. Therefore, pre-test controls are of particular importance to ensure that participants arrive as fresh as possible and

that results represent a typical day. This would enhance the reliability of results and decrease the measurement error.

2.1.7.1 Physical Activity, Exercise Tolerance and Walking Mobility

Definitions

Exercise, physical activity, exercise tolerance and walking mobility are all important measures in the assessment of exercise and physical activity based interventions.

- Exercise can be defined as a potential disruption to homeostasis by muscle activity that is either exclusively, or in combination, concentric, eccentric, or isometric' (Winter and Fowler, 2009). Exercise is often planned and structured activity designed to improve fitness and health (Bouchard and Shephard, 1994).
- Physical activity is often referred to as exercise that includes activities of daily living such as household jobs, walking the dog manual labour etc (Bouchard and Shephard et al., 1994).
- Exercise tolerance can be defined as 'the point at which a participant in a physical activity attains the limit of acceptable effort before succumbing to weariness' (Stedman and Thomas, 2011).
- Walking Mobility can be defined as 'as the ability to independently and safely move oneself from one place to another' (MS Trust, 2011)

In addition, to the core outcome measures recommended by Paul et al., (2014), interventions that have the primary aim of increasing exercise and or physical activity would benefit from more comprehensive measurement of this variable,

as it is important to determine not only has the intervention had an impact on MS, but also have PwMS become more active and fitter because of it. Within this domain it is important to not only examine physical activity, but also whether fitness and walking mobility have improved. Walking mobility is particularly important for PwMS as it is reported to be one of the 'most visible manifestations' of the condition (Bethoux and Bennett, 2011) and has a further impact on Quality of Life (LaRocca, 2011).

A triangulation of methods as recommended by Schäfler et al., (2013) is suggested, to ensure that a clear picture of the impact of exercise interventions can be determined. Measures should include PROMS such as the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003) or the Godin Leisure-time exercise Questionnaire (GLTEQ) (Godin and Shephard, 1985), alongside objective measures such as accelerometry and timed functional tests such as the 6MWT (ATS Committee, 2002) as recommended by Paul et al., (2014) to assess exercise tolerance and walking endurance and the 25 foot walk as recommended by Potter et al., (2013) to assess walking ability and speed.

Patient reported outcome measures (PROMS)

Probably the most obvious assessment to measure physical activity for PwMS is the Physical Activity and Disability Survey (PADS-R), which is specifically designed to measure physical activity in people with chronic neurological conditions (Kayes et al., 2009a). However, this test as yet has had limited use in the MS literature and does not provide results that are comparable with the general population. Currently the two primary measures utilised for measuring physical activity through self-report, are the GLTEQ and the IPAQ (Craig et al.,

2003). Both of these measures are quick and easy to complete and there is strong evidence to suggest that they are both valid and reliable for assessing physical activity in PwMS (Motl et al., 2013; Weikert et al., 2010; Snook, Motl and Gliottoni, 2009; Gosney et al., 2007; Motl et al., 2006a). The GLTEQ in particular has shown excellent correlations with physical activity (Gosney et al., 2007) and good test re-test reliability with PwMS (Motl et al., 2013). In addition to this some studies have used the 7-day PAR, which has shown excellent correlations with physical activity (Motl et al., 2006a). However, this is administered using an interview, which makes it more time consuming for both the researcher and the study participant. The GLTEQ and the IPAQ do not correlate well with walking mobility and should only be used as a physical activity outcome measure (Snook, Motl and Gliottoni, 2009; Motl et al., 2006a). In both the feasibility study and main trial reported in this thesis, home exercise compliance was also monitored via self-report exercise diaries that were reviewed weekly by the practitioner. This type of approach is simple and easy to administer and enables the client to benefit from self-monitoring of their exercise programme. However, it is noted that this method could lead to miss-reporting, with more objective measures such as video monitoring or accelerometry potentially providing more robust data.

Accelerometry

Less than 20% of PwMS are reported to meet the current physical activity recommendations in the UK (Klaren et al 2013), with 41% of PwMS reporting to have difficulty with walking (LaRocca, 2011). There is therefore a need for a tool to better understand walking mobility, exercise behaviour, and the ability to determine time spent participating in physical activity of at least a moderate

intensity (Sandroff et al 2014). Accelerometry provides a possible solution enabling a more objective measurement of these variables to take place, in a community setting and with minimum participant burden (Motl et al., 2012). Moreover, accelerometry has the potential to measure walking mobility, which is of particular significance to PwMS, due to its ability to offer insight into both disability and disease progression (Pearson et al., 2004).

Research regarding the use of accelerometry as both a measure of physical activity and walking mobility is variable, with the use of accelerometry for measurement of physical activity coming under scrutiny. Kayes et al., (2009b), suggested that caution should be taken when using with PwMS, due to poor test re-test reliability at low levels of activity, whilst several researchers have reported it to correlate better with walking mobility than physical activity (Hale, Pal and Becker, 2008; Weikert et al., 2012). However, other researchers have suggested that it can be used to measure both variables (Snook, Motl and Gliottoni, 2009; Weikert et al., 2010). Its usefulness as a reliable and valid measure of walking mobility and exercise behaviour has gained momentum over recent years with many studies supporting its use (Hale, Pal and Becker, 2008: Snook, Motl and Gliottoni, 2009; Weikert et al., 2010; Weikert et al., 2012; Motl et al., 2013). However, it has been indicated that there is a significant difference in results between different types of accelerometer, which may limit comparisons between studies (Coote and Dwyer, 2012). The majority of studies have small samples sizes and have only used a single type of accelerometer, so may not be able to be generalised across the MS population and when using different types of device. Recently Klaren et al., (2013) and Sandroff et al., (2014), have reported recommended activity count cut off points to take into account the increased energy cost of walking in this population group. The

study by Klaren et al., (2013) used treadmill based walking, whilst the more recent research by Sandroff et al., (2014) had the added advantage of measuring in the real world and also developing different activity count cut points for people with different levels of disability from MS. This offers the potential to provide a better correlation between accelerometers and physical activity measures and to provide a good indication of whether PwMS are meeting current physical activity guidelines.

Walking assessments

The most commonly used timed walking assessments for MS are the shorter 25ft walk or 10 metre walk (Cutter et al., 1999) and the longer two-minute or six-minute walk test (Butland et al., 1992). Whilst the most widely used self-report test is the Multiple Sclerosis Walking Test-12 (MSWT-12) (Hobart et al., 2003). The longer 2MWT and 6MWT have been reported to have better test retest reliability Feys et al., (2014) and perform better when detecting improvements after physical rehabilitation (Baert et al,, (2014). With the 6MWT recommended in reviews on outcome measures by Paul et al., (2014) and Potter et al., (2013), alongside the 25ft walking test and the MSWT-12, which were also recommended by Potter et al., (2013). However, the six-minute test is time consuming and tiring for the participant, current research indicates that the two-minute test correlates well with the six-minute test Gijbels, Eijnde and Feys (2011), and has recently been shown to responsive to detecting improvements Baert et al., (2014). This indicates that the two-minute test may be a valuable alternative to the more commonly used six-minute assessment in future MS and exercise research trials.

VO_{2max} is often considered to be the best method of assessing endurance capacity in the general population (Stickland et al., 2012) and has been suggested to be feasible for use in PwMS, with a ten percent day to day variance (Langeskov-Christensena, 2014). However, the exertion required for this test can be off-putting, particularly for PwMS, where fatigue is reported as one of the most common symptoms (Zajicek, 2010). Exercise interventions in this population have therefore focused on walking based assessments (Butland et al., 1992) or sub-maximal protocols on cycle ergometers usually starting with the bike unloaded and proceeding at increments of 10-15 watts per minute until volitional termination of the test (Sutherland and Anderson, 2001; and Motl and Fernhall, 2012) in order to reduce the level of participant risk and burden experienced from the research assessment process.

2.1.7.2 Fatigue

Fatigue is poorly defined in MS, yet is often reported as one of the most common and disabling symptoms (Flachenecker et al., 2002). Some reports show that 80-90% of PwMS experience fatigue (Krupp et al., 2006; Weiland et al; 2015), with approximately two thirds of PwMS describing it as their most disabling symptom (Branas et al., 2000). Exercise interventions suggest that improved fitness may positively impact fatigue (Carter et al., 2014), with rehabilitation interventions such as exercise and education reported to have a more significant impact than pharmacological treatments (Asano and Finlayson, 2014). A variety of PROMS are used to assess the impact of exercise interventions on fatigue in PwMS. These include the Fatigue Severity Scale

(Krupp et al., 1989); the MS-Specific FSS (MS-FS) (Krupp et al., 1995); the Fatigue Impact Scale (FIS) (Fisk et al., 1994ab) and the Modified Fatigue Impact Scale (MFIS) (MS Council, 1998). The most frequently used fatigue outcome measure in exercise interventions is the MFSS (Asano and Finlayson, 2014). MS fatigue is generally considered to be a multidimensional construct (Kesselring and Beer, 2005), with some fatigue scales measuring different aspects of fatigue which are poorly correlated (Flaschenecker et al., 2002) and others providing a single (unidimensional) fatigue score (Elbers et al., 2012). There is a need for a multidimensional scale to be developed that covers all dimensions of MS fatigue if we are to provide a robust assessment of the impact of research trials in the future (Flachenecker et al., 2002). It is recommended that based on current available measures, a multidimensional assessment tool such as the MFIS is used to determine the impact of exercise interventions on fatigue (Paul et al., 2014; Potter et al., 2014). However, it is suggested that should only a unidimensional measure be required then the FSS is sufficient (Paul et al., 2014), with well-defined cut points available for sub-group analysis (Roelcke et al., 1997; Bakshi et al., 2000).

2.2 Theoretical Underpinning

Current research suggests that there is an increased interest in using behavioural interventions to improve long-term physical activity in PwMS (Ellis and Motl 2013; Motl, 2014). Behavioural interventions including theories such as the Social Cognitive Theory (SCT) (Bandura, 1986) have been reported to have a positive impact on physical activity behaviour in PwMS (Motl et al., 2011; Dlugonski et al., 2012; Pilutti et al., 2014). It therefore makes sense that a combined approach using an exercise intervention alongside a behavioural

intervention that is theoretically underpinned may have a greater long-term impact on physical activity behaviour (Coote et al., 2014).

2.2.1 Psychological approach

Pharmacological agents are only moderately effective in managing MS symptoms. Physical activity is considered to be an important self-management tool for PwMS, with increased physical activity linked to improved health outcomes such as quality of life and fatigue (Reitberg et al., 2005; Heesen et al., 2006; Dalgas et al., 2008; Döring et al., 2012; Latimer-Cheung et al., 2013; Sá, 2013). Despite this PwMS are less physically active than the general population (Motl, McAuley and Snook, 2005), with symptoms reported to be linked to physical inactivity and partially explained by low exercise self-efficacy (Motl et al., 2006b). It is reasonable to hypothesise that this could be linked to MS symptoms and their ability to impact on physical ability, self-efficacy and intentions to engage in physical activity (Plow, Finlayson and Cho, 2011). It is therefore important to consider strategies to enhance self-efficacy and intentions in the design of any pragmatic exercise intervention aimed at promoting improved long-term autonomous physical activity behaviour for PwMS.

There are many barriers to changing complex health behaviours such as physical activity (Sallis et al., 2006), with early exercise and physical activity interventions for PwMS (Petajan et al., 1996; Sutherland and Anderson, 2001) predominantly focusing on the physiological content of the intervention. However, a psychology based approach that is theoretical underpinned is required to promote long-term behaviour change and enable interventions to be

replicated. Contemporarily, the most commonly used theories in exercise and physical activity literature to date have come from pre-existing approaches to behaviour change developed in the social psychology arena (Buchan et al., 2012). These include theories such as Social Cognitive Theory (SCT) (Bandura, 1986), The Theory of Planned Behaviour (TPB) (Ajzen, 1991), The Self-Determination Theory (SDT) (Deci and Ryan, 2002), and The Transtheoretical Model (TTM) (Prochaska and Diclemente, 1983) (Nigg et al., 2008). A practical yet tailored approach to exercise intervention design is required that follows a model with structure that enables it to be repeated if successful. One such approach often used to inform physical activity behaviour change is the Transtheoretical model (TTM) (Prochaska and DiClemente, 1983).

2.2.1.1 The Transtheoretical Model

The TTM (Prochaska & DiClemente, 1983; Prochaska, DiClemente, & Norcross, 1992; Prochaska & Velicer, 1997) focuses on an individual's ability to make volitional decisions about their behaviour and utilises existing theories to underpin its approach. Subsequently, it's a comprehensive theory of change comprising of 4 key constructs; stages of change (SOC), decisional balance, self-efficacy and processes of change (Prochaska and Diclemente, 1983). The model seeks to explain how individuals make positive changes to their behaviour and features the SOC as one of its core constructs (Figure 2.1).

The stages of change offer a temporal dimension looking at change as a process containing five (Oka, 2000) or six (Horiuchi et al., 2012) stages rather than a single event, with individuals going through a series of set processes of change to move through the stages.

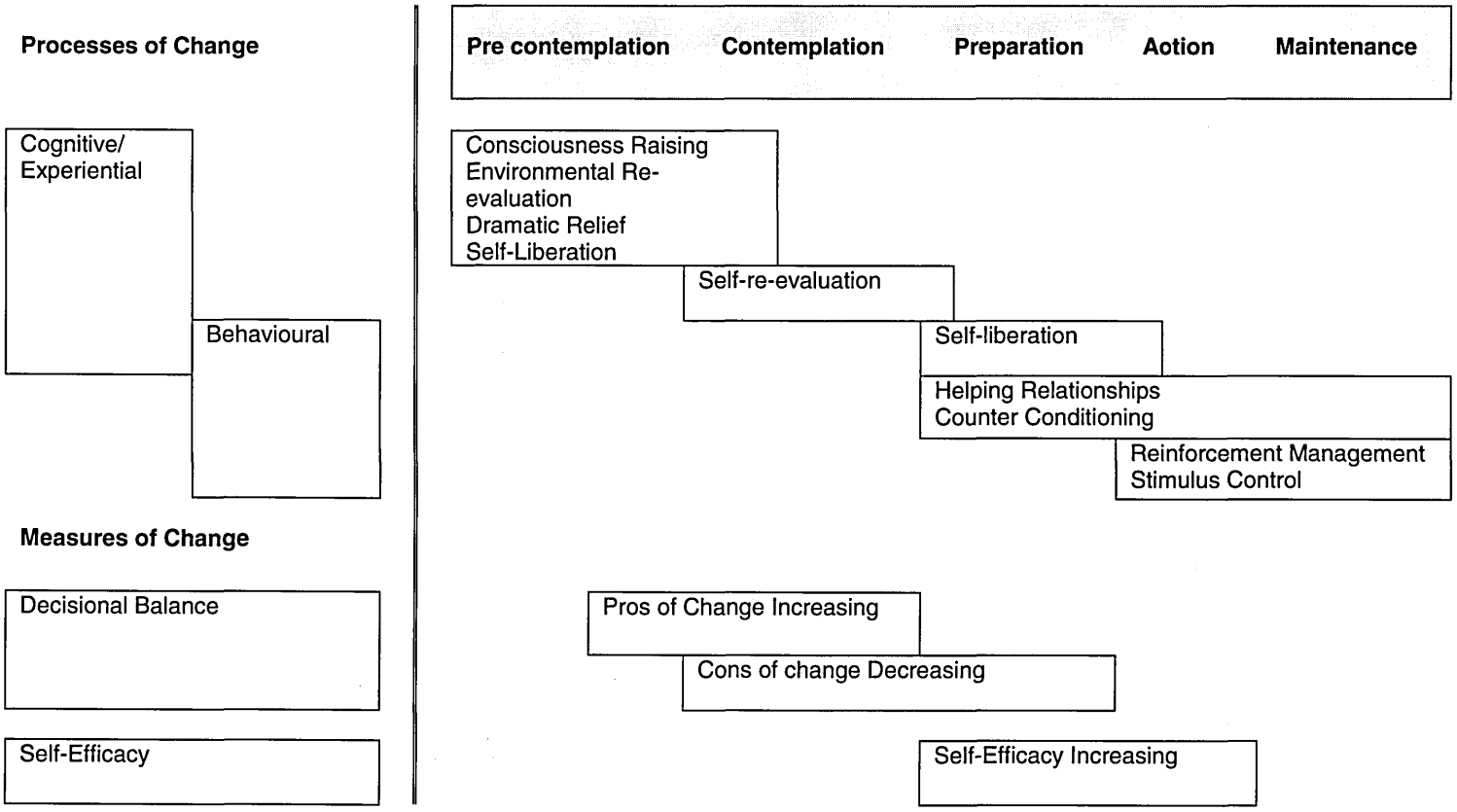

Figure 2.1. Overview of Transtheoretical model and its key constructs (stages of change, processes of change, decisional balance and self-efficacy). Adapted from http://www.prochange.com/transtheoretical-model-of-behavior-change

Table 2.2 outlines the five most common stages of change. However, recent research in adults with physical disabilities validated a four stage model, combining the later fourth and fifth stages into a single action stage (Kosma and Ellis, 2010).

The TTM also includes measures sensitive to progression through the stages such as decisional balance (weighing up the advantages and disadvantages to change) and self-efficacy. In addition the ten processes of change are divided into two main sub-groups, cognitive and behavioural, which help to explain how changes occur. Interventions designed using the principles of the TTM take into account the varying needs of individuals, tailoring the intervention to their stage of change and accounting for both forward and backward movement between the stages (Khatta, 2008).

Table 2.2. Description of stages of change as linked to the TTM (Horiuchi et al., 2012).

Stages Of Change	**Description**
Pre-contemplation	No. I have no intention to begin in the next six months
Contemplation	No. But I intend to begin in the next six months
Preparation	No. But I exercise irregularly
Action	Yes. I have been practicing for at least six months
Maintenance	Yes. I have been practicing for at least six months
Termination	Yes. I have been practicing for more than five years (termination stage)

This approach was originally used in helping to prevent negative health behaviours such as smoking (Prochaska and DiClemente, 1983). However, over the last decade it has been used to promote positive health behaviours such as physical activity (Fahrenwald et al., 2004).

A recent Cochrane library systematic review (2014) reported that current research utilising the TTM in physical activity and dietary interventions is reported to be of low quality, providing limited evidence for its use in physical activity interventions (Mastellos et al., 2014). This highlights the need for more 'well-designed RCTs that apply the principles of the TTM SOC appropriately to produce conclusive evidence about the effect of TTM SOC on lifestyle interventions' (Mastellos et al., 2014).

The complex and varied symptoms experienced by PwMS are reported to interfere with their intention to be physical activity (Plow, Resnik and Allen, 2009), with constructs of the TTM such as self-efficacy reported to be mediators of intention to engage in physical activity in this population group (Motl et al., 2006c). Research into the TTM and SOC with PwMS has suggested that this approach is worth exploring in exercise interventions with PwMS (Plow et al., 2011) and has the potential for motivating PwMS to exercise (Levy et al., 2009). Moreover, longitudinal changes in the TTM constructs have been linked to changes in physical activity behaviour in PwMS, suggesting that long-term maintenance of autonomous exercise requires cognitive change first, before behavioural strategies are introduced (Kosma, 2012). It would therefore seem valid to utilise this approach in future exercise interventions for PwMS.

2.3 Trial Design

2.3.1 Randomised-Control Trials (RCT)

The National Institute of Clinical Excellence has defined an RCT as; 'A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all'.

RCTs are often reported to be the most robust method for assessing the effect of a treatment and its cost-effectiveness (Sibbald, 1998). RCTs also include double blinding where appropriate and intention to treat analysis (i.e. analyzed in the group that they were originally assigned regardless of adherence to the intervention) (Sibbald, 1998). The most commonly cited limitation of this method are with ethical and practical concerns regarding the withholding of a treatment thought to be beneficial to the trials participants (Edwards et al., 1998).

2.3.2 Mixed Methods Approach

Outcomes based research has typically utilised quantitative approaches to determine the effectiveness of an intervention. This method does not enable the researcher to fully understand many aspects of health care research such as patient perceptions that are crucial in determining the effectiveness of a pragmatic intervention (Curry et al., 2009). Therefore for pragmatically designed trials a mixed methods approach is recommended (Creswell et al., 2011). Mixed methods research can be defined as research that; 'focuses on questions that call for real-life contextual understandings, multi-level perspectives, and cultural

influences; employ rigorous quantitative research assessing magnitude and frequency of constructs and rigorous qualitative research exploring the meaning and understanding of constructs; utilize multiple methods (e.g., intervention trials and in-depth interviews); intentionally integrate or combine these methods to draw on the strengths of each; and frame the investigation within philosophical and theoretical positions' (Creswell et al., 2011). The use of a mixed methods approach is becoming increasingly important when designing pragmatic research trials, as using this approach enables us to gain a much broader understanding of real-world interventions and the context in which they work (Albright et al, 2013).

2.4 Barriers to participation

Current knowledge suggests that people with MS benefit from taking part in regular and appropriate physical activity, despite this PwMS still engage in less physical activity than the general population and even those with other chronic illnesses (Motl et al., 2005). There are currently only a handful of papers exploring both, what factors help people with MS to take part in physical activity and what creates barriers to participation (Kayes et al., 2011a). Understanding this is crucial if we are to design interventions that help to promote autonomous long-term participation. The complexity of MS in terms of symptoms and its unpredictable nature suggest that it may have a unique set of barriers.

The majority of research has explored the facilitators and barriers to physical activity participation utilising questionnaire based studies to determine which variables correlate best with amount of physical activity in PwMS (Motl et al., 2006c; Motl et al., 2009; Vanner et al., 2008; Kayes et al., 2011a). Numerous

studies to date have reported the importance of exercise self-efficacy in promoting participation (Motl et al., 2006b; McAuley et al., 2007; Snook and Motl, 2008; Motl et al., 2009; Stroud, Minahan, Sabapathy, 2009), with people with greater self-efficacy reporting more enjoyment and greater adherence to exercise interventions (McAuley et al., 2007). In addition, the importance of MS symptoms and there management in terms of promoting exercise self-efficacy is also noted (Motl et al., 2006b; Snook and Motl, 2008), indicating that monitoring symptoms during exercise and maintaining a flexible approach to exercise prescription may help to promote self-efficacy and exercise adherence. Moreover, the importance of designing programmes to limit fatigue and the provision of education around the benefits of exercise on this variable may enhance exercise self-efficacy (Stroud et al., 2009). More recently Kayes et al., (2011a) explored the facilitators and barriers to participation in a large group (n=282) of individuals with MS, reporting that the most frequently cited barrier was being 'too tired'. In addition this study supported the notion that physical activity participation is significantly correlated with both self-efficacy and the number of perceived barriers to physical activity participation. Importantly the study highlighted potentially modifiable factors such as self-efficacy, mental fatigue and perceived barriers to participation that could be used to improve the design of future exercise interventions.

Qualitative studies are capable of providing a more personal and detailed insight into exercise participation. However, only a few studies have used this approach to explore the barriers and facilitators to physical activity participation for PwMS (Kayes et al., 2011b; Brown, Kitchen and Nicoll, 2012; Learmouth et al., 2013). Kayes et al. (2011b) highlighted that the decision to take part in physical activity is complex amongst PwMS and there is a need for a highly

individual approach to barrier management taking into account personal beliefs. Studies by Brown, Kitchen and Nicoll (2012) and Learmonth et al., (2013) explored barriers and facilitators to participation in specific types of group based exercise programme (aqua fitness and leisure centre). Both studies sited that knowledge of MS amongst staff and lack of opportunities as key barriers to participation. Moreover, knowledge on benefits, inadequate transport, lack of one-to-one support, participation fears and accessibility were also highlighted as potential barriers to aqua fitness (Brown, Kitchen and Nicoll, 2012). Exercising with healthy people, the perceived attitudes of others and MS symptoms where additionally reported as barriers to exercising in a leisure facility (Learmouth et al., 2013). However, both groups were small and covered a limited range of abilities and activity types, with a potentially biased sample of participants who were already engaging in an activity based intervention. More detailed research in this area is needed if we are to gain a full understanding of the unique set of variables that may both facilitate and provide barriers to physical activity participation in PwMS.

2.5 Scoping review: exercise and physical activity interventions for the treatment of Multiple Sclerosis

The purpose of this scoping review was to map the existing literature on exercise and MS in order to provide a general update on what is currently understood about exercise and MS and provide reference for the discussion and conclusion in this thesis. A scoping review was chosen as a recognised method of summarising research findings and identifying gaps in existing literature (Levac et al., 2010). This scoping review followed the framework recommended by Arksey and O'Malley (2005) (figure 2.2).

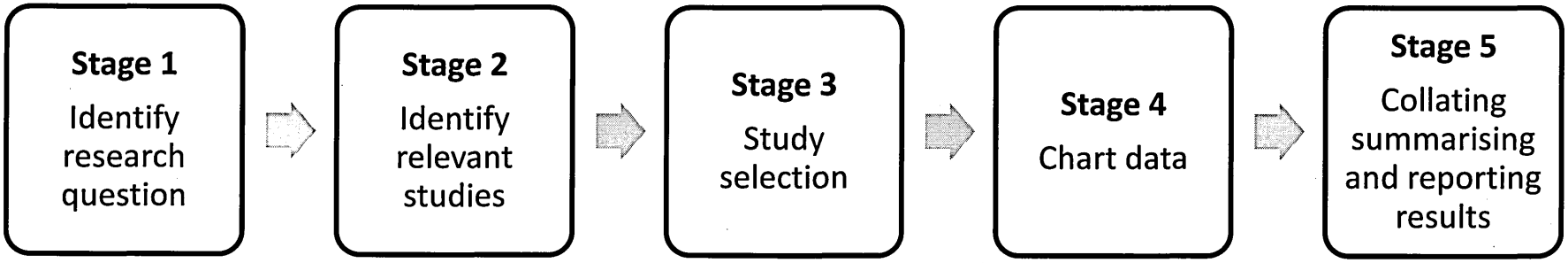

Figure 2.2. Scoping review framework (Arksey and O'Malley, 2005)

It is recognised that this type of review generally fails to evaluate the quality of the literature or provide any synthesis regarding intervention effectiveness. Due to the volume of information available, it was decided to include an element of quality review in stage 2 (only including RCT's) in order to select the most pertinent literature and some synthesis within the narrative in stage 5.

2.5.1 Research question for scoping review

What is currently understood about the impact of different exercise and physical activity intervention on functional and health outcomes for PwMS?

2.5.2 Scoping review methods

Search Strategy

Literature searches were conducted using Scopus and PubMed from 1996 to August 2014. Only articles printed from 1996 onwards were included as several previous systematic reviews (Rietberg et al., 2005; Asano et al., 2009; Latimer-Cheung et al., 2013) have reported Petajan, (1996) to be the first published MS and exercise RCT. Research published from this thesis was excluded from this review.

Inclusion Criteria

The review included studies containing PwMS of any age, gender or disease type that were not experiencing a relapse or exacerbation. Studies must have been published in an English language peer review journal and be an RCT where exercise training/therapy was the main treatment. Where exercise training/therapy is defined as "a series of movements with the aim of training or

developing the body by a routine practice or as a physical training to promote good physical health" (Webster's New World Dictionary, 1982). Randomised controlled trials, with both wait list control and cross-over design were included as well as the standard RCT.

Exclusion Criteria

Reviews, editorials or notes were excluded and used for cross reference only. Interventions that were only behavioural, balance rehabilitation, qualitative or utilised vibration therapy were also excluded. Non-English languages were also excluded due to no translation service available.

Search Criteria:

A list of keywords was generated based on keywords and search terms used in existing exercise and physical activity literature and reviews. The search criteria used was; ("exercise" AND "multiple sclerosis") OR ("exercise therapy" AND "multiple sclerosis") OR ("physical activity" AND "multiple sclerosis") OR ("physical therapy" AND "multiple sclerosis") OR ("training" AND "multiple sclerosis") OR ("rehabilitation" AND "multiple sclerosis").

Date of search 28/08/2014

2.5.3 Process

The search yielded 1876 papers (SCOPUS), 1956 (PubMed). The titles and abstracts were then screened to exclude non RCT's where exercise therapy/training was not the main treatment. The use of the Physiotherapy Evidence Database Scale (PEDro Scale) (Verhagen et al., 1998) was

considered as a method of rating methodological quality of the RCT's and eliminating further low quality studies from the search. However, it was decided that based on the low quality of many studies and to remain as inclusive as possible this search would be based on the primary PEDro criteria of an RCT, without looking further at the additional sub criteria.

75 (SCOPUS) and 52 (PubMed) articles were retained. Duplicate articles were removed and the remaining 83 articles were obtained and read. Following this 34 papers were deemed relevant for inclusion in the review. It is recognised that the ideal scenario would have been to have this process carried out by two independent reviewers; however this was outside the scope of this thesis. To minimise the impact of this further checking was carried out by cross checking the references from five previous MS and exercise reviews (Rietberg et al., 2005; Asano et al., 2009; Döring et al., 2012; Kjølhede, Vissing and Dalgas, 2012; Sá, 2013 and Latimer-Cheung et al., 2013) to determine if any further relevant papers needed to be included. This process revealed a further, eight papers that needed to be included. In total 42 papers (38 studies) were retained in the final review. Figure 2.3.outlines a flow chart of the review process.

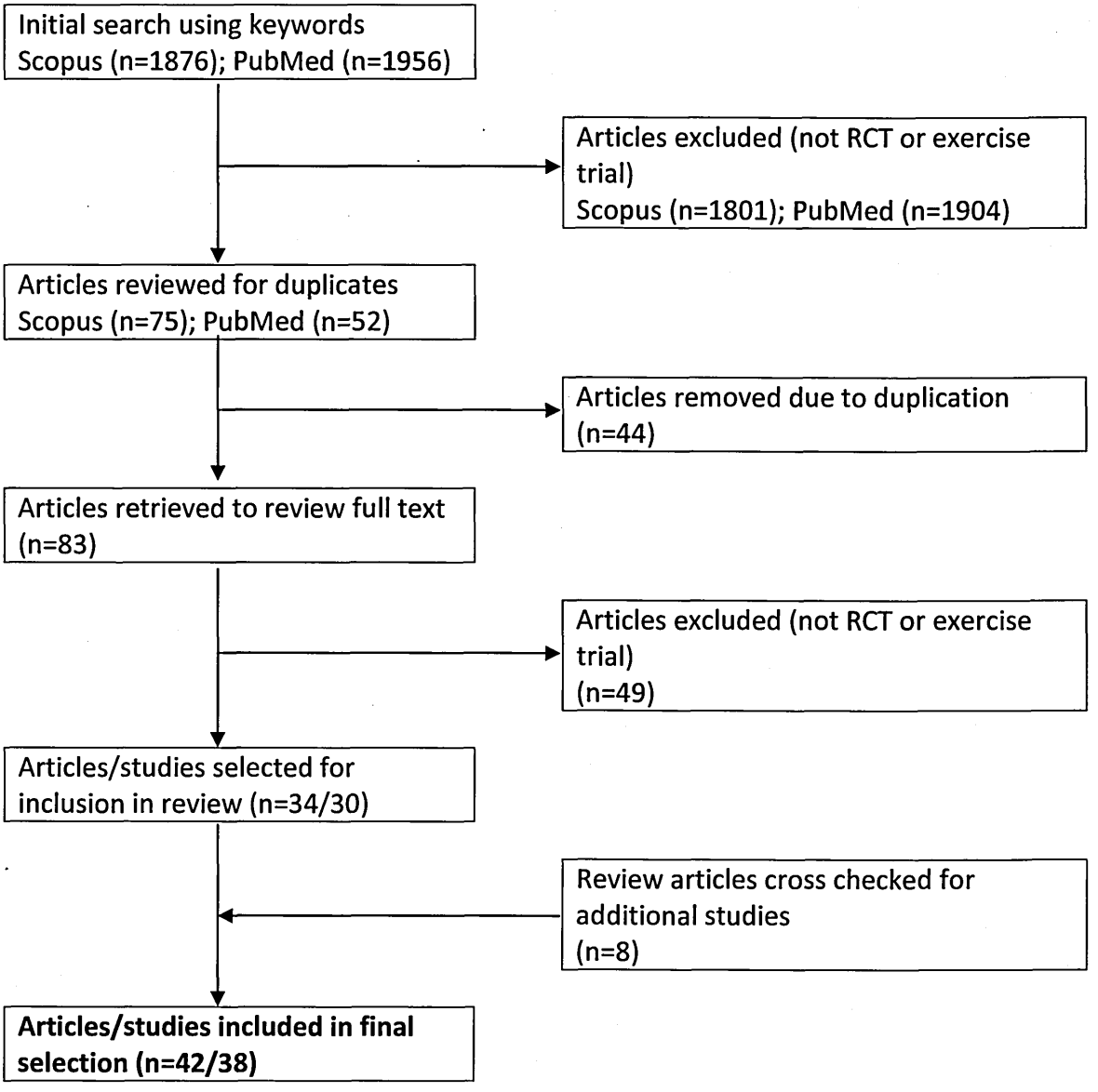

Figure 2.3. Flow chart outlining the review process.

Table 2.3a. Aerobic exercise interventions for PwMS (Articles: n=11, Studies: n=11).

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Complianoe
Effects of exercise on fitness and cognition in progressive MS: a randomized, controlled pilot trial								
Briken et al., 2014 Germany	42 C: 10 (4M, 6F) Ex (arm): 10 (5M, 5F) Ex (row): 11 (4M, 7F) Ex (bike): 11 (5M, 6F)	C: 50.4 (7.6) Ex (arm): 49.1 (8.5 Ex (row): 50.9 (9.2) Ex(bike): 48.8 (6.8)	C: 4.9 (0.9) AE: 5.2 (0.9) R: 4.7 (0.8) BE: 5.0 (0.8)	Design	Randomised to 3 exercise groups and wait list control	Aerobic (cycle test, for max power and AT), 6MWT, IDS-SR, MFIS	Increased aerobic fitness and walking ability Decrease in depressive symptoms and fatigue	Retention: 89.4%
				Groups	Arm ergometry, rowing or bicycle ergometry, plus wait list control			
				Frequency/ Duration	2-3 x week (15-45 minutes), 8-10 weeks, (aim 20 sessions)			
				Intensity	120-130% of anaerobic threshold			
				Assessments	Baseline, 10 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Endurance training is feasible in severely disabled patients with progressive multiple sclerosis								
Skjerbæk et al., 2014 Denmark	11(3M, 8F) Ex: 6 UC: 5	Ex: 62.0 (5.9) C: 55.2 (8.2)	6.0 – 8.0	Design	RCT feasibility	VO_2 Peak, MDI, MSIS-29, FSMC, 9-hole peg test, hand-grip strength, 6 minutes wheelchair test	Increased VO_2 peak	Retention: 90.9%
				Groups	Exercise (inpatient rehabilitation plus aerobic upper body training), usual care (inpatient rehabilitation)			
				Frequency/ Duration	4 weeks in patient rehabilitation, plus 10 exercise sessions			
				Intensity	5 minute warm up, 6 x 3 minute intervals at 65-75% VO_2 peak			
				Assessments	Baseline 4 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in ms patients								
Ahmadi et al., 2013 Iran	31 (31F)	35.2 ± 9.0	2.2 ± 1.2	Design	Randomised with wait list control	BBS, FSS, BDI, BAI, 10MWT, 6MWT	Improvements in BBS, 6MWT, FFS, BDI and BAI (both groups). 10MWT treadmill only	Retention: 100%
				Groups	3 groups: treadmill training, yoga and wait list control			
				Frequency/ Duration	3 x week (treadmill: 30 minutes, yoga: 60-70 minutes), for 8 weeks			
				Intensity	Treadmill: 40-75% APHRM			
				Assessments	Baseline, 8 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Effect of treadmill training on fatigue in multiple sclerosis: a pilot study								
Gervasoni et al., 2013 Italy	30 (18M, 12F)	47.6 ± 9.2	5.25 (3.0-6.5)	Design	Randomised control trial	BBS, DGI, FSS, PANAS,HR, RPE	Improved perceived exertion, and exercise HR	Retention: 100%
				Groups	2 groups: treadmill training and attention control			
				Frequency/ Duration	12 sessions over a 2 week period treadmill: 30 minutes conventional therapy, plus 15 minute treadmill, control: 45 minutes conventional therapy			
				Intensity	11-12 on the Borg RPE scale			
				Assessments	Baseline, immediately after first session and the day after the intervention.			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Endurance exercise improves walking distance in MS patients with fatigue								
Dettmers et al., 2009 Germany	31	Ex: 45.8 (7.9) C: 39.7 (9.1)	Ex: 2.6 (1.2), Control: 2.8 (0.7)	Design	RCT	Maximal walking distance, MFIS, FSMC, BDI, HAQUAMS	Improved walking distance in exercise group	Retention: 96.8%
				Groups	Endurance exercise (interval) or control (stretching, balance and coordination)			
				Frequency/ Duration	3xweek (45 minutes) for 3 weeks			
				Intensity	Not reported			
				Assessments	Baseline, 3-weeks			
				Behaviour Change	Theoretical basis for behaviour change absent, no techniques described			
Effects of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomised crossover controlled trial								
Rampello et al., 2007 Italy	19 (14F, 5M)	41 (8)	3.5 (1.0-6.0)	Design	Randomised crossover controlled	EDSS, MFIS, MSQOL-54, lung function, 6MWT, VO_2 peak	Improved 6MWT and VO_2 peak after aerobic training	Retention: 57.9%
				Groups	Aerobic (leg cycle ergometry) or neurological rehabilitation (respiratory exercises and stretching)			
				Frequency/ Duration	3xweek (30 minutes) for 8 week			
				Intensity	Aerobic (60% up to 80% max work load)			
				Assessments	Baseline, 8 weeks			
				Behaviour Change	Theoretical basis for behaviour change absent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Treadmill training for individuals with multiple sclerosis: a pilot randomised trial								
Van den Berg et al., 2006 UK	17 Ex: 8 (7F, 1M) C: 9 (7F, 2M)	30-65 yrs	-	Design	RCT – cross over design	10MWT 2MWT, GNDS, FSS	Improved 10MWT at follow-up 1	Retention: 89.4%
				Groups	Treadmill exercise and control			
				Frequency/ Duration	3xweek (30 minutes) for 4 weeks			
				Intensity	55-85% APHRM			
				Assessments	Baseline, week-7, week-12			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis								
Schulz et al., 2004 Germany	28 Ex: 15 C: 13	Ex: 39.0 (9.0) C: 40.0 (11.0)	Ex: 2.0 (1.4) C: 2.5 (0.8)	Design	RCT	Fitness (Blood lactate), HAQUAMS, FIS	Improved fitness and QoL	Not reported
				Groups	Aerobic and control			
				Frequency/ Duration	2 x week (30 minutes) a week for 8 weeks			
				Intensity	Interval training on cycle ergometer at 60% VO_{2max}, maximum of 75% max power output achieved on max test			
				Assessments	Baseline and 8 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis								
Mostert and Kesselring, 2002 Switzerland	26 Ex: 3 (10F, 3M) C: 13 (11F, 2M)	Ex: 45.2 (8.7) C: 43.9 (13.9)	Ex: 4.6 (1.2) C: 4.5 (1.9)	Design	RCT	EDSS, physical activity (BQ), SF-36, FSS, maximum aerobic capacity	Improved anaerobic threshold, health perception, activity levels	Retention: All: 70% Compliance: Ex: 65%
				Groups	Exercise (cycle ergometry) and control			
				Frequency/ Duration	5 x week (30 minutes) for 4 weeks			
				Intensity	Individual intensity based on heart rate at AT			
				Assessments	Baseline and 4-weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	**Age (years) Mean (SD)**	**EDSS (analogue scale) Mean (SD)**	**Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change**		**Main Measures**	**Significant Findings**	**Retention/ Compliance**
Can aerobic exercise training affect health-related quality of life for people with multiple sclerosis?								
Sutherland et al., 2001 Australia	22 Ex: 11 (6F, 5M) C: 11 (6F, 5M)	Ex: 47.2 (4.8) C: 45.5 (5.1)	Not reported	Design	Matched for age and gender and randomly assigned (procedure not described)	MSQOL-54, POMS, MSPSS, Aerobic Fitness (only measured in exercise group)	Improved fitness, increased energy and vigour and reduced fatigue	Retention: Ex: 100%, C: 100% Compliance: Ex: 90%
				Groups	Supervised exercise (aerobic water based) and non-control			
				Frequency/ Duration	3xweek (45 minutes) for 10 weeks			
				Intensity	Not reported			
				Assessments	Baseline and 10 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Impact of aerobic training on fitness and quality of life in multiple sclerosis								
Petajan et al., 1996 USA	54 Ex: 21 (15F, 6M) C: 25 (16F, 9M)	Ex: 41.1 (2.0) C: 39.0 (1.7)	Ex: 3.8 (0.3) C: 2.9 (0.3)	Design	RCT	VO_2 max, isometric strength, POMS, SIP, FSS, EDSS	Improved fitness and factors impacting QoL	Retention: Ex: 77% C: 92% Compliance: Ex: 97%
				Groups	Supervised aerobic exercise (combined arm and leg ergometry) and control			
				Frequency/ Duration	3xweek (40 minutes) for 15 weeks			
				Intensity	60% of Vo2 max			
				Assessments	Baseline and 15 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Table 2.3b. Resistance exercise interventions for PwMS (Studies: n=6, Articles: n=8).

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Home-based exercise program and fall-risk reduction in older adults with multiple sclerosis: phase 1 randomized controlled trial								
Sosnoff et al., 2014 US	27 (23F, 4M)	60 (6.1)	2.5 – 6.5	Design	Randomised control pilot trial	Falls Risk (PPA), BBS, walking test (25-ft Walk, 6MWT, MSWS-12)	Decreased falls risk and increased walking mobility	Retention: 81.5% Compliance: 68.3%
				Groups	Home-based exercise (targeting strength and balance to reduce falls) and wait list control			
				Frequency/ Duration	3 x week for 12 weeks			
				Intensity	Not reported			
				Assessments	Baseline, 12 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Progressive resistance training did not improve walking but can improve muscle performance, quality of life and fatigue in adults with multiple sclerosis: a randomized control trial								
Dodd et al., 2011 Australia	71 Ex: 36 (26F, 10M) C: 35 (26F, 9M)	Ex: 47.7 (10.8) C: 50.4 (9.6)	-	Design	Single blind randomised control trial	2MWT, muscle strength (IRM leg press), muscle endurance (reps at 50% 1RM), MFIS, WHOQoL-BREF, MSSS-88, MSIS-29	No significant difference in walking performance. Increased leg strength, improved fatigue (physical) and QoL (physical)	Retention: 88.2% Compliance: 92%
				Groups	Progressive resistance training (leg press, knee extension, calf raise, leg curl, reverse leg press) or usual care (with social programme)			
				Frequency/ Duration	Ex: 2 x week (45 minutes) for 10 weeks C: attention and social program 1 x week			
				Intensity	2 x 10-12 repetitions, at 11-12 repetition max, with 2 minutes rest between sets			
				Assessments	Baseline, 10 and 22 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis								
Broekmans et al., 2011 Belgium	36	47.8 (10.6)	2.0-6.5	Design	Randomised controlled trial	Strength, TUG, 25 ft walk, 2MWT, functional reach	Improved leg strength, no difference between exercise groups	Retention: 91.6% Compliance: 99%
				Groups	Ex (Standard light to moderate unilateral leg resistance training), Ex(resistance training with simultaneous electrical stimulation), control group			
				Frequency/ Duration	5 sessions every 2 weeks (60 minutes) for 20 weeks			
				Intensity	Light to moderate			
				Assessments	Baseline, 10 and 20 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Cycling progressive resistance training for people with multiple sclerosis: a randomised controlled study								
Cakt et al., 2010 Turkey	33 Ex: 14 Ex: 10 C: 9	36.4 (10.5)	≤6	Design	3-group randomised control trial	Fitness, TUG, DGI, functional reach, falls efficacy scale, 10MWT, FSS, BDI	Improved fitness, TUG, 10MWT, FSS, SF-36 (physical)	Retention: 73.3%
				Groups	Cycle progressive resistance training and balance, home-based lower limb strength and balance, control			
				Frequency/ Duration	2 x week (60 minutes) for 8 weeks			
				Intensity	15 sets of 2 minutes high resistance pedalling and 2 minutes low resistance pedalling (30-40w)			
				Assessments	Baseline, 8 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
a Muscle fiber size increases following resistance training in multiple sclerosis b Fatigue, mood and quality of life improve in MS patients after progressive resistance training c Resistance training improves muscle strength and functional capacity in multiple sclerosis								
Dalgas et al., 2009a, 2010b, 2010c Denmark	31 (20F, 11M) Ex: 15 C:16	Ex: 47.7 (41.9-53.4) C: 49.1 (44.6-53.6)	Ex: 3.7 (3.2-4.2) C: 3.9 (3.5-4.4)	Design	2-arm randomised control trial	FSS, MDI, SF-36, muscle strength (isometric, knee extensor) and functional capacity (6MWT,10MWT)	Improved muscle strength and functional capacity (6 and 10 MWT) at 12 and 24 weeks. Improved fatigue, SF-36	Retention: 81.5%
				Groups	Progressive resistance training group and control			
				Frequency/ Duration	2 x week for 12 weeks			
				Intensity	3-4 sets of 8-12 reps at 8-15RM, 2-3 minute rest between sets			
				Assessments	Baseline, 12 weeks, 24 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis								
DeBolt and McCubbin, 2004 USA	29 Ex:19 (15F, 4M) C:17 (13F, 4M)	Ex: 51.6 (7.3) C: 47.8 (10.5)	Ex: 4.0 (1.8) C: 3.5 (1.5)	Design	RCT	Balance (postural sway and sway velocity), leg extensor power, TUG	Improved leg extensor power	Compliance: 95%
				Groups	Exercise (home based resistance of lower extremity) and control			
				Frequency/ Duration	3 x week for 8 week			
				Intensity	Not reported			
				Assessments	Baseline and 8 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Table 2.3c. Combined (aerobic/resistance) exercise for PwMS (Studies: n=7, Articles: n=8).

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Effect of combination exercise therapy on walking distance, postural balance, fatigue and quality of life in multiple sclerosis patients: a clinical trial study								
Sangelaji et al., 2014 Iran	59 Ex: 39(15M, 24F) C: 20 (7M, 15F)	Ex: 33.1(7.7) C: 32.1 (6.4)	Not reported	Design	RCT	BBS, 6MWT, EDSS, QoL	10 weeks: Improved balance, walking mobility, and QoL 1 year: No change	Not reported
				Groups	Combination therapy: aerobic (static bike and treadmill), strength (resistance bands), balance and stretching or control			
				Frequency/ Duration	3 x week (20-90 minutes) for 10 weeks			
				Intensity	Progressive, 40-70% APHRM			
				Assessments	Baseline, 10 weeks and 1 year			
				Behaviour Change	Theoretical basis for behaviour change absent, participants received knowledge on benefits of exercise and encouraged to exercise long-term.			
The effects of a 12-week leisure centre-based, group exercise intervention for people moderately affected with multiple sclerosis: a randomised controlled pilot study								
Learmounth et al., 2012 UK	32 Ex: 20 (5M, 15F) C: 12 (4M, 8F)	Ex: 51.4 (8.1) C: 51.8 (8.0)	Ex: 6.1 (0.4) C: 5.8 (0.5)	Design	Randomised control pilot trial	25ft walk, 6MWT, BBS, TUG, FSS, quad strength	Improved balance confidence and physical activity	Retention: 87.5% Compliance: 71%
				Groups	Exercise (community, group, mobility, balance and resistance), control (usual care)			
				Frequency/ Duration	2 x week (60 minutes) for 12 weeks			
				Intensity	Not reported			
				Assessments	Baseline, 8 and 12 weeks			
				Behaviour Change	Theoretical basis for behaviour change absent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Combined exercise training reduces IFN-γ and IL-17 levels in the plasma and the supernatant of peripheral blood mononuclear cells in women with multiple sclerosis								
Golzari et al., 2010 Iran	20 Ex: 10 C: 10	32.2 (7.6)	2.1 (1.1)	Design	RCT	EDSS, VO_{2max}, muscle strength, balance	Improved muscle strength and balance	Not reported
				Groups	Exercise (combined aerobic and resistance) or control			
				Frequency/ Duration	3 x week (60 minutes) for 8 weeks			
				Intensity	Not reported			
				Assessments	Baseline and 8 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Long-term benefit of exercising on quality of life and fatigue in multiple sclerosis patients with mild disability: a pilot study								
McCullagh et al., 2008 Ireland	24 Ex: 12 C: 12	Ex: 40.5 (12.7) C: 33.6 (6.1)	Not reported	Design	Allocated by blind ballot	MFIS, MSIS-29, FAMS, exercise capacity	Improved exercise capacity, QoL and fatigue, with improved fatigue and QoI lasting up to 6-months	Retention ex: 80%
				Intervention groups	Exercise (4 stations (i.e. treadmill, bike, arm strength etc.) and control			
				Frequency/ Duration	Ex: 2 x week (40-60 minutes) class, 1 x week home for 3-months C: monitored monthly			
				Intensity	11-13 RPE 'fairly light to somewhat hard'			
				Assessments	Baseline, 3 months, 6 months			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
a Effects of a 6-month exercise program on patients with multiple sclerosis: a randomised study **b Long-term exercise improves functional impairement but not quality of life in multiple sclerosis**								
Effects of aerobic and strength exercise on motor fatigue in men and women with multiple sclerosis: a randomised controlled trial								
Romberg et al., 2004a; Romberg et al., 2005b Finland	95 Ex: 47 (30F, 17M) C: 48 (31F, 17M)	Ex: 43.8 (6.3) C: 43.9 (7.1)	Ex: 2.0 (1.0-5.5) C: 2.5 (1.0-5.5)	Design	RCT	25ftWT, 500 m walk, maximal isometric torque (knee extensors/ flexor),MSQOL-54, EDSS, MSFC, CES-D	Improved walking speed, endurance and MSFC score	Retention: 96% Compliance: Ex Overall 93%, home strength 59%
				Groups	Mixed (aerobic and resistance) and control			
				Frequency/ Duration	1xweek (aerobic), 3-4xweek (resistance) for 6 months Aerobic: aquatic (weeks 1-3), mixed after Resistance: circuit of 10 exercises (upper, lower body and core), using therabands			
				Intensity	Not reported			
				Assessments	Baseline and 6 months			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Surakka et al., 2004 Finland	95 Ex: 47 (30F, 17M), C: 48 (31F, 17M)	Ex (F): 43 (6) Ex (M):45(6) C (F): 44 (7) C(M): 44 (7)	Ex (F): 2.9 (1.2) Ex (M): 2.0 (0.8) C (F): 3.1 (1.2) C (M): 2.5 (1.0)	Design	RCT	Motor fatigue of knee extensor and flexor muscles	Reduced motor fatigue in women, but not men	Compliance: Home strength- F: 62% and M: 53% Aerobic and strength sessions, F: 98% and M: 85%
				Groups	Mixed supervised / home and control			
				Frequency/ Duration	Supervised: 3-4 x week (60 minutes) for 3 weeks Home: 4-5xweek for 23 weeks Supervised: 5 sessions water based aerobic, 5 sessions land based resistance Home (25% aerobic, 75% resistance) resistance (theraband)			
				Intensity	Supervised: water based aerobic (65-75% APHRM), land based resistance, 10 exercises, 2 sets of 10-15 reps (50-60% max load)			
				Assessments	Baseline, week-3 and week-23			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Multiple sclerosis and brief moderate exercise: A randomised study								
Bjarnadottir et al., 2002 Iceland	16 Ex: 6 C:10	38.7	2.1	Design	RCT	Fitness (VO_2 peak, AT, peak workload), SF-36, EDSS	Increased VO_2 peak, AT and peak workload Improved SF-36 (vitality)	Retention: 69.6%
				Groups	Exercise: aerobic (cycle ergometry) and resistance training (major muscle groups) and control			
				Frequency/ Duration	3 x week (60 minutes), for 5 weeks			
				Intensity	Aerobic: 15-20 minutes at 55% VO_2 peak (AT) Resistance: 15-20 repetitions			
				Assessments	Baseline, 5 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Table 2.3d. Exercise (mixed activities such as Yoga, Pilates, Ai-Chi etc.) interventions for PwMS (Studies: n=12, Articles: n=13).

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue Scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
A task oriented circuit training in multiple sclerosis: a feasibility study								
Straudi et al., 2014 Italy	24 Ex: 12 (7 F; 5 M) C: 12 (10F/2M)	52.6 ± 11.2	4.9 ± 0.5	Design	Single blind RCT feasibility (block randomisation)	6MWT, 10MWT, TUG, dynamic balance, FSS, MSWS-12, MSIS-29	2 weeks: ↑ Walking ability ↑ HRQoL 3 months: No significant difference	Retention: 100% (2-weeks), 87.5% (3-months) Compliance: ExH-58.3%
				Groups	Experimental (task oriented circuits) and control			
				Frequency/ Duration	Supervised ;5 x week (120 minutes), 2 weeks, Home; 3 x week (60 minutes) for 3 months			
				Intensity	Not reported			
				Assessments	Baseline, 2 weeks and 3 months			
				Behaviour Change	Theoretical basis for behaviour change abscent, exercise diaries used and individual feedback			
The effect of an aquatic training program on walking ability and quality of life of patients with multiple sclerosis.								
Garopoulou et al., 2014 Greece	10(4M, 6F)	30.4 (3.0)	1.0 – 2.5	Design	RCT - Pilot	EQ-5D, timed 500m walk (treadmill)	↑ Walking mobility ↑EQ-5D	Not specified
				Groups	Exercise (aquatic training) or control			
				Frequency/ Duration	2 x week (40 minutes) for 12 weeks			
				Intensity	Not reported			
				Assessments	Baseline, 12 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue Scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Randomized controlled pilot study of customized pamphlets to promote physical activity and symptom self-management in women with multiple sclerosis								
Plow et al., 2014 USA	30 (30 F)	Immediate: 47 (9) Delayed: 48 (10)	Not reported	Design	Randomly allocated, 2 group repeated measures, delayed treatment contact acting as control	PADS, PDDS, GLTEQ, SF-12, SMSS, 6MWT	Increased physical activity, improved perception of physical function and increased 6MWT	Not reported
				Groups	Prescribed home exercise (indoor cycling, stretching, balance and strength)and customised pamphlets on physical activity and symptom management, matched to stage of readiness to change and barriers			
				Frequency/ Duration	Prescribed home exercise: 3-5 x week (45 minutes) Customised pamphlets: every 3 weeks for 12 weeks			
				Intensity	Not reported			
				Assessments	Baseline, 12 weeks			
				Behaviour Change	Guided by Social Cognitive Theory and the Transtheoretical Model, with pamphlets adapted to Stages of Change			
a. Exercise in the community for people with minimal gait impairment due to MS: an assessor-blind randomized controlled trial **b. Exercise in the community for people with multiple sclerosis- a follow-up of people with minimal gait impairment**								
Garrett et al., 2013a and b Ireland	314 Physio (80) Yoga (77) Fitness (86) Control (71)	Physio 51.7 ± 10, Yoga 49.6 ± 10, Fitness 50.3 ±10, Control 48.8 ± 11	Not assessed	Design	Multi centre, block randomised, assessor blinded, controlled trial	MSIS-29, MFIS, 6MWT	10 weeks: Improved MSIS-29 (psych) and MFIS (Phys) Physio and Fitness only improved MSIS-29 (Phys) and 6MWT. 3 months improved psych. and fatigue only	Retention: 10-weeks 77.1%
				Groups	4 groups (n=8) of community based exercise: Physiotherapy lead, yoga lead, fitness instructor lead and control			
				Frequency/ Duration	1x week (60 minutes) for 10 weeks			
				Intensity	Not reported			
				Assessments	Baseline, 10 weeks, 3 months			
				Behaviour Change	Theoretical basis for behaviour change abscent, advice given on continuing after the programme			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue Scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Comparison of the effect of 8 weeks aerobic and yoga training on ambulatory function, fatigue and mood status in ms patients								
Ahmadi et al., 2013 Iran	31 (31F)	35.2 ± 9.0	2.2 ± 1.2	Design	Randomised with wait list control	BBS, FSS, BDI, BAI, 10MWT, 6MWT	Improvements in BBS, 6MWT, FFS, BDI and BAI (both groups). 10MWT treadmill only	Retention: 100%
				Groups	3 groups: treadmill training, yoga and wait list control			
				Frequency/ Duration	3 x week (treadmill: 30 minutes, yoga: 60-70 minutes), for 8 weeks			
				Intensity	Treadmill: 40-75% APHRM			
				Assessments	Baseline, 8 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis								
Kargarfard et al., 2012 Iran	32 (32F) Ex: 16 C: 16	Ex: 33.7 ± 8.6 C: 31.6 ± 7.7	Ex: 2.9 ± 0.9 C: 3.0 ± 0.7	Design	Randomised control trial (sealed envelope)	MFIS, MSQol-54	Improved MFIS and MSQol-54 at 4 and 8 weeks	Retention: 65.6%
				Groups	Exercise (aquatic), or control			
				Frequency/ Duration	3 x week (60 minutes) for 8 weeks			
				Intensity	50-75% MHRR			
				Assessments	Baseline, 4 weeks and 8 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue Scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Evaluation of a home-based physiotherapy programme for those with moderate to severe multiple sclerosis: a randomised controlled pilot study								
Miller et al., 2011 UK	30 (19F, 11M) Ex: 15 C: 15	Ex: 56.3 (9.0) C: 52.9 (6.3)	Ex: 7.0 (0.5) C: 7.1 (0.8)	Design	RCT	Knee flexion and extension strength, MSIS-29	Improved right and left knee flexion strength	Retention: 93.3% Compliance: 92.5%
				Groups	Exercise (upper and lower limb task specific strengthening exercises using therabands, mobile pedals and weights) and usual care control			
				Frequency/ Duration	2 x week (60 minutes) for 8 weeks			
				Intensity	Not reported			
				Assessments	Baseline, week 8 and week 16			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
A home-based walking program using rhythmic auditory stimulation improves gait performance in patients with multiple sclerosis: a pilot study								
Conklyn et al., 2010 USA	10 Ex: 5 C: 5	47.0 (10.5)	Not reported	Design	RCT	25ft walk	No significant difference	Retention: 100%
				Groups	Exercise (walk to music) and control			
				Frequency/ Duration	7 x week (20 minutes) for 4 weeks			
				Intensity	Songs to replicate progression in cadence			
				Assessments	Baseline, 4 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue Scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
The effects of a twelve-week home walking program on cardiovascular parameters and fatigue perception of individuals with multiple sclerosis: a pilot study								
Geddes et al., 2009 USA	12 Ex: 8 C: 4	51.3	4.7	Design	RCT	FSS, 6MWT	No significant difference	Not reported
				Groups	Exercise (walking) or control			
				Frequency/ Duration	3 x week (15-30 minutes) for 12 weeks			
				Intensity	Not reported			
				Assessments	Baseline and 12 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, exercise log kept			
The efficacy of multidisciplinary rehabilitation in stable multiple sclerosis patients								
Storr et al., 2006 Denmark	90 Ex: 38 C: 52	Ex: 53.0 (8.9) C: 50.1 (10.0)	Ex: 6.5 C:6.5	Design	RPG: Double-blinded	MSIS-29, EDSS GNDS, 9 hole peg test, 10MWT	No significant differences	Not reported
				Groups	Supervised physiotherapy (Stretch, relaxation, balance) and aerobic (horse riding), with patients in hospital			
				Frequency/ Duration	4-5 x week (45 minutes) for 3-5 weeks			
				Intensity	Not reported			
				Assessments	Baseline, 5 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

Reference/ Location	Population: Exercise (Ex)/Control (C)			Intervention		Outcomes		
	n	Age (years) Mean (SD)	EDSS (Analogue Scale) Mean (SD)	Design, Intervention groups, Frequency/Duration, Intensity, Assessments, Behaviour Change		Main Measures	Significant Findings	Retention/ Compliance
Randomized controlled trial of yoga and exercise in multiple sclerosis								
Oken et al., 2004 USA	69 Ex (Aero): 21 (15) Ex (Yoga): 26 (22) C: 22 (20)	Ex (Aero): 48.8 (10.4), Ex (Yoga): 49.8 (7.4), C: 48.4 (9.8)	Ex (Aero): 2.9 (1.7) Ex (Yoga): 3.2 (1.7) C: 3.1 (2.1)	Design	RCT	Cognition, MFI, POMS, SF-36	Both Groups improved fatigue scores	Retention: 82.6% Ex (Aero): 71.4% Ex (Yoga): 84.6% C: 90.1%
				Groups	Yoga, Aerobic exercise, control			
				Frequency/ Duration	Yoga: 1 x 90 minutes per week for 6 months Aerobic: 1 x up to 60 minutes per week for 6 months Both groups encouraged to exercise at home			
				Intensity	Not reported			
				Assessments	Baseline and 6 months			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			
Controlled randomised crossover trial of the effects of physiotherapy on mobility in chronic multiple sclerosis								
Wiles et al., 2001 Wales	42 Ex/ExH/C: 42	47.2 Range (28.2-68.8)	6.0 Range (4.0 – 6.5)	Design	Randomised (sealed envelopes) control crossover	6MWT, balance time, 9-hole peg, cognitive and mood	Improved mobility, subjective wellbeing, and mood in both ex groups at week 8, but not week 16	Retention: All: 95%
				Groups	Physiotherapy at home, physiotherapy as outpatient, no therapy			
				Frequency/ Duration	2 x week (45 minutes) for 8 weeks Physiotherapy: Outpatient focusing on specific facilitation techniques. Home focusing on functional activities			
				Intensity	Not reported			
				Assessments	Baseline, 8 weeks and 16 weeks			
				Behaviour Change	Theoretical basis for behaviour change abscent, no techniques described			

2MWT: 2 minute walk test, 6MWT: 6 minute walk test, 10MWT: 10 metre walk test, APHRM: Age Predicted Heart Rate Maximum, AT: Anaerobic Threshold, BAI: Beck Anxiety Inventory, BBS: Borg Balance Scale, BDI: Becks Depression Inventory, BMI: Body Mass Index, BQ: Baecke physical activity Questionnaire, C: Control, CES-D: Centre for Epidemiologic Studies Depression scale, DGI: Dynamic Gait Index, EDSS: Expanded Disability Status Scale, Ex: Exercise, EQ-5D: EuroQol 5-D, FAMS: Functional Assessment of MS Scale, FIS: Fatigue Impact Scale, FSMC: Fatigue Scale for Motor and Cognition, FSS: Fatigue Severity Scale, GLTEQ: Godin Leisure-Time Exercise Questionnaire, GNDS: Guys Neurological Disability Scale, HAQUAMS: Hamburg Quality of Life in MS, HRQoL: Health Related Quality of Life, IDS-SR: Inventory of Depressive Symptoms, MDI: Major Depression Inventory, MFIS: Modified fatigue impact scale, MHRR: Maximum Heart Rate Reserve, MSFC: MS Functional Capacity, MSIS-29: Multiple Sclerosis Impact Scale-29, MSQoL-54: Multiple Sclerosis Quality of Life-54, MSSS-88: Multiple Sclerosis Spasticity Subscale, MSWS-12: Multiple Sclerosis Walking Scale-12, PASAT: Paced Auditory Serial Addition Test, PADS: Physical Activity Disability Survey, PANAS: Positive and Negative Affect Schedule, PDDS: Patient Determined Disease Steps, POMS: Profile of Mood States, PPA: Physiological Profile Assessment, QoL: Quality of Life, RCT: Randomised Control Trial, RM: Repetition Maximum, SF-12: Short Form health survey, SF-36: Short Form health survey, SIP: sickness impact profile, SMSS: Symptoms of Multiple Sclerosis Scale, TUG: Timed up and go test, WHOQoL-BREF: World Health Organisation's Quality of Life assessment

2.5.4 Interventions

2.5.4.1 Aerobic exercise

Eleven studies comparing aerobic exercise (Table 2.3a) with a usual care control group were included in this review; three of these were feasibility or pilot work only. The studies included 342 PwMS, the majority of which were individuals with mild-to-moderate disability from the condition. The largest study so far was that of Petajan et al., (1996), leaving most trials inadequately powered. The modality of exercise used in these trials included arm, cycle, combined (arm/cycle) and rowing ergometry, treadmill walking and water based activity. Sessions lasted between 30 and 60 minutes, and were carried out for two to three times per week (except one which was five times per week) for between three and 20 weeks. The intensity of the sessions was generally light to moderate and included both continuous and interval style training. Outcome measures were generally assessed at baseline and immediately following the intervention period. Only two studies (Van den Berg et al., 2006; Ahmadi et al., 2013) included a follow-up, but neither of these would be considered to be of sufficient duration to be classified as long-term. Retention on the trials varied from 57.9% up to 100%, with the majority being between 80 and 90%. Compliance to exercise was less well reported with only three trials reporting this measure. Most of these were supervised sessions and reported good compliance of between 90 and 97%.

Outcome measures suggested no negative effects of mild-to-moderate aerobic exercise and several positive outcomes for PwMS. Most studies reported improvements in aerobic fitness as measured directly by either VO_2 peak, VO_2 max or anaerobic threshold (Petajan et al., 1996; Mostert and Kesselring et al., 2002; Briken et al., 2014) or indirectly through the walking distance covered

during a six minute walk test (Ahmadi et al., 2013) or as maximum walking distance (Dettmers et al., 2009). Walking speed has been commonly measured either using the 10 metre walk test or the 25 foot walk test. Results on the impact of exercise training on this variable are mixed with Ahmadi et al., (2013) and van den Berg et al., (2006) both showing an improvement in walk speed. These two studies used treadmill training only for their aerobic intervention. Thus, indicating that specificity of training may be important to gain an improvement in walking speed for PwMS.

The impact of aerobic exercise on fatigue was less conclusive, with some studies showing evidence for improvement (Sutherland et al., 2001; Ahmadi et al., 2013; Briken et al., 2014) and others failing to show any significant difference (Petajan et al., 1996; Schulz et al 2004; van den Berg et al., 2006; Rampello et al., 2007; Dettmers et al., 2009; Skjerbæk et al., 2014). This difference may have been due to the different outcome measures used to report on this variable. The majority of those reporting a significant improvement utilised the Modified Fatigue Impact Scale (MFIS), which is a multidimensional tool. Whereas the majority of those that did not, utilised either the Fatigue Scale for Motor and Cognition (FSMC) or the Fatigue Severity Scale (FSS), both of which are uni-dimensional. In a recent review of outcome measures for MS and exercise interventions Paul et al., (2014) recommended using the MFIS as a measure of energy and drive due to its ability to provide a multidimensional assessment.

Health related quality of life (HRQoL) was assessed in the majority of studies. Different measures used include the Multiple Sclerosis Quality of Life-54 (MSQol-54), Multiple Sclerosis Impact Scale-29 (MSIS-29) and the Hamburg Quality of Life in MS (HAQUAMS). The majority have shown some

improvements in various sub-domains and overall quality of life (Petajan et al., 1996; Sutherland et al., 2001; Mostert and Kesselring, 2002; Schulz et al., 2004; Rampello et al., 2007), but there is little consistency over what domains are impacted most, or evidence to describe what it was about the intervention that caused that impact.

2.5.4.2 Resistance exercise

Six studies (eight articles) were included where the primary exercise intervention was resistance training (Table 2.3b). The studies included 227 PwMS, most of which were individuals with mild-to-moderate disability from the condition. The majority of studies had small sample sizes (n=27 to 36), with the exception of one study (n=71). As with the studies reported into aerobic exercise this leaves most inadequately powered. The type of resistance exercises used ranged from home-based functional body weight and resistance band exercises (DeBolt and McCubbin 2004; Sosnoff et al., 2014), to resistance cycling (Cakt et al., 2010) and gym based (machine/free weights) (Dalgas et al., 2009; Dodd et al., 2011) work. Sessions lasted between 45 and 60 minutes, and were carried out two to three times per week for between eight and 20 weeks. Where recorded the intensity of the sessions was between eight and 12 repetitions, at between eight and 15 repetition maximum. Retention to the trials was good at between 73.3% and 91.6%, with reported compliance to the intervention varying from 68.3% up to 99%. No long-term follow-ups were reported.

Outcome measures suggested no negative impact from this type of training for PwMS, with several positive outcomes. In those studies that assessed muscle

strength or power as a main outcome measure improvements were reported in the intervention groups (DeBolt and McCubbin, 2004; Dalgas et al., 2010b; Broekmans et al., 2011; Dodd et al., 2011), suggesting that PwMS can improve their strength through appropriate training. Several studies used more functional outcome measures such as the timed up and go test (TUG) (Debolt and McCubbin, 2004; Cakt et al., 2010; Broekmans et al., 2011), falls risk (Sosnoff et al., 2014) or walking ability (Cakt et al., 2010; et al., 2011; Sosnoff et al., 2014). DeBolt and McCubbin et al., (2004) reported no difference in TUG during home-based resistance training, despite improved leg extensor power, whereas a significant improvement was seen following cycle resistance training. Sosnoff et al., (2014) reported home-based exercise to be sufficient to reduce risk of falls. With regard to walking mobility, walking speed as measured by the 10 metre walk and the 25 foot walk, was reported to be improved following home-based (Sosnoff et al., 2014), cycle resistance (Cakt et al., 2010) and gym weights (Dalgas et al., 2010c), with only Broekmans et al., (2011) reporting no significant improvement in this measure. However, the exercise training used was very specific containing unilateral leg raises, with and without additional functional electrical stimulation and may not have been targeted enough to improve the strength, balance and coordination required to walk faster. Walking endurance as measured using the six minute walking test (6MWT) and the 2 minute walking test (2MWT) were reported to be significantly improved by both home based exercise (Sosnoff et al., 2014) and gym based exercise (Dalgas et al., 2010b; Dodd et al., 2011), with the study by Broekmans et al., (2011) again not showing a significant difference.

Three of the included studies measured self-reported fatigue using either the multidimensional MFIS or the unidimensional FSS. Gym based (Dalgas et al.,

2010b; Dodd et al., 2011), and cycle resistance (Caikt et al., 2010) training both reported improvements in fatigue, suggesting that resistance training may have a positive impact on this variable.

Only two of the RCT's included in this review repored the impact of resistance training on quality of life. Dalgas et al., (2010b) utilised the SF-36 and reported improvements in the physical component of the QoL score following 12 weeks of progressive resistance training. This was supported by Dodd et al., (2011), who utilised the WHOQol-Bref and again found improvements following progressive resistance training, in the physical domain. Findings regarding the impact on this variable suggest a potentially positive impact on the physical domain of quality of life, but not enough research is available to conclude the impact of resistance training on the various domains of health related quality of life.

2.5.4.3 Combined (Aerobic, balance/mobility and resistance) exercise

Seven studies (eight articles) were included where the prescribed exercise intervention was a combination of either aerobic or balance and mobility and resistance training (Table 2.3c). The studies included 341 participants, the majority of which had mild-to-moderate disability from MS. However, Learmounth et al., (2012) looked at community based resistance and mobility/balance work in individuals with moderate to severe MS. The structure and content of the interventions was diverse. The modality of aerobic exercises included varied from combinations of, treadmill and cycle ergometry (McCullagh et al., 2008; Sangelaji et al., 2014), cycle ergometry (Bjarnadottir et al., 2002; Mostart and Kesselring, 2002) and aquatic exercises (Romberg et al., 2004;

Surakka et al., 2004), with resistance exercises varying from gym based to resistance band work, with sessions taking place both in the community, at home or in a more structured gym environment. Sessions lasted between 20 and 90 minutes, and were carried out between two and five times per week, for between eight and 24 weeks. Recorded exercise intensity was generally fairly light to moderate (40-75% APHRM). Retention to the trials was good at between 70% and 96%, with reported compliance to the interventions varying from 59% up to 98%. Two studies reported long term follow-up data of three months (McCullagh et al., 2008) and one year (Sangelaji et al., 2014).

The majority of studies that measured aerobic fitness reported improvements in this measure (Bjarnadottir et al., 2002; Romberg et al., 2004; McCullagh et al., 2008; Sangelaji et al., 2014), with only Learmonth et al., (2013) reporting no change as measured by the 6MWT and Golzari et al., (2010) as measured by VO_2 peak. It is unlikely that the study by Learmonth et al., (2013) contained enough of an aerobic stimulus to improve this area, as the exercise intervention focused around mobility, balance and resistance work, whereas the study by Golzari et al., (2010) although containing an aerobic component, was only 8 weeks long and fails to provide detail on exactly what the aerobic component involved. The evidence for the impact of resistance training on muscle strength when combined with an additional aerobic component is less convincing with only Golzari et al., (2010) demonstrating an improvement in absolute muscle strength, although Surakka et al., (2004) demonstrated an improvement in muscle fatigue index in women (but not men) and Romberg et al., (2004) demonstrated an improvement in upper body strength endurance. It can therefore be suggested that providing an appropriate aerobic component is

included in a combined intervention, aerobic fitness can be improved. However, improvements in absolute strength may require a more targeted approach.

The impact of combined exercise on fatigue is sparse, with few studies reporting this as an outcome measure (McCullagh et al., 2008; Learmonth et al., 2012). Out of these two studies only McCullagh et al., (2008) reported an improvement in this measure. This is likely to be due to the much greater dose of exercise in this study, which also had an impact on fitness, unlike the Learmonth et al., (2012) study, which failed to report a significant increase in exercise capacity.

Quality of Life was also not frequently assessed in this section of research, with only the recent study by Sangelaji et al., (2014) assessing this variable and demonstrating improvements.

2.5.4.4 Other exercise programmes

Twelve studies (thirteen articles) were included where the prescribed exercise intervention contained training that could not be definitively defined as containing either aerobic or resistance training (Table 2.3d). Types of studies include those looking at pilates, yoga and tai-chi. The studies included 694 participants, the majority of which had mild-to-moderate disability from MS.

The majority of studies had small sample sizes (n=10 to 42), with the exception of three studies containing 69 (Oken et al., 2004), 90 (Storr et al., 2006) and 314 (Garrett et al., 2013) participants. The type of exercise interventions included contained home-based exercises such as walking, physiotherapy and indoor aerobic, strength and balance exercises (Wiles et al., 2001; Geddes et al., 2009; Conklyn et al., 2010; Miller et al., 2011; Plow et al., 2014;), supervised

exercises such as aquatic (ai-chi), yoga, treadmill, horse riding and physiotherapy (Oken et al., 2004; Storr et al., 2006; Kargarfard et al., 2012; Ahmadi et al. 2013; Garrett et al., 2013; Bayraktar et al., 2013; Garpoulou et al., 2014;) and mixed supervised and home-based interventions (Straudi et al., 2014). Sessions lasted between 20 and 120 minutes, and were carried out between one and seven times per week for between four and 24 weeks. Intensity of these interventions was poorly recorded with only one study reporting intensity of between 50-75% of maximum heart rate reserve (Kargarfard et al., 2012). Retention to the trials was again good at between 77.1% and 100%, compliance to the intervention was only reported in one study at 58.3% (Straudi et al., 2014).

Aerobic capacity has predominantly been assessed using the 6-minute walking test, with most studies (Ahamadi et al., 2013; Garret et al., 2013; Plow et al., 2014; Garpoulou et al., 2014; Straudi et al., 2014) demonstrating an improvement in this measure following the exercise intervention. Only two studies (Wiles et al., 2001; Geddes et al., 2009) failed to show an improvement. Wiles et al., (2001) utilised a physiotherapy programme and Geddes et al., (2009) a home-based walking programme. The exercise interventions that were successful in improving this area reported a greater aerobic exercise dose.

Fatigue was assessed in seven out of 13 studies and improvements were reported in 5 of these. Both of the studies that failed to show an impact also reported no improvements in aerobic capacity Geddes et al., 2009; (Straudi et al., 2014), indicating that the aerobic stimulus may have not been sufficient to bring about an improvement in fatigue.

As with the mixed exercise group quality of life was not commonly assessed. However, in the two studies that did assess this (Kargarfrad et al., 2012; Straudi

et al., 2014) a positive impact was reported. However, Straudi et al., (2014) only reported this after the supervised portion of the intervention this along with other measures, was not significant following the home portion of the programme, where compliance was much lower. This suggests that to sustain impact following a supervised programme, a different approach is required to ensure compliance and impact.

2.6 Current physical activity recommendations for people with Multiple Sclerosis

2.6.1 What is known?

The current evidence base is sufficient to suggest that for people with mild-to-moderate disability from MS, supervised, facility based exercise is safe and can improve aerobic capacity and muscle strength, and may improve other health outcomes such as fatigue, mobility and quality of life for PwMS (Reitberg et al., 2005; Śa, 2013; Latimer-Cheung et al., 2013). It is recommended that exercise is promoted for PwMS not experiencing an exacerbation (Rietberg et al., 2005) and that exercise twice a week at a moderate intensity is appropriate for achieving improvements in fitness and health outcome measures (Latimer-Cheung et al., 2013).

2.6.2 What needs to be determined?

MS and exercise research is generally of poor quality, leading to insufficient evidence to provide accurate information for individuals with different degrees of disability from MS and different types of MS (Döring et al., 2012). In addition, evidence on the short and long-term impact of exercise on symptoms, and

information capable of providing accurate exercise prescription to guide long-term exercise participation is currently unavailable (Döring et al., 2012; Latimer-Cheung et al., 2013). Therefore the challenge now is to assess the efficacy of pragmatic and cost-effective ways to implement exercise interventions for PwMS. Although one-to-one supervised facility-based exercise programmes can offer more support and guidance to MS patients, over the long-term they may prove difficult for many PwMS due to time barriers, transport issues and health constraints (e.g. fatigue). Moreover, they are very labour intensive, require specialist equipment, and are unlikely to be cost-effective. Hence, the purpose of the proposed investigation is to investigate whether a pragmatically-designed exercise intervention is effective for evoking improvements in physical activity behaviour and health outcomes in PwMS.

2.7 Research Question

Does a pragmatically designed exercise programme enable PwMS to benefit from improved health outcomes both in the short and long-term and is this a cost-effective approach to the treatment of MS?

2.8 Research Aims

2.8.1 Feasibility study

The primary aim of this study was to investigate the feasibility of a pragmatic exercise intervention in PwMS. The secondary aim was to obtain preliminary data on the impact of the intervention on key health outcomes by comparison with PwMS randomised to a standard care control group.

2.8.2 Main trial

Primary aims for the main study trial were;

1. Will PwMS who are randomised to pragmatic exercise have increased structured exercise and free living physical activity in comparison to usual care only controls at three-months and nine-months of follow-up?

2. Will PwMS who are randomised to pragmatic exercise have improved functional and health outcomes in comparison to usual care only controls at three-months and nine-months of follow-up?

3. Is inclusion of a pragmatic exercise intervention in the patient care pathway a more cost-effective treatment strategy than current medical care alone in PWMS?

Secondary aims for the main study trial were;

1. What dose of exercise is achievable by PwMS during facility-based supervised and home-exercise portions of the intervention?

2. Is the dose of physical activity associated with improvement in outcomes in people with mild-to-moderate MS and those more severely affected?

2.9 References

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3.0 PRAGMATIC EXERCISE INTERVENTION IN PEOPLE WITH MILD TO MODERATE MULTIPLE SCLEROSIS: A RANDOMIZED CONTROLLED FEASIBILITY STUDY

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3.1 Preface to Chapter 3

Chapters one and two explored the current literature on exercise for people with Multiple Sclerosis and the current recommendations for trial design. It was concluded that further knowledge was required on the feasibility of a pragmatic exercise intervention for PwMS to inform a robust RCT that could influence clinical practice.

Chapter three investigates the feasibility of an exercise therapy intervention designed using a pragmatic approach, alongside principles from the transtheoretical model to increase long-term exercise behaviour change in people with mild to moderate MS. Permission for its reprint in this thesis has been gained from the publishers (Appendix 9.14).

3.2 Abstract

Background: People with Multiple Sclerosis (PwMS) are less physically active than the general population and pragmatic approaches designed to equip them with the skills and confidence to participate in long-term physical activity are required.

Objective: To determine the feasibility of a pragmatic exercise intervention in PwMS.

Methods: A voluntary sample of 30 PwMS (male *n*=4, female *n*=26; mean age = 40 years; range = 24-49 years), with mild to moderate disability (EDSS ≤ 5.5), were recruited from eligible participants attending outpatient clinics (26, retained immediate follow-up, 24, 3-month follow-up). Participants were randomised to a 10 week pragmatic exercise intervention (2 x supervised and 1 x home-based session per week) or standard care. Clinical, functional and quality of life (MSQoL-54) outcomes were assessed at baseline, immediately and 3 months after the intervention.

Results: Attrition was low (10 weeks, 13%; 3 months, 20%), with high compliance rates (> 75% of all sessions). The intervention group achieved progression of exercise volume (24.3 ± 7.0 to 30.9 ± 5.5 min per session), intensity (60.4 ± 8.8 to 67.7 ± 6.9 % HR max) and training impulse (min x average HR = Training Impulse/load [arbitrary units; AU]) (2600 ± 1105 to 3210 ± 1269 AU) during the intervention, whilst significantly increasing (*P*=0.050) their physical composite score (MSQOL-54) at 10 weeks and readiness to exercise (*P*=0.003) at 3 months compared with standard care.

Conclusion: This pragmatic intervention was feasible for PwMS, but further research is needed to assess its long-term impact on physical activity behaviour.

3.3 Introduction

Evidence suggests that people with multiple sclerosis (PwMS) are less physically active than the general population [1], but exercise self-efficacy has consistently been reported to influence participation [2, 3]. Current research supports the health benefits of supervised, one to one facility based exercise interventions for people with mild to moderate disability from Multiple Sclerosis (MS). These include, increased muscle strength and aerobic capacity, improved mood state and enhanced quality of life (QoL), with no evidence of patient harm [4, 5]. In the long-term, this approach may prove difficult for PwMS and is unlikely to be cost effective. More high quality randomised control trials (RCT) to assess the efficacy of pragmatic interventions for equipping PwMS with the skills and confidence needed to exercise independently long-term are required [6]. Moreover, given that despite the benefits PwMS appear to find long-term exercise behaviour change difficult, interventions based on behaviour change theories are likely to optimise the chances of long term behaviour change taking place. One approach to this is the Transtheoretical Model [7] of behaviour change which outlines a series of stages that people move through in the behaviour change process and suggests strategies or processes that can be used to facilitate movement through the stages. This model has been applied to several health-related behaviours, including exercise, and is often used in research and as a basis to develop health related interventions that are person specific. It is hypothesised that PwMS will find a pragmatic approach to

exercise feasible, with results indicating improvements in function and quality of life.

Hence, the primary aim of this study was to investigate the feasibility of a 'pragmatic' exercise intervention that included cognitive-behavioural strategies to facilitate long term behaviour change in PwMS. Feasibility was measured in terms of recruitment, acceptability of the intervention, compliance and attrition, safety and suitability of exercise dose and appropriateness of outcome measures. A secondary aim was to obtain preliminary data on the impact of the intervention on key health outcomes by comparison with PwMS randomized to a standard care control group. In this study 'pragmatic' is defined as a practical, achievable and flexible programme that allows for individual choice and utilises behaviour change tools to enhance self-efficacy and promote long-term behaviour change.

3.4 Method

3.4.1 Participant inclusion/exclusion criteria:

A total of 30 participants were recruited from MS clinics at Sheffield Teaching Hospitals NHS Foundation Trust (UK). All participants were aged 18-65 years, fulfilled the modified McDonald diagnostic criteria for MS [8], had an Expanded Disability Status Score (EDSS; [9]) ≤ 5.5 and were stable on disease modifying treatment for ≥ 3 months prior to recruitment. Participants who experienced relapses within the preceding 3 months, had other illness substantially affecting their ability to exercise (confirmed by consultant) or who were physically active (≥2 x week, ≥ 30 minutes per session, during previous 3 months) were excluded. Ethics and research governance approval for this study was obtained

through Sheffield Research Ethics Committee and the Sheffield Teaching Hospitals NHS Foundation Trust respectively.

3.4.2 Study design

This feasibility study was a parallel randomised controlled trial (RCT). Following completion of baseline assessments, participants were randomly assigned to either pragmatic exercise or standard care control groups. The randomisation list was computer generated by an independent researcher and was concealed from those conducting assessments. Both groups had access to standard medical care.

3.4.2.1 Pragmatic exercise therapy intervention

Participants attended two supervised sessions and undertook one home session per week for 10 weeks. Supervised sessions were delivered one-to-one and led by an exercise researcher, qualified up to postgraduate level in sport and exercise science, with applied accreditation in exercise delivery. The project lead observed the delivery of the intervention at the start to ensure that protocols were interpreted correctly and consistently. Each session lasted approximately 1 hour, with participants being offered a range of aerobic exercise options (rowing, walking, upright cycle, recumbent bike and cross-trainer), delivered as short bouts (e.g. 5 x 3 minutes, with 2 min rest) at 50 to 69% age predicted maximum heart rate (ratings of perceived exertion [RPE] 11 to 13 on the Borg RPE Scale). Training impulse (TRIMP), calculated as average exercise heart rate (bpm) x duration (minutes); arbitrary units (AU), was used to quantify overall exercise training load [10].

The exercise programme was progressive and tailored towards individual capabilities and preferences. Participants were encouraged to try all appropriate exercise options, but were given choice over the exact modality, duration and intensity of the sessions. Sessions were then designed and progressed on the basis of individual preferences. Each session contained a warm-up, followed by an aerobic component, tailored functional body conditioning exercises based on individual need (balance, strength and flexibility) and a cool down, with content recorded (exercise modality, heart rate, RPE and duration). This type of tailored approach is recommended for PwMS [6]. Using the Transtheoretical Model [7] as a guiding framework, a variety of cognitive behavioural techniques (e.g. consciousness raising, goal setting and finding social support for exercise) were also used during sessions to promote motivation and confidence for exercise. Exercise researchers were trained in the delivery of the intervention and detailed guidelines on weekly content were provided. The behavioural techniques were integrated into the exercise sessions and the instructor used strategies appropriate to the conversation, the stage of change participants were at, and difficulties/questions participants raised during sessions. Full details of the behaviour change strategy have been published previously [11].

Home session content comprised both aerobic exercise and body conditioning activities, and was agreed with the participant after taking into account their needs, preferences, goals and exercise opportunities in their community. The duration and intensity of the home exercise sessions mirrored the level and progression achieved in the supervised sessions. Home sessions were included to promote independent exercise participation following the intervention. Participants completed a physical activity diary to log compliance and diaries

were checked and confirmed weekly, with participants being made aware of the importance of recording accurate data.

3.4.2.2 Standard care control

The standard care group continued with their usual National Health Service Care (NHS) and were offered the opportunity to receive advice and take part in 3 supervised sessions once they had completed the study.

3.4.3 Assessment of outcomes

All participants were assessed at baseline, immediately following the intervention (week 10) and 3 months post intervention. Participants were initially assessed on the hospital site by a neurologist (BS) who assigned EDSS [9] and Guy's Neurological Disability Scale (GNDS, [12]) scores. All other assessments were undertaken at Sheffield Hallam University.

Height (m) and body mass (kg) for body mass index (BMI) and waist and hip circumferences (cm) were measured using standard techniques [13]. Aerobic capacity was determined using a continuous, resistance incremented, sub-maximal cycle ergometer test. The test was terminated when participants reached a rating of perceived exertion of 17 (very hard), with time to termination recorded [14]. The 25ft walk from the multiple sclerosis functional composite (MSFC) assessment was included as a measure of clinical functional ability [15]. QoL was assessed using the Multiple Sclerosis Quality of Life-54 (MSQOL-54 [16]), which includes a generic health related QoL instrument (Rand 36-item health survey 1.0 [17]) and 18 additional items relevant to PwMS. Current physical activity and readiness to exercise was assessed using

the Godin Leisure-Time Questionnaire [18] and a visual-analogue stage of change ladder [19], with anchored labels for the five items from the standard stages of change for exercise questionnaire [20]. Additionally, participants assigned to the exercise arm completed a series of open-ended questions focusing on their reasons for taking part, confidence, side effects, barriers and attitudes towards exercise following the intervention.

3.4.4 Data analysis

Data were analysed using SPSS for Windows version 18.0 (SPSS Inc, Chicago, Illinois, USA). Statistical significance was set at $P<0.05$. Data were first checked for normality using Kolmogrorov-Smirnov test and found to be normally distributed. Data analysis was conducted using the intention to treat principle, with missing data points checked to be random (Little's Chi Squared test), and then imputed using the SPSS Expectation Maximization (EM) method. Data were analysed using analysis of covariance (ANCOVA), with baseline values used as the covariate, to compare differences between groups at each time point (Follow-up 1 / week 10 and Follow-up 2 /3 months) [21]. Results are presented as mean (± SD) at each time point. As this was a feasibility study, changes in outcome data are considered to be preliminary, and a cautious approach to interpretation has been taken.

3.5 Results

3.5.1 Recruitment, retention and compliance

Thirty PwMS were recruited at a rate of 1.4 participants per month, of these 28 were randomised to pragmatic exercise (n=15) or standard care control

(n=13).Two participants withdrew prior to randomisation (increased commitments, opted to participate in drugs trial). Table 3.1 shows the baseline characteristics of participants.

Table 3.1. Baseline characteristics of pragmatic exercise and usual care groups.

	Mean (SD)	
	Pragmatic Exercise (*n*=16)	Usual Care (*n*=14)
Gender (male/female)	2/14	2/12
Age (years)	39.5 (6.5)	40.9 (8.7)
Height (m)	1.66 (0.08)	1.68 (0.09)
Mass (kg)	72.9 (13.3)	75.0 (17.0)
EDSS (analogue scale)	3.0 (1.1)	3.1 (1.7)

From the standard care group, one participant withdrew in week 10 (MS relapse), whilst in the intervention group, one participant withdrew in week 5 due to increased work and fatigue. Attrition was low with 87% completing the week 10 assessments. A further two participants from the intervention group were lost to follow-up at 3 months, when they failed to respond to study visit invitations (80% completion; Figure 3.1). No adverse effects resulting from the intervention were reported. Compliance was high, with participants attending 76% of supervised exercise sessions (15.2 ± 2.7) and an average of 75% of prescribed home sessions (7.5 ± 2.2).

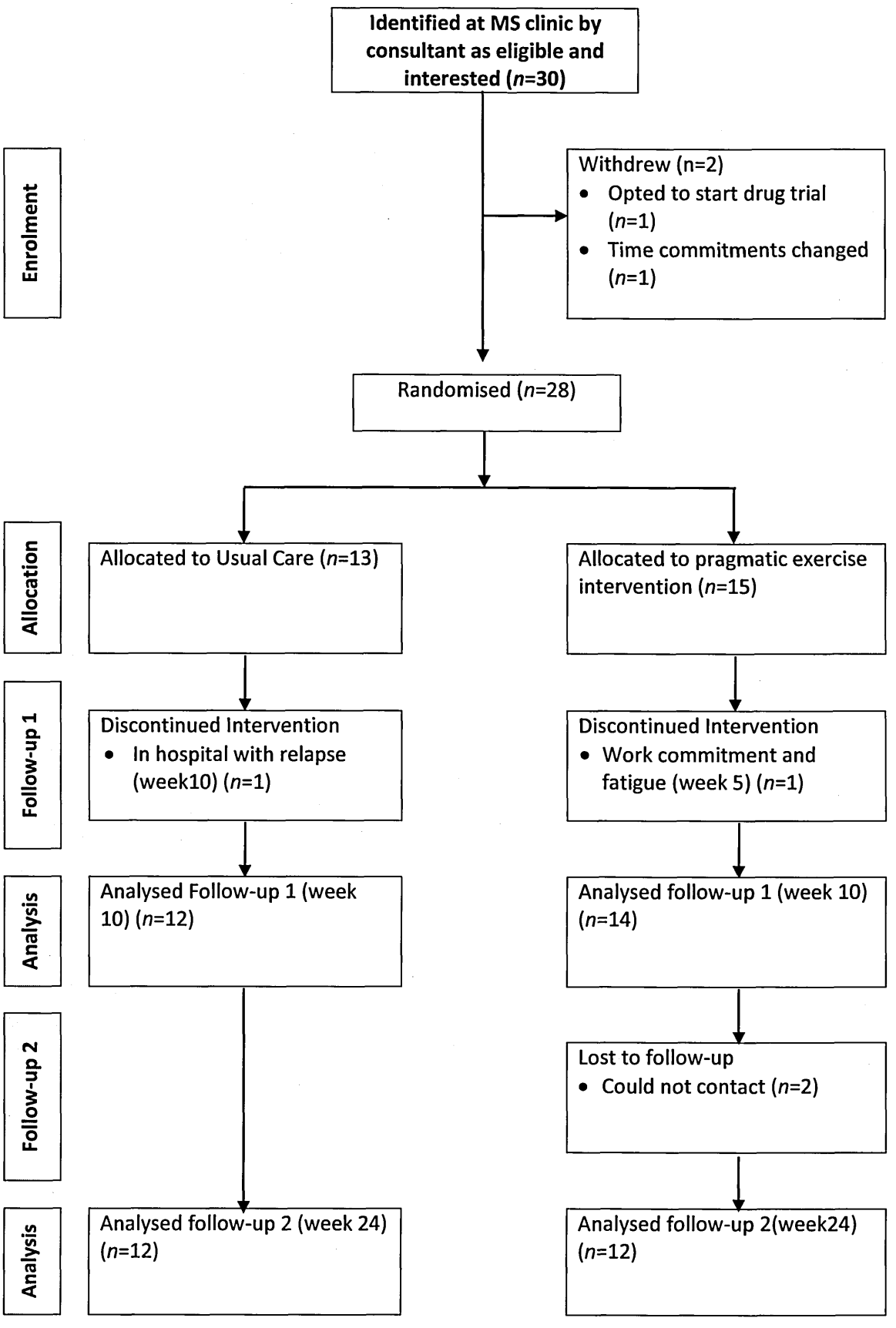

Figure 3.1. CONSORT diagram of patient recruitment and retention during the study.

3.5.2 Exercise dose and preference

The mean duration of the aerobic component of supervised sessions progressed from 24.3 ± 7.0 to 30.9 ± 5.5 min across the 10 weeks, with 11 participants showing an increase. This was accompanied by an increase in intensity (mean percentage of age predicted [HR max]), with participants progressing from 60.4 ± 8.8 to 67.7 ± 6.9 % HR max. Overall training impulse (TRIMP) showed steady progress from 2600 ± 1105 to 3210 ± 1269 Arbitrary Units (AU). Increased TRIMP was achieved with only small changes in RPE, 11.2 ± 0.8 to 11.6 ± 0.8, excluding the first session (RPE 10.8 ± 0.8) which was intentionally light to assess individual responses to exercise (Figure 3.2).

During supervised exercise, the most used mode of exercise was the treadmill, with a mean duration of 14.0 ± 5.5 min per session (Figure 3.3). The most popular activity for home sessions was walking (68%), although participants also used public gyms and swimming pools (14%), engaged in activities of daily living (gardening and housework) (10%) and used exercise equipment at home (8%).

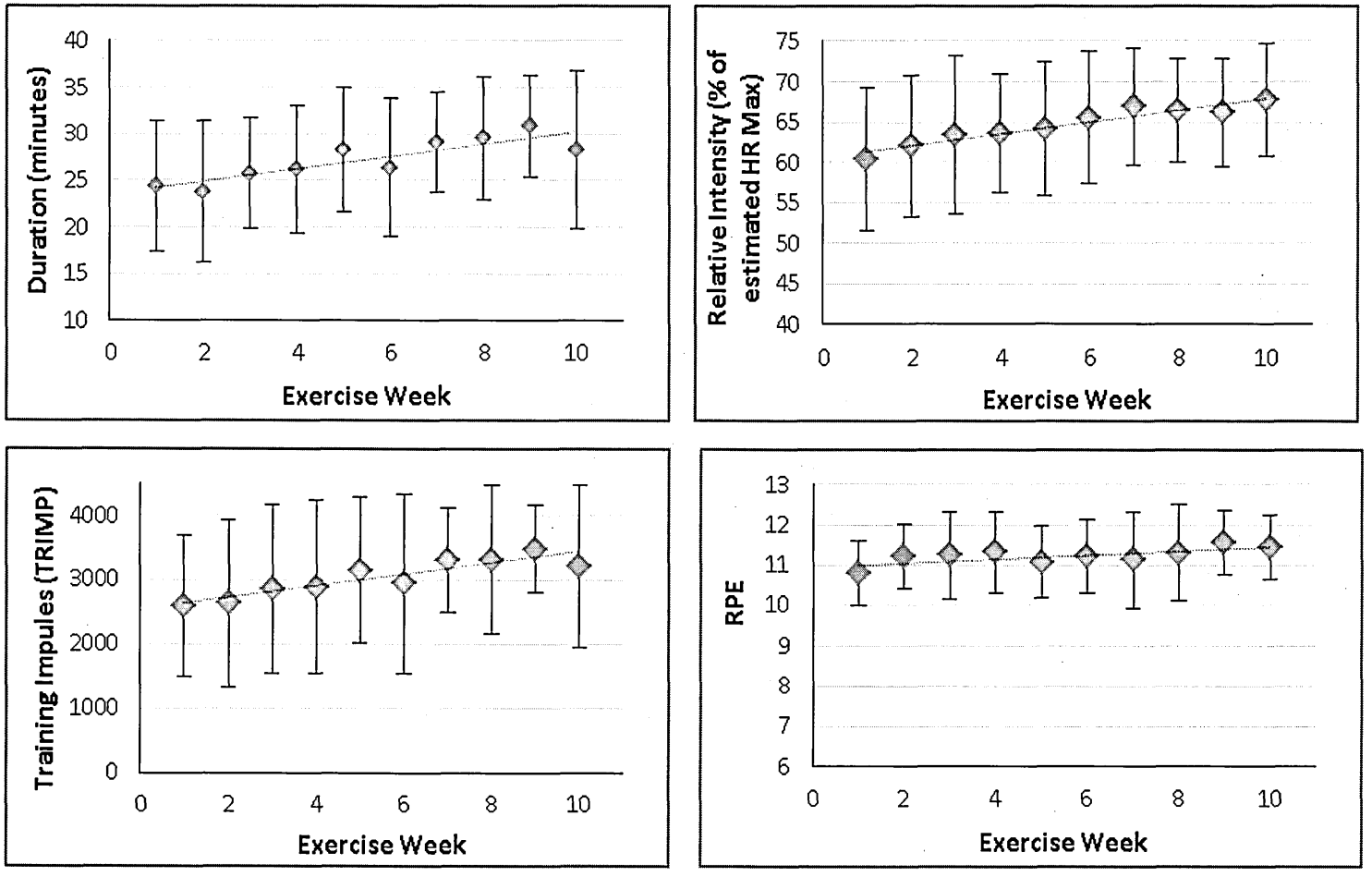

Figure 3.2. Change in exercise load over a pragmatic 10-week supervised programme, with error bars reflecting SD (n=15).

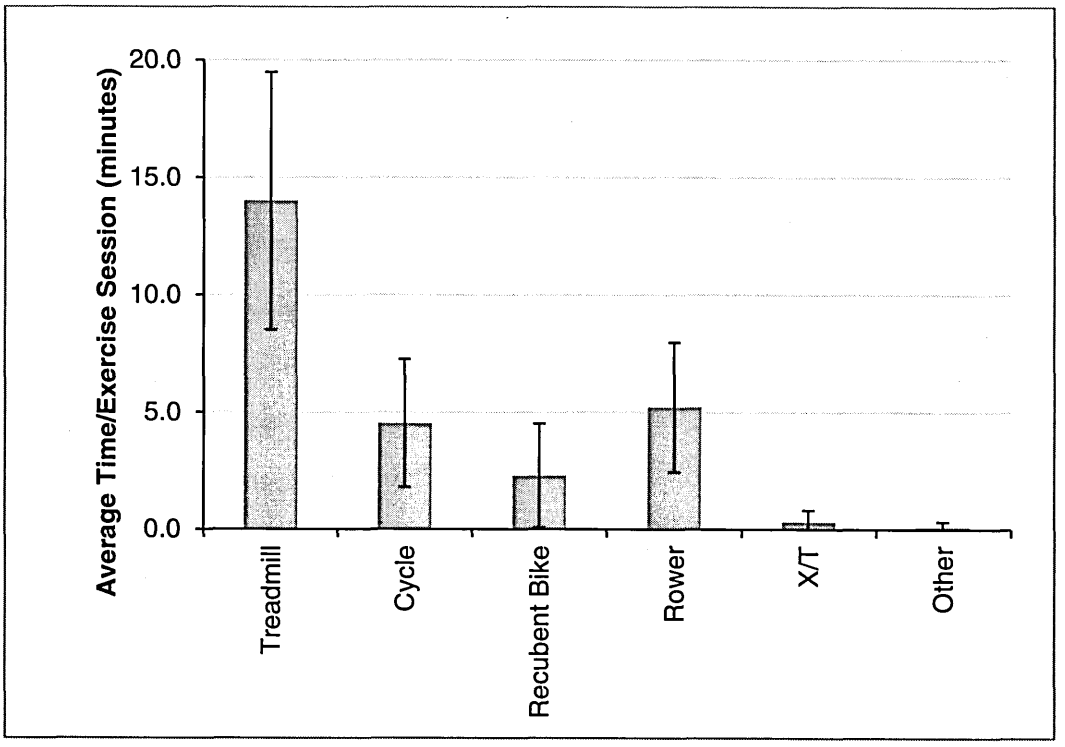

Figure 3.3. Exercise preference during supervised exercise sessions, with error bars reflecting SD (n=15).

Table 3.2. Physiological, Functional and anthropometric outcomes at baseline, follow-up 1 (week-10) and follow-up 2 (week-24) in the pragmatic exercise and usual care groups.

	Pragmatic Exercise			Usual Care			*P* Value	
	BL mean (SD)	FU1 mean (SD)	FU2 mean (SD)	BL mean (SD)	FU1 mean (SD)	FU2 mean (SD)	BL - FU1	BL - FU2
Antropometric								
Body Mass Index (m/kg^2)	26.7 (5.7)	26.1 (5.4)	27.0 (5.7)	26.6 (5.4)	26.8 (5.6)	27.0 (5.1)	0.13	0.80
Waist:Hip Ratio	0.79 (0.07)	0.81 (0.07)	0.79 (0.06)	0.80 (0.08)	0.83 (0.08)	0.82 (0.09)	0.63	0.26
MSFC								
25ft Walk (s)	6.1 (2.0)	5.2 (1.7)	5.5 (1.4)	5.2 (2.0)	5.1 (2.2)	5.8 (1.9)	0.33	0.08
9-hole peg test, dominant hand (s)	24.0 (4.7)	22.2 (4.5)	21.5 (3.1)	23.3 (4.3)	21.1 (3.5)	20.5 (3.4)	0.38	0.35
9-hole peg test, non-dominant hand (s)	29.6 (17.0)	25.4 (8.6)	22.8 (2.7)	24.6 (5.1)	22.8 (3.9)	22.2 (3.8)	0.88	0.90
PASAT	41.5 (14.7)	42.8 (15.9)	46.4 (9.3)	43.2 (12.3)	48.9 (8.3)	51.0 (6.3)	0.29	0.27
EDSS								
Score	3.0 (1.1)	2.8 (1.1)	2.7 (1.0)	3.1 (1.7)	3.2 (1.2)	3.0 (1.4)	0.07	0.48
GNDS								
Score	9.9 (5.8)	9.1 (6.3)	8.8 (5.5)	8.9 (6.3)	10.8 (8.6)	10.1 (9.1)	0.23	0.24
Aerobic Fitness Test								
Time to RPE 17 (s)	584.1 (358.2)	642.0 (415.6)	648.1 (269)	541.8 (351.3)	550.1 (401.4)	553.5 (401.4)	0.54	0.57

BL= Baseline, FU1= follow-up1, week-10, FU2= follow-up 2, week-24, 3-month post intervention

3.5.3 Functional, Clinical and Anthropometric Outcomes

There was encouraging evidence of improvements in walking speed between baseline and 3 months and EDSS between baseline and 10 weeks in the intervention group compared with standard care, but with changes being of border-line statistical significance (P=0.08 and 0.07 respectively) (Table 3.2). There were no improvements in anthropometric variables over the duration of the trial.

3.5.4 Quality of Life and Physical Activity Outcomes

The exercise group increased their readiness to exercise (P=0.003), based on the visual analogue stages of change ladder [19] (Figure 3.4) and there was a trend for an increase in moderate intensity physical activity (P=0.08) based on results from the Godin Leisure-Time Questionnaire [18] (table 3.3) at 3 months. In addition, this group also scored higher on the physical health composite component (P=0.05) of the MSQOL-54 [16] at 10 weeks (table 3.3).

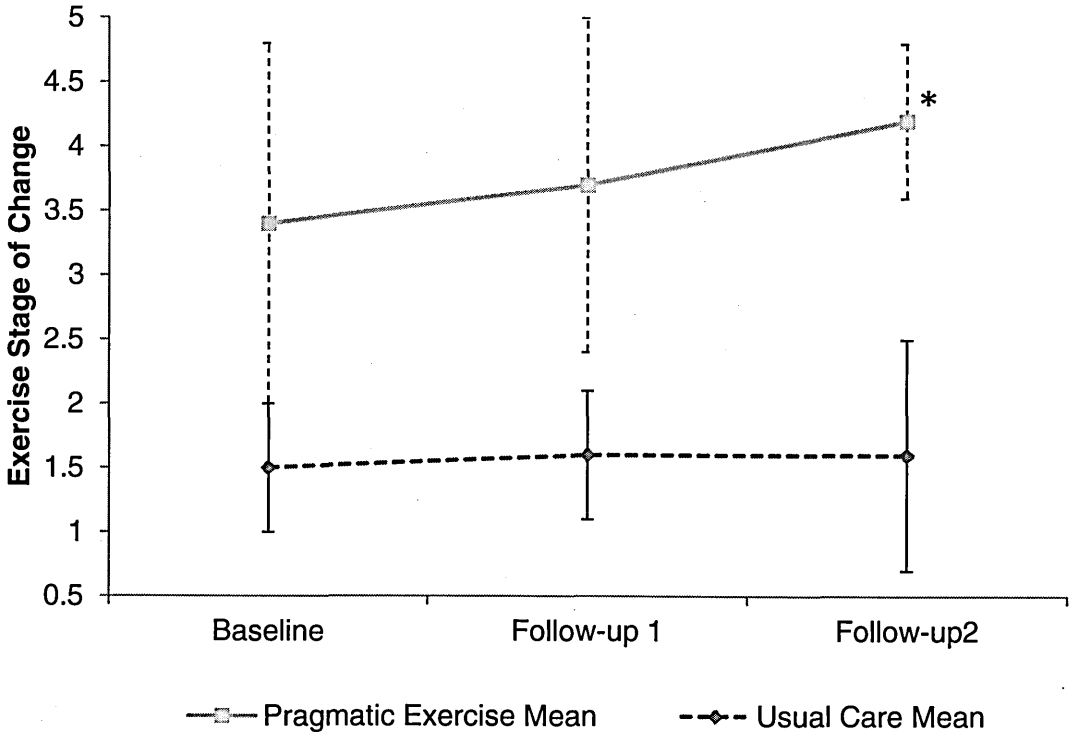

Figure 3.4. Change in exercise stage of change from baseline to follow-up 1 and baseline to follow-up 2 in the pragmatic exercise and usual care groups. * indicates significant change from baseline.

Table 3.3. Exercise and quality of life outcomes at baseline, follow-up 1 (week-10) and follow-up 2 (week-24) in the pragmatic exercise and usual care groups.

	Pragmatic Exercise			Usual Care			*P* Value	
	BL mean (SD)	FU1 mean (SD)	FU2 mean (SD)	BL mean (SD)	FU1 mean (SD)	FU2 mean (SD)	BL - FU1	BL - FU2
Godin leisure-time exercise Questionnaire								
Mild	3.8 (5.0)	4.1 (4.9)	1.9 (1.5)	3.2 (2.5)	3.2 (2.4)	3.0 (1.9)	0.588	0.088
Moderate	0.7 (1.4)	0.7 (1.3)	1.7 (1.5)	0.4 (0.9)	0.4 (0.9)	0.8 (1.0)	0.577	0.079
Vigorous	0.0 (0.0)	0.0 (0.0)	0.4 (0.9)	0.2 (0.6)	0.2 (0.6)	0.2 (0.4)	0.649	0.295
Weekly leisure activity score	14.7 (14.9)	14.7 (14.4)	17.8 (12.5)	13.2 (12.0)	13.3 (11.8)	14.4 (8.4)	0.585	0.457
MSQOL-54								
Overall Quality of Life	69.3 (24.3)	69.0 (15.4)	66.3 (15.8)	62.3 (20.1)	61.2 (19.8)	63.5 (18.0)	0.423	0.877
Physical Health Composite	45.4 (15.7)	52.6 (11.9)	50.0 (12.7)	47.8 (16.8)	47.9 (18.5)	54.0 (20.7)	0.050*	0.645
Mental Health Composite	60.7 (20.6)	65.5 (15.7)	62.7 (14.4)	62.3 (20.1)	58.6 (22.4)	58.0 (22.5)	0.115	0.413

BL= Baseline, FU1= follow-up1, week-10, FU2= follow-up 2, week-24, 3-month post intervention

3.5.5 Qualitative analysis

Data are reported as frequency counts for each of the questions asked. Over 90% of participants felt confident they would continue to exercise. When asked about feelings during and after exercise, 100% (n=14) gave positive comments, with remarks such as 'exercise made them feel more awake', 'eased aches and pains', and that they 'only occasionally felt tired'. Following exercise, 36% (n=5) reported feeling more energetic, 29% (n=4) reported that they felt tired at first but this improved and 29% (n=4) continued to feel occasional tiredness, but this was reported as manageable. All participants liked the session structure as it was tailored, built up gradually, manageable and they liked having goals and targets. However, 14% (n=2) did suggest a wider variety of equipment would have been preferable.

3.6 Discussion

This study evaluated the feasibility of a mixed (supervised and home-based) pragmatic exercise intervention, designed to promote confidence and motivation for self-directed exercise in people with mild to moderate disability due to MS. Our findings suggest that this type of intervention is feasible, with excellent retention (10 week, 87%; 3 month, 80%) and high compliance (> 75% of all sessions) rates, with this pragmatic approach leading to progression in exercise duration and intensity over the 10 week intervention period. Our preliminary data also suggests that PwMS might experience important behavioural and QoL benefits that are retained for at least 3 months. However, caution should be heeded when interpreting outcome data from feasibility studies, as participant numbers are not powered for statistical significance,

3.6.1 Recruitment, retention and compliance

Study recruitment rates (1.4 PwMS / month) are comparable a cognitive behavioural trial that recruited via clinics in Sheffield [22]. Recruitment to future large scale interventions could be enhanced by using a range of different methods to reach eligible patients (mail-outs, advertisements, patient notes and a multi-centre approach). The implementation of an efficient and effective recruitment strategy for patients on clinical trials is critical to avoid expensive delays and failures [23].

Trial retention was excellent (87% at 10 week; 80% at 3 month). Previous supervised interventions using similar exercise frequency and intensity have reported slightly lower retention rates (73 to 85% at follow-up 1) [24, 25, 26, 27]. The inclusion in our study of home exercise, individually tailored sessions and a framework to promote motivation and confidence to exercise may have increased retention rates. Previous home-based interventions focusing on resistance or physiotherapy exercises, have reported excellent retention rates of 95% to 100% [28, 29]. However, to our knowledge McCullagh *et al.* [30] is the only other exercise intervention with PwMS reporting long-term follow-up data (83% retention at follow-ups 1 and 2), which is comparable to rates reported here.

Compliance to exercise was also excellent, with 80% of participants completing at least 70% of both supervised and home sessions and with no adverse events reported. Petajan *et al.* [24] reported 97% compliance to a moderate intensity aerobic exercise programme (3 x week; 15 week), whilst Mostert and Kesselring [31] reported only 65% compliance (5 x week; 4 week) during exercise at the individually determined anaerobic threshold. Home-based exercise compliance rates are also variable, with a physiotherapy lead resistance programme (3 x

week; 8 weeks) reporting 95% compliance [28]. However, a combined supervised and home-based aerobic programme, reported 83% compliance for supervised exercise, with no participants achieving more than half of home-based sessions [30]. This is much lower than our home session compliance rates. However, their study [30] did not contain any cognitive strategies to enhance self-efficacy and promote positive behaviour change, suggesting that strategies used in the current study, could have had a positive impact on home exercise adherence, with 90% feeling confident to continue exercise after the programme. This is supported by previous research linking the importance of increased self-efficacy for physical activity participation in PwMS [32, 33, 34]. Future exercise interventions should consider the importance of this component when designing trials for PwMS.

3.6.2 Exercise progression and preferences

This study aimed to progress exercise sessions by increasing intensity and duration whilst keeping RPE between 11 and 13 (fairly light to somewhat hard). Exercise dose, intensity and TRIMP all increased across the programme, whilst RPE remained relatively constant, suggesting progression was well tolerated. Motl *et al.* [35] reported a relatively fast progression rate with PwMS (EDSS 4.0-6.0), from 15 to 60 min per session during an 8 week, moderate intensity, supervised programme. Rassova *et al* [36] reported progression from between 2 and 10 min of cycling during week 1 (60% VO_2 max), up to between 10 and 30 min at week 10, with progression dependent of disability. This progression rate is similar to results from our study, where progression was participant lead.

During the intervention PwMS were encouraged to try all suitable ergometers and provide feedback on preferences, to inform programme design. During supervised exercise, the treadmill was utilised the most. Rowing and cycling ergometers were also used frequently, but were not as well tolerated for long durations, either due to the higher intensity of the activity (rower) or localised muscle fatigue (cycle). This conflicts with suggestions that rowing was only likely to be tolerated by well-functioning patients [5], as after initial training on correct usage all our participants included rowing in their programme. Previous exercise research with PwMS has focused on treadmill or cycle ergometry [6] and to our knowledge no other intervention has utilised rowing. Anecdotally, for participants experiencing muscle fatigue, alternating between equipment using different muscle groups was found to assist with more continuous exercise. At home 68% of total exercise time was spent walking, in accordance with previous research [36].

3.6.3 Outcome measures

Changes in the outcome measures should be interpreted with caution due to the small sample size. However, high retention rates in both groups suggest that despite the large number of measures, the volume and type of assessments were feasible and did not discourage participation.

We observed significant improvements in stages of change and QoL (Physical Health Composite) reported. There was also encouraging evidence of an improvement in 25 ft walk, EDSS and increases in self-reported moderate intensity activity (borderline statistical significance). In addition, participants reported that they felt confident in continuing to be active and enjoyed exercise.

Anecdotally, participants commented on having the energy to do more at home, and using walking aids less. This suggests that PwMS can gain important clinical, physical and QoL benefits from exercise, with some improvements present after 3 months of follow-up. This is consistent with systematic reviews of exercise and MS, which concluded that mild to moderate exercise can be beneficial for PwMS, without any negative effects [4, 6]. Pilot work by McCullagh et al., [30] supports the possible benefits 3 months after an exercise intervention, suggesting significant improvements in both fatigue and QoL. However, a larger scale trial with long-term follow-up needs to be conducted before conclusions regarding exercise maintenance and long-term benefits can be drawn.

3.6.4 Study Limitations

Changes in physical activity and home exercise were assessed by questionnaire, a subjective fitness assessment and self-report activity diaries. This may have impacted on results given the social desirability response. The inclusion of an objective physical activity measure such as 7-day accelerometry would enhance future trials. The current study utilised strategies to enhance self-efficacy and confidence. However, it is recommended that these behaviour change constructs are explored in more detail in future trials to gain more insight into their impact on long-term-behaviour change in PwMS. This study used TRIMP as a non-intrusive method of monitoring changes in exercise load. This method does not take into account the limitations of using absolute heart rate as a measure of exercise intensity, particularly given the cardiovascular dysfunction reported in PwMS [37]. However, as TRIMP results compared the same individual over time, it is unlikely to have significantly impacted on the

findings. Future studies would benefit from using more precise measurements of change in exercise training load. Furthermore future studies would benefit from monitoring the other services such as physiotherapy that were accessed by PwMS during the trial, as this may have impacted on outcome measures. It is recommended that this not only monitored in future trials, but also that this pragmatic tailored approach could be further enhanced if both the expertise of a physiotherapist and an exercise researcher were used in the programme design.

3.7 Conclusions

Our findings suggest that this type of pragmatic exercise intervention is feasible for people with mild to moderate MS, with good compliance reported for both aspects of the programme. No other studies to date have investigated the feasibility of this type of pragmatic exercise programme, combining individually tailored aerobic (supervised and home-based) exercise, with flexibility, balance and core work, and behavioural strategies to encourage PwMS to be more physically active. In addition, a cautious consideration of the outcome data suggests that PwMS can experience behavioural and QoL benefits from participation and that these changes may be sustained for up to 3 months after the intervention. Future larger-scale definitive trials, with longer follow-up are required to corroborate the results from this preliminary study.

3.8 Acknowledgements

This project was funded by Sheffield Teaching Hospitals NHS Foundation Trust, a larger scale RCT is currently being funded by the MS Society.

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4.0 PRAGMATIC EXERCISE INTERVENTION FOR PEOPLE WITH MULTIPLE SCLEROSIS (EXIMS): RANDOMISED CONTROLLED TRIAL STUDY PROTOCOL.

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4.1 Preface for Chapter 4.0

Chapter three explored the feasibility of running a pragmatically designed exercise intervention for people with mild to moderate MS. Results suggested that this type of exercise intervention was not only feasible, but has the potential to elicit long-term exercise behaviour change, with a further large scale trial required to support these findings.

The results from the feasibility trial outlined in chapter three informed the design of a larger RCT in this population group. The methods of which are reported in chapter four. Permission for its reprint in this thesis has been gained from the publishers (Appendix 9.14).

4.2 Abstract

Exercise is an effective intervention for improving function, mobility and health-related quality of life in people with multiple sclerosis (PwMS). Questions remain however, regarding the effectiveness of pragmatic exercise interventions for evoking tangible and sustained increases in physical activity and long-term impact on important health outcomes in PwMS. Furthermore, dose–response relationships between exercise and health outcomes have not previously been reported in PwMS. These issues, and improved knowledge of cost effectiveness, are likely to influence key decisions of health policymakers regarding the implementation of exercise therapy as part of the patient care pathway for PwMS. Hence, the primary aim of this study is to investigate whether a 12-week tapered programme of supervised exercise, incorporating cognitive-behavioural techniques to facilitate sustained behaviour change, is effective for evoking improvements in physical activity and key health outcomes in PwMS over 9 months of follow-up. A total of 120 PwMS will be randomised (1:1) to either a 12-week pragmatic exercise therapy intervention or usual care control group. Participants will be included on the basis of a clinical diagnosis of MS, with an expanded disability status score (EDSS) between 1 and 6.5. Outcome measures, to be assessed before and after the intervention and 6 months later, will include physical activity, clinical and functional measures and health-related quality of life. In addition, the cost effectiveness of the intervention will be evaluated and dose– response relationships between physical activity and the primary/ secondary outcomes in those with mild and more severe disease will be explored.

4.3 Introduction

Living with multiple sclerosis (MS) can be a difficult experience, both physically and psychologically [1,2], with common symptoms including visual problems, motor abnormalities, bowel and bladder incontinence, loss of balance and sexual dysfunction [2,3]. Research also indicates that there is an increased prevalence of falls in people with MS (PwMS) [4,5] and a high proportion of patients who experience debilitating symptoms of fatigue, defined as a 'a subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual and desired activities' [6]. Hence, there is a need to assess the effectiveness of therapeutic strategies that could have a long-term impact on health-related quality of life of PwMS, particularly given that MS affects many young and middle-aged individuals [7], who have a life expectancy close to normal [8].

A growing body of evidence supports the beneficial effects of exercise in terms of wide-ranging health outcomes for PwMS [9–13]. However, a major challenge is to develop pragmatic and cost-effective interventions that engage PwMS in exercise therapy and have a long-lasting impact on physical activity behaviour. Supervised facility-based exercise programmes offer comprehensive support and guidance but over the long-term they are likely to prove difficult due to time barriers, transport issues and health constraints (e.g. fatigue) in PwMS. In addition, they are very labour intensive, require specialised equipment, and may not be cost-effective. Pragmatic physical activity interventions, involving cognitive-behavioural techniques to promote confidence for self-directed exercise are likely to be more cost-effective than long-term supervised programmes of exercise therapy.

We undertook a small-scale study (N=30) to investigate the feasibility of a

pragmatic exercise intervention which was designed to promote sustained changes in physical activity behaviour in PwMS. The intervention involved two supervised and one home-based exercise session each week for 10 weeks, using a variety of cognitive-behavioural techniques (e.g. consciousness raising, goal setting and finding social support for exercise) and the Transtheoretical Model [14] as a guiding framework, to promote motivation and confidence for exercise. Outcomes were assessed at baseline, after the 10 week intervention and after a further 3 months. Adherence to the intervention was excellent (80% of participants completed ≥70% of the exercise sessions), attrition was low (20%) and trends for improvement in key health outcomes (i.e. quality of life and readiness to exercise) were observed up to 3 months of follow-up in the intervention group. Focus groups showed that PwMS enjoyed the intervention, including the structure and content of the sessions. Qualitative analysis also revealed that the exercise sessions provided participants with feelings of energy, vitality and a sense of achievement. On completing the 10-week intervention, over 90% of the participants indicated that they felt confident they would continue to exercise in their communities.

On the basis of these positive feasibility data and the qualitative feedback received from PwMS, this definitive randomised controlled trial was designed to investigate the effectiveness of this pragmatic approach to implementing exercise therapy in a larger population of PwMS. The main aims of this trial are to investigate the effects of the pragmatic exercise intervention on physical activity behaviour and important health outcomes up to 9 months of follow-up, as well as cost-effectiveness of the intervention in relation to standard care.

In addition, dose–response relationships between exercise therapy and the primary/secondary outcomes in those with mild and more severe disease will be explored.

4.4. Methods

4.4.1. Patient recruitment

A total of 120 PwMS will be recruited by consultant neurologists at the collaborating hospitals and via flyers/community adverts displayed at the local South Yorkshire MS Society branches. All patients will be seen by a neurologist prior to entering the trial, regardless of their route of recruitment. In total, around 50 potential participants per week are seen at the collaborating hospital centres. In addition, we will have access to several hundred PwMS who are affiliated with local South Yorkshire MS Society branches. We will seek to feature the trial in the MS matters newsletter during recruitment and aim to recruit the required sample of 120 PwMS over 24-months; this equates to a recruitment rate of 5 PwMS per month. Participant travel expenses will be reimbursed. Ethics approval for the study has been granted by the South Yorkshire Research Ethics Committee.

4.4.2 Randomisation and allocation concealment

The study is a randomised controlled trial with participants being randomised to the pragmatic exercise intervention or standard care control group (Fig. 4.1). Stratification will be used to balance the potentially confounding variables of gender and Expanded Disability Status Scale (EDSS) score (low: up to 3.5, high: up to 6.5). Randomisation will be undertaken by a distant randomisation service at the University of York, UK. The randomisation sequence will not be

disclosed until participants have completed their baseline assessments.

4.4.3 Inclusion and exclusion criteria

The inclusion criteria for the trial are: clinical diagnosis of MS with an EDSS score of between 1.0 and 6.5, and able to walk 10 m distance; aged 18–65 years; clinically stable for at least 4 weeks prior to entering the study; participants on disease modifying therapy (Interferon, Glatiramer Acetate, Mitoxantrone and Natalizumab) must have been stable on this treatment for at least 3 months prior to entering the study; physically able to participate in some form of exercise three times per week; able to provide written informed consent. The exclusion criteria for the trial are: failure to meet any of the above inclusion criteria; experiencing illness that impairs the ability to be physically active three times per week; unwilling to be randomised to either the exercise intervention or usual care control group; living more than 20 miles from the trial centre; already engaged in purposeful structured exercise or brisk walking ≥3 times per week for ≥30 min per session for at least 6-months.

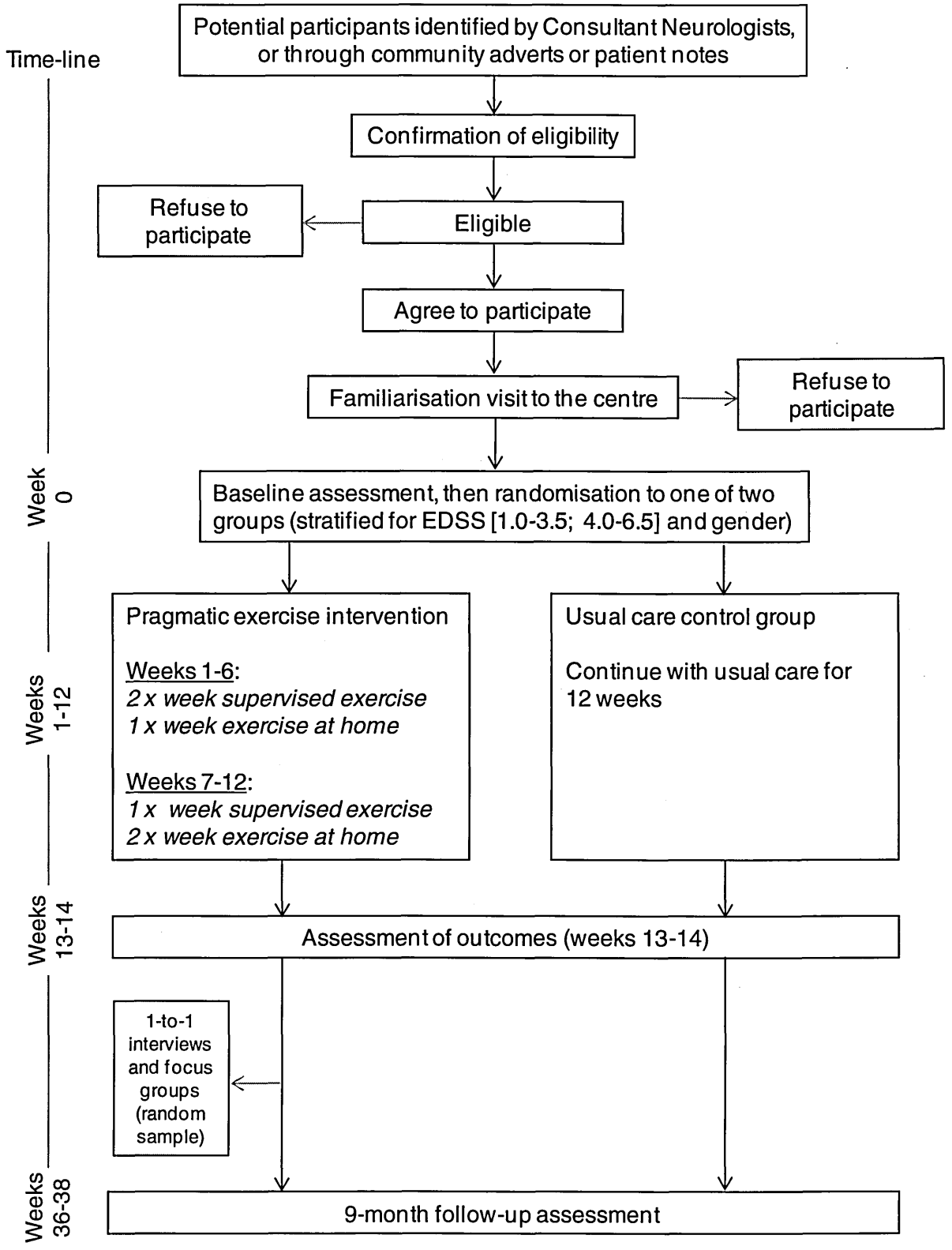

Figure 4.1. Flow of participants through the trial.

4.4.4 Sample size calculations and expected loss to follow-up

The sample size estimation is based on physical activity behaviour change data from our pilot study [15,16] and an estimated post-intervention difference in 6-min walk test (6MWT) between the groups [17]. A sample of 50 patients randomised to each group will be sufficient to detect a moderate effect size difference (80% power and a 5% significance level) of 1.3 units on the Godin physical activity scale (standard deviation=2.29 [our pilot study data]) and an increase of 56 m (sd=99.4 m) in 6MWT [17] (an increase in 6MWT of 56 m was accompanied by improved neurological function after a 12 week aerobic exercise programme in PwMS) [17]. This figure rises to 60 in each group to allow for a 15% loss to follow-up.

4.4.5 Exercise intervention

At baseline, participants in the intervention group will receive a pack of printed information that details important information about exercise and MS (e.g. safely increasing exercise over time, minimising injuries, dealing with fatigue, taking heart rate and appropriate shoes for exercise, etc.). The intervention period will be 12 weeks in duration, with more frequent participant contact during weeks 1–6 (2 supervised exercise sessions), and reduced contact during weeks 7–12 (one supervised exercise session). In accordance with recent recommendations for PwMS [13], and as used in our pilot study, the intervention will be staged-adapted and participants will be encouraged to exercise within their own capabilities, which will be influenced by individual symptomatology. An exercise physiologist and specialist physiotherapist will oversee the delivery of the intervention.

During weeks 1–6, participants will attend two supervised sessions per week at

the Centre for Sport and Exercise Science (CSES) and will be required to undertake one additional session in their home environment. Supervised sessions will involve small groups of up to three participants led by an exercise therapist/researcher. Each session will last approximately 1 h and participants will be offered a range of aerobic exercises (e.g. stepping, cycle-ergo, walking, rowing, and arm-cranking). Participants will be asked to complete short bouts (e.g. 5×3-min, with 2-min rest intervals) of low to moderate intensity aerobic exercise (50–69% of maximum heart rate). As the intervention progresses and when appropriate, participants will be encouraged to participate in longer periods of aerobic exercise (e.g. 5×4-min) or to take shorter rests between bouts. Sessions will also incorporate exercises that focus upon developing muscle strength. Participants will undertake 1–3 sets of strength training exercises for large skeletal muscle groups using light weights, Therabands and body resistance, which will be progressed according to individual capabilities. Balance board and static stretching exercises for large skeletal muscle groups will also be incorporated into the sessions. Heart rate, ratings of perceived exertion and minutes of specific exercises completed in each session will be recorded by the researcher to allow for an assessment of the exercise dose achieved each week.

During weeks 7–12 participants will attend CSES once per week and complete two home sessions per week on their own. We hypothesise that the gradual increase in home-based sessions within the intervention group will help to facilitate independent exercise participation after the intervention phase is completed. As for the supervised sessions, the home sessions will be geared towards the mobility and symptoms of each participant. During the single weekly supervised session at CSES, they will undertake aerobic exercise (as in

weeks 1–6) and discuss and receive advice on the content of their home-based exercise sessions, which will aim to mirror that of the supervised sessions, in terms of intensity and duration of aerobic exercise and additional tailored exercises for strength, flexibility and balance. Participants will be encouraged to seek out opportunities to exercise either in the home or in the local community (e.g. healthy living centres, health walks, fitness centres, swimming pools, etc.), based on their individual needs and preferences, and will receive instructions on how to complete a physical activity log for quantification of structured exercise sessions achieved outside of the supervised sessions.

4.4.6 Theoretical model for facilitating physical activity behaviour change

The supervised exercise sessions will also incorporate cognitive-behavioural techniques (e.g. goal setting, finding social support, understanding the costs/benefits of exercise etc.) to promote long-term participation in physical activity. Using the Transtheoretical Model [14] as a guiding framework, this aspect of the intervention will be aimed at equipping PwMS with the skills, knowledge and confidence to engage in a more physically active lifestyle (Table 4.1).

Table 4.1. Strategies used in exercise counselling.

Suggested time-frame (individual)	Processes and mediators of change	Exercise counselling framework: Examples of skills and techniques to be used
Weeks 1–2 of the intervention	Consciousness Raising (benefits), Dramatic relief (risks) Tools: decisional balance	*Review first session:* • How did it feel? Was it difficult/easy? • Did you enjoy it? • What to expect in the coming weeks • Finding time for exercise - fitting it in the gaps. • Your exercise preferences. Consider previous exercise experiences *Exercise knowledge* • Benefits of exercise/consequences of inactivity • How often, how hard and for how long? • Where and when? • Contra-indications to exercise—when and when not to exercise • Importance of hydration • Importance of warming up and cooling down
Weeks 3–4 of the intervention	Self re-evaluation Decisional balance Consciousness raising	*Which physical exercises do I prefer?* • Previous exercise experiences, why this worked/failed. • What other exercises might you like to try? *Are you enjoying the sessions?* • What do you like/dislike? • What would you change? • Is it what you had expected? • What benefits have I noticed? *Exercise knowledge* • Training principles—de-training, overload and adaptation
Weeks 5–6 of the intervention	Self re-evaluation Goal setting/self-regulation Social support	*Introduce goal setting* • What is it and how might it help? • Set one SMART goal *Exercise review* • How do you feel after 5–6 weeks? • What do you enjoy most? *Findings support for exercise* • Thinking of others who might encourage participation in exercise • Consider ways in which to exercise with other people • What opportunities are there, how available are they?
Weeks 6–12 of the intervention	Goal setting/self-regulation Stimulus control (identify situations and relapse prevention) Reinforcement management (reward success) Self-liberation (making commitments, goal setting)	*Review goals* • Did you achieve them? • If yes well done! If not, why not? What can we do to help change this? Cues for action • Think of tasks that might prompt participation in exercise *Thinking about moving on from the programme* • Avoiding relapse from exercise • Future exercise options *Looking/planning ahead—SWOT analysis* • What will help me to exercise in the future? • What will stop me? *What have I achieved so far* • Review exercise, what has been learned? • Thinking positively and taking positive action *Moving on* • Action plan for home

4.4.7 Outcome measures

4.4.7.1 Timing of assessments and setting

Unless otherwise stated, outcomes will be blindly assessed at three time-points: baseline, after the 12-week intervention and 6-months later. Personal characteristics (e.g. postcode, marital status, ethnicity, etc.) and condition specific data (e.g. time since diagnosis, medication, onset of symptoms, use of health care resources etc.) will be collected. Large print versions of the questionnaires will be available. Clinicians at the collaborating hospitals will perform the neurological tests and an experienced researcher will assess other outcomes at the SHU site. Self assessment questionnaires (for participants to take home) will be used where indicated to reduce the assessment burden for PwMS. These will take approximately 1.5 h to be completed. Patients in the usual care control group will be assessed at the same time points.

4.4.7.2 Primary outcomes

Physical activity levels will be monitored over a 7-day period, using a combination of self-report physical activity questionnaire/recall diary and accelerometry (Actigraph GT1M, Actigraph, LLC, Fl, USA). The advantages of using both measures are that the objective measures can provide a more accurate measure of physical activity, whilst the subjective measure gives context. The Leisure Score Index (LSI) of the Godin Leisure Time Exercise Questionnaire [15,16] will be used to measure self-reported physical activity behaviour. Quantification of structured exercise sessions at the CSES and in the home environment will be verified using a physical activity log comprising a checklist for type, duration, and intensity of exercise achieved. The Actigraph is reported to be amongst the most extensively validated accelerometers and has

been proven to correlate reasonably with doubly labelled water derived energy expenditure techniques [18]. Functional exercise capacity (proxy measure of compliance to the intervention) will also be assessed using the 6-minute walking test (6MWT), according to a standardised protocol [19]. This test is sensitive to change following exercise interventions in PwMS [17,20].

4.4.7.3 Secondary outcomes

4.4.7.3.1 Neurological impairment and clinical functional ability.

The EDSS [21] will be assessed according to standard clinical procedures by the neurology consultant using two standardised methods. The EDSS has been shown to be reliable and valid and is frequently used for evaluating neurological impairment in research involving adults with MS. The Multiple Sclerosis Functional Composite (MSFC) [22] is a measure of clinical functional ability. It includes a timed 25-foot walk and measures of arm/hand function (9-hole peg test) and cognitive function (paced auditory serial addition).

4.4.7.3.2. Quality of life, fatigue and qualitative analysis of patient experiences.

The Multiple Sclerosis Quality of Life-54 questionnaire (MSQOL-54) [23] is a generic HRQOL instrument based on the Medical Outcome Short Form-36 (SF-36) Health Survey, but with 18 additional items relevant to PwMS. Both dimensional and composite scores will be used in the analyses. This will be self-assessed by the participants. Perceived effects of fatigue will be assessed using the Modified Fatigue Impact Scale (MFIS), which has been validated for PwMS [24,25]. This will be self-assessed by the participants. At the end of the intervention, a random sample of 30 PwMS from the intervention group will be invited to participate in a one-to-one, semi-structured interview and focus group

sessions to elicit detailed and confidential accounts of their experiences. The interview schedule will be similar to that used by Dodd et al. [26] and will concentrate on patients' experiences, barriers and attitudes towards exercise, perceived benefits and adverse effects of the intervention. This qualitative aspect will help to overcome the limitations of rating scales in assessing treatment benefits in PwMS.

4.4.7.3.3 Cost effectiveness of the pragmatic exercise intervention.

An economic evaluation will be undertaken alongside the trial Service (NHS) perspective will be used in the primary economic analysis. This and other methods will be in accordance with UK National Institute for Health and Clinical Excellence (NICE) Technology Appraisal Guidelines [28]. Data collection will also account for costs incurred by the participants themselves for supplementary analysis, to allow for a broader perspective to be taken. The cost of the programme for each participant at each arm of the trial will need to be estimated. This is achieved by collecting costs for staff time, facilities hire, equipment and staff travel. Resource use data will be recorded for all participants, accounting for their health service use over the 3-months of follow-up. Use of primary care will be obtained from self-completed resource use items included in the health follow-up questionnaires. Use of hospital services, i.e. inpatient admission (including length of stay and speciality), outpatient attendances and A&E visits, will be obtained from hospital records. To enable a broader-base costing, PwMS will also be asked about their use of social services. The Medical Outcome Short Form-36 (SF-36) Health Survey generates summary measures for physical and mental health which can be used for the assessment of effectiveness [29]. The SF-36 summary measures

can be derived from the MSQOL-54 [23]. The one-page EuroQoL EQ-5D [30] will be included to provide an additional preference-based measure.

4.4.7.3.4 Data analysis.

Differences in primary and secondary outcomes between groups will be compared using intention to treat analysis. Outcomes will be compared over the follow-up period using mixed model analysis, adjusting outcomes for baseline scores. Effect size statistics will be determined to indicate the clinical impact of the intervention. Multiple regression will be used to explore dose–response effects on outcome. Associations between 'exercise dose' (product of total exercise duration x average intensity of each session) and change in health outcomes will be assessed using regression modelling, adjusting for gender and EDSS score. Imputation methods will be used to assess data losses through level drop-out and loss to follow-up. All results will be reported as means and 95% confidence intervals. Our medical statistician (AR) blinded to group allocation will undertake the analysis.

The main cost effectiveness analysis will be an intention to treat comparison of the costs of providing a pragmatic exercise therapy intervention as opposed to the standard treatment for PwMS, compared to gains in the SF-36 scores at the individual patient level. The final result will be presented as a ratio of the differences in costs and quality-adjusted life years (QALYs) between the two arms of the trial, with a 95% confidence interval estimated by bootstrapping. Results will be plotted on the cost effectiveness plane and then transformed into cost effectiveness acceptability curves with their associated frontier [27]. There will be considerable uncertainty in many of the cost estimates and the underlying estimate of benefit. Furthermore, an important consideration in the

long term cost effectiveness of this intervention is likely to be the longevity of the benefits and cost consequences, therefore highlighting the importance of undertaking sensitivity analysis.

The qualitative analysis (both interviews and focus groups) will be guided by a 'framework approach' to data collection and analysis. A thematic analysis will be used to explore the narrative accounts of individuals within (and across) the focus groups and interviews. Interview and focus group audio recordings will be transcribed verbatim. Three researchers will verify the identification and refinement of themes from the research. The analytical process will be facilitated by the use of QSR Nvivo software.

4.5 Discussion

MS affects around 100,000 people in the UK [31] and the clinical symptoms of the disease impose a significant burden to patients, the healthcare system and wider economy. This study intends to generate new knowledge on the effectiveness of a pragmatic approach to implementing exercise therapy in relation to physical activity behaviour change up to 9 months of follow-up and a range of other key health outcomes in PwMS of varying disability levels (EDSS range: 1.0–6.5). Dose–response relationships between exercise therapy and health outcomes will also be explored. In addition, the study will yield novel data on exercise preferences and rate of exercise progression in the facility and home-based settings, cost-effectiveness in relation to service usage and an abundance of rich qualitative data on participant experiences and subjective health benefits.

Systematic reviews and a meta-analysis show that exercise therapy is a safe, non-pharmacological treatment strategy for PwMS and can bring many health

benefits, including improvements in muscle power, physical and psychosocial functioning and quality of life [32–34]. Exercise therapy may also have an important role to play in the management of fatigue [35], which affects ≥75% of PwMS either persistently or sporadically [36] and with up to 55% of PwMS describing it as their most severe symptom [37]. Fatigue negatively affects quality of life [38,39], mental alertness [40] and cognitive processing [41] and has a major impact on the high levels of unemployment in PwMS [42,43]. A systematic review of clinical fatigue treatments for PwMS concluded that the effectiveness of pharmacological and psychosocial interventions was likely to be modest at best but was most often reported to be ineffective [44]. Hence, alternative approaches to fatigue management are clearly needed and treatment modalities that can be incorporated into self-management strategies could have particular appeal to patients, their carers and healthcare providers.

Further research is needed to understand the relative effectiveness of different exercise regimens for evoking improvements in clinical symptoms in PwMS of different disability levels. There is also a need to assess the impact of interventions designed to equip PwMS with the skills and confidence needed to become independent exercisers. Evidence suggests that PwMS is less physically active than the general population [45]. Physical inactivity resulting from a predominantly sedentary lifestyle has the potential to exacerbate functional impairments and increase the risk of developing other health concerns such as cardiovascular disease, obesity, type-2 diabetes and some cancers [13]. Pragmatic physical activity interventions, involving cognitive behavioural techniques to promote confidence for self-directed exercise, have been effectively implemented in other populations, including those with chronic diseases [46–49] and are likely to be more cost-effective than long-term

supervised programmes of exercise therapy.

We have designed an exercise therapy intervention which is predominantly home-based in the latter stages, but with a tapered programme of supervised sessions to guide and support PwMS. The rationale is to provide PwMS with the skills, knowledge and confidence to engage in a more physically active lifestyle, hence promoting better self-management of the condition. A stronger evidence-base for the long-term impact of such approaches on exercise participation and important health outcomes will help to build greater confidence in exercise therapy amongst health professionals and motivate a greater number of PwMS to engage in exercise for improved self-management of their condition. Consequently, this could mean fewer GP visits, lower overall burden on healthcare systems and further tangible economic returns resulting from improved occupational productivity. If effective, the intervention could also become part of the treatment pathway for PwMS within the National Health Service and other healthcare organisations.

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5.0 PARTICIPANT RECRUITMENT INTO A RANDOMISED CONTROLLED TRIAL OF EXERCISE THERAPY FOR PEOPLE WITH MULTIPLE SCLEROSIS.

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5.1 Preface to Chapter 5

Chapter four outlines the Methods used for the main study trial, whilst chapter five provides detailed information on the recruitment strategies, rates and estimated costs for the main study trial. Results from which suggested that recruitment via MS clinics yielded the greatest number of participants, whilst recruitment from consultant mail-outs was the most cost effective strategy, suggesting that to reach recruitment targets a variety of methods need to be employed.

Chapters six and seven report the results from the main trial, including clinical, functional, quality of life and cost effectiveness outcomes. Permission for its reprint in this thesis has been gained from the publishers (Appendix 9.14).

5.2 Abstract

Background: The success of a clinical trial is often dependant on whether recruitment targets can be met in the required timescale. Despite an increase in research into the benefits of exercise in people with Multiple Sclerosis (PwMS), no trial has reported detailed data on effective recruitment strategies for large-scale Randomised Control Trials (RCTs). The main purpose of this report is to provide a detailed outline of recruitment strategies, rates and estimated costs for the Exercise intervention for Multiple Sclerosis (EXIMS) trial to identify best practice for future trials involving MS patient recruitment.

Methods: EXIMS recruited 120 PwMS, to a 12-week exercise intervention, with participants randomly allocated to either exercise or usual care control groups. Participants were sedentary, aged 18-65 years and had an Expanded Disability Status Scale (EDSS) score of 1.0-6.5. Recruitment strategies included attendance at MS outpatient clinics, consultant mail-out and trial awareness raising activities.

Results: 120 participants were recruited over 34-months. To achieve this, 369 potentially eligible and interested participants were identified. A total of 60% of participants were recruited via MS clinics, 29.2% from consultant mail-outs and 10.8% through trial awareness. The randomisation yield was 33.2%, 31.0% and 68.4% for MS Clinic, consultant mail-outs and trial awareness strategies respectively. The main reason for ineligibility was being too active (69.2%), whilst for eligible participants the most common reason for non-participation was the need to travel to the study site (15.8%). Recruitment via consultant mail-out was the most cost-effective strategy, with MS clinics being the most time consuming and costly.

Conclusions: To reach recruitment targets in a timely fashion a variety of methods were employed, although consultant mail-outs were the most cost-effective recruitment strategy, use of this method alone would have not reached the required number of participants in the required time period, leading to costly extensions to the project or failure to reach the number required for statistical power. Thus a multifaceted approach to recruitment is recommended for future trials.

5.3 Background

One of the most difficult challenges in clinical trials is whether appropriate participants can be identified and consented quickly (Lindbald, Zingeser and Sismanyazici, 2011). Many trials either fail to reach recruitment targets or have to be extended (McDonald et al., 2006). This then either leads to an under-powered study, or an extension to the duration of the study often at additional cost, impacting on the time required to inform clinical practice and utilising funds that could have been used for other research (Treweek et al., 2011; McDonald et al., 2011). The implementation of an efficient and effective recruitment strategy for patients on clinical trials is critical if expensive delays and failures to meet predetermined targets are to be avoided (Probstfield and Frye, 2011).

The introduction of CONSORT guidelines (Moher et al., 2001) has improved the quality of recruitment information reported for randomised control trials. However, detailed data on recruitment, including methods used, rates achieved and cost are still underreported. More detailed data would help to identify strategies to improve recruitment, benefiting both researchers and research (Treweek et al., 2011) and ultimately patients.

In recent years there has been an increase in the number of studies that have investigated the possible health benefits of exercise for people with multiple sclerosis (PwMS) (Asano et al., 2009; Latimer-Cheung et al., 2013 and Sá 2014). Although detailed recruitment data for exercise interventions in other clinical populations, such as breast cancer patients and wheelchair users, are available (Ott et al., 2006; Daley et al., 2007; Nary et al., 2011), to date no study has reported recruitment data for a large-scale randomised control exercise trial for PwMS. In recent years, the number of clinical trials in MS has increased, leading to an increased need to recruit research participants from a limited patient pool, and with modern trials often needing large sample sizes to ensure adequate statistical power (Montalban, 2011).

The Exercise Intervention for Multiple Sclerosis (ExIMS) trial was a large-scale randomised control trial involving 120 people with mild to moderate MS. It was designed to investigate the short and longer-term health impacts of a 12-week pragmatic exercise programme (Carter et al., 2014; Tosh et al., 2014). The main purpose of this report is to provide a detailed outline of the recruitment methods, rates and estimated cost to help inform future research of this type. In addition, we aim to determine which recruitment method provided the highest yield of participants and the lowest cost per participant.

5.4 Methods

5.4.1 Trial Design

A brief description of the trial design is reported here as detailed protocol and outcomes papers for this study have been published elsewhere (Saxton, et al., 2013; Carter et al., 2014; Tosh et al., 2014). Power calculations indicated that we would need 100 PwMS to complete the trial. This alongside the retention rates observed in our feasibility study of 87% immediately following the intervention and 80% at 3-months (Carter et al., 2013), lead to a recruitment target of 120 PwMS (60 in each group). The project was funded for three years, and an initial recruitment target of five participants per month, over 24 months was set, with recruitment beginning in February 2009. A sample of 120 PwMS, with mild to moderate disability (EDSS ≤ 6.5) was recruited. Participants were randomized to a 12-week pragmatic exercise intervention (2 x supervised and 1 x home-based session per week for 6-weeks followed by 1 x supervised and 2 x home-based sessions per week for 6-weeks, plus usual care) or usual care alone. The primary outcome was self-reported exercise behaviour at 3-months using the Godin Leisure Time Exercise Questionnaire (GLTEQ) (Godin et al., 1985). In addition accelerometry was used to provide an objective measure of daily activity and step count (Actigraph GT2M accelerometer, Actigraph, LLC, FL, USA). Secondary outcome measures included fatigue, health related quality of life, functional ability and neurological impairment. Outcomes were assessed at baseline, immediately post intervention (3 months) and 6 months post intervention (9 months). This study was approved by the South Yorkshire Research Ethics Committee (08/H1310/69) according to the principles of the declaration of Helsinki and all participants provided informed consent prior to enrolment.

5.4.2 Eligibility Criteria

Regardless of the recruitment method used, all participants were screened by a consultant neurologist prior to entering the trial. Participants were included if they; had a clinical diagnosis of MS using the McDonald diagnostic criteria for MS (Polman et al 2011); had an Expanded Disability Status Score (EDSS) (Kurtze, 1983) between 1.0 and 6.5; aged 18-65 years; were stable on disease modifying treatment for ≥ three months prior to recruitment; were clinically stable (had not experienced a relapse in at least four weeks); were physically able to participate in exercise three times per week and were able to provide written informed consent. Exclusion criteria were; failure to meet any of the inclusion criteria; experiencing illness that would be a contra indicator to exercise; living further than 20 miles from the trial centre; unwilling to be randomised to either group; already engaged in moderate structured exercise ≥ three times per week for ≥ 30 min per session consistently for the last six months. Participants who were initially screened out due to either having changed their drug treatment in the last three months or having had a relapse in the previous four weeks were re-assessed following the required lapse of time and recruited if the eligibility criteria were then met.

5.4.3 Recruitment Methods

Participants were recruited continuously until the required sample size was obtained. All recruitment methods and procedures were approved by the South Yorkshire Research Ethics Committee. Regardless of recruitment method the following procedures were adhered to (table 5.1).

Table 5.1. Recruitment process for ExIMS trial.

Recruitment Process
• **Potentially eligible participants identified (consultant neurologist, mail-out, other)** • **Trial manager made aware of participants interest** • **Trial manager speaks (phone or in person) with participant to outline study, answer questions and screen participants for all eligibility criteria** • **If interested and eligible participant booked in for trial familiarisation session (phone or in person)** • **Potential participant attends trial familiarisation at trial site and is given 7 days to consider participation** • **Participant booked in for initial appointment to provide informed consent and participate in baseline assessment**

5.4.3.1Consultant Referral at MS Outpatient Clinic

Consultant referral at MS outpatient clinics was the primary recruitment strategy, as consultant recommendations are thought to play a crucial role in participants' decisions to enrol in a clinical trial (Lindbald et al., 2012; Probstfield and Frye, 2011). In addition, recruitment by this method would reduce the possibility of patients being contacted who did not meet the eligibility criteria.

MS outpatient clinics took place at the Royal Hallamshire Hospital, Sheffield on a weekly basis. The project's lead consultant (BS) and two other neurology consultants assisted with identifying potentially eligible and interested

participants. Each consultant saw approximately 13 patients per clinic (10 follow-ups and three new patients) over a 3.5-hour period. A trial researcher attended all clinics, enabling any participants identified to speak with them about the trial, ask any questions and confirm eligibility. If interested, participants were booked in for a familiarisation session at the trial site.

5.4.3.2 Consultant Mail-out

To maintain a consistent flow of patients onto the study, participant mail-outs were timed to take place during periods of low recruitment. Letters were sent in batches of no more than 125 to manage the flow of patients onto the study and ensure that all participants who responded could be contacted in a timely manner. All mail-outs were sent from the project's lead consultant (BS) and contained the logos of the Hospital, the University and the funding body (MS Society). The details of the participants to be included in the mail-outs were obtained from the local MS Risk Sharing Scheme database and clinic waiting lists. Notes of potential participants were screened for all available eligibility criteria (clinical diagnosis of MS, distance from trial centre, EDSS score and age). In addition, those that had been previously contacted about the project through other means and stated that they did not wish to take part were screened out at this stage. Letters contained a reply slip, stamped addressed envelope and the participant information sheet, along with a contact number for further information. The trial manager contacted all interested participants on receipt of the reply slip to answer any questions and confirm eligibility. No attempt was made to contact patients who did not respond to the invitation letter from their consultant.

5.4.3.3 Trial Awareness Strategies

Other trial awareness strategies included leaflets and posters at clinics, therapy centres and regional MS Societies, presentations and attendance at regional MS Society events and to local MS physiotherapy teams, referral from other professionals such as MS nurses and word of mouth. Despite being reported as a potentially successful recruitment method (Daley et al., 2007), we chose not to use local media (radio, television and newspapers) as it was felt that this may attract too many individuals who did not meet the study eligibility criteria. It was agreed that this strategy would be used only as a last resort.

5.4.3.4 Incentives

Participants were reimbursed travel costs (40 p per mile up to a maximum of £10 per visit) for all visits to the trial centre, with free parking made available. Those more severely disabled were also offered the option of a taxi service if other methods of transport would restrict their ability to participate. Flexible appointment times and start dates were made available to help participants fit the trial commitments around work, children and fatigue patterns. To encourage participation the usual care group were offered up to 4 exercise sessions following the study. This option was taken up by 20% of the usual care participants who completed the study.

5.4.3.5 Data analysis

Participant recruitment rates were calculated as the average number of participants recruited per month over the duration of the recruitment period. Response rates were reported as percentage interested and percentage

recruited. Recruitment yields were calculated as total recruited divided by the number of interested participants. Recruitment time was estimated based on time taken to ascertain interest and eligibility in the study and does not include any other time taken to carry out familiarisation visits and consent as this was the same for all recruitment methods. The time cost of each method is calculated per participant recruited, based on the average salary cost per hour of the trial researcher.

5.5 Results

A total of 349 potentially eligible participants were identified via the recruitment methods (217 MS Clinic, 113 consultant mail-out and 19 trial awareness) (See Figure 5.1). For CONSORT checklist and flow diagram please see Additional file 1.

5.5.1 Recruitment Rates

The original recruitment period was planned to take place over a period of 24 months. This was extended to a period of 34 months (February 2009 to November 2011), due to lower than expected recruitment rate of 3.5 ± 0.32 (mean ± 95% CI) participants per month (See Fig. 5.2). Recruitment was carried out by attending MS Clinics and using trial awareness strategies throughout this period. Mail outs were conducted in the second year of the trial at time-points where lower levels of recruitment from the clinic were observed in the trials first year (July, August and February and October).

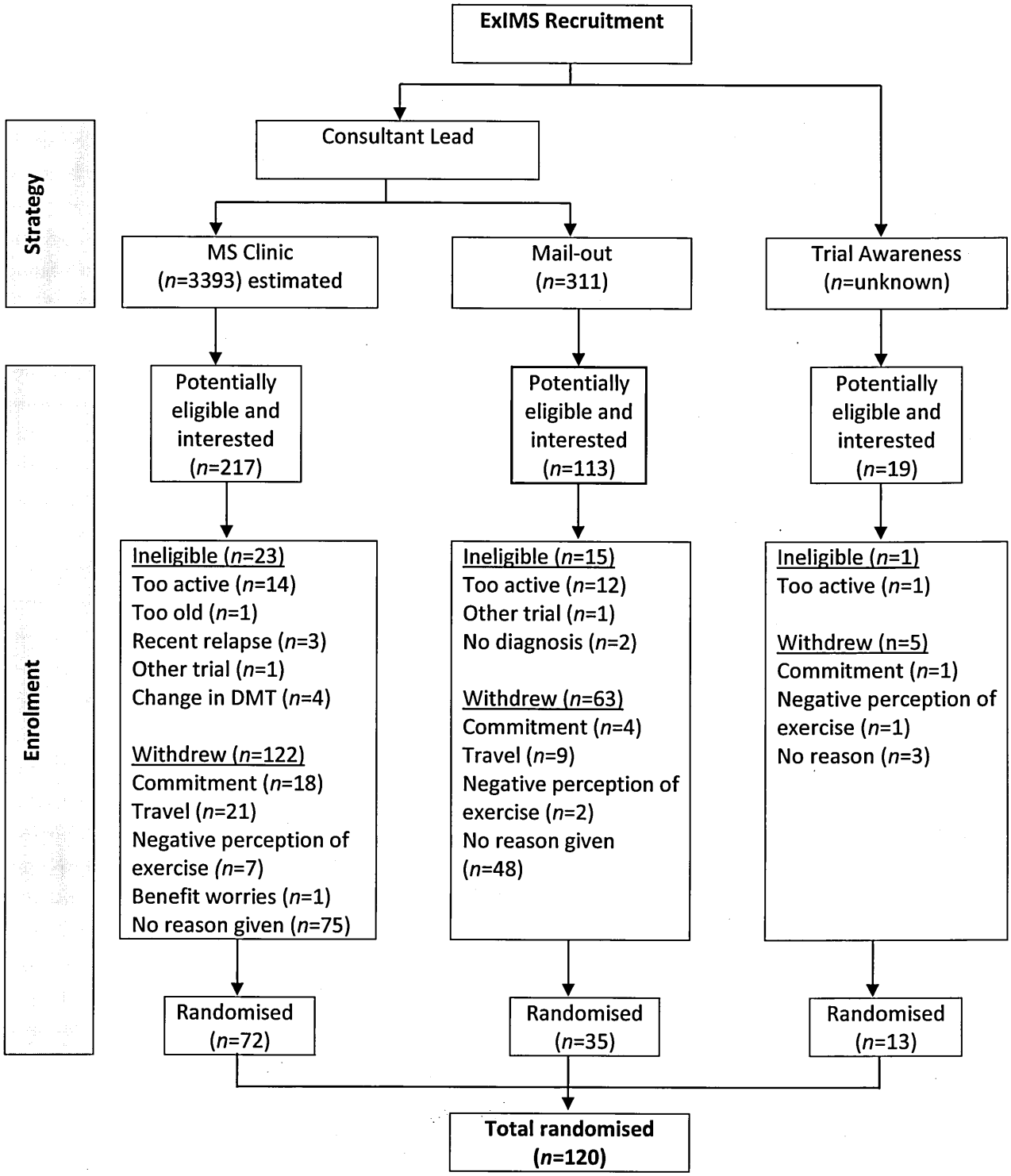
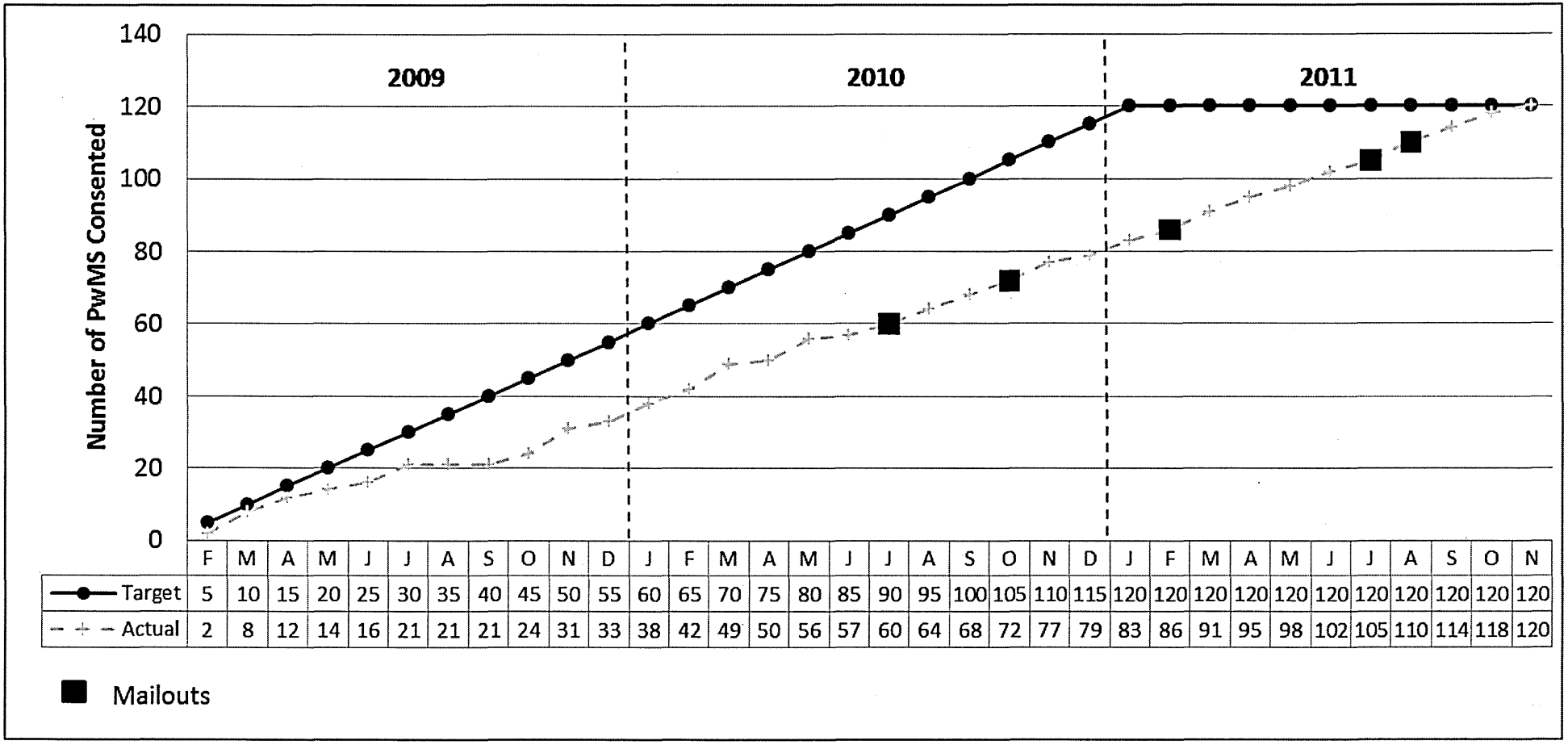


Figure 5.1. Flow diagram of participant recruitment to the ExIMS trial.



	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N
Target	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	120	120	120	120	120	120	120	120	120	120
Actual	2	8	12	14	16	21	21	21	24	31	33	38	42	49	50	56	57	60	64	68	72	77	79	83	86	91	95	98	102	105	110	114	118	120

Figure 5.2. Predicted and actual recruitment rates for participants in the ExIMS research trial.

5.5.2 Response Rates

Out of approximately 3,393 people with MS who attended the MS outpatient clinic during the recruitment period, 217 were identified as potentially interested and eligible, 6.4% (n=217/3393). Of these, 10.6% were ineligible (n=23/217) and 56.2% (122/217) declined to participate.

Mail outs were sent to 311 potentially eligible participants. From this, 133 (42.8%) PwMS expressed an interest in the trial, 11.2% of which were ineligible (n=15/133) and 47.3% of whom (63/133) declined to participate.

Our trial awareness strategies provided 19 interested individuals from an unknown pool of potential participants, from which 5% (n=1/19) were ineligible and 21.1% (n=4/19) declined to participate.

5.5.3 Randomisation Yields/Accrual Rates

The randomisation yield was 33.2% (72/217) from the MS Clinic, 31.0% (35/113) for consultant mail-outs and 68.4% (13/19) for those contacted via trial awareness strategies. This lead to 60% (72/120) of participants being recruited via MS clinics, 29.2% (35/120) via mail-outs and 10.8% (13/120) via trial awareness strategies.

5.5.4 Reasons for Ineligibility

A total of 39 (23 MS Clinic, 15, mail-out and 1 trial awareness) participants who had expressed an interest were ineligible. In order of prevalence the main reasons for ineligibility were; too active 69.2% (27/39), recent change in disease modifying therapy 10.3% (4/39), recent MS relapse 7.7% (3/39), participating in

another trial 5.1% (2/39), no definitive diagnosis of MS 5.1% (2/39) and too old 2.6% (1/39).

5.5.5 Reasons for Declining Participation

The reasons that eligible participants declined to participate in order of prevalence were; gave no reason 66.3% (126/190), issues with transport/travel to the trial site 15.8% (30/190), other commitments 12.1% (23/190), negative perceptions of exercise 5.3% (10/190) and loss of benefit worries 0.5% (1/190).

Table 5.2. Estimated time to identify and recruit participants and the associated costs.

Recruitment Method	Time Spent Recruiting (hours)	Time per potential Participant (hours)**	Time per Recruited participant (hours)***	Cost Per Recruit (based on estimated cost of a researcher - £25/hour)
MS outpatient clinic	304.5 (87 clinics)	1.4 (304.5/217)	4.2 (304.5/72)	£105 (£25x4.2)
Consultant mail-out	20 (5 mail-outs)	0.2 (20/113)	0.6 (20/35)	£15 (£25x0.6)
Trial awareness strategies	26 *	1.5 (29/19)	2.2 (29/13)	£55 (£25x2.2)
All Strategies	350.5	1.4 (350.5/349)	2.9 (350.5/120)	£72.50 (£25x2.9)

* An estimated 26 hours were spent raising awareness of the trial, this included producing a flyer and attending and giving talks at various MS events. **Time per potential participant (hours) is calculated as time spent recruiting (hours)/number of potentially eligible participants. ***Time per recruited participant (hours) is calculated as time spent recruiting/number of participants recruited.

5.5.6 Recruitment Time/Cost

MS clinics required the longest recruitment time of 4.2 hours per participant, whilst the consultant mail-out had the shortest recruitment time of 0.6 hours per participant (See table 5.2).

5.6 Discussion

5.6.1 Recruitment Rates

Recruitment to this study was slower than anticipated at 3.5 ± 0.32 (mean ± 95% CI) participants per month, leading to the trial failing to recruit on time and an extended recruitment period of 34 months (from an initial target of 24 months) needed to reach the target number of participants. Recruitment rates have not previously been reported for large-scale exercise trials in PwMS, but a non-exercise intervention using computerised cognitive behavioural therapy for PwMS reported slightly lower rates of 2.6 per month (Cooper et al., 2011), whilst a multi-centre RCT for a group based fatigue management programme reported recruitment of 13.0 participants per month (across three sites), equating to 4.3 per trial site (Thomas et al., 2013). However both these trials had a lower patient time commitment than ExIMS. Exercise trials with other clinical groups have reported similar recruitment rates, for example, wheel chair users, 2.9 per month (Nary et al., 2011), breast cancer survivors, 3.8 per month (Daley et al., 2007) and elderly stroke survivors, 4.0 per month (Taylor-Piliae et al., 2014). This suggests that our observed recruitment rate of 3.5 participants per month is a realistic target for future randomised controlled exercise trials for PwMS that require regular attendance.

5.6.2 Response Rates

The response rate from a potentially large pool of participants at MS clinics was low at 6.4%. Reasons for this may either be related to patients being ineligible (changing to new medication, suffering a relapse, new patient, other neurological condition), consultants too busy to recruit during clinic and/or patients not being interested in the study. As might be expected response rates to personalised consultant study invitation letters were higher (42.8%), as this strategy was much more targeted towards eligible individuals. However, this still leaves nearly 60% of potential participants who did not respond to the invitation. As suggested by Daley et al., (2007) it is possible that non-responders, were either deterred by the 'demanding nature of exercise trials' or were already engaged in regular physical activity. The latter seems less likely due to the lower physical activity rates reported in PwMS (Motl and Pilutti, 2012).

5.6.3 Randomisation Yields/Accrual Rates

The trial recruited 60% of the 120 participants from the MS outpatient clinic, with 29.2% recruited via consultant mail-out and 10.8% via trial awareness strategies. However, the randomisation yield (number recruited/number interested) was similar for both the MS Clinic and consultant mail-outs (33.2 and 31.0% respectively), suggesting that both methods are useful in attaining recruitment targets. Values reported in the exercise literature are varied, with an exercise trial for wheelchair users reporting a randomisation yield of 41.8% (Nary et al., 2011) and an exercise trial with breast cancer survivors reporting yields of 13.3% from consultant letters and 29.7% from community strategies. In addition, a cognitive behavioural trial for PwMS had relatively low yields of 4.5% for the MS Clinic and 4.0% from mail-outs (Cooper et al., 2011). Hence, our

data suggest that PwMS are as interested as other clinical populations in participating in a supervised exercise trial and may be more interested in an exercise trial than other behavioural interventions with similar time constraints.

5.6.4 Reasons for Ineligibility

There were a number of reasons why people interested in the trial were ineligible to take part. The most common reason for ineligibility was already being too active to participate (69.2%), as they were already engaged in moderate structured exercise ≥ three times per week for ≥ 30 min per session consistently for the last six months. This is consistent with reasons for non-eligibility reported in a similar exercise intervention with breast cancer survivors where 55% of those interested were ineligible due to being already too active (Daley et al., 2007). The number of potential participants screened out through being already too active was much less (8.5%) in a group of wheelchair users (Nary et al., 2011), suggesting that physical disability may impact heavily on current exercise levels. Our data suggests that despite the physical disabilities of MS, there are many people with mild to moderate levels of disability from the condition that are managing to participate in moderate intensity exercise over a prolonged time period. However, data from the wheelchair exercise study (Nary et al., 2011) would suggest that PwMS having higher levels of disability may be less physically active.

5.6.5 Reasons for Choosing not to Participate

The reasons that eligible participants have given for choosing not to take part in exercise intervention studies has rarely been reported, but can give a valuable

insight into areas of trial design that maybe improved to enhance recruitment. Many PwMS (66.3%) did not specify why they had declined to take part. However, out of those that did, the need to travel to the trial site, negative perceptions of exercise and loss of benefit worries are all factors that could potentially be overcome in future trials through design modifications and patient education.

5.6.6 Recruitment Time/Cost

Recruitment is a time consuming process with some community based trials reporting up to 10-hours per participant to recruit (Rdesinski et al. 2008). This study averaged 2.9 hours per participant. Study mail-outs were reported to be the most efficient recruitment method at only 0.6 hours per participant. However, this only recruited 29.2% of the studies overall cohort, suggesting the importance of the more time consuming method of recruitment through MS outpatient clinics. Although this method required 4.2 hours per participant, it yielded 60% of the study's total cohort. In the present study costs are based on a researcher doing all the recruitment regardless of method, however, it is noted that if recruitment at clinic had incurred additional consultant time, costs would be much higher for this method.

5.6.7 Limitations

There was the potential for cross-contamination across recruitment pathways, as participants may have been reached by more than one method (for example PwMS may have seen trial awareness information, before attending an appointment at the MS clinic, which may have made them more likely to recruit

from this method). This could be improved in future studies by asking participants if they have been made aware of the study by any other means. In addition, it was not a requirement of the study for individuals to provide reasons for declining to take part in the study/ it would be useful to include methods for collecting this data so that strategies can be developed to increase recruitment yield and hence decrease recruitment costs.

5.7 Conclusion

Achievement of pre-determined recruitment targets is a critical factor influencing the success of RCTs. Well-designed feasibility work and a combination of recruitment methods can help to ensure that a trial is appropriately designed to reach targets. Although consultant mail-outs were shown to be the most cost-effective recruitment strategy, this method alone may well be insufficient to meet recruitment targets in time-limited RCTs. This study reports for the first time the pros and cons of different recruitment methods in randomised controlled exercise trials involving PwMS and would recommend a combination of methods to meet recruitment targets. The results provide novel insights into challenges of trial recruitment in this context and can be used to inform the design of future trials in this population; recruitment for other types of trial such as drugs trials may be different.

5.8 Acknowledgements

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5.9 Additional File

Additional file 1: CONSORT Checklist and Flow Diagram (DOCX 193 kb)

5.10 References

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6.0 PRAGMATIC INTERVENTION FOR INCREASING SELF-DIRECTED EXERCISE BEHAVIOUR AND IMPROVING IMPORTANT HEALTH OUTCOMES IN PEOPLE WITH MULTIPLE SCLEROSIS: A RANDOMISED CONTROLLED TRIAL.

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6.1 Preface to Chapter 6

Chapter five provides detailed information regarding recruitment to a large scale randomised control exercise trial, whilst chapter six provides the results from the primary and secondary outcome data, immediately and after six months of follow-up. Results suggest that significant improvements in self-reported physical activity levels, fatigue and health related quality of life, with sustained improvements in some of the domains of quality of life.

In order for this research to influence practice cost effectiveness data is required. Results from this analysis are outlined in chapter seven. Permission for its reprint in this thesis has been gained from the publishers (Appendix 9.14).

6.2 Abstract

Background: Exercise programmes that can demonstrate evidence of long-lasting clinical effectiveness are needed for people with multiple sclerosis (PwMS).

Objective: The objective of this study was to assess the effects of a practically implemented exercise programme on self-directed exercise behaviour and important health outcomes in PwMS to nine months of follow-up.

Methods: We conducted a parallel-arm, randomised controlled trial: 120 PwMS (Expanded Disability Status Scale (EDSS) 1.0–6.5) randomised to a three-month exercise intervention plus usual care, or usual care only. Two supervised plus one home-exercise session (weeks 1–6) were followed by one supervised and two home-exercise sessions (weeks 7–12). Cognitive-behavioural techniques promoted long-term exercise behaviour change. Outcomes were blindly assessed at baseline and at three and nine months after randomisation. The primary outcome was self-reported exercise behaviour (Godin Leisure Time Exercise Questionnaire (GLTEQ)). Secondary outcomes included fatigue and health-related quality of life (HRQoL).

Results: The intervention increased self-reported exercise (9.6 points; 95% CI: 2.0 to 17.3 points; $p = 0.01$) and improved fatigue ($p < 0.0001$) and many HRQoL domains ($p \leqslant 0.03$) at three months. The improvements in emotional well-being ($p = 0.01$), social function ($p = 0.004$) and overall quality of life ($p = 0.001$) were sustained for nine months.

Conclusion: This pragmatic approach to implementing exercise increases self-reported exercise behaviour, improves fatigue and leads to a sustained enhancement of HRQoL domains in PwMS.

6.3 Introduction

Supervised facility-based exercise programmes can offer comprehensive support and guidance for people with multiple sclerosis (PwMS) but over the long-term are likely to prove difficult because of time barriers, transport issues and ealth constraints (e.g. fatigue).[1] A major challenge is to develop pragmatic and cost-effective exercise programmes that can safely engage PwMS in exercise and provide robust evidence of a long-lasting impact on important health outcomes. Interventions that promote and provide support for sustainable home-based exercise, including use of community facilities, may help to overcome some of these problems but, to date, only very few studies have assessed the health impacts of exercise in community-based settings.[2–4] The inclusion of cognitive-behavioural strategies might also be effective for increasing confidence for self-directed exercise, as reported in other clinical populations.[5–7]

Here, we report the effects of a pragmatic Exercise Intervention for people with MS (EXIMS) on self-directed exercise behaviour and important health outcomes, including fatigue and health-related quality of life (HRQoL). We hypothesised that participants randomised to the intervention group (EXIMS) would show an increase in physical activity levels and improvements in a range of health outcomes up to nine months of follow-up in comparison with participants randomised to usual care alone.

6.4 Materials and Methods

6.4.1 Controlled Trial

This was a two-arm, parallel, randomised controlled trial. PwMS were randomised (1:1) to receive the EXIMS intervention plus usual care or usual care only. Full details of the protocol have been published previously.[8] This study was approved by the South Yorkshire Research Ethics Committee and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from participants before entering the study.

6.4.2 Recruitment of participants and baseline assessment

A total of 120 PwMS were recruited via the Sheffield MS Clinic and flyers/community adverts displayed at the local South Yorkshire MS Society branches. All patients were assessed by a consultant neurologist with an interest in MS prior to entering the trial. The inclusion criteria for the trial were clinical diagnosis of MS, as defined by the modified McDonald criteria,[9] with an Expanded Disability Status Scale (EDSS) score of 1.0–6.5, and able to walk a 10-metre distance; aged 18–65 years; clinically stable for at least four weeks prior to entering the study; physically able to participate in exercise three times per week; able to provide written informed consent. Participants on disease-modifying therapy (interferon beta, glatiramer acetate and natalizumab) had been stable on this treatment for at least three months. Exclusion criteria were comorbid conditions impairing the ability to be physically active three times per week; unwilling to be randomised; living more than 20 miles from the trial centre; already engaged in structured exercise or brisk walking $\geqslant$ 3 times per week for $\geqslant$ 30 minutes per session for at least six months.

6.4.3 Randomisation and concealed allocation

Minimisation was used to balance the potentially confounding variables of gender and EDSS score (low: 1.0–3.5; higher: 4.0–6.5). Treatment allocation was concealed from the study researchers by using a distant randomisation service at the University of York, UK. The allocation was not disclosed to members of the research team until participants had completed their baseline assessments. Due to the nature of the intervention, neither the participants nor researchers involved in the day-to-day running of the trial could be blinded to treatment allocation.

6.4.4 Pragmatic exercise intervention

An exercise physiologist supervised the delivery of the intervention but with physiotherapist input during the early stages of the programme. During weeks 1–6, participants attended two supervised sessions per week at a university exercise research facility and engaged in one additional self-directed exercise session in their home environment. Supervised exercise sessions involved up to three participants and lasted for approximately one hour. Studies show that aerobic exercise, resistance exercise and combined programmes bring health benefits to PwMS.[10,11] Hence, the programme was designed to be pragmatic and accessible, taking into account exercise preferences and giving choices. Aerobic exercise was the core exercise modality as it is accessible (i.e. includes community-based walking exercise) and does not require equipment. Participants were asked to complete short bouts (e.g. 5 × 3 minutes, with two-minute rest intervals) of low to moderate intensity aerobic exercise (e.g. stepping ergometer, cycle-ergometer, treadmill walking, rowing ergometer, arm-

cranking) at 50%–69% of predicted maximum heart rate (220–age) or 12–14 on the Borg Ratings of Perceived Exertion Scale.[12] Intensity was monitored continuously during exercise training sessions. As the intervention progressed, participants were encouraged to participate in longer periods of aerobic exercise (e.g. 5 × 4 minutes) or to take shorter rests between bouts.

Where appropriate, participants also performed exercises for strength and control. The prescribed strength training was based on individual functional needs, as assessed by the trial physiotherapist (NS). Strength training was undertaken by 48 of 60 participants in the intervention group and typically involved two to six different resistance exercises (e.g. wall press-ups, arm-curls, leg abduction, wall squats and/or regular squats, knee extensions, calf raises, sit-to-stand) each session. Body resistance, light weights and Therabands were used to provide resistance and one to three sets of five to 20 repetitions were performed, depending on level of disability and strength, as well as stage of the programme (exercises were progressed according to individual capabilities and strength gains). Balance board, balance exercises and exercise ball work were included where control and coordination were a problem and static stretching exercises for large skeletal muscle groups were also included in the sessions if appropriate.

During weeks 7–12 participants attended the centre once per week and completed two additional self-directed exercise sessions in their home or local community. The home-exercise sessions were intended to mirror the supervised sessions in terms of intensity and duration of aerobic exercise, and also included tailored exercises for strength, flexibility and balance. Participants were encouraged to seek out opportunities to exercise in the local community (e.g. healthy living centres, health walks, fitness centres, swimming pools, etc.),

based on their individual preferences. Details of supervised and home-exercise sessions were recorded in an exercise log.

The supervised exercise sessions incorporated cognitive-behavioural techniques (e.g. goal setting, finding social support, understanding the costs/benefits of exercise, etc.) to promote long-term participation in physical activity. Using the Transtheoretical Model[13] as a guiding framework, this aspect of the intervention was aimed at equipping PwMS with the skills, knowledge and confidence to engage in a more physically active lifestyle. The cognitive-behavioural elements were integrated into the exercise sessions using strategies appropriate to the conversation, stage of change and concerns/questions raised by participants. Further details of the theoretical model for facilitating physical activity behaviour change have been published previously.[8] Participants in the usual care group were offered three exercise sessions at the university exercise research facility and individual exercise advice after the study.

6.4.5 Outcome measures

Outcomes were assessed at baseline, and at three months (post-intervention) and nine months after randomisation. The primary outcome was self-reported exercise behaviour at three months using the Godin Leisure Time Exercise Questionnaire (GLTEQ).[14] The GLTEQ asks participants to recall the frequency of strenuous, moderate and mild intensity exercise for periods >15 minutes over the past seven days and is a valid measure of habitual exercise in PwMS.[15] Daily movement and step counts were objectively assessed using an accelerometer (Actigraph GT2M accelerometer, Actigraph, LLC, FL, USA), worn

on the waist during waking hours, except when bathing/showering or swimming. Accelerometers were programmed for an epoch length of one minute and the average daily movement count (vertical axis) and daily step count over a seven-day period were recorded.

Secondary outcomes included fatigue, HRQoL, functional ability and neurological impairment. Fatigue was assessed using the Modified Fatigue Impact Scale (MFIS).[16] HRQoL was measured using the MSQoL-54.[17] The Multiple Sclerosis Functional Composite (MSFC)[18] was used as a measure of clinical functional ability. It includes a timed 25-foot walk and measures of arm/hand function (9-hole peg test) and cognitive function (Paced Auditory Serial Addition Test: PASAT). Functional exercise capacity was assessed using the six-minute walk test (6MWT).[19] The EDSS[20] (neurological impairment and disability) was assessed by a single trained consultant neurologist according to standard clinical procedures[21] in the hospital setting. Other outcomes were blindly assessed by an experienced researcher not directly involved with the day-to-day running of the trial.

6.4.6 Sample size

The sample size estimation was based on self-reported physical activity data (GLTEQ) from our pilot study.[22] It was estimated that a sample of 50 patients for each group would be sufficient to detect a moderate effect size difference (80% power and a 5% significance level) in GLTEQ (standard deviation, SD = 2.29). Hence, we aimed to recruit 60 participants for each group to allow for a 15% loss to follow-up at the primary time point (based on our pilot study data).[22]

6.4.7 Statistical analysis

Repeated-measures mixed modelling was used to compare outcomes between the randomised groups at the three- and nine-month follow-ups, adjusting for baseline score, EDSS and gender. The distribution of the majority of outcomes were skewed, therefore the analyses were bootstrapped (1000 replications) to provide more reliable estimates. All analyses were by intention to treat, whereby participants were analysed in the arm to which they were randomised irrespective of whether they complied with the intervention. Multiple imputation of missing values was performed using the imputation by chained equations (ICE) command in STATA 12. Variables included in the imputation were age, gender, baseline EDSS, and baseline, three- and nine-month follow-up scores for all outcomes. Five imputations were carried out and mixed-model analysis was performed on each imputed dataset. The adjusted means and confidence intervals (CIs) from each analysis were then consolidated using Rubin's rules. Sensitivity analysis was performed to determine the effect of outliers in the GLTEQ scores by their removal from the analysis. Bivariate associations between key variables were analysed using the Pearson Product Moment correlation coefficient. No corrections for multiple testing were made in the analysis. Analyses were undertaken by the trial statistician, blinded to treatment allocation, using STATA 12 and results are generally reported as means and CIs.

6.5 Results

6.5.1 Participant flow and recruitment

The trial took place from March 2009 to August 2012. Of 349 potential participants who were assessed for eligibility, 120 (34%) were randomised (Figure 6.1). The two groups had similar demographic, anthropometric and MS disease characteristics at baseline (Table 6.1). In the two years preceding the study, 55 relapses were experienced by 30 participants in the usual care group in comparison to 54 relapses experienced by 33 participants in the exercise group.

Table 6.1. Baseline characteristics of participants allocated to usual care only or usual care plus EXIMS. Values are numbers (percentages) or mean ± SD.

Characteristics	Usual care group(n = 60)	EXIMS group(n = 60)
Age (years)	46.0 ± 8.4	45.7 ± 9.1
Female	43 (71.7%)	43 (71.7%)
White	57 (95%)	54 (90%)
Employed full time	16 (27%)	9 (15%)
Employed part time	14 (23%)	17 (28%)
Time since MS diagnosis (years)	9.2 ± 7.9	8.4 ± 7.4
EDSS score subgroup	3.8 ± 1.5	3.8 ± 1.5
0–3.5	28 (47%)	29 (48%)
4.5–6.5	32 (53%)	31 (52%)
Mean score	3.8 ± 1.5	3.8 ± 1.5
MS subtype		
Relapsing–remitting	47 (78%)	51 (85%)
Secondary progressive	11 (18%)	7 (12%)
Primary progressive	2 (3%)	2 (3%)
Anthropometric variables and blood pressure		
Height (m)	1.68 ± 0.07	1.68 ± 0.08
Body mass (kg)	76.4 ± 15.5	79.4 ± 17.8
BMI (kg/m^2)	27.1 ± 5.8	28.0 ± 5.4
Waist circumference (cm)	92.8 ± 13.6	95.1 ± 14.4
Waist:Hip ratio	0.86 ± 0.08	0.87 ± 0.09
Systolic blood pressure (mm Hg)	129 ± 16	126 ± 14
Diastolic blood pressure (mm Hg)	82 ± 10	83 ± 10

MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; BMI: body mass index.

6.5.2 Loss to follow-up and MS relapses

A total of 13 participants (six from the intervention group and seven from the usual care group) were lost to follow-up at three months. An additional eight participants were lost to follow-up at nine months (five from the intervention group and three from the usual care group; Figure 6.1). Participants that dropped out of the study were slightly younger than the study completers (43.3 vs 46.3 years) and had higher baseline EDSS and total fatigue scores (4.5 vs 3.6 and 48.0 vs 42.6, respectively). During the nine-month study period, 16 MS relapses were experienced by 14 of the usual care participants in comparison to 10 MS relapses experienced by nine participants in the exercise group. Participants were encouraged to rejoin the trial following recovery, and complete or partial follow-up data were obtained for 21 of the 23 relapsing participants.

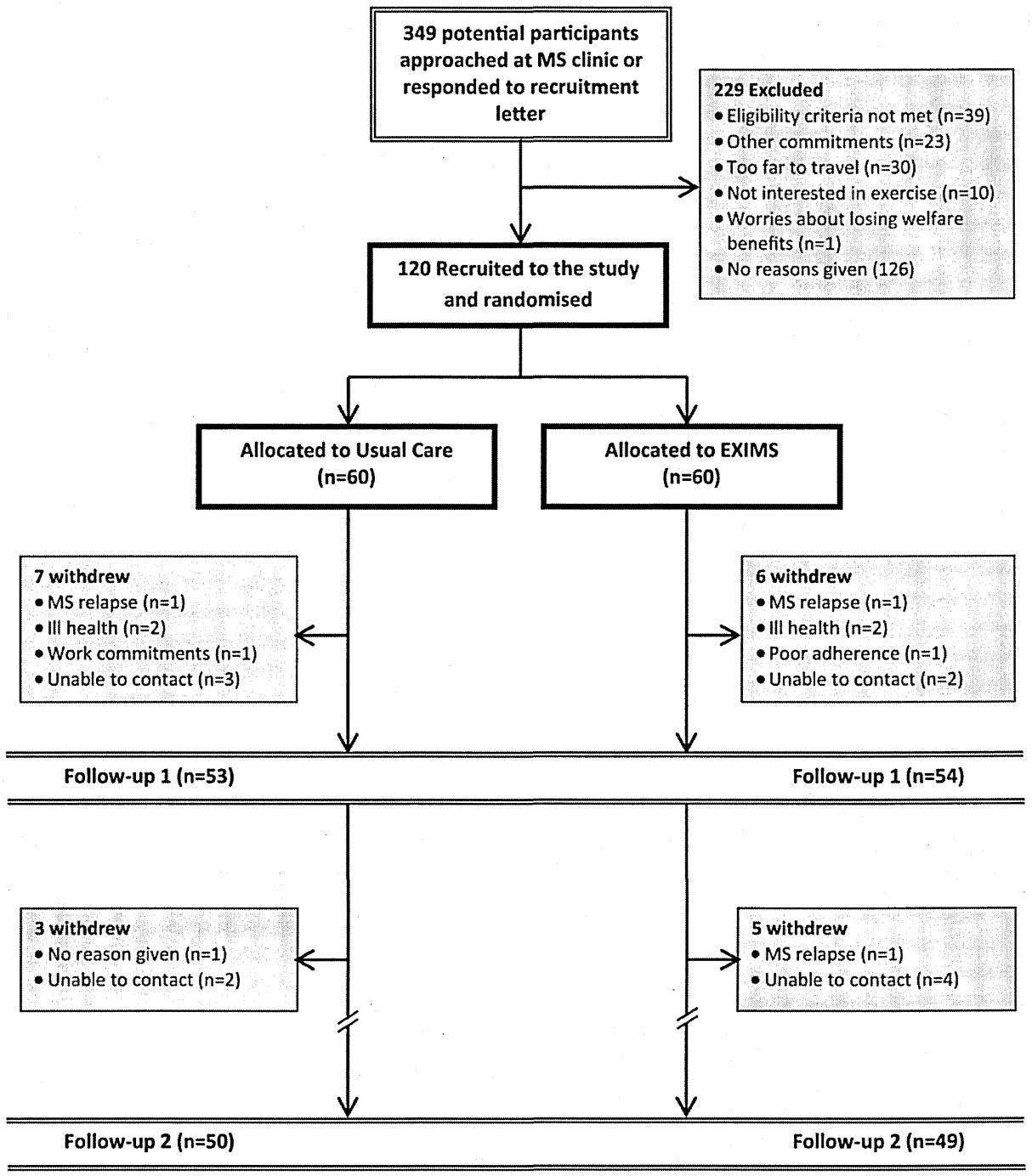

Figure 6.1. Flow of participants through the trial. EXIMS: pragmatic Exercise Intervention for people with MS.

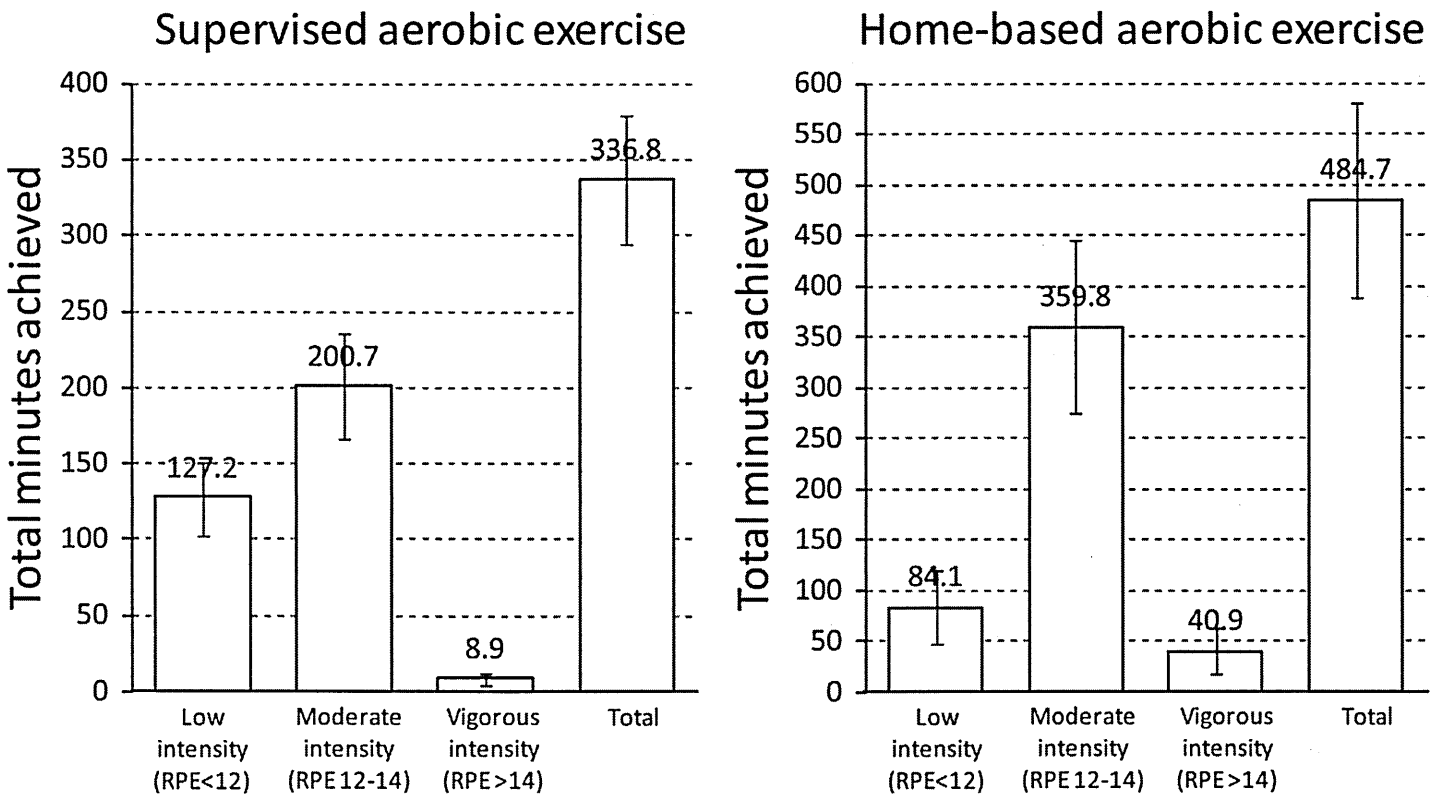

Figure 6.2. Minutes of supervised and home-based aerobic exercise achieved by the intervention group at different intensities over the supervised period of the study (weeks 1–12). Values are means with error bars representing 95% confidence intervals. RPE: Ratings of Perceived Exertion.

6.5.3 Adherence to the EXIMS intervention

Adherence to the supervised and home-exercise sessions was very good, with participants attending an average of 16.2 of the 18 supervised sessions (90%; range 7–18 sessions) and participating in an average of 14.6 of the 18 prescribed home-exercise sessions (81%, range 2–18 sessions). Home exercise during the intervention period comprised walking, use of home exercise equipment, public facilities (including swimming) and gardening for the majority of participants. The volumes of supervised and home-based aerobic exercise are presented in Figure 6.2. No serious adverse events or serious symptom exacerbations were recorded.

6.5.4 Primary and secondary outcomes

Baseline scores for the primary and secondary outcomes were comparable for the two groups (Table 6.2). An increase in GLTEQ was observed in the exercise group versus usual care at the primary time point of three months (p = 0.01) and a non-significant increase was still apparent after nine months (p = 0.08; Figure 6.3). The improvement in self-reported exercise behaviour was accompanied by increases in objectively measured daily step counts at three months (p = 0.009) in the exercise group versus usual care, but at nine months daily step counts were similar to baseline levels (Figure 6.3). All dimensions of fatigue were significantly improved in the exercise group in comparison with usual care at three months (p <0.0001), with the change in total fatigue scores being positively correlated with baseline levels (Table 6.3). Interestingly, volume of supervised aerobic exercise achieved was negatively correlated with the change in total fatigue scores at the three-month follow-up (Table 6.3).

Table 6.2. Baseline primary and secondary outcome data for participants allocated to usual care only and usual care plus EXIMS. Values are presented as mean ± SD.

Characteristics	Usual care group		EXIMS group	
	Mean (SD)	*N*	Mean (SD)	*N*
Physical activity				
Godin LTEQ score	17.5 (14.8)	59	20.3 (21.9)	58
Accelerometer daily step counts	4695 (2711)	59	4488 (2251)	60
Fatigue				
Physical	21.6 (7.5)	60	22.7 (7.9)	60
Cognitive	17.2 (8.1)	60	18.3 (9.2)	60
Psychosocial	4.0 (2.1)	60	4.1 (2.0)	60
Total MFIS	42.8 (15.7)	60	45.0 (17.0)	60
MSQoL-54				
Physical health	52.2 (30.1)	60	45.7 (28.7)	60
Role limit physical	32.9 (38.6)	60	31.8 (40.7)	59
Role limit emotional	60.6 (43.2)	60	58.8 (43.9)	59
Pain	65.7 (24.1)	60	63.0 (29.6)	60
Emotional well-being	65.1 (18.3)	60	64.2 (18.8	60
Energy	39.0 (16.5)	60	39.9 (20.1)	60
Health perceptions	42.3 (18.4)	60	42.0 (23.3)	60
Social function	65.3 (24.8)	60	66.0 (23.3)	60
Cognitive function	67.5 (21.0)	60	61.3 (25.0)	60
Health distress	57.8 (26.4)	60	52.5 (28.4)	60
Sexual function	70.0 (32.7)	55	64.4 (31.8)	55
Change in health	45.4 (19.3)	60	44.6 (24.0)	60
Sex satisfaction	52.3 (28.6)	55	53.1 (29.5)	57
Overall quality of life	62.4 (20.3)	60	58.3 (21.8)	60
Physical health component	51.2 (18.8)	60	48.8 (21.5)	60
Mental health component	62.8 (21.7)	60	59.5 (22.5)	60
MSFC				
25-ft walk test (s)	8.9 (10.6)	59	8.2 (6.6)	60
9-hole peg test DH average	25.0 (6.1)	59	26.0 (8.9)	59
9-hole peg test NDH average	29.6 (13.4)	60	27.7 (7.6)	59
PASAT	43.3 (14.2)	60	40.6 (13.8)	60
Six-minute walk test (m)	395 (140)	57	373 (134)	59

EXIMS: pragmatic EXercise Intervention for people with MS; LTEQ: Leisure Time Exercise Questionnaire; MFIS: Modified Fatigue Impact Scale; MSQoL-54: MS quality of life-54; MSFC: Multiple Sclerosis Functional Composite; PASAT: Paced Auditory Serial Addition Test; DH: dominant hand; NDH: non-dominant hand.

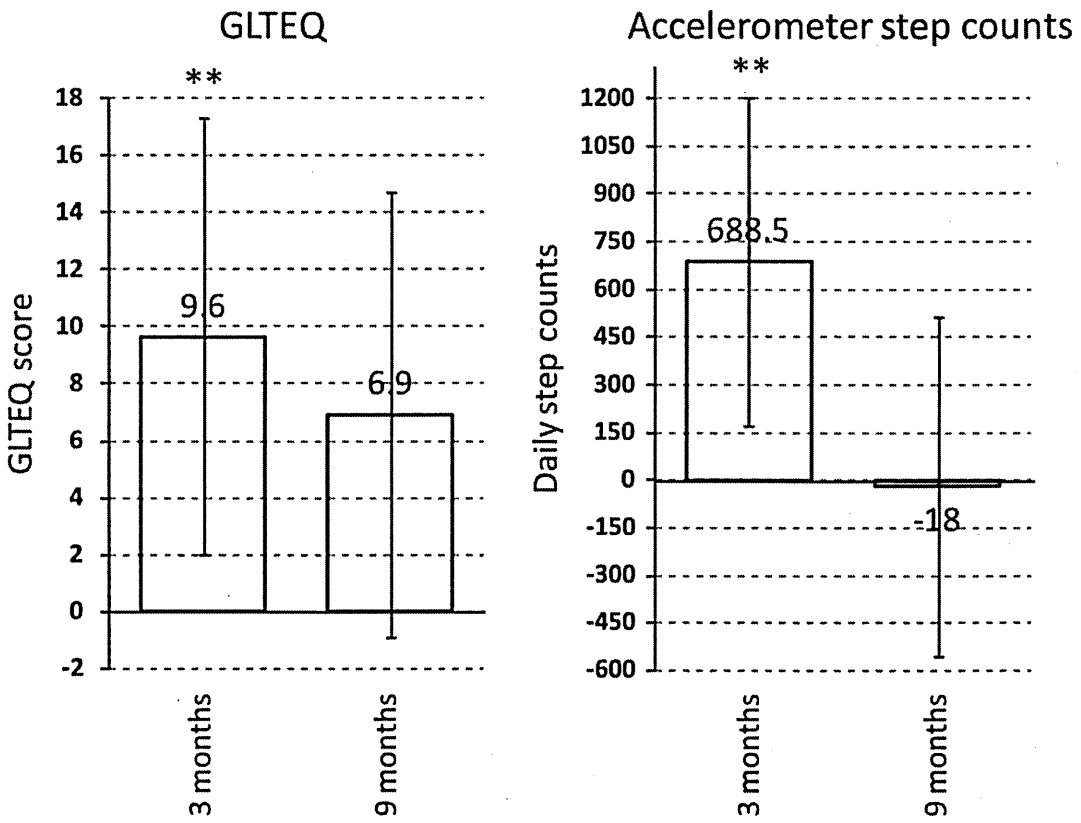

Figure 6.3. Adjusted mean differences in self-reported exercise (GLTEQ) and accelerometry step counts between the intervention and usual care control groups at 3 months and 9 months (adjusted for baseline, gender and EDSS). Values are means with error bars representing 95% confidence intervals. $^{**}p \leqslant 0.01$ between the groups. GLTEQ: Godin Leisure Time Exercise Questionnaire.

The improvements in fatigue were not maintained at nine months (Table 6.4). Positive changes in many quality of life domains in favour of the exercise group were also observed at three months, with improvements in emotional well-being ($p = 0.01$), social function ($p = 0.004$) and overall quality of life ($p = 0.001$) being maintained for nine months (Table 6.4). The exercise intervention had no effect on functional ability or neurological impairment (Table 6.4). At baseline, EDSS scores were positively correlated with total fatigue scores and negatively correlated with the volume of aerobic exercise achieved (Table 6.3). Body weight also remained unchanged in both groups but there was evidence of a reduction in waist circumference at both follow-up time points (non-significant at three months) and reduction in diastolic blood pressure at nine months in the exercise group versus usual care (Table 6.5). Multiple imputation analysis gave similar results to the primary available case analyses, and exclusion of outliers in GLTEQ scores had no impact.

Table 6.3. Bivariate association between EDSS, total fatigue, GLTEQ and total volumes of supervised and home-based aerobic exercise for the intervention group.

	Total fatigue (B/L)	Δ GLTEQ	Δ Total fatigue	Supervised aerobic exercise (min)	Home-based aerobic exercise (min)
EDSS (B/L)	0.36[b]	–0.12	0.24	–0.62[b]	–0.29[a]
Total fatigue (B/L)		0.03	0.37[b]	–0.41[b]	–0.12
Δ GLTEQ			–0.08	0.00	0.03
Δ Total fatigue				–0.32[a]	–0.05

EDSS: Expanded Disability Status Scale; GLTEQ: Godin Leisure Time Exercise Questionnaire. Values in the table show Pearson Product Moment correlation coefficients. B/L indicates baseline measures; Δ indicates difference between baseline and three-month follow-up; Total volumes of supervised and home-based aerobic exercise are shown in minutes; [a]$p < 0.05$; [b]$p < 0.01$.

Table 6.4. Secondary outcomes at three months and nine months in participants allocated to usual care and usual care plus EXIMS.

	Follow-up time point (months)	Usual care group mean (sd)	EXIMS group mean (sd)	Difference in adjusted means (95% CI)	Bootstrapped *p* value
Fatigue					
Physical	3	21.2 (8.9)	17.9 (8.3)	−4.3 (−6.2 to −2.5)	**<0.0001**
	9	20.7 (8.5)	20.1 (7.8)	−1.2 (−3.0 to 0.7)	0.22
Cognitive	3	17.7 (8.2)	14.9 (9.6)	−3.6 (−5.5 to −1.8)	**<0.0001**
	9	16.7 (9.6)	16.0 (8.8)	−1.4 (−3.3 to 0.5)	0.15
Psychosocial	3	4.2 (2.1)	2.9 (2.2)	−1.2 (−1.7 to −0.7)	**<0.0001**
	9	4.0 (2.4)	3.5 (1.9)	−0.3 (−0.8 to 0.3)	0.36
Total MFIS	3	43.2 (17.3)	35.8 (18.2)	−9.2 (−12.8 to −5.7)	**<0.0001**
	9	41.3 (18.8)	39.6 (16.6)	−2.9 (−6.6 to 0.8)	0.12
MSQoL-54					
Physical health	3	51.4 (31.2)	52.8 (27.4)	6.9 (2.8 to 11.0)	**0.001**
	9	54.3 (33.1)	51.9 (28.8)	2.9 (−1.5 to 7.3)	0.20
Role limit physical	3	40.2 (42.2)	47.1 (40.4)	7.6 (−1.9 to 17.2)	0.12
	9	39.4 (43.6)	39.6 (41.2)	−0.8 (−10.2 to 8.7)	0.88
Role limit emotional	3	64.1 (42.1)	70.6 (41.4)	7.7 (−4.9 to 20.2)	0.23
	9	61.0 (46.3)	67.4 (39.8)	4.8 (−8.2 to 17.9)	0.47
Pain	3	67.2 (26.6)	70.2 (25.9)	5.4 (0.5 to 10.2)	**0.03**
	9	64.0 (25.6)	64.5 (28.3)	1.0 (−4.2 to 6.2)	0.70
Emotional well being	3	54.3 (14.2)	60.2 (12.9)	7.3 (3.5 to 11.1)	**<0.001**
	9	66.2 (21.9)	71.4 (17.5)	5.9 (1.2 to 10.5)	**0.01**
Energy	3	38.1 (18.9)	53.2 (18.2)	13.6 (8.8 to 18.3)	**<0.0001**
	9	41.3 (18.3)	46.1 (19.4)	2.5 (−2.2 to 7.2)	0.29
Health perceptions	3	40.3 (20.0)	50.2 (24.0)	9.4 (4.7 to 14.1)	**<0.001**
	9	44.0 (19.5)	43.9 (19.7)	−1.4 (−6.7 to 3.9)	0.61
Social function	3	67.5 (25.0)	76.9 (21.3)	8.9 (4.2 to 13.5)	**<0.001**
	9	65.8 (25.1)	74.1 (21.7)	7.1 (2.2 to 12.0)	**0.004**
Cognitive function	3	67.6 (21.1)	67.0 (27.4)	4.4 (−0.2 to 9.0)	0.06
	9	69.9 (22.9)	66.4 (27.8)	1.1 (−4.0 to 6.2)	0.68
Health distress	3	61.8 (26.9)	68.7 (24.9)	11.5 (6.6 to 16.4)	**<0.001**
	9	63.2 (25.8)	61.6 (26.4)	1.3 (−4.5 to 7.0)	0.67
Sexual function	3	70.4 (29.4)	74.1 (30.3)	7.5 (1.3 to 13.7)	**0.02**
	9	69.4 (29.6)	71.8 (25.9)	4.2 (−2.9 to 11.2)	0.25
Change in health	3	44.5 (22.2)	62.0 (24.5)	17.6 (10.9 to 24.4)	**<0.0001**
	9	47.3 (20.3)	50.0 (21.9)	3.0 (−3.8 to 9.9)	0.39
Sex satisfaction	3	51.6 (33.5)	64.1 (27.7)	9.8 (2.3 to 17.3)	**0.01**
	9	56.9 (31.0)	58.0 (25.2)	0.19 (−7.7 to 8.1)	0.96
Overall quality of life	3	60.6 (19.2)	68.1 (20.3)	9.9 (6.3 to 13.5)	**<0.0001**
	9	60.4 (21.1)	65.9 (20.1)	6.7 (2.6 to 10.7)	**0.001**
Physical health component	3	52.5 (21.4)	59.7 (20.6)	9.0 (5.6 to 12.4)	**<0.0001**
	9	53.3 (21.1)	54.1 (21.7)	2.0 (−2.0 to 6.0)	0.32
Mental health component	3	60.8 (20.0)	65.5 (20.2)	7.3 (2.6 to 12.0)	**0.002**
	9	63.8 (24.1)	65.9 (21.0)	3.5 (−2.1 to 9.2)	0.22
MSFC					
25-ft walk test (s)	3	9.9 (16.4)	6.7 (4.1)	−1.4 (−3.0 to 0.2)	0.09
	9	8.8 (10.8)	7.2 (4.7)	0.4 (−1.0 to 1.9)	0.58
9-Hole pin test DH average	3	25.2 (7.4)	26.4 (13.1)	−0·6 (−1.7 to 0.5)	0.26
	9	25.8 (10.5)	26.9 (14.7)	−1.5 (−3.0 to 0.1)	0.06
9-Hole pin test NDH average	3	28.4 (14.8)	26.8 (7.8)	−0.6 (−1.8 to 0.6)	0.30
	9	29.4 (14.9)	27.0 (7.7)	−0.7 (−1.7 to 0.4)	0.21
PASAT	3	46.0 (13.7)	41.9 (15.0)	−1.8 (−4.4 to 0.8)	0.17
	9	46.9 (13.9)	47.4 (9·9)	2.3 (−0.4 to 5.0)	0.10
Six-minute walk test (m)	3	398 (152)	406 (128)	13 (−6 to 31)	0.18
	9	382 (169)	394 (137)	18 (−9 to 46)	0.20

MFIS: Modified Fatigue Impact Scale; MSQoL-54: MS quality of life-54; MSFC: Multiple Sclerosis Functional Composite; PASAT: Paced Auditory Serial Addition Test; DH: dominant hand; NDH: non-dominant hand; 95% CI: 95% confidence intervals; values are presented as mean (±SD), with difference scores adjusted for baseline, gender and Expanded Disability Status Scale (EDSS).

Table 6.5. Anthropometric, blood pressure and EDSS scores at three- and nine-month follow-ups in participants allocated to usual care only and usual care plus EXIMS.

	Follow-up time point (months)	Usual care group mean (SD)	EXIMS group mean (SD)	Difference in adjusted means (95% CI)	Bootstrapped *p* value
Body mass (kg)	3	77.0 (15.6)	79.1 (18.0)	0.4 (–0.8 to 1.5)	0.52
	9	77.3 (15.6)	78.8 (18.7)	0.1 (–1.2 to 1.5)	0.88
BMI (kg/m^2)	3	27.2 (5.9)	28.0 (5.2)	0.2 (–0.3 to 0.7)	0.51
	9	27.2 (6.1)	28.0 (5.5)	0.3 (–0.4 to 1.0)	0.40
Waist circumference (cm)	3	90.9 (14.0)	90.5 (14.3)	–1.4 (–2.8 to 0.1)	0.07
	9	91.3 (14.2)	90.5 (14.7)	–2.0 (–3.7 to –0.2)	**0.03**
Waist:Hip ratio	3	0.85 (0.09)	0.85 (0.09)	–0.002 (–0.02 to 0.01)	0.71
	9	0.85 (0.09)	0.84 (0.09)	–0.01 (–0.02 to 0.002)	0.10
Systolic blood pressure (mm Hg)	3	129.6 (18.4)	125.6 (13.0)	–1.1 (–4.0 to 1.7)	0.44
	9	127.2 (16.4)	124.8 (13.6)	0.1 (–3.1 to 3.3)	0.94
Diastolic blood pressure (mm Hg)	3	83.0 (10.7)	81.9 (8.6)	–1.1 (–3.2 to 0.9)	0.28
	9	83.8 (10.1)	81.5 (8.6)	–2.3 (–4.6 to –0.1)	**0.04**
EDSS	3	3.9 (1.6)	3.5 (1.3)	–0.1 (–0.4 to 0.2)	0.41
	9	3.9 (1.7)	3.7 (1.5)	–0.1 (–0.4 to 0.2)	0.36

EXIMS: pragmatic EXercise Intervention for people with MS; BMI: body mass index; EDSS: Expanded Disability Status Scale. Values are presented as mean (±SD), with difference scores adjusted for baseline, gender and EDSS.

6.6 Discussion

This was the first robustly designed randomised controlled trial to investigate the effects of a practically implemented progressive exercise programme on self-directed exercise behaviour and important health outcomes in PwMS up to nine months of follow-up. Significant increases in self-reported exercise behaviour (GLTEQ) and step counts were observed in the intervention group versus controls at three months. A smaller difference in GLTEQ score (6.9 points, 95% CI: –0.9 to 14.7) in favour of the intervention group was also apparent after nine months, though this was not statistically significant and there was no evidence of a sustained increase in step counts at this time point.

Whilst the GLTEQ is reported to be a valid measure of habitual exercise behaviour in PwMS,[15] the possibility that self-reporting bias explains the

discrepancy between GLTEQ scores and accelerometry step counts at nine months cannot be overlooked. However, difficulties interpreting accelerometer step-count data in PwMS have been highlighted,[23] and activities such as stationary cycling, seated upper-body exercise, gardening and swimming can go undetected when using accelerometry. Although body weight remained unchanged, evidence of a reduction in waist circumference at both follow-up time points (non-significant at three months) and the reduction in diastolic blood pressure at nine months provides support for the maintenance of physical activity in the exercise group. These findings also show that the exercise intervention had an important impact on risk factors for cardiovascular disease. Hence, the apparent discrepancy between GLTEQ score and accelerometry step counts may reflect a shift to predominantly undetectable non-ambulatory activities over the study follow-up period, but this needs to be verified by future research. Despite this, our results suggest that the magnitude of change in self-directed exercise behaviour at nine months was reduced and was less clinically relevant.

The exercise group experienced improvements in multidimensional fatigue and in most HRQoL dimensions at three months. These improvements are consistent with previous systematic reviews,[24,25] although some conflicting evidence also exists.[26,27] Fatigue negatively affects HRQoL[28] and has a major impact on the high levels of unemployment in PwMS,[29] with $\geqslant$75% of the MS population experiencing symptoms persistently or sporadically.[30] For these reasons, pragmatic interventions that can alleviate fatigue are likely to have an important impact on HRQoL and ability to remain in employment. Baseline fatigue scores in the exercise group were positively associated with EDSS scores at baseline and the reduction in symptoms observed at the three-month

follow-up. This suggests that PwMS experiencing the highest levels of fatigue also experienced the greatest improvements with exercise training. However, higher volumes of supervised aerobic exercise were associated with less pronounced reductions in fatigue, suggesting that there could be an optimum level of aerobic exercise for symptom relief in PwMS. The changes in fatigue and GLTEQ scores were unrelated.

Improvements in emotional well-being, social function and overall HRQoL were maintained to nine months in the exercise group (versus controls), whereas the difference between groups in other HRQoL domains and fatigue was diminished at the final follow-up. The lack of a sustained improvement in other HRQoL domains and fatigue might be explained by a reduction in self-directed exercise over the follow-up period. Although previous studies suggest that short-term exercise interventions can have lasting effects on fatigue and HRQoL up to three months,[2,31,32] continued engagement in exercise is likely to be needed for the longer-term enhancement of many HRQoL dimensions and MS fatigue. A higher level of contact with participants after the intervention period could have been used to provide additional support and motivation for self-directed exercise. Although this has resource implications, our results suggest that strategies for maintaining contact with participants after an initial period of supervision (e.g. posted literature, mobile phone text messaging, social media, etc.) warrant further investigation.

There were no changes in measures of functional ability (6MWT) or neurological impairment (EDSS and MSFC) and these results are consistent with some[4,26,31,33,34] but not all previous exercise intervention studies.[3,26,27] Evidence suggests that regular exercise may be more effective in retarding

disease progression in PwMS,[35] rather than reversing the neuropathological changes that underpin neurological and functional impairments.[36]

A key limitation of the study is that it included ambulatory participants with only mild to moderate disease (EDSS $\leqslant$ 6.5) and at the present time, the effectiveness of exercise interventions for people with more severe disability is unknown. Many eligible PwMS declined to take part in the study without giving a reason (N = 126; 66%) and a more comprehensive understanding of the barriers and facilitators to exercise in PwMS could be used to inform the design of future programmes. In the remaining 34%, unwillingness to travel, other commitments, not being interested in exercise and worries about losing welfare benefits were cited as the reasons for not taking part. At least 30 potentially eligible PwMS considered the distance too far to travel (Figure 1), hence, providing the supervised component in a broader range of community settings may help to engage more PwMS in exercise programmes.

In conclusion, the observed improvements in self-directed exercise behaviour, HRQoL and fatigue suggest that EXIMS could be an effective way to practically implement progressive exercise rehabilitation within health care settings. EXIMS provides a tailored programme of preferred supervised and home-based exercises that are appropriate for individuals with different physical abilities and the level of uptake (39%) and high level of adherence (>80%) provides evidence that it is accessible to many PwMS. This study recruited participants with a range of neurological impairment (EDSS: 1.0–6.5), suggesting the results can be generalised to a broad spectrum of ambulatory PwMS. Strategies for promoting continued contact between participants and exercise practitioners beyond the initial period of supervision, however, may be needed to maintain meaningful improvements in important health outcomes.

6.7 Acknowledgments

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7.0 GENERAL DISCUSSION

7.1 Review of Findings

This thesis includes five published papers based around the design and implementation of a pragmatic exercise trial for PwMS. The first study paper (chapter three) investigated the feasibility of such an approach. The following chapters (chapter four to seven) contain the study protocol, recruitment details, key findings and cost-effectiveness data from the main trial (ExIMS).

7.1.1 Feasibility Trial

The feasibility trial presented in this thesis (chapter three) explored the feasibility of a pragmatic exercise intervention (supervised and home-based), that was both tailored to the individual and designed to promote confidence and motivation for long-term exercise behaviour change. Our results suggest that this type of trial design is feasible and effective for PwMS, with excellent retention (10 weeks, 93%; 3 months, 86%) and high compliance (>75% of all sessions) alongside a good progression in training load (duration and intensity). Moreover, our initial data suggests that important behavioural and QoL benefits might be experienced by PwMS and retained for up to three months follow-up. However, the impact of this type of intervention long-term should be viewed with caution as this may not reflect adherence to exercise beyond three month. Despite the reported benefits of exercise (Latimer-Cheung et al., 2013; Sá, 2013) PwMS participate in less physical activity (Ellis and Motl, 2013) than the general population and appear to find long-term adherence to exercise interventions difficult (Hale et al., 2012). Therefore our results suggest that a pragmatically designed and theoretically underpinned exercise intervention may

have the potential to increase the likelihood of long-term exercise behaviour change.

When retention was compared with previous supervised interventions of similar exercise load (73 to 85% at follow-up 1) (Petajan et al., 1996; Klieff and Ashburn, 2005; Van den Berg et al., 2006; Cakt et al., 2010) and other home-based trials (95 to 100% at follow-up 1) (DeBolt and McCubbin, 2004; Finkelstein et al., 2008) for PwMS, results were favourable. Moreover, retention in the feasibility trial was comparable to data reported after three months of follow-up (83% at 3 months follow-up) (McCullagh et al., 2008). Compliance was also excellent (80% of participants completing at least 70% of both supervised and home sessions), with the supervised component reporting similar figures to previous research (65 to 97%) (Petajan et al, 1996; Mostert and Kesselring, 2002; McCullagh et al., 2008). In addition, when compared to compliance in home-sessions during a similar combined exercise programme (100% of participants completing <50%) (McCullagh et al., 2008), this study design proved beneficial. Thus, suggesting that the addition of cognitive behavioural strategies to the study design may have had a positive impact on home-exercise behaviour.

The progression of exercise load was patient led and involved increasing intensity and/or duration whilst maintaining an RPE of between 11 and 13 (Fairly light to somewhat hard). The progression reported in this study is similar to other participant led progression rates (Rasova et al., 2006) and was well tolerated (no adverse events). Exercise type was also participant led, with all participants including treadmill, rowing and cycling ergometry in their supervised programme, despite rowing only previously being recommended for well-functioning patients (Dalagas et al., 2008). In addition, the most popular home

exercise was walking, in accordance with previous research (Rasova et al., 2006).

Cautious consideration of the outcome data reported indicated that PwMS can experience important clinical, physical and QoL benefits that may still be present after three months follow-up, as previously suggested by McCullagh et al., (2008). A large-scale trial, with a longer follow-up was warranted before conclusions regarding exercise benefits and maintenance could be determined.

7.1.2 Main Trial

7.1.2.1 Study Protocol

With this in mind chapter four outlines the protocol for an adequately powered two-group randomised control trial. The trial design aimed to generate new knowledge by investigating the effects of a pragmatic exercise trial containing cognitive behavioural strategies in a large population of PwMS for up to six-months of follow-up, reporting impact on physical activity behaviour, key health outcomes, and cost-effectiveness. In addition, the design included participants with slightly higher levels of disability from MS (up to EDSS 6.5 - Constant bilateral support required to walk 20 metres without resting) to determine impact on different disability levels, as suggested by Latimer-Cheung et al., (2013).

The study design was similar to that used in the feasibility study, containing cognitive behavioural strategies to promote long-term exercise behaviour change, exercise programmes that were individually tailored and a combination of home and supervised exercise sessions. However, the programme was extended from 10 to 12 weeks and changed to include a tapering of contact and

an increase in home exercise sessions during the second six weeks to build the skills and confidence for long-term self-management.

The majority of exercise and physical activity research studies in MS prior to this thesis have been inadequately powered and of poor research design. With regard to intervention design most have included either home or supervised exercise interventions, with only a few using a combined (supervised and home-based) approach (Surakka et al., 2004). Moreover to our knowledge no previous research has looked at the impact of a combined tapered approach to exercise for PwMS, although this has been used in other clinical groups, such as prostate and breast cancer patients (Bourke et al., 2011a, 2011b, 2014; Rogers et al., 2014). In addition, only more recent research trials have included a cognitive behavioural approach in combination with an exercise intervention in PwMS (Beckerman et al., 2013; Coote et al., 2014), thus making this study design unique, with design elements included to promote long-term exercise behaviour change.

7.1.2.2 Trial Recruitment

Chapter five provides a detailed account of the recruitment methods, rates and estimated costs for the main study trial. The main purpose of this chapter was to provide recruitment data to inform future research of this type and to determine which recruitment methods were the most successful in terms of numbers and cost per participant. This type of in-depth data for exercise interventions in MS is currently unavailable and will assist the design of future trials, enabling them to achieve recruitment targets in a timely fashion. This is essential if we are to ensure that research is adequately powered and does not require costly

extensions to enable completion (Treeweek et al., 2011; Polman et al., 2011). The recruitment data show that a variety of recruitment methods need to be employed if participants are to be recruited efficiently to exercise trials. Targeted consultant mail-outs were reported to be the most cost effective approach. However, insufficient numbers could be reached via this method and additional more time consuming methods, such as recruiting at MS outpatient clinics, was required for sufficient numbers of participants to be reached.

The recruitment rate of 3.5 participants per month achieved in this trial is comparable to other non-pharmacological intervention trials in MS. Previous interventions using PwMS have reported either marginally lower (Cooper et al., 2011) or higher (Thomas et al., 2013) rates per month, with exercise intervention trials in other clinical populations again reporting similar rates of between 2.9 and 4.0 participants per month (Daley et al., 2007; Nary et al., 2011; Taylor-Piliae et al., 2014). This indicates that this is a realistic target to use.

Response rates were highest from targeted consultant invite letters (42.8%) and lowest from attendance at MS outpatient clinics (6.4%), despite the large number of PwMS attending clinics, many did not meet the eligibility criteria. These methods should not however be discounted as the trial recruited 60% of its participants from this route, with only 29.2% coming from consultant letters and 10.8% from other trial awareness strategies. Randomisation yield (number recruited/number interested) for recruitment from the MS outpatient clinics and consultant letters was similar (33.2% and 31.0% respectively), suggesting both methods are useful in attaining targets.

The most common reason given for ineligibility to participate in the trial was already being too active (69.2%), this is consistent with results reported for

similar exercise trials in cancer survivors, where 55% were to active (Daley et al., 2007). This is surprising given the low levels of physical activity reported in the UK, with PWMS reported to be even more inactive than the general population (Klaren et al., 2013). However, those who wish to take part in an exercise study are likely to have an interest in and be more motivated to exercise. This suggests that we may not be reaching those who have limited interest in exercise and may need to look at more appealing interventions and other ways to incentivise this group to volunteer to take part in trials of this type. Options could include offering taster sessions prior to consent.

Many eligible participants (66.3%) chose not to give a reason for declining to participate. However, of those who did, travel to the site was the most commonly cited reason. Ensuring adequate travel arrangements or arranging community venues for exercise sessions could alleviate these concerns and should be considered in the design of future exercise trials in MS.

To adequately budget for recruitment to future trials it is important to not only understand where participants were recruited from, but how long it took to recruit each participant, with some community-based interventions reporting to take up to 10 hours per participant to recruit (Rdesinski et al., 2008). This trial reported that consultant mail-out was the most efficient method of recruitment at 0.6 hours per participant, with MS outpatient clinics requiring seven times this amount at 4.2 hours per participant. This provides an indicator of the time allocation required for recruitment in future trials. The results from this study provide a unique insight into trial recruitment for exercise interventions in MS and may be used to inform the design of future trials of this type.

Future trials would benefit from using a comprehensive recruitment strategy that includes methods to recruit individuals less keen on exercise, to ensure that a

representative sample of patients is recruited in an efficient and timely fashion. If the project is of a similar design and requires more than three patients a month to be recruited, a multi-centre trial is recommended. This would have the added benefits of testing generalisability across a variety of different settings.

7.1.2.3 Main Trial Results

Following on from the design of the ExIMS trial reported in chapter four and the recruitment strategies reported in chapter five, chapter six reports the primary and secondary outcome data from the main trial. Additional cost-effectiveness data is reported in appendix 8.15. The paper reported in chapter six aims to demonstrate if a robust pragmatically designed intervention, containing cognitive behavioural strategies to promote long-term participation, would show an increase in physical activity levels and improved health outcomes at up to nine months of follow-up, when compared with usual care. In addition the paper looks at dose response relationships and whether level of disability from MS has an impact on outcomes.

This research fills an essential gap in knowledge, as despite a large volume of literature in the area of exercise and MS, many questions have remained unanswered (Reitberg et al., 2005; Asano et al., 2009). The majority of current trials have been of poor quality and have not involved a pragmatic approach with cognitive behavioural strategies to promote long-term adherence to exercise (Asano et al., 2009). Moreover, none have begun to answer the questions regarding the dose response relationship and the impact of disability status on outcomes. The ExIMS trial reported significant improvements in exercise behaviour (GLTEQ and accelerometer step counts), fatigue and health

related QoL at three months follow-up, with significant improvements in emotional wellbeing, social function and overall QoL being sustained at up to nine months follow-up. These improvements were reflected in the effect sizes calculated, where small to moderate effects were reported (Appendix 8.14).

In line with previous systematic reviews on exercise interventions for PwMS (Latimer-Cheung et al., 2013) ExIMS reported a significant increase in physical activity (GLTEQ and step count) at three months follow-up. However, only the self-report data (GLTEQ) showed a notable sustained increase at nine months. There are two possible reasons for this, firstly self-report bias could have impacted on the data reported in the questionnaire and secondly, accelerometry for PwMS can be difficult to interpret (Weikert et al., 2010) and does not account for activities such as swimming, cycling and rowing ergometry, which were reported to be popular in the feasibility trial for this study (Carter et al., 2013). However, physiological data collected for diastolic blood pressure and waist circumference did indicate that there may still have been some increase in physical activity levels at nine months follow-up, with both showing significant improvement. Thus, suggesting that the programme may have an important long-term impact on cardiovascular health for PwMS. This is essential as PwMS are reported to have 2.4 times greater risk of death due to cardiovascular disease than the general population (Lalmohamed et al., 2012).

In addition to the significantly increased physical activity reported for the intervention group, when compared with usual care control at three months follow-up, multidimensional fatigue and most dimensions of health related QoL were also significantly improved. This is comparable with data reported in previous systematic reviews on exercise interventions for PwMS (Motl and Gosney, 2008; Andreason et al., 2011). When physical activity was no longer

reported to be significantly enhanced at nine months, follow-up improvements were no longer noted in fatigue and some of the health related QoL domains, despite improvements in emotional wellbeing, social function and overall quality of life remaining significant when compared with usual care control.

Previous research suggests that improvements in fatigue and QoL can be maintained up to three months follow-up even when improvements in exercise capacity have returned back to normal (McCullagh et al., 2008). No measures were taken in the current study at three months post intervention and it is possible that by six months post intervention that these changes had diminished. Thus, suggesting that continued engagement in exercise is required to maintain improvements in fatigue. This is supported by current literature that suggests that although the cause of MS fatigue is unknown it may be linked to immune dysfunction, with pilot work suggesting that aerobic exercise activates genes responsible for the immune response not observed in healthy controls. However, this disappears when exposure to exercise is removed (Mulero et al., 2015).

The study also reported that individuals experiencing the highest levels of fatigue at baseline, experienced the greatest improvements from the exercise intervention. This is comparable with the hypothesis drawn in the systematic review by Andreasen et al., (2011), who suggested that exercise interventions that demonstrated an impact on fatigue were those that had clinically fatigued patients at baseline. Chapter six also indicates that PwMS achieving high volumes of exercise during the intervention reported less pronounced improvements in fatigue, implying that an optimum level of training may exist. This finding warrants further research as data reported in a systematic review by Andreasen et al., (2011), suggests that at present 'it is not possible to draw

solid conclusions on optimal exercise duration, frequency and intensity'. It is likely that maintenance of exercise and hence fatigue and health related QoL domains during the follow-up may have been enhanced if the protocol had included additional contact with participants in the six month period following the intervention. However, this additional resource would increase the cost of the intervention and may impact on the cost-effectiveness results reported in chapter seven.

The ExIMS trial did not show any significant changes in functional ability (6MWT) or neurological impairment (MSFC, EDSS) when compared with usual care control. However, the study was not powered to demonstrate a change in these outcomes. In addition, studies lasting less than a year have only been reported to show subtle differences in EDSS (Brown and Kraft, 2005).

7.1.2.4 Economic Evaluation

Chapter six builds on current evidence that suggests that exercise can be beneficial for PwMS. However, if exercise is to be integrated into services provided for PwMS an economic evaluation is required to determine if the pragmatic approach used in the ExIMS trial provided a cost effective treatment strategy. The published article reporting the results of the economic evaluation for the ExIMS trial is contained in appendix 8.15. Data collected on hospital admissions suggested that there were four admissions during the trial, despite the scoping review in this thesis suggesting exercise to be safe. Due to the relapsing remitting nature of most of the participants in this trial, this is not considered abnormal or related to the intervention, with admissions in the usual care and exercise groups being similar. Data collected from ExIMS suggests

that the exercise intervention group was both more expensive and more effective than usual care alone, with no significant differences in cost or benefit between groups at six months follow-up. However, the intervention reported a high probability of being cost effective, with the calculated incremental cost effectiveness ratios (ICER) falling comfortably within the excepted thresholds of £20,000 per quality adjusted life years (QALY) used by NICE (Appleby et al., 2007). These results were maintained regardless of whether ExIMS was to be provided in the NHS or privately. Furthermore, the intervention was likely to become more cost effective over time, with the costs occurring in the first three months. This suggests that the ExIMS intervention is likely to be cost effective and provide cost benefits to the NHS. In addition, sub-group analysis suggested that if the intervention were to be targeted towards those who were less active and more severely affected by MS then the cost effectiveness of the ExIMS trial may be even greater.

7.2 Limitations of the Present Research

The results reported in this thesis suggest that the pragmatically designed ExIMS trial increases self-reported exercise behaviour, improves fatigue and provides a sustained improvements in many of the health related QoL domains, leading to a high probability of the intervention being cost effective. However, these findings should be interpreted based on the strengths and limitations of the research. The inclusion of a feasibility trial and a robust research design offers considerable improvement on previous aerobic exercise trials in PwMS, where participant numbers were much lower (between 11 and 54) (see Table 3a) and methodology often of poor quality (Döring et al., 2012). To our knowledge the ExIMS trial is the first MS and exercise RCT, with concealed

allocation, blind assessment and sample size based on statistical power calculations derived from a feasibility study. However, despite this, the research studies presented here do have some methodological weaknesses that should be taken into consideration when interpreting the findings presented in this thesis. The limitations fall into four main categories; research design, treatment fidelity, data interpretation and choice of outcome measures.

With regard to research design it should be noted that due to the nature of the intervention (exercise therapy) double blinding of participants and researcher was not possible, with only assessments able to be blinded. This is reported to possibly lead to exaggerated estimates of treatment impact (Schulz et al., 1995). In addition, the use of a usual care control group, instead of an attention control, could impact on the internal validity of the study as it may not be clear if some of the improvements in outcome measures were due to the additional attention rather than the specific nature of the intervention. However, it is felt that the chosen study design of usual care control would be the most desirable in order to answer the question of whether the new treatment could improve outcomes over and above usual practice. The option of a three group design, with intervention plus usual care, attention plus usual care and usual care only (Freedland, 2013), may have resolved this issue. However this would have been beyond the scope of the funding for the ExIMS trial and would have involved more participants having to take part who were not receiving the potentially beneficial intervention treatment arm.

It is noted that the study could have contained more stringent assessment of treatment fidelity, where treatment fidelity is defined as 'the degree to which an experimental manipulation has been implemented as intended' (Taylor et al., 2015). With regard to the physiological protocol it is felt that this was adequately

controlled, as the study intervention was delivered by experienced researchers who followed a detailed protocol, with appropriate data collected on intervention dose (compliance and adherence). Nevertheless the study would have benefited from a built in treatment fidelity assessment to ensure the integrity of the behavioural element of the intervention. However, this was beyond the scope of the funding provided for the feasibility work and the main ExIMS research trial reported in this thesis.

With regard to the intervention design it is felt that the post intervention follow-up duration of three month (feasibility trial reported in chapter three) and six months (ExIMS trial reported in chapters four to seven), although longer than that reported in previous exercise trials in MS (Latimer-Cheung, 2013) may have still benefited from being extended further, in order to determine the true long-term impact of the programme. With some of the clinical outcome measures such as EDSS and MSFC reported to require at least one year before meaningful differences can be observed (Brown and Kraft, 2005). Moreover, it is felt that an extension to 12 months of follow-up would have improved the results from the cost effectiveness analysis (chapter seven), as intervention costs were front loaded. In addition, further contact during the follow-up phase may have been beneficial in providing additional support and motivation for long-term improvements in exercise behaviour, thus enhancing the maintenance of improved exercise behaviours during the follow-up phase. However, it is noted that this would have resource implications, which would have to be measured up against the potential benefits to be gained.

The generalizability of the results may have been limited as eligible and interested participants who volunteered to participate in both the feasibility study (chapter three) and the ExIMS trial (chapters four to seven) may not be

representative of the broader MS population. This is likely to be due to the inclusion criteria limiting the study to participants that were ambulatory with an EDSS of up to 6.5, thus meaning that the results cannot be utilised with higher disability levels. In addition, there was only a limited number of individuals recruited at the higher end of the disability spectrum (5.0 - 6.5), limiting the ability of the study to determine the impact across different disability levels. Employing a recruitment strategy that ensured a balance of participants from each disability sub-group would have assisted with this, but may have led to an inadequate number of participants being recruited to the trial or a lengthy delay in completion. In addition, data from our recruitment paper (chapter five) suggested that those interested in being recruited to the trial had an interest in exercise participation with 69.2% being ineligible due to already being too active. This indicates that the impact of this intervention for PwMS not already contemplating exercise participation may differ to the results reported in this trial. Therefore, different recruitment strategies would be required to recruit this subset of the MS population.

There are two major considerations when interpreting the meaningfulness of the data reported in this thesis. Firstly, the study team were unable to conduct reliability and repeatability testing on the study population. This would have been the ideal scenario as it would have enabled better interpretation of the results in relation to the exact setting and population that they were based upon. However, data conducted independently on the reliability and repeatability of outcome measures used with PwMS does exist in the literature, a summary of which is outlined in the consensus meeting recommendations by Paul et al., (2014). In addition, this work was not covered by the ethics approval for this

study and any further assessments would have increased participant burden, something the ethics committee had already raised concerns over.

Secondly, it must also be noted that the data from the ExIMS trial (chapter six) is generally reported in terms of means, *p* values and confidence intervals. How best to analyse and report data from RCT's is often debated by statisticians. However, there is a growing body of literature reporting the need for the data to be reported as *p* values, confidence intervals and effect sizes to enable the meaningfulness of the data to be correctly interpreted (Maher et al., 2013). Therefore, it is suggested that the data reported in this paper could be strengthened, if effects sizes were reported, in addition to the confidence intervals and *p* values reported in chapter six. These have been calculated and presented in appendix 8.14.

The final set of limitations reported for this thesis pertains to the outcome measures used. Firstly, as noted in the review of findings, self-report data formed part of the economic evaluation and exercise behaviour assessment. Although this is common procedure for economic results reported alongside clinical trials, it must be noted that this can lead to inaccurate results and incomplete data sets. However, the finite funding available for the ExIMS trial meant that this was the only option available to the study team. In addition, despite the GLTEQ used being reported as a valid measure of exercise behaviour in PwMS (Motl et al., 2006), there is a possibility of self-report bias inflating the results. Secondly, the general variability of outcome measures used to report findings from clinical trials with PwMS must be mentioned, as this makes the comparison of the results from ExIMS with other similar trials for PwMS difficult.

7.3 Implications for Practice

There is a lack of quality evidence regarding exercise training and physical activity for PwMS (Reitberg et al., 2005; Asano et al., 2009). Therefore, many questions such as; what is the long-term impacts of exercise; is there an optimum dose and does this differ for different disability levels, remain unanswered (Döring et al., 2012; Sá, 2013). Current evidence is sufficient to suggest that mild to moderate intensity exercise is safe and effective at increasing fitness and may improve symptoms of fatigue and quality of life in patients with mild to moderate disability from MS (Latimer-Cheung et al., 2013; Sá, 2013). The ExIMS trial reported in chapter's four to seven was the first robustly designed pragmatic exercise trial for people with mild to moderate MS, designed to begin to answer some of these questions. The results from this thesis can be inferred for ambulatory individuals with mild to moderate disability from MS, with the effectiveness of the intervention for those with more severe disability from MS remaining unclear.

The ExIMS trial demonstrated that a pragmatic approach is effective at enhancing self-directed exercise behaviour and retaining some important health outcomes at up to six months of follow-up and is likely to be cost effective if implemented by the National Health Service (NHS).

In addition, it suggests that there is an optimum level of exercise for improvements in fatigue and that exercise is likely to be more beneficial for people experiencing higher levels of fatigue. Moreover, it indicates that some long-term benefits in health related QoL are retained at up to six months follow-up. However, it is suggested that for long-term improvements in fatigue participants need to maintain the elevated levels of fitness achieved following the three month intervention. Therefore it is recommended that cognitive

behavioural strategies form an essential component in the design of future exercise interventions, with further contact during follow-up required to maintain participant's confidence and motivation to exercise following the intervention. It should also be noted that the ExIMS trial is the only study to our knowledge to use an individually tailored programme guided by the individual, with input and advice from both specialist exercise scientists and physiotherapists. This approach is recommended in the future for the design of exercise programmes that provide PwMS with the ability to become more physically active and participate in more regular exercise.

This thesis provides valuable evidence to guide the design of future exercise interventions and provides robust and detailed data to enable more comprehensive guidelines for exercise and physical activity to be drawn up. On the basis of this new evidence it is recommended that exercise becomes part of the treatment pathway for PwMS within the NHS.

The broadcasting of the new knowledge made available from this thesis has been carried out within the scientific community through publication of the results (Saxton et al., 2013; Carter et al., 2013; Carter et al., 2014; Tosh et al., 2014; Carter et al., 2015) and presentation at research conferences (Society for Research and Rehabilitation, 2009; European Committee for Treatment and Research in MS, 2010; Physiotherapy UK, 2014; British Association of Sport and Exercise Science, 2014). In addition, results and take-home messages have been presented at practitioner (MS Frontiers, 2009, neuroinflamation forum, 2011; newly diagnosed course, 2009; neurological enablement service, 2010) and patient (MS Society living with MS days, 2009, 2010, 2012) led events to ensure the message is delivered to a wider audience. Moreover the

published results from this trial have been cited in the updated 'NICE Guidelines for Management of Multiple Sclerosis in Primary and Secondary Care' (2014).

7.4 Directions of Future Research

To date review articles in the area of exercise and MS have consistently stated that there is a need for more high quality RCT's, with sample sizes based on statistical power calculations (Sa, 2013; Doring et al., 2012) and interventions tailored to individuals symptoms and lifestyle (Asano et al., 2009). In addition, there is also a need for studies to take into account different disability levels and longer-term impact (Doring et al., 2012). For exercise interventions to have the greatest impact there is a need for future studies to use a mixed methods approach, examining the motivational responses that determine exercise behaviour and enabling the barriers to exercise participation in this population group to be fully explored (Kasser, 2009), with studies also designed to include cognitive behavioural strategies to promote long-term exercise behaviour change (Coote et al., 2014; Giedl et al., 2014).

The publications presented in chapter three to seven of this thesis, begin to answer these questions. However, there are still many questions that need to be answered as most studies have involved people with mild to moderate disability from MS, exercising at a moderate intensity (Asano et al., 2009). Therefore, there is a requirement for further high quality RCT's designed to explore the following research topics:

- Exercise for people with more severe disability from MS (EDSS greater than 6.5).

- The feasibility of higher intensity exercise for people with mild disability from MS.
- Early educational intervention to prevent rapid decline in exercise participation on diagnosis.
- The optimum type and dose of exercise for fatigue management for people with clinical levels of fatigue from MS.

7.4.1 Exercise for people with more severe disability from MS

Despite the rapid increase of research into exercise for people with mild to moderate MS over the last 10 to 15 years, research into exercise for those with more severe disability has been sparse. The results from this thesis (chapters three to seven) have looked at the acceptability of a pragmatic tailored approach to exercise for PwMS (EDSS 1.0-6.5) and whether the dose able to be achieved is different for those with more severe disability. Results suggest that although some participants at the upper limits of our inclusion criteria were able (EDSS 6.0-6.5) to achieve excellent compliance levels, with 1 achieving 100%. Most however found attending the supervised sessions difficult, with high drop-out levels experienced in this population group, thus supporting research suggesting the need for a tailored approach to physical activity interventions, directed by disability status (Cavanaugh et al., 2011). The challenge now is to explore the type of physical activity interventions that would be acceptable and achievable for people with more severe MS and what benefits could potentially be gained from participation in interventions aimed at decreasing sedentary behaviour and increasing physical activity in this population group. Such research has the potential to have a significant impact on the lives of PwMS and

their families. Hence, there is a need to investigate what type of intervention would be feasible for people with moderate to severe MS and what potentially benefits this could have on physical activity behaviour and health outcomes.

7.4.2 Feasibility of high intensity exercise for people with mild disability from MS.

Current guidelines recommend that people with MS exercise at a moderate intensity (Reitberg et al., 2005; Latimer-Cheung et al., 2013), as most current exercise research is conducted at this intensity (Rognomo et al, 2004). Thus, meaning that even if individuals have very mild or benign MS they are still advised to avoid high intensity exercise as there is no current research available to suggest whether it is safe or not. This may lead to the type of scenario where an individual whom is currently very active may be recommended to significantly alter their current exercise habits on diagnosis, when they may not have to. High intensity interval training (HIIT) has grown in popularity over recent years, as it has been shown to be an effective alternative to traditional endurance training (Bird and Hawley, 2012), despite having a substantially lower time commitment (Gibala et al., 2012). In addition, this type of exercise has also been used successfully with other clinical populations such as diabetics (Adams, 2013) and obesity (Lunt et al., 2014). It is therefore recommended that future research investigates the feasibility of higher intensities of exercise for people with mild disability from MS to determine if it is safe and beneficial for this population group.

7.4.3 Early educational intervention to prevent rapid decline in exercise participation on diagnosis of MS

PwMS participate in less physical activity than the general population (Motl et al., 2005; Plow and Motl., 2012), by nearly one standard deviation, with almost 60% of individuals with MS participating insufficient physical activity to provide minimal health benefits (Motl et al., 2015). Unpublished qualitative data collected during the ExIMS trial suggests that at diagnosis PwMS currently receive little if any advice and support on what type of exercise is beneficial and that this continues long-term, with health professionals and gym instructors unable to provide adequate advice. In addition, if PwMS wish to access additional information on exercise and physical activity, their preferred source is the Internet (Sweet et al., 2013). This is a resource also utilised by health care professionals wishing to promote physical activity (Cullen, 2002). Unfortunately, current information found on websites such as the MS Society and MS Trust is generic, lacks detail and contains limited use of behaviour change techniques (Shirazipour et al., 2015).

Qualitative research suggests that fear of making the condition worse (Kayes et al., 2011) and fatigue (Smith et al., 2011) may contribute to the observed decline in physical activity and structured exercise following a diagnosis of MS.

Therefore, cost effective strategies that provide support to individuals to help them maintain and or take up new forms of exercise and physical activity both at diagnosis and as disability levels and symptoms change are crucial. This would enable PwMS to maintain a healthy relationship with exercise that enables them to better self-manage their condition and gain maximum benefits from being more physically active.

Survey research with 318 PwMS based in the United Kingdom, reported that PwMS are looking for 3 key things from the health care service; information on management, relevant tailored advice and access to appropriately skilled professionals (Somerset, 2011). Therefore, an education based programme combining individual therapy and group education sessions on exercise and lifestyle issues, ran by appropriately trained professionals would go some way to meeting the needs of PwMS (Plow et al., 2009). Lifestyle education programmes have been used successfully to increase physical activity participation with other clinical populations i.e. diabetes (DESMOND) (Skinner etal, 2006) and claudication (CEDRIC) (Tew et al., 2015). Positive benefits of educational sessions have also been reported for PwMS, with Feys et al., (2013), reporting that a one day practical and theory based education programme for physical activity may have a long-term impact on physical activity and perceived impact of MS. This positive impact is supported by Ng et al., (2013), who reported short and long-term increases in self-efficacy and health related quality of life from a four day interdisciplinary wellness education programme. However, both of these studies did not include a usual care control group and contained only self-report outcome measure which may have positively biased the results. In addition, these studies lacked a theoretical underpinning designed to increase self-efficacy and promote long-term adherence to positive behaviour change.

It is, therefore, recommended that future research investigates the impact of a robustly designed trial containing both individual tailored advice and group sessions, with the theoretical underpinning to increase knowledge and confidence to exercise and promote long-term exercise adherence for PwMS.

This has the potential to provide a cost effective solution to declines in exercise participation observed in PwMS.

7.4.4 The optimum type and dose of exercise for fatigue management for people with clinical levels of fatigue from MS.

Data synthesis from systematic reviews (Latimer-Cheung et al., 2013; Andreasen et al., 2013) and meta-analysis (Pilluti et al., 2013; Asano and Finlayson, 2014) suggests that exercise may provide a useful approach to managing fatigue for PwMS. However, quality research is sparse and does not enable inference across different types of MS and disability levels (Asano and Finlayson, 2014), or what type and dose provide optimum results (Latimer-Cheung et al., 2013; Asano and Finlayson, 2014). Results from this thesis (Chapter six) suggest that individuals experiencing the highest levels of fatigue have the potential to experience the greatest improvements, as supported by Andreason et al (2011). In addition, our data also suggests that there may be an optimum dose of exercise, with individuals achieving the highest dose of exercise during the ExIMS trial not achieving the greatest improvements in fatigue.

Therefore, it is recommended that future research explores the optimum type and dose of exercise required to gain benefits in PwMS presenting with clinical levels of fatigue.

7.5 Conclusion

The studies presented in chapter's three to seven of this thesis report on the feasibility, design, recruitment, health outcomes and cost effectiveness of a

pragmatically designed exercise intervention. The intervention uses a unique approach that is individually tailored, employs cognitive behavioural techniques to promote long-term adherence and is designed to contain tapered supervision, being predominantly home-based in the latter stages. Data suggest that to recruit to this type of study a mixture of approaches are required for targets to be met, with an average recruitment rate of 3.5 participants a month being a realistic goal. Our main outcomes suggest that this pragmatic approach was not only feasible, but results from ExIMS indicate that this type of intervention can provide significant increases in self-directed exercise behaviour, fatigue and health related QoL, with significant improvements for some domains of QoL being sustained at up to nine months follow-up. In addition, this intervention is highly likely to be cost effective if implemented by the NHS.

Prior to this research systematic reviews and meta-analysis into the benefits of exercise for people with MS have consistently highlighted a need for more robustly designed research trials, containing long-term follow-up and participants with higher levels of disability from MS. This thesis has taken a notable step towards filling in the gaps in the literature, by providing data from a robustly designed pragmatic exercise trial, which has recruited people with a range of neurological impairment (EDSS 1.0-6.5) and has included a longer-term follow-up (six months).

Our results provide a strong evidence base to suggest that a pragmatic approach to exercise can have important long-term health benefits that improve self-management and should encourage health professionals to motivate individuals with MS to exercise. It is hoped that exercise will now be considered as part of the treatment pathway for PwMS within the NHS, with results

presented in this thesis already cited in the 'NICE Guidelines for Management of Multiple Sclerosis in Primary and Secondary Care' (2014). However, if outcomes are to be optimised and increased levels of activity maintained, there is a need for strategies to provide continued contact between participants and the delivery team following the intervention.

Furthermore, there are still many questions that remain unanswered, as the majority of exercise research has involved people with mild to moderate levels of disability from MS, exercising at a moderate intensity. There is a need for more high quality RCT's exploring the benefits of exercise for people with more severe disability from MS, and the feasibility of higher intensity exercise for people with mild disability from MS. In addition, further details are required on the optimum dose of exercise for improvements of important health outcomes such as fatigue.

7.6 References

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8.1

NHS

National Research Ethics Service

South Yorkshire Research Ethics Committee
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S5 7AU

Telephone: 0114 226 8153
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30 September 2008

Dr John M Saxton
Reader in Clinical Exercise Physiology
Sheffield Hallam University
Centre for Sport and Exercise Science
Sheffield
S10 2BP

Dear Dr Saxton

Full title of study: **The effects of a pragmatic exercise therapy intervention on physical activity and important health outcomes influencing maintenance in people with multiple sclerosis.**
REC reference number: **08/H1310/69**

The Research Ethics Committee reviewed the above application at the meeting held on Thursday 25 September 2008. Thank you for attending to discuss the study.

Discussion

This was a well prepared study that did not present any major ethical issues apart from the fact you were expecting a huge amount of commitment from the participants. The study required several visits by participants and completion of lots of questionnaires. It was queried whether you felt you would be able to recruit the numbers required. You believed adequate numbers were available in the area and felt that from previous experience patients seemed to be quite keen on this kind of intervention. Advice had been taken from the consultants involved and you had satisfactorily carried out similar RCTs with other patient groups and believed it would be possible to recruit sufficient numbers for the study. The committee accepted this explanation.

It was observed that Chesterfield was outside the domain of the South Yorkshire REC and you were asked to assure the committee that no research procedures would be carried out there, including the taking of informed consent or data collection. You explained that participants would be travelling to Sheffield and confirmed that no research procedures would be carried out in Chesterfield. The committee accepted this assurance but would like it confirmed in writing.

It was noted that you intended to store the research data for 20 years and it was felt this was too long. After discussion it was agreed that the data would be stored for five years after the study had been completed and then destroyed. The committee accepted this assurance.

The study was being carried out as part of a PhD qualification but the student concerned i.e. Anouska McConnell was not mentioned anywhere in the application as a Co-investigator/ Collaborator. Please confirm she should be included as a Co-investigator/Collaborator.

Some additions were required to the Participant Information Sheet (see below).

Ethical opinion

Members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

- Confirm the following in writing:
  - No research procedures will be carried out at Chesterfield including the taking of informed consent or collection of data.
  - Research data will be stored for five years after the study had been completed and then destroyed.
  - Anouska McConnell should be named as a Key Investigator/Collaborator

- Submit an amended Participant Information Sheet (Version 2 with a new date) to include the following:
  - Under a heading "General information about research" insert "Independent advice can be obtained from the Patients' Advisory Liaison Service (PALs) and give contact details"
  - Under the heading "Who has reviewed this study?" insert "South Yorkshire Research Ethics Committee"

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Application		15 August 2008
Investigator CV	1	15 August 2008
Protocol	1	15 August 2008

Covering Letter		15 August 2008
Questionnaire: Validated - Health Questionnaire EQ-5D		
Questionnaire: Validated - Modified Fatigue Impact Scale (MFIS)		
Questionnaire: Validated - International Physical Activity Questionnaire (August 2002)		
Questionnaire: Validated - Multiple Sclerosis Quality of Life (MSQOL)-54 Instrument		
Advertisement	1	15 August 2008
Letter of invitation to participant	1	15 August 2008
Participant Information Sheet (awaiting Version 2)	1	15 August 2008
Participant Consent Form	1	15 August 2008
CV - Anouska McConnell		
Study Flow Chart	1	15 August 2008
GP Letter	1	15 August 2008
Letter from Funding Body		11 August 2008

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

08/H1310/69 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

J Brown

pp Jo Abbott
Chair

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers" SL-AR2
Site approval form (SF1)

Copy to: STH R & D Department

South Yorkshire Research Ethics Committee

Attendance at Committee meeting on 25 September 2008

Committee Members:

Name	Profession	Present	Notes
Jo Abbott	Senior Nurse Manager, Public Health, Rotherham PCT	Yes	
Dr A H Abdelhafiz	Consultant Physician, Elderly Medicine	Yes	
Reverend Joan Ashton	Co-ordinator of Chaplaincy Services	Yes	
Miss Helen Barlow	Knowledge Manager	Yes	
Professor Nigel Beail	Consultant Clinical Psychologist & Professor of Psychology	Yes	
Mr Ian Cawthorne	Chief Pharmacist	Yes	
Mr Paul Fryers	Public Health Specialist	Yes	
Dr Peter Matfarlane	Consultant Paediatrician	Yes	
Mr Neil Marsden	Police Communications Officer	Yes	
Dr Anton Mayer	Consultant in Paediatric Intensive Care	No	
Mrs Andrea Porritt	District Nurse/Practice Educator	No	Written comments
Dr Ganesh Rao	Consultant Clinical Neurophysiologist	No	
Mr Jaydip Ray	ENT Consultant	No	
Ms Stephanie Rhodes	Neonatal Sister	Yes	
Dr Salil R. Sen	General Practitioner	Yes	
Dr Paul Spencer	Consultant Radiologist	No	
Dr Jonathan Train	Consultant Anaesthetist	No	

South Yorkshire Research Ethics Committee

LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION

For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For Issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.

REC reference number:	09/H1310/69	**Issue number:**	1	**Date of Issue:**	29 September 2009
Chief Investigator:	Dr John M Saxton				
Full title of study:	The effects of a pragmatic exercise therapy intervention on physical activity and important health outcomes influencing maintenance in people with multiple sclerosis.				

This study was given a favourable ethical opinion by South Yorkshire Research Ethics Committee on 25 September 2009. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.

Principal Investigator	*Post*	*Research site*	*Site assessor*	*Date of favourable opinion for this site*	*Notes* [1]
Dr Basil Sharrack	Consultant Neurologist	Sheffield Teaching Hospitals NHS Trust, 8 Beech Hill Road Sheffield	North Sheffield Local Research Ethics Committee	29/09/2009	

Approved by the Chair on behalf of the REC:

J Brown ..... (Signature of ~~Chair~~Co-ordinator)

(delete as applicable)

JOAN BROWN ..... (Name)

(1) *The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension or termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.*

RESEARCH IN HUMAN SUBJECTS OTHER THAN CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS

After ethical review – guidance for sponsors and investigators

This document sets out important guidance for sponsors and investigators on the conduct and management of research with a favourable opinion from a NHS Research Ethics Committee. Please read the guidance carefully. A failure to follow the guidance could lead to the committee reviewing its opinion on the research.

1. Further communications with the Research Ethics Committee

1.1 Further communications during the research with the Research Ethics Committee that gave the favourable ethical opinion (hereafter referred to in this document as "the Committee") are the personal responsibility of the Chief Investigator.

2. Commencement of the research

2.1 It is assumed that the research will commence within 12 months of the date of the favourable ethical opinion.

2.2 In the case of research requiring site-specific assessment (SSA) the research must not commence at any site until the Committee has notified the Chief Investigator that the favourable ethical opinion is extended to the site.

2.3 The research must not commence at any site until the local Principal Investigator (PI) or research collaborator has obtained management permission or approval from the organisation with responsibility for the research participants at the site.

2.4 Should the research not commence within 12 months, the Chief Investigator should give a written explanation for the delay. It is open to the Committee to allow a further period of 12 months within which the research must commence.

2.5 Should the research not commence within 24 months, the favourable opinion may be suspended and the application would need to be re-submitted for ethical review.

3. Duration of ethical approval

3.1 The favourable opinion for the research generally applies for the duration of the research. If it is proposed to extend the duration of the study as specified in the application form, the Committee should be notified.

3.2 Where the research involves the use of "relevant material" for the purposes of the Human Tissue Act 2004, authority to hold the material under the terms of the ethical approval applies until the end of the period declared in the application and approved by the Committee.

4. Progress reports

4.1 Research Ethics Committees are expected to keep a favourable opinion under review in the light of progress reports and any developments in the study. The Chief Investigator should submit a progress report to the Committee 12 months after the date on which the favourable opinion was given. Annual progress reports should be submitted thereafter.

4.2 Progress reports should be in the format prescribed by NRES and published on the website (see www.nres.npsa.nhs.uk/applicants/after-ethical-review).

4.3 The Chief Investigator may be requested to attend a meeting of the Committee or Sub-Committee to discuss the progress of the research.

5. Amendments

5.1 If it is proposed to make a substantial amendment to the research, the Chief Investigator should submit a notice of amendment to the Committee.

5.2 A substantial amendment is any amendment to the terms of the application for ethical review, or to the protocol or other supporting documentation approved by the Committee, that is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the trial participants
(b) the scientific value of the trial
(c) the conduct or management of the trial.

5.3 Notices of amendment should be in the format prescribed by NRES and published on the website, and should be personally signed by the Chief Investigator. The agreement of the sponsor should be sought before submitting the notice of amendment.

5.4 A substantial amendment should not be implemented until a favourable ethical opinion has been given by the Committee, unless the changes to the research are urgent safety measures (see section 7). The Committee is required to give an opinion within 35 days of the date of receiving a valid notice of amendment.

5.5 Amendments that are not substantial amendments ("minor amendments") may be made at any time and do not need to be notified to the Committee.

6. Changes to sites *(studies requiring site-specific assessment only)*

6.1 Where it is proposed to include a new site in the research, there is no requirement to submit a notice of amendment form to the Committee. The SSI Form together with the local Principal Investigator's CV should be submitted to the relevant local REC for site-specific assessment (SSA).

6.2 Similarly, where it is proposed to make significant changes in the management of a site (in particular, the appointment of a new PI), a notice of amendment form is not required. A revised SSI form for the site (together with the CV for the new PI if applicable) should be submitted to the relevant local REC for SSA.

6.3 The relevant local REC will notify the Committee whether there is any objection to the new site or Principal Investigator. The Committee will notify the Chief Investigator of its opinion within 35 days of receipt of the valid application for SSA.

6.4 For studies designated by the Committee as exempt from SSA, there is no requirement to notify the Committee of the inclusion of new sites.

7. Urgent safety measures

7.1 The sponsor or the Chief Investigator, or the local Principal Investigator at a trial site, may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety.

7.2 The Committee must be notified within three days that such measures have been taken, the reasons why and the plan for further action.

8. Serious Adverse Events

8.1 A Serious Adverse Event (SAE) is an untoward occurrence that:

(a) results in death
(b) is life-threatening
(c) requires hospitalisation or prolongation of existing hospitalisation
(d) results in persistent or significant disability or incapacity
(e) consists of a congenital anomaly or birth defect
(f) is otherwise considered medically significant by the investigator.

8.2 A SAE occurring to a research participant should be reported to the Committee where in the opinion of the Chief Investigator the event was related to administration of any of the research procedures, and was an unexpected occurrence.

8.3 Reports of SAEs should be provided to the Committee within 15 days of the Chief Investigator becoming aware of the event, in the format prescribed by NRES and published on the website.

8.4 The Chief Investigator may be requested to attend a meeting of the Committee or Sub-Committee to discuss any concerns about the health or safety of research subjects.

8.5 Reports should not be sent to other RECs in the case of multi-site studies.

9. Conclusion or early termination of the research

9.1 The Chief Investigator should notify the Committee in writing that the research has ended within 90 days of its conclusion. The conclusion of the research is defined as the final date or event specified in the protocol, not the completion of data analysis or publication of the results.

9.2 If the research is terminated early, the Chief Investigator should notify the Committee within 15 days of the date of termination. An explanation of the reasons for early termination should be given.

9.3 Reports of conclusion or early termination should be submitted in the form prescribed by NRES and published on the website.

10. Final report

10.1 A summary of the final report on the research should be provided to the Committee within 12 months of the conclusion of the study. This should include information on whether the study achieved its objectives, the main findings, and arrangements for publication or dissemination of the research including any feedback to participants.

11. Review of ethical opinion

11.1 The Committee may review its opinion at any time in the light of any relevant information it receives.

11.2 The Chief Investigator may at any time request that the Committee reviews its opinion, or seek advice from the Committee on any ethical issue relating to the research.

NHS

National Research Ethics Service

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28 October 2008

Dr John M Saxton
Reader in Clinical Exercise Physiology
Sheffield Hallam University
Centre for Sport and Exercise Science
Sheffield
S10 2BP

Dear Dr Saxton

Full title of study: **The effects of a pragmatic exercise therapy intervention on physical activity and important health outcomes influencing maintenance in people with multiple sclerosis.**
REC reference number: **08/H1310/69**

I acknowledge receipt of your letter dated 23 October 2008 complying with the conditions specified in the REC's favourable opinion letter dated 30 September 2008 and enclosing the following document:

- Participant Information Sheet, Version, 2, dated 23 October 2008

Yours sincerely

Joan Brown

Joan Brown
South Yorkshire REC Co-ordinator

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

MS Multiple Sclerosis Society

Sheffield Hallam University

The effects of a pragmatic exercise intervention in people with multiple sclerosis.

Patient Information Sheet

Version 2: 23rd October 2008

Introduction

Exercise is increasingly being accepted as a component of symptom management in people with Multiple Sclerosis. High quality research evidence exists to support the benefits of exercise on physical function, muscle power, exercise tolerance, quality of life and mobility-related activities in people with MS.

In this study you will be randomly allocated to either an exercise or usual care group. The randomisation is generated by a computer sequence, we have to do this in order to make sure the results are scientific.

At the beginning and following the study we will measure your physical function, asking you to complete a series of physical tests. We will also assess your feelings of quality of life, physical activity levels and fatigue by asking you to complete some questionnaires and take a blood sample for immunological analysis. The data from this study will contribute to the evidence-base for exercise therapy in MS and inform health policy through clinical guideline recommendations.

This patient information sheet for the study answers the most frequently asked questions and is your copy to keep.

Frequently asked questions

Q: What is the main purpose of the study?

A: The aim of the study is to investigate whether a practically designed exercise programme is effective in providing improvements in physical activity and health outcomes which are likely to have a positive impact on your physical function and quality of life. We will also explore what amounts of exercise are most effective and whether exercise is more or less beneficial for people with different disability levels.

Q: Why has my Doctor told me about this study?

A: You have been selected as being a suitable patient from your medical history, and because you are receiving treatment for multiple sclerosis.

Q: What will I have to do?

A: All patients who are interested in entering the study will be initially invited to attend an appointment with the study researcher at The Centre for Sport and Exercise

Science at Sheffield Hallam University. You will have the opportunity to go through this information sheet again and ask any questions you might have about the study. You will also be shown around the exercise training facility and assessment room and taken through the procedures. You will be given a consent form to take home and complete. This is so that you can have time to decide whether or not you would like to take part in the study.

Assessment

If you decide to take part you will be asked to attend the University for an initial assessment session before you are randomised to either the exercise intervention or the usual care group. You should bring your completed consent form with you to the first session. You will be assessed on a total of 3 occasions; at the start of the programme, immediately following the 12 week intervention and 6-months following the intervention. In addition, at the end of the supervised exercise sessions some individuals will be randomly chosen to participate in a 1-to-1 interview and focus group sessions at the University to discuss you experiences of the research study.

At the University

During the assessment session we will take a small blood sample and complete series of functional and physical tests. These include measurement of resting heart rate and blood pressure, height, weight and waist:hip girths, completion of the MS Functional composite test (25 ft walk, 9 hole peg test and paced auditory serial addition test) and a six minute walk test. These visits should last no more than 45 minutes.

At Home

You will also be asked to complete a self assessment questionnaire. This can be completed at home and will include measures of physical activity behaviour, quality of life, fatigue and cost effectiveness. This should take no longer than 1 hour to complete. You will also be asked to wear an accelerometer (a small device worn like a pedometer) for a 7 day period and keep a physical activity recall diary during this period. In addition, salivary cortisol will be measured on three consecutive days at 4 time points. A special watch will be provided to help you remember.

At the Hospital

You will also be required to have an appointment with a consultant at the Royal Hallamshire Hospital to assess your disability score (EDSS). This appointment should take no more than 30 minutes.

Q: What will I have to do if I am allocated to the exercise intervention group?

A: After the baseline assessment sessions, you will be asked to participate in 3 exercise sessions a week over a 12 week period. For the first 6-weeks this will consist of 2 supervised exercise sessions and 1 exercise session at home. In the second 6-weeks you will be asked to complete 1 supervised exercise session a week and 2 exercise sessions at home. Supervised sessions will take place at The Centre for Sport and Exercise Science at Sheffield Hallam University, Collegiate Crescent Campus (off Ecclesall Road) and are lead by experienced exercise professionals, with programmes overseen by the project physiotherapist.

Supervised exercise will take place in small groups (up to 3-4 people) and will begin with a gentle warm up. Each exercise session will consist of completing short bouts of exercise (1-5 mins), with rest intervals, at a low-moderate intensity. Where appropriate, strength, balance and flexibility work may also be performed. Heart rate, ratings of perceived exertion and minutes of specific exercises achieved will be recorded by the researcher to allow for an assessment of the exercise dose achieved each week. Please allow 45-60 minutes for your exercise session. All exercise sessions are tailored to your level of ability, according to your symptoms, fitness and personal goals.

Q: What will I have to do if I am allocated to the usual care group?
A: Patients allocated to the usual care group will be asked to continue with their usual daily routine. You will only be required to attend the complete the assessments (outlined previously), which will be at the beginning, end of the 12-week study period and after a further 6-months for a follow up.

Q: How long will the study last?

A: The exercise intervention will last 12 weeks. We will monitor your progress throughout, to make sure that the exercise programme progresses at an appropriate rate. You will then be assessed 6 months after the end of the intervention to see if it has had a more long term impact.

Q: Will there be any effects on my follow-up treatment?

A: No, your participation in this study will not affect your follow-up treatment in any way.

Q: What are the possible benefits of taking part in this study?

A: Previous research suggests that the exercise intervention has the potential to improve your physical and mental wellbeing. Possible benefits specifically include; increased endurance, increased mobility (walking/balance), improved mood, increased quality of life and possible improvements to fatigue.

Q: Are there any side-effects of taking part?

A: If you haven't exercised for a while, it might initially make you feel you are breathing harder than usual or slightly sweaty. Exercise may also initially make you feel tired, but as you do it more regularly this should feel increasingly better.

Q: What are the possible disadvantages and risks of taking part?

A: The potential for risks of anything untoward happening during the exercise will be minimal.

Q: If I decide to participate, will my GP be notified?

A: With your consent, we will write and inform your family doctor that you are taking part in this study.

Q: Do I have to take part?

A: It is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form.

Q: What if I do not wish to take part?

A: Your participation is entirely voluntary. If you decide not to take part, this will not affect the standard of care you receive from the hospital or any health professional.

Q: What if I change my mind during the study?

A: You are free to withdraw from the study at any time without it affecting your future treatment.

Q: What will happen to the information from the study?

A: The overall conclusions of the study will be available to you; however, it will not be possible to produce an individualised report of your performance.

Q: Will my taking part in this study be kept confidential?
A: Yes, the confidentiality of our study participants and their data is of utmost importance. All data from this study will be annonymised. This means that you will be allocated a number during the study and this will be used to store data. In addition, we will need to obtain your permission to allow the research team access to your medical records, and to information collected during the study. This is one of the clauses, which you will sign in agreement on the official consent form.

Our procedures for handling, processing and storage of and destruction of data are compliant with the Data Protection Act 1998.

Q: Who is organising and funding the research?
A: The research is organised by The Centre for Sport and Exercise Science, Sheffield Hallam University in collaboration with the Sheffield Teaching Hospitals NHS Foundation Trust. Funding for the research has been provided by the Multiple Sclerosis Society.

Q: Who has reviewed this study?
A: The South Yorkshire Research Ethics Committee has reviewed this study.

Q: What if I have further questions?
A: f you have any further questions with regards to this study you may phone:-

Name: Dr. John Saxton (Project Co-ordinator) Tel: 0114 225 4414

Name: Anouska McConnell (Study researchers) tel. 0114 225 5633

Name: Mr. Basil Sharrack (Consultant Neurologist) Tel: 0114 271 3608

Q: What if I wish to complain about the way this study has been conducted?

A: f you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you and are not compromised in any way because you have taken part in a research study. The normal hospital complaints procedure applies, and you should contact the following person:

Name: Professor Chris Welch (Medical Director) Tel: 0114 271 1900

You can also complain to any individual of the research team

Name: Dr. John Saxton (Project Co-ordinator) Tel: 0114 225 4414

Name: Anouska McConnell (Study researchers) tel. 0114 225 5633

Name: Mr. Basil Sharrack (Consultant Neurologist) Tel: 0114 271 3608

Sheffield Hallam University has the following policies in place for the legal liability of the University; (a) Professional indemnity (£10 million); and (b) Public liability (£20 million)

Q: What if I am Harmed?

A: n the event that something does go wrong and you are harmed during the research study, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you might have grounds for legal action for compensation, but you could have to pay your legal costs.

Thank you for taking the time to consider participating in this study

Dr.John Saxton (Project co-ordinator)

General Information about Research

Independent advice can be sort from the Patients' Advisory Liaison Service (PALS), Royal Hallamshire Hospital, B Floor, Glossop Road, Sheffield, South Yorkshire, S10 2JF, (0114 271 2450).

Appendix 8.3 - Informed consent form

Sheffield Teaching Hospitals NHS Foundation Trust | Multiple Sclerosis Society | Sheffield Hallam University

PATIENT CONSENT FORM

Sheffield Hallam University and The Sheffield Teaching Hospitals Trust

The effects of a pragmatic exercise intervention in people with multiple sclerosis.

Patient Identification Number for this study:

Study Investigators: Dr John Saxton, Dr Basil Sharrack, Miss Anouska McConnell.

Name of researcher:

tick box

1. **I confirm that I have read and understood the information sheet dated 23rd October 2008 Version 2 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.** ☐
2. **I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.** ☐
3. **I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals of the research team, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.** ☐
4. **I agree to my G.P. being informed of my participation in the study.** ☐
5. **I agree to take part in the above study.** ☐

Name of Patient	Date	Signature
Name of individual taking consent (if not researcher)	Date	Signature
Researcher	Date	Signature

3 copies to be kept; 1 for site file; 1 for patient; original to be kept in medical notes

Appendix 8.4 - Letter to general practitioner

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

MS
Multiple Sclerosis Society

Sheffield Hallam University

-- date here --

Dear Dr <NAME>

Re: Patient Name (D.O.B: Date)

I am writing to inform you that Patient Name has consented to participate in an exercise intervention based at The Centre for Sport and Exercise Science, Sheffield Hallam University.

The new project is offering individuals with mild to moderate Multiple Sclerosis (MS) the opportunity to exercise in a safe and supportive environment. This study is generously supported by the Multiple Sclerosis Society and is in collaboration with consultant neurologists at the Royal Hallamshire Hospital. The study aim is to investigate whether a pragmatically designed exercise intervention is effective in evoking improvements in physical activity behaviour and health outcomes which are likely to have a positive impact on maintenance and quality of life in people with MS. In addition, we will be exploring the dose-response relationship between exercise and the primary/secondary outcomes in those with mild and more severed disease and evaluating the cost effectiveness of the intervention.

If you have any concerns or questions regarding your patient participating in this study please do not hesitate to contact me, my direct line telephone number is 0114 225 5633.

Yours sincerely,

Anouska McConnell, MSc, BSc, BASES Accredited (physiology support)

Senior Sport and Exercise Science Officer, The Centre for Sport and Exercise Science, Sheffield Hallam University

Appendix 8.5 - Protocol

PROPOSED INVESTIGATION

1. BACKGROUND AND PURPOSE OF PROPOSED INVESTIGATION

1.1 General background

Living with MS can be a difficult experience, both physically and psychologically.1-3 Some of the most common symptoms for people with MS (PWMS) include excessive fatigue,4 limb weakness,5 motor abnormalities and sexual dysfunction.6 Research has also indicated that there is an increased prevalence of falls in this population.7-8 In addition, poor mental health9 and symptoms of fatigue affecting quality of life4,10 represent a substantial problem for PWMS. Hence, there is a need for clinicians and researchers to address issues that could have an impact on the long-term health-related quality of life of PWMS, particularly given that MS affects many young and middle-aged individuals,11 who have a life expectancy close to normal.12 There is evidence that PWMS are involved in fewer recreational activities than the general population.13 Physical inactivity however, contributes to a sedentary lifestyle that increases the risk of developing other health concerns (e.g. heart disease, obesity, isolation, depression and infections).

1.2 Pilot study

This research team recently completed a pilot study which investigated the effects of a supervised exercise therapy intervention, relative to usual care, upon physical functioning and other health-related outcomes in PWMS. A total of 30 (4 male and 26 female) PWMS (EDSS $\leq$ 5.5) were recruited. The intervention involved patients attending one-to-one supervised exercise sessions at a dedicated exercise therapy room at Sheffield Hallam University twice per week over 10 weeks. Participants were also asked to complete one home session each week during the intervention phase of the trial. Analysis of covariance showed that the exercise group participated in more moderate intensity exercise ($P<0.003$) and had better perceptions of general health status ($P<0.03$). There were also strong trends for less pain ($P<0.054$) and greater aerobic capacity (time to a perceived exertion of 17 on the Borg RPE Scale) ($P<0.053$) in the exercisers versus usual care controls. Adherence to the exercise therapy intervention was excellent, with 80% of patients able to attend 70% (14/20 sessions) or more of the supervised exercise sessions. PWMS also self-reported completing an average of 7/10 the prescribed home exercise sessions. PWMS in the intervention group were asked to complete a series of open-ended questions about their experiences. The responses showed that PWMS enjoyed the intervention, including the structure and content of the sessions. The sessions also provided patients with feelings of energy, vitality and a sense of achievement. On completing the 10-week intervention, over 90% of patients indicated that they felt confident they would continue to exercise in their communities.

1.3 Purpose of the proposed investigation

The results from our pilot study are in agreement with a growing evidence-base supporting the beneficial effects of exercise therapy for PWMS.14-19 Our experience shows that supervised exercise interventions are acceptable to PWMS and that they can reap important health benefits from participation. The challenge now is to assess the efficacy of pragmatic and cost-effective ways to implement exercise therapy. Although one-to-one supervised facility-based exercise programmes can offer more support and guidance to MS patients (as clearly demonstrated in our pilot study), over the long-term they may prove difficult for many PWMS due to time barriers, transport issues and health constraints (e.g. fatigue). In addition, they are very labour intensive, require specialist equipment, and are unlikely to be cost-effective. Hence, the purpose of the proposed investigation is to investigate whether a pragmatically-designed exercise intervention is effective for evoking improvements in physical activity behaviour and health outcomes in PWMS. We will also explore dose-response relationships between physical activity and the primary/secondary outcomes in those with mild and more severe disease and evaluate the cost effectiveness of the intervention.

1.4 Study research questions

1.4.1 Primary research questions

1. Will PWMS who are randomised to pragmatic exercise therapy have improved functional and health outcomes in comparison to usual care only controls at 3-months and 6-months of follow-up?

2. Will PWMS who are randomised to pragmatic exercise therapy have increased structured exercise and free living physical activity levels in comparison to usual care only controls at 3-months and 6-months of follow-up?

3. Is inclusion of a pragmatic exercise therapy intervention in the patient care pathway a more cost-effective treatment strategy than current medical care alone in PWMS?

1.4.2 Secondary research questions

1. What dose of exercise is achievable by PWMS during facility-based supervised and home-exercise portions of the intervention?

2. Is dose of physical activity associated with improvement in outcomes in people with mild to moderate MS and those more severely affected?

3. Are improvements in physical function and fatigue as a result of the exercise intervention associated with positive changes in serum cytokine and salivary cortisol levels?

2. PLAN OF INVESTIGATION

2.1 Study design

The proposed study is a randomised controlled trial with participants being stratified according to gender and EDSS score (low: up to 3.5, high: up to 6.5). Research Ethics Committee approval will be sought and all patients will provide informed written consent prior to involvement in the trial.

2.2 Patient recruitment

A total of 120 people with MS (PWMS) will be recruited by Consultant Neurologists at the collaborating hospitals and via flyers/community adverts displayed at the local South Yorkshire MS Society branches. All patients will be seen by a neurologist prior to entering the trial, regardless of their route of recruitment. In total, around 50 potential participants per week are seen at the collaborating hospital centres. In addition, we will have access to several hundred PWMS who are affiliated with local South Yorkshire MS Society branches. We will seek to feature the trial in the msmatters newsletter during recruitment and aim to recruit the required sample of 120 PWMS over 24-months; this equates to a recruitment rate of 5 PWMS per month. Patient travel expenses will be reimbursed.

2.2.1 Inclusion criteria

- Clinical diagnosis of MS with an EDSS score of between 1.0-6.5, and able to walk 10 m distance
- Aged 18-65 years
- Participants must have been clinically stable for at least 4 weeks prior to entering the study
- Participants on disease modifying therapy (Interferon and Grateramer Acetate) must have been stable on this treatment for at least 3 months prior to entering the study
- Physically able to participate in some form of exercise three times per week
- Able to provide written informed consent

2.2.2 Exclusion criteria

- Failure to meet any of the above inclusion criteria
- Experiencing illness that impairs their ability to be physically active three times per week
- Not willing to be randomised to either the exercise intervention or usual care control group
- Living more than 20 miles from the trial centre

- Already engaged in purposeful structured exercise or brisk walking exercise □ 3 times per week for □ 30 min per session and have been so on a consistent basis during the previous 6-months

2.2.3 Sample size calculations and expected loss to follow-up

The sample size estimation is based on physical activity behaviour change data from our pilot study20,21 and an estimated post-intervention difference in 6-minute walk test (6MWT) between the groups.22 A sample of 50 patients randomised to each group will be sufficient to detect a moderate effect size difference (80% power and a 5% significance level) of 1.3 units on the Godin physical activity scale (sd = 2.29 [our pilot study data]) and an increase of 56 m (sd = 99.4 m) in 6MWT22 (an increase in 6MWT of 56 m was accompanied by improved neurological function after a 12 week aerobic exercise programme in PWMS).22 This figure rises to 60 in each group to allow for a 15% loss to follow up.

2.3 Pragmatic exercise therapy intervention

2.3.1 General overview and rationale

At baseline, participants in the intervention group will receive a pack of printed information that details important information about exercise and MS (e.g. safely increasing exercise over time, minimising injuries, dealing with fatigue, taking heart rate and buying shoes, etc). The intervention period will be 12 weeks in duration, with a more frequent contact phase during the first 6-week block, and reduced contact during the second 6-week block. Programmes of at least 10 weeks are more likely to provide sufficient time for patients to adapt to exercise. In accordance with recent recommendations for PWMS,23 and as used in our pilot study, the intervention will be staged-adapted and participants will be encouraged to exercise within their own capabilities, which will be influenced by individual symptomatology. Several leaders in the field of exercise adherence suggest that allowing patients to exercise at their preferred intensity enhances compliance.24 A physiotherapist will oversee the delivery of the intervention. The Centre is easily accessible by public transport and there is dedicated parking.

2.3.2 Pragmatic exercise therapy intervention

During weeks 1-6, participants will attend two supervised sessions per week at the Centre for Sport and Exercise Science (CSES) and will be required to undertake one additional session in their home environment. Supervised sessions will involve small groups of up to three participants led by an exercise therapist/researcher. Each session will last approximately 1-hour and participants will be offered a range of exercises (e.g. stepping, cycle-ergo, walking, arm-cranking). Sessions will also incorporate exercises that focus upon developing muscle strength, function, balance and flexibility. Participants will be asked to complete short bouts (e.g. 5 x 3-min, with 2-min rest intervals) of low to moderate intensity exercise (50-69% of maximum heart rate). As the intervention progresses and when appropriate, participants will be encouraged to participate in longer periods exercise (e.g. 5 x 4-min) or to take shorter rests between bouts. Heart rate, ratings of perceived exertion and minutes of specific exercises completed in each session will be recorded by the researcher to allow for an

assessment of the exercise dose achieved each week. Supervised exercise will also include cognitive-behavioural techniques (e.g. goal setting, finding social support, understanding the costs/benefits of exercise etc.) to promote long-term participation in physical activity. Using the Transtheoretical Model25 as a guiding framework, this aspect of the intervention will be aimed at equipping PWMS with the skills, knowledge and confidence to engage in a more physically active lifestyle.

During weeks 7-12 participants will attend CSES once per week and complete two home sessions per week on their own. We hypothesize that the gradual increase in home-based sessions within the intervention group will help to facilitate independent exercise participation after the intervention phase is completed. As for the supervised sessions, the home sessions will be geared towards the mobility and symptoms of each participant. During the single weekly supervised session at CSES, they will undertake aerobic exercise (as in weeks 1-6) and receive instructions on how to complete muscle/strength and body-conditioning exercises in the home environment. They will also be encouraged to access exercise facilities/opportunities in their community (e.g. healthy living centres, health walks, fitness centres, swimming pools, etc) and receive instructions on how to complete a physical activity log for quantification of structured exercise sessions achieved outside of the supervised sessions.

2.4 Outcome measures

2.4.1 Timing of assessments & setting

Unless otherwise stated, outcomes will be blindly assessed at three time-points: baseline, after the 12-week intervention and 6-months later. Personal characteristics (e.g. postcode, marital status ethnicity, etc.) and condition specific data (e.g. time since diagnosis, medication, onset of symptoms, use of health care resources etc) will be collected. Large print versions of the questionnaires will be available. Clinicians at the collaborating hospitals will perform the neurological tests and an experienced researcher will assess other outcomes at the SHU site. Self-assessment questionnaires (for participants to take home) will be used where indicated to reduce the assessment burden for PWMS. These will take approximately 1.5 hr to complete. Patients in the usual care control group will be assessed at the same time points.

2.4.2 Primary outcome measures

Physical activity levels will be monitored over a 7-day period, using a combination of self-report physical activity questionnaire/recall diary and accelerometry (Actigraph GT1M, Actigraph, LLC, Fl, USA). The advantages of using both measures are that the objective measures can provide a more accurate measure of physical activity, whilst the subjective measure gives context. The Leisure Score Index (LSI) of the Godin Leisure Time Exercise Questionnaire20,21 will be used to measure self-reported physical activity behaviour. Quantification of structured exercise sessions at the Centre (intervention group) and in the home environment (experimental and control groups) will be verified using a physical activity log comprising a checklist for type, duration, and intensity of exercise achieved. The Actigraph is reported to be amongst the most extensively validated accelerometers and has been proven to correlate reasonably with

doubly labeled water derived energy expenditure techniques.26 Functional exercise capacity (proxy measure of compliance to the intervention) will also be assessed using the 6-minute walking test (6MWT), according to a standardised protocol.27 This test is sensitive to change following exercise interventions in PWMS.22,28

2.4.3 Secondary outcome measures

2.4.3.1 Neurological impairment and clinical functional ability

- Expanded Disability Status Scale Score (EDSS)29 will be assessed according to standard clinical procedures by the neurology consultant. The EDSS has been shown to be reliable and valid and is frequently used for evaluating neurological impairment in research involving adults with MS.

- Multiple Sclerosis Functional Composite (MSFC)30 is a measure of clinical functional ability. It includes a timed 25-foot walk and measures of arm/hand function (9-hole peg test) and cognitive function (paced auditory serial addition).

2.4.3.2 Quality of life, fatigue and qualitative analysis of patient experiences

- The Multiple Sclerosis Quality of Life-54 questionnaire (MSQOL-54)31 is a generic HRQOL instrument based on the Medical Outcome Short Form-36 (SF-36) Health Survey, but with 18 additional items relevant to PWMS. Both dimensional and composite scores will be used in analyses. This will be self-assessed by the participants.

- Perceived effects of fatigue will be assessed using the Modified Fatigue Impact Scale (MFIS), which has been validated for PWMS.32,33 This will be self-assessed by the participants.

- At the end of the intervention, a random sample of 30 PWMS from the intervention group will be invited to participate in a one-to-one, semi-structured interview and focus group sessions to elicit detailed and confidential accounts of their experiences. The interview schedule will be similar to that used by Dodd et al. (2006)34 and will concentrate patients' experiences, barriers and attitudes towards exercise, perceived benefits and adverse effects of the intervention. Both interviews and focus groups will be guided by a "framework approach" to data collection and analysis. A thematic analysis will be used to explore the narrative accounts of individuals within (and across) the focus groups and interviews. Interview and focus group audio recordings will be transcribed verbatim. Three researchers will verify the identification and refinement of themes from the research. The analytical process will be facilitated by the use of QSR Nvivo software. This qualitative aspect of the study is considered very important and could help to overcome some of the limitations of rating scales in assessing treatment benefits in PWMS.

2.4.3.3 Immunological analysis

Disruption to the neuroendocrine axis and alterations in immune activation have been implicated in MS.35,36 As exercise is known to be an important modulator of immune and endocrine parameters and may have an impact on circulating cytokines in PWMS37, levels of serum IL-6, TNF-□, IL-4, IL-10 and CRP and salivary cortisol will be measured by ELISA. This exploratory component of the study may shed light on the

complex mechanisms underlying symptoms of fatigue in MS and the role of exercise in alleviating such symptoms.

2.4.3.4 Cost effectiveness of the pragmatic exercise intervention

An economic evaluation will be undertaken alongside the trial using recommended practice.38 The NHS perspective will be used in the primary economic analysis. This and other methods will be in accordance with NICE Technology Appraisal Guidelines.39 Data collection will also account for costs incurred by the participants themselves for supplementary analysis, to allow for a broader perspective to be taken.

Cost data: The cost of the programme for each participant at each arm of the trial will need to be estimated. This is achieved by collecting costs for staff time, facilities hire, equipment and staff travel. Resource use data will be recorded for all participants, accounting for their health service use over the 3-months of follow-up. Use of primary care will be obtained form self-completed resource use items included in the health follow-up questionnaires. Use of hospital services, i.e. inpatient admission (including length of stay and speciality), outpatient attendances and A&E visits, will be obtained from hospital records. To enable a broader-base costing, PWMS will also be asked about their use of social services. Effectiveness data: The Medical Outcome Short Form-36 (SF-36) Health Survey generates summary measures for physical and mental health which can be used for the assessment of effectiveness.40 The SF-36 summary measures can be derived from the MSQOL-54.31 The one-page EuroQoL EQ-5D41 will be included to provide an additional preference-based measure.

2.5 Data analysis

Differences in primary and secondary outcomes between groups will be compared using intention to treat analysis. Outcomes will be compared over the follow-up period using mixed model analysis, adjusting outcomes for baseline scores. Effect size statistics will be determined to indicate the clinical impact of the intervention. Multiple regression will be used to explore dose-response effects on outcome by examining the relationship between recorded physical activity and outcomes. A sub-group analysis of the effect of disease severity on dose-response will be performed by the inclusion of the interaction of severity of disease and physical activity in the regression analysis. Imputation methods will be used to assess data losses through level drop-out and loss to follow-up. All results will be reported as means and 95% confidence intervals. Our medical statistician (AR) blinded to group allocation will undertake the analysis.

Cost effectiveness analysis will be undertaken by a Health Economist (YO: co-applicant). The main analysis will be an intention to treat comparison of the costs of providing a pragmatic exercise therapy intervention as opposed to the standard treatment for PWMS, compared to gains in the SF-36 scores at the individual patient level. The final result will be presented as a ratio of the differences in costs and QALYs between the two arms of the trial, with a 95% confidence interval estimated by bootstrapping. Results will be plotted on the cost effectiveness plane and then transformed into cost effectiveness acceptability curves with their associated frontier.38 There will be considerable uncertainty in many of the cost estimates and the underlying estimate of benefit. Furthermore, an important consideration in the long term cost

effectiveness of this intervention is likely to be the longevity of the benefits and cost consequences, therefore highlighting the importance of undertaking sensitivity analysis.

2.6 Timescale and milestones

Milestone number	Target date	Milestone title
1	01.08.08	Apply for Ethics and Research Governance approval
2	01.11.08	Project start date: begin to recruit PWMS
3	31.10.10	Complete recruitment of 120 PWMS and baseline assessments
4	15.02.10	Complete the 12 wk intervention in all PWMS
5	31.08.11	Complete all 6-month follow-up assessments
6	15.09.11	Complete collation of all 12 wk and 6-month follow-up data
7	30.09.11	Complete statistical analysis of the data
8	31.10.11	Complete final report/prepare manuscripts for publication

3.0 INVESTIGATOR EXPERTISE

This research team already has an established track-record of working together on exercise trials with PWMS and other patient populations. The experience of the research team covers a wide range of disciplines that are highly relevant to the requirements of this project. We have an excellent track record of running randomised controlled exercise trials that have been funded by the BHF, Cancer Research-UK, The Health Foundation, American Institute for Cancer Research, the Department of Health (MidRec), the Medical Research Council and Heart Research UK.

3.1 Applicants, roles and responsibilities

Dr John Saxton (Principal Investigator: Clinical Exercise Physiology) is Reader in Clinical Exercise Physiology at Sheffield Hallam University. He is a member of the Physiological Society and a BASES accredited research physiologist. Role: Trial management and co-ordination, responsible for day-to-day supervision of research assistants, oversee assessment and evaluation of physiological outcomes.

Dr Amanda Daley (Lead Co-applicant: Health Psychology) is a British Psychological Society (BPS) chartered psychologist and a BASES accredited Sport and Exercise Psychologist. Amanda is Lecturer in Health Psychology at the University of Birmingham Medical School. Role: Trial management and co-ordination, oversee quality control of the interventions, health psychology input.

Dr Basil Sharrack (Co-applicant: Neurology) is Consultant Neurologist at the Royal Hallamshire Hospital with considerable expertise in conducting research trials and

studies with PWMS. He has published widely in the field of MS research. Role: Patient recruitment, assessments and clinical input.

Ms Jane Petty (Co-applicant: Physiotherapy) is National Lead for the Physiotherapy Programme for the MS Society in England and Wales and previously employed as a physiotherapist at the Royal Hallamshire hospital, Sheffield. Role: Clinical input, oversee exercise interventions, patient recruitment.

Ms Yemi Oluboyede (Co-applicant: Health Economics) is a Health Economist at the University of Sheffield. Yemi is been involved in the design analysis and reporting of several RCTs, which have compared new and existing health technologies. Role: Overlook the cost effectiveness analysis.

Ms Andrea Roalfe (Co-applicant: Medical Statistics) is Senior Lecturer in Medical Statistics at the University of Birmingham and Research Facilitator for the Primary Care Clinical Research and Trials Unit. Role: Sample size calculations, overlook the analysis of all trial data.

3.2 Research staff

Ms Anouska McConnell (named research assistant). Anouska is a BASES Accredited Sport and Exercise Physiologist who gained extensive experience of delivering exercise interventions to PWMS in our recent pilot study. Role: Hands-on delivery of exercise interventions in PWMS.

Ms Sue Green (named research assistant). Sue is an experienced exercise scientist, who has worked on a number of research projects with different patient populations at Sheffield Hallam University. Role: Assisting the delivery of exercise intervention and related tasks.

3.3 Collaborator and advisors

Professor Nicola Woodroofe (Collaborator), Sheffield Hallam University will advise on MS research issues, help to coordinate trial management meetings and supervise the immunological analysis in her laboratory. Dr S J L Howell (Collaborator) and Dr S Price (Collaborator), Consultant Neurologists at the Royal Hallamshire Hospital, Sheffield) will assist with clinical decisions and neurological assessments. Dr Jeremy Hobart (advisor), Consultant Neurologist at the Peninsula Medical School, will form part of the trial steering group and will advise on interpretation of the results. Dr Helen Crank (advisor), Sheffield Hallam University, has considerable expertise in qualitative analysis techniques and will overlook that aspect of the research.

5.0 JUSTIFICATION FOR FINANCIAL SUPPORT (TOTAL FUNDING REQUESTED: £197,536)

Personnel: Funding is requested to support the salary costs for a 0.6 FTE Research Assistant (AM) (£91873). She would be responsible for recruiting the PWMS and

delivery of intervention. A second 0.2 FTE research assistant (SG) is required to assist AM in organising and delivering supervised exercise (£15,531). To ensure scientific rigour, a third 0.1 FTE Research Assistant is requested for the blind assessment of outcomes and data collation (£8,437) and £12,196 is requested to meet the salary costs of hands-on physiotherapy support for one session per week (0.1 FTE). This would ensure that the delivery of supervised exercise and advice to PWMS is in accordance with good physiotherapy practice. Part-time administrative support (£6028) is requested for 0.5 days per week (0.1 FTE) to help with the booking of patients, and other project-specific administrative tasks, including the transcribing of interview and focus group qualitative accounts. Consumables/miscellaneous costs: A sum of £5474 is requested for the objective statistical analysis of the research data and £12,537 is requested for the evaluation of cost effectiveness. Funding to cover participant travel expenses is also being requested. At an average of £10.00 per visit for 18 supervised exercise sessions and two assessment visits at baseline, post-intervention and 6-months in the intervention group (N=60) and for two assessment visits at baseline, post-intervention and 6-months in the usual care controls (N=60), this amounts to £19,136 over the lifetime of the project. We are also requesting funding of £1275 to meet expenses incurred by the research team attending project management meetings and £2157 to meet the costs of presenting the research data at scientific/clinical conferences. To ensure scientific rigour, patients will be randomised using a distant randomisation service (£2095). As the trial will need to be registered with the ISRCTN scheme, a sum of £206 is requested to cover this expense. Consumables funding of £13368 is requested to support the costs of the circulating cytokine analysis. Finally, in order to optimise dissemination of the results, and especially among PWMS, we are requesting £2064 towards the development of resources for the MS Society website and regional 'Awareness Days', etc. Equipment: We are requesting a sum of £5160 to support the costs of purchasing 20 Actigraph accelerometers. This is an unobtrusive device, worn on the thigh, which would enable us to collect more objective data on free living physical activity levels over a 7-day time period in all participants.

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Appendix 8.6 - Recruitment Flyer

What are we doing?

- We are offering people with mild to moderate Multiple Sclerosis (MS) the opportunity to take part in an exercise study examining the effects of a practically designed exercise programme on people with MS.

Why are we doing it?

- Current evidence regarding the beneficial effects of supervised exercise on physical function, mobility and quality of life for people with MS is strong. This study aims to look at the impact of a more practically designed exercise programme on improvements in physical activity and health. In addition, we are going to explore what amount of exercise is most beneficial and whether the benefits vary between those with different disability levels.

Can you help us?

- We are hoping to recruit 120 people, living within 20 miles of the University. We are looking for people with a clinical diagnosis of MS who are physically able to participate in some form of exercise 3 times a week.

Where does the project take place?

- At the Centre for Sport and Exercise Science, Sheffield Hallam University. People who take part will be asked to either follow standard advice from their health care team or follow a 12 week exercise programme.

Where can I find out more?

- For further information on the eligibility criteria or an informal chat about the study, please contact Anouska McConnell on 0114 225 5633 or e-mail a.mcconnell@shu.ac.uk.

Sheffield Hallam University

Sheffield Teaching Hospitals NHS

Appendix 8.7 - Assessment protocol

ExIMS: Assessment Procedures

If required the participant attends an initial hospital visit for their EDSS assessment and signs their consent (X3).The participant then attends the University for their assessment, if a hospital visit has not been required then the consent is signed here. At the first University visit the participant is provide with the questionnaires, saliva kit and accelerometer for the home data collection and booked in to return in 1-week. At this second University visit the blood sample will be taken and home assessment materials collected. Repeat tests are conducted at the same time of day where possible.

Hospital Visit - Neurology consultant

- Expanded Disability Status Score (EDSS)

University Visit (1)

Equipment: Blood pressure monitor, heart rate monitor, MSFC kit, scales, stadiometer, small tape measure (Waist:Hip), large tape measure (6MWT), lap counter, 2 cones, stop watch, chair.

Pre-test questionnaires:

- Complete Medical, Demographic and health related events information

Blood Pressure/Resting Heart Rate

- Contra indicators to 6MWT = resting HR >120, BP>190/100

Anthropometry

- Body Mass - Measured to the nearest 0.05kg
- Waist-hip ratio - Measured to the nearest 0.5 cm using an inelastic measurement tape

The Multiple Sclerosis Functional Composite

- 25 Foot walk to assess leg function/ambulation:
  - The subject is instructed ***'I'd like you to walk 25 ft as quickly as possible, but safely. Do not slow down until you have passed the finish line. Ready, go.'***
  - Timing begins when the lead foot crosses the start line and ends when the lead foot crosses the finish line.
  - Time is recorded to the nearest 0.1 s.
  - Two trials are carried out, one in each direction.
  - Record if a walking aid is used

- 9 hole peg test to assess Arm/hand function
  - Place the 9-hole peg test on the table directly in front of the patient.
  - Arrange the pg test so that the side with the pegs is directly in front of the hand to be tested and the empty peg board is in front of the other hand.
  - The test will be ran twice with the dominant hand and then twice with the non-dominant hand.
  - The subject is instructed ***'On this test, I want you to pick up the pegs one at a time, using one hand only, and put them into the holes as quickly as***

you can in order until all the holes are filled. Then, without pausing, remove the pegs one at a time and return them to the container as quickly as you can. We'll have to do this 2 times with each hand. We'll start with your dominant hand. You can hold the peg board steady with your non dominant hand. If a peg falls on the table, please retrieve it and continue the task. If a peg falls on the floor, keep working on the task and I will retrieve it for you. See how fast you can put all the pegs in and take them out again. Are you ready? begin.'

- Paced auditory serial addition test to assess cognitive function
    - Read the following instructions to the patient ***'On this tape you are going to hear a series of single digit numbers that will be presented at the rate of one every 3 seconds. Listen for the first two numbers, add them up, and tell me your answer. When you hear the next number, add it to the one you heard on the tape right before it. Continue to add the next number to each proceeding one. Remember you are not being asked to give me a running total rather the sum of the last two numbers that were spoken on the tape'.***
    - For ***example 'if the first two numbers are 5 and 7, you would say 12. If the next number is 3 you would say _____'*** (pause and wait for answer). ***'Then if the next number is 2 you would say _____'***
    - ***'This is a challenging task. If you lose your place, just jump back in - listen for 2 numbers in a row and add them up and keep going. There are some practice items on the tape. Let's try these first.'***
    - Play the sample items, if the patient gets 2 or more answers correct proceed to test. If not redo practice items a maximum of 3 times
    - Before starting the test remind the patient ***'if you get lost, just jump back in because I can't stop the test once it has begun.'***
    - After 5 consecutive no responses remind the patient by saying ***'jump back in'***.
    - On the answer sheet circle correct answers, write in patients response for incorrect answers. For no response place a dash, if patient emends cross out initial response and write SC (self-corrected).

<u>6MWT</u>

- The course should be marked out with a starting line at one end and a cone at the other to mark the turning point.
- Participants should wear comfortable clothes and shoes and use their usual walking aid and should not have exercised vigorously within 2-hours of the visit.
- The test does not require a warm-up and the participants should sit and rest in a chair near the start position for at least 10-minutes before the test.
- Take start heart rate and overall fatigue and RPE using the Borg scale (10-point scale).
- Participant instructions;

"The object of this test is to walk as far as possible for 6-minutes. You will walk back and forth in this hallway. Six-minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, stop, and rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around the cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6-minutes, but don't run or jog. Start now or whenever you are ready."

Home Assessment

- Stand near the start line throughout the test. As the patient starts to walk start the timer. Do not talk during the walk, except for standard phrases where an even tone of voice should be used. Each time the participant returns to the start line click the lap counter letting the participant see that you have done this.
- If the participant stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like: then continue walking whenever you feel able." Do not stop the timer. If the participants stops and refuses to continue (or you decide they should not) fetch a chair and record time, distance and reason for stopping."
- Instructions;
    - 1-minute: "You are doing well. You have 5-minutes to go."
    - 2-minute: "Keep up the good work. You have 4-minutes to go."
    - 3-minutes: "You are doing well. Halfway done."
    - 4-minutes: "Keep up the good work you have 2-minutes left."
    - 5-minutes: "You are doing well. You only have 1-minute left to go."
    - 5:45 minutes: "In a moment I am going to tell you to stop. When I do, just stop right where you are and I will come to you."
    - 6-minutes: "Stop" Walk over to the patient taking a chair with you if required. Mark the floor and record distance, laps etc.

Home Assessment

Information provided at first university assessment and returned 7 days later at second visit.

<u>Health Questionnaire booklet</u>

- Multiple Sclerosis Quality of Life-54 questionnaire
- Modified Fatigue Impact Scale (MFIS)
- Godin Leisure-Time Exercise Questionnaire & IPAQ (Short)
- EuroQol EQ-5D

<u>Accelerometer</u>

- Wear accelerometer on dominant hip for 7 days, except when sleeping, washing or swimming.
- Complete brief activity diary during this time period

Saliva Samples

- Collect 3-days of saliva samples as outlined on instruction sheet

University Visit (2)

Bloods

- Collect venous blood sample - 3 serum tubes (yellow) and 3 EDTA plasma tubes (purple) and label with date time and patient ID.
- Spin plasma straight away, at ~ 2500-3000 rpm for 20-mins. Allow Serum to clot for about 20-mins before doing the same (use the centrifuge that can be cooled to 4 degrees and always keep the blood cool after taking it and while processing it, i.e. put it in the fridge/put it on ice or place one of those cold packs on it. Make sure centrifuge is well balanced or there could be a bit of a mess when you open it up!).

ExIMS: Assessment Data Collection Sheet

STH Study Number:	15153	**Date:**	
Patient ID Number:		**Time point:**	

QUESTIONNAIRES

- **MSQL-54/ MFIS/EuroQoL/Godin** ☐
- **EDSS (consultant)** ☐
- **Health Related Events** ☐
- **Demographics** ☐

Accelerometer Number ____

MSFC

- **25ft Walk** ☐
- **9 Hole Peg Test** ☐
- **Cognitive Function** ☐

IMMUNOLOGY

- **Blood Sample** ☐
- **Saliva Sample** ☐

HEALTH SCREENING

Blood Pressure

	1	2
Systolic (mmHg)		
Diastolic (mmHg)		
Resting HR		

- **Medical Questionnaire** ☐
- **Consent Form** ☐

ANTHROPOMETRY

Body Measurements

	Measurement
Body Mass (kg)	
Stature (cm)	
BMI (kg/m^2)	

Girths

Girth Location	Circumference (cm)			
	1	2	3	Average
Waist (cm)				
Hip (cm)				
Waist/Hip				

AEROBIC CAPACITY (6MWT)

Temperature (°C): ..... Humidity (%): .....

Time (min)	Heart Rate (bpm)	RPE	
		Fatigue	breathless-ness
Start			
0-1			
1-2			
2-3			
3-4			
4-5			
5-6			
Finish			

Circuit Length: _____

Number of laps: _____

Total Dist. (m): _____

Walking aid: _____

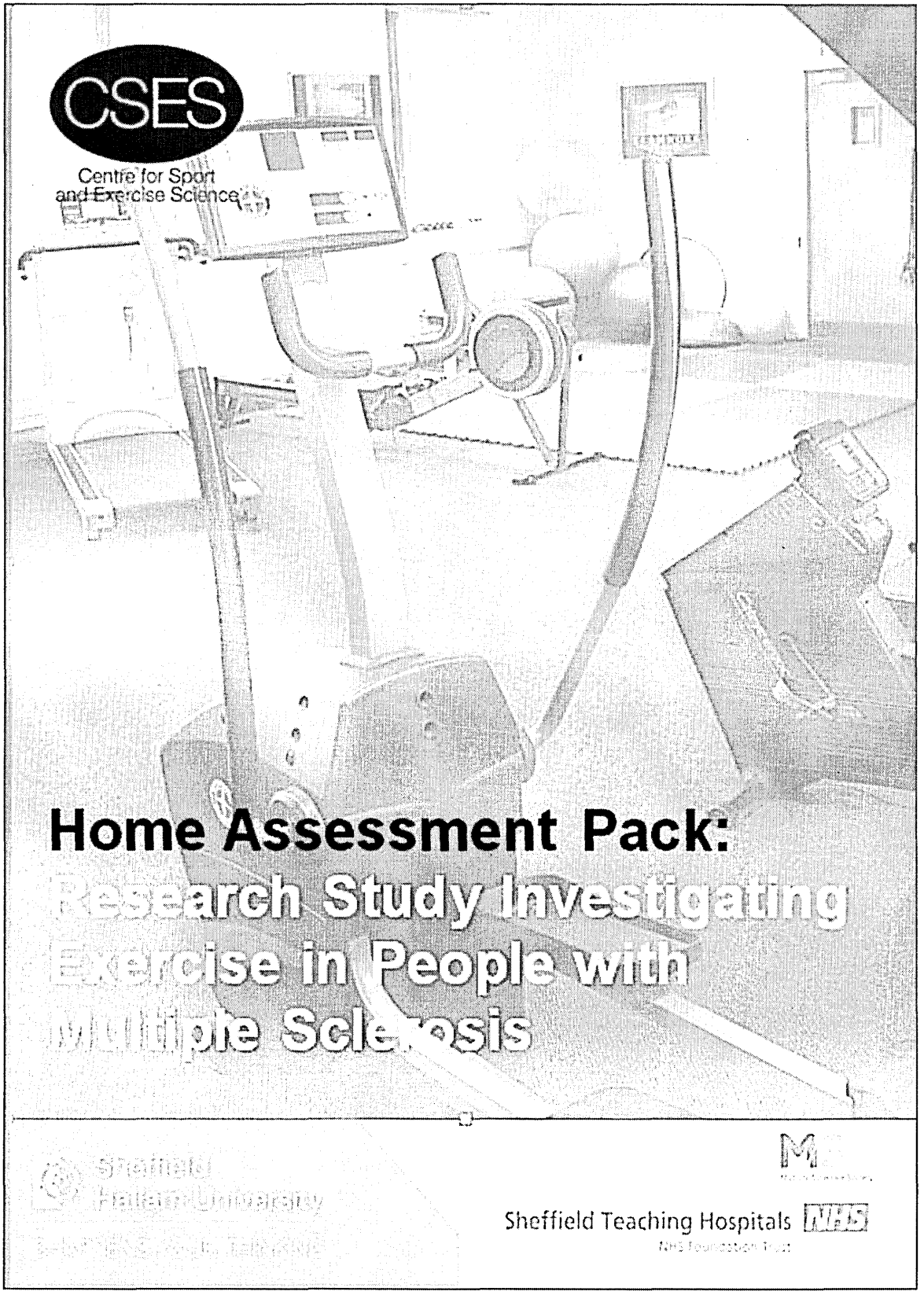
Stop/Pause Reason: _____

What stopped you walking further? _____

Predicted Max HR(bpm): _____ % Max HR reached: _____

Signature of Person Completing Form: _____

Name of Person Completing Form: _____


CSES
Centre for Sport and Exercise Science
Home Assessment Pack:
Research Study Investigating Exercise in People with Multiple Sclerosis
Sheffield Hallam University
Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Home Assessment: Checklist

STH Study Number: 15153	**Date:** _____
Participant ID: _____	**Time point:** _____

	Date		
	Start of Day	**End of Day**	✓
• Complete ***Health Questionnaire***			
• Wear ***Accelerometer*** and complete ***7-Day Exercise Diary***			
• Collect ***Saliva Samples*** (3-days) and complete ***Record Sheet***			

Next Appointment: _____

You will need to arrive at this visit having fasted for 12-hr so that we can take a blood sample from you. You should also bring with you this completed booklet, your saliva samples and accelerometer. This visit should take ~ 15-30 minutes.

CONTACT DETAILS

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Faculty of Health and Wellbeing
Sheffield Hallam University
Collegiate Crescent Campus
Sheffield, S10 2BP

Tel: 0114 225 5633 **E-Mail:** a.mcconnell@shu.ac.uk

Accelerometer: 7 Day Exercise Diary

STH Study Number: 15153 **Date:** _____

Participant ID: _____ **Time point:** _____

INSTRUCTIONS

This diary is to be completed for the 7-days that you where your accelerometer. Your accelerometer should be worn around your waist, with the device placed on your dominant hip. The device can be worn above or below clothing but must be held snugly against the body. Remember the device should be removed when sleeping at night and must not get wet, so **please remove before showering, bathing or swimming**.

Please record the total amount of time you have spent doing physical activity (of moderate intensity or higher) on every day of the week.

Please note, by **moderate intensity** we mean a level of activity that noticeably increases your heart rate and breathing rate. You may sweat, but you are still able to hold a conversation, but you can't sing (e.g. fast walking, swimming, dancing, cycling and heavy gardening).

Week commencing: _____

Please give your answers to the nearest 10mins *(tick one box for each day).*

	0 mins	1-10 mins	11-20 mins	21-30 mins	30 + mins	Main Activities
Monday	☐	☐	☐	☐	☐	_____
Tuesday	☐	☐	☐	☐	☐	_____
Wednesday	☐	☐	☐	☐	☐	_____
Thursday	☐	☐	☐	☐	☐	_____
Friday	☐	☐	☐	☐	☐	_____
Saturday	☐	☐	☐	☐	☐	_____
Sunday	☐	☐	☐	☐	☐	_____

Additional Comments: _____

Saliva Sample: Record Sheet

STH Study Number: 15153 **Date:** _____

Participant ID: _____ **Time point:** _____

How to take a sample using the tubes:

1. Identify the tube labelled with the correct time
2. Remove the stopper and cotton swab
3. Place the swab in your mouth and chew on it for one minute
4. Place the swab back into the tube and firmly replace the stopper
5. Refrigerate the sample as soon as possible

When to take samples:

We would like you to take samples four times a day for three days, at 8am, 12noon, 5pm and 9pm. Please take each sample as close as possible to these times and make a note of the exact time in the table below. Up to 30mins before or after the target time is fine, so if you remember slightly before the target time, take the sample while you are thinking about it!

Sample Time Record:

	Alarm time	*Actual time the sample was taken*
DAY 1:	8 am	
	12 noon	
	5 pm	
	9pm	
DAY 2:	8 am	
	12 noon	
	5 pm	
	9pm	
DAY 3:	8 am	
	12 noon	
	5 pm	
	9pm	

Health Questionnaire

Exercise Intervention for Multiple Sclerosis (ExIMS)

STH Study Number:	15153	**Date:**	
Participant ID:		**Time point:**	

Sheffield Teaching Hospitals NHS Foundation Trust

Multiple Sclerosis Society

Sheffield Hallam University

Health and Daily Activities

1. In general, would you say your health is:

	(circle one number)
Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago**, how would you rate your health in general **now**?

	(circle one number)
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

3-12. The following questions are about activities you might do during a typical day. Does **your health** limit you in these activities? If so, how much?

			(Circle 1, 2 or 3 on each line)
	Yes, limited a lot	**Yes, limited a little**	**No, not limited at all**
3. *Vigorous activities*, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. *Moderate activities*, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing *several* flights of stairs	1	2	3
7. Climbing *one* flight of stairs	1	2	3
8. Bending, kneeling or stooping	1	2	3
9. Walk *more than a mile*	1	2	3
10. Walking *several blocks*	1	2	3
11. Walking *one block*	1	2	3
12. Bathing and dressing yourself	1	2	3

13-16. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle one number on each line)

	YES	NO
13. Cut down on the *amount of time* you could spend on work or other activities	1	2
14. *Accomplished less* than you would like	1	2
15. Were limited in the *kind* of work or other activities	1	2
16. Had *difficulty* performing the work or other activities	1	2

17-19. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious).

(Circle one number on each line).

	YES	NO
17. Cut down on the *amount of time* you could spend on work or other activities	1	2
18. *Accomplished less* than you would like	1	2
19. Didn't do work or other activities as *carefully* as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

	(circle one number)
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

PAIN

21. How much **bodily** pain have you had during the **past 4 weeks**?

	(circle one number)
None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very Severe	6

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

	(circle one number)
Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

23-32. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the **past 4 weeks**.....

(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6
32. Did you feel rested on waking in the morning	1	2	3	4	5	6

33. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with you social activities (like visiting with friends, relatives, etc)?

	(circle one number)
All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

HEALTH IN GENERAL

34-37. How TRUE or FALSE is **each** of the following statements for you.

	(Circle one number on each line)				
	Definitely true	**Mostly true**	**Not sure**	**Mostly false**	**Definitely false**
34. I seem to get sick a little easier than other people	1	2	3	4	5
35. I am as healthy as anybody I know	1	2	3	4	5
36. I expect my health to get worse	1	2	3	4	5
37. My health is excellent	1	2	3	4	5

Health Distress

How much of the time during the **past 4 weeks.....**

	(Circle one number on each line)					
	All of the time	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the tine**	**None of the time**
38. Were you discouraged by your health problems?	1	2	3	4	5	6
39. Were you frustrated about your health?	1	2	3	4	5	6
40. Was your health a worry in your life?	1	2	3	4	5	6
41. Did you feel weighed down by your health problems?	1	2	3	4	5	6

Cognitive function

How much of the time during the **past 4 weeks**....

(Circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
42. Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
43. Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
44. Have you had trouble with your memory?	1	2	3	4	5	6
45. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?	1	2	3	4	5	6

Sexual function

46-49. The next set of questions are about your sexual function and your satisfaction with your sexual function. Please answer as accurately as possible about your function **during the last 4 weeks only.**

How much of a problem was each of the following for you ***during the past 4 weeks?***

(Circle one number on each line)

MEN	Not a problem	A little of a problem	Somewhat of a problem	Very much of a problem
46. Lack of sexual interest	1	2	3	4
47. Difficulty getting or keeping an erection	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

(Circle one number on each line)

WOMEN	Not a problem	A little of a problem	Somewhat of a problem	Very much of a problem
46. Lack of sexual interest	1	2	3	4
47. Inadequate lubrication	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

50. Overall, how satisfied were you with your sexual function **during the past 4 weeks**?

	(circle one number)
Very Satisfied	1
Somewhat Satisfied	2
Neither satisfied or dissatisfied	3
Somewhat dissatisfied	4
Very Satisfied	5

51. During the **past 4 weeks,** to what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbours or groups?

	(circle one number)
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

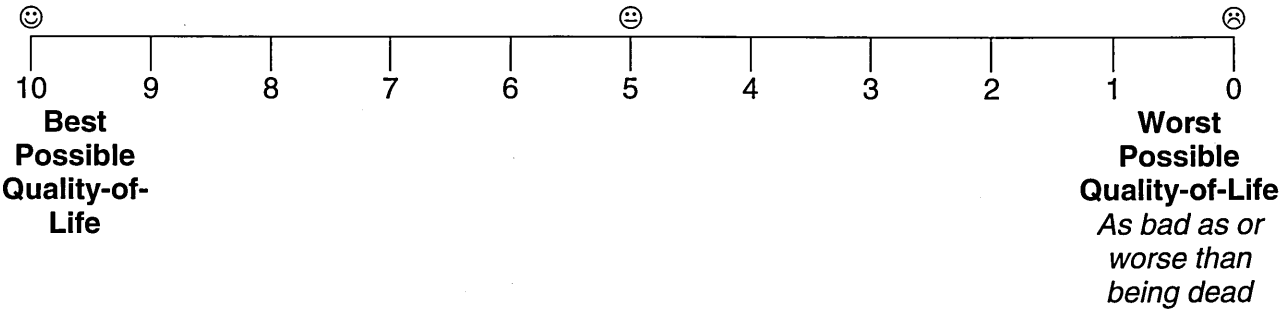
52. During the **past 4 weeks**, how much did ***pain*** interfere with your enjoyment of life?

	(circle one number)
Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

QUALTIY OF LIFE

53. Overall, how would your rate your quality-of-life?

Circle one number on the scale below:



54. Which best describes how you feel about your life as a whole?

	(circle one number)
Terrible	1
Unhappy	2
Mostly dissatisfied	3
Mixed - about equally satisfied and dissatisfied	4
Mostly satisfied	5
Pleased	6
Delighted	7

Fatigue

INSTRUCTIONS
Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. But people who have medical conditions like MS experience stronger feelings of fatigue more often and with greater impact than others.

Following 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 answer to select, chose the one that comes closest to describing you.

Because of my fatigue during the past 4 weeks I have .....

	Never	Rarely	Sometimes	Often	Almost Always
1. been less alert	0	1	2	3	4
2. had difficulty paying attention for long periods of time	0	1	2	3	4
3. been unable to think clearly	0	1	2	3	4
4. been clumsy and uncoordinated	0	1	2	3	4
5. been forgetful	0	1	2	3	4
6. had to pace myself in physical activities	0	1	2	3	4
7. been less motivated to do anything that requires physical effort	0	1	2	3	4
8. been less motivated to participate in social activities	0	1	2	3	4
9. been limited in my ability to do things away from home	0	1	2	3	4
10. had trouble maintaining physical effort for long periods	0	1	2	3	4
11. had difficulty making decisions	0	1	2	3	4
12. been less motivated to do anything that requires thinking	0	1	2	3	4
13. been feeling as though my muscles are week	0	1	2	3	4
14. been physically uncomfortable	0	1	2	3	4
15. had trouble finishing tasks that require thinking	0	1	2	3	4
16. had difficulty organising my thoughts when doing things at home/work	0	1	2	3	4
17. been less able to complete tasks that require physical effort	0	1	2	3	4
18. been thinking more slowly	0	1	2	3	4
19. had trouble concentrating	0	1	2	3	4
20. limited my physical activity	0	1	2	3	4
21. needed to rest more often or for longer periods	0	1	2	3	4

Physical Activity

FREE TIME ACTIVITY

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your **free time**?

Please place a number in each box

a) STRENUOUS EXERCISE (heart beats rapidly)
(e.g. jogging, vigorous swimming, netball, aerobics, circuits) ☐

b) MODERATE EXERCISE (not exhausting, but tiring)
(e.g. fast walking, tennis, cycling, easy swimming, dancing) ☐

c) MILD (minimal effort)
(e.g. yoga, archery, bowling, golf, easy walking) ☐

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

Often ☐ Sometimes ☐ Never/Rarely ☐

EVERYDAY ACTIVITY

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard/garden work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days. Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?	_____ **days per week** ☐ no vigorous activity ➔ ***Skip to question 3***
2. How much time did you usually spend doing **vigorous** physical activities on one of those days?	_____ **hours per day** _____ **minutes per day** ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days. Moderate** activities refer to activities that take moderate physical effort and make you breathe

somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.	_____ **days per week** ☐ No moderate physical activities ➔ ***Skip to question 5***
4. How much time did you usually spend doing **moderate** physical activities on one of those days?	_____ **hours per day** _____ **minutes per day** ☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?	_____ **days per week** ☐ No walking ➔ ***Skip to question 7***
6. How much time did you usually spend **walking** on one of those days?	_____ **hours per day** _____ **minutes per day** ☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?	_____ **hours per day** _____ **minutes per day** ☐ Don't know/Not sure

Health and Daily Activities

INSTRUCTIONS

This survey asks about your health and daily activities. *Answer every question* by circling the appropriate number. **If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.**

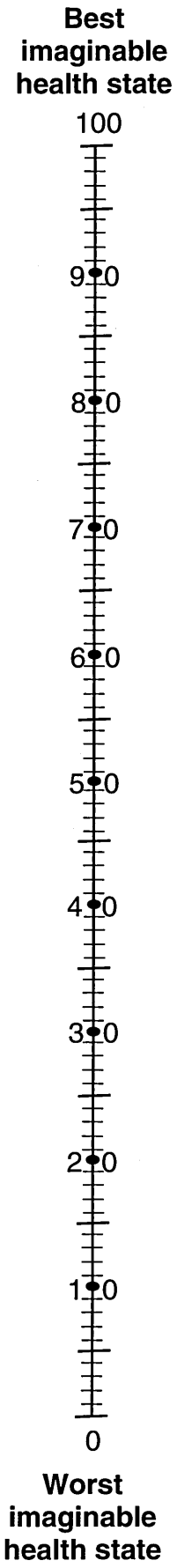
Please feel free to ask someone to assist you if you need help reading or marking the form.

Please indicate which statements best describe your own health state today.

	(circle one number)
Mobility	
I have no problems in walking about	1
I have some problems in walking about	2
I am confined to bed	3
Self-Care	
I have no problems with self-care	1
I have some problems washing or dressing myself	2
I am unable to wash or dress myself	3
Usual Activities *(e.g. work, study, housework, family or leisure activities)*	
I have no problems with performing my usual activities	1
I have some problems with performing my usual activities	2
I am unable to perform my usual activities	3
Pain/Discomfort	
I have no pain discomfort	1
I have moderate pain discomfort	2
I have extreme pain or discomfort	3
Anxiety/Depression	
I am not anxious or depressed	1
I am moderately anxious or depressed	2
I am extremely anxious or depressed	3

Your own health state today
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line on the scale at whichever point indicates how good or bad your health state is today.



This is the end of the questionnaire, thank you for participating.

ExIMS - Supervised Exercise Session
Data Collection Sheet

STH Study Number: 15153 **Week:** _____

Patient ID Number: _____

1. SUPERVISED SESSION **DATE** ..... **TIME** .....

Duration	Mode	Intensity	HR (bpm)	RPE

Additional Work Done (i.e. strength, function, balance, R of M):

Additional Comments:

2. SUPERVISED SESSION **DATE** ..... **TIME** .....

Duration	Mode	Intensity	HR (bpm)	RPE

Additional Work Done (i.e. strength, function, balance, R of M):

Additional Comments:

Signature of Person Completing Form: _____

Name of Person Completing Form: _____

ExIMS - Home Exercise Session
Data Collection Sheet (Weeks 1-6)

STH Study Number: 15153 **Week:** _____

Patient ID Number: _____

1. HOME SESSION **DATE .....** **TIME .....**

	Suggested Exercise	Achieved Exercise
Activity (walking, swimming etc)		
Intensity (RPE Scale)		
Time (minutes)		
Additional Comments		

Intensity - Borg's RPE Scale

6	
7	Very, very light
8	
9	Very light
10	
11	Fairly Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
19	Very, very hard

Signature of person completing the form

_____

Name of person completing the form

_____

Appendix 8.12 - Action Plan

ExIMS - Final Exercise Session (Wk11)

STH Study Number:	15153
Patient ID Number:	

1 a. Review Goals (did you achieve them? If yes well done, if not why not, what can we do to help?)

b. What is your long-term goal over the next 6-months (SMART)?

c. What short term goals are going to enable you to reach this goal (SMART)?

2 a. What do you see as potential barriers to continuing to be physical activity (SWOT-strengths, weaknesses, opportunities and threats)?

b. How might you avoid or overcome these?

3 a. Exercise Achievements. What have I achieved so far, what have I learnt, is there anything that I still would like to know?

4. Action Plan for Home (Session menu, tailored plan, progression and relapse strategy)

Exercise and MS - Home Plan

Aerobic exercise Session Plan: 3 x week

Gentle Aerobic Warm-up

- Light walk/cycle to gradually increase your heart rate (RPE ~10-11)

Light Stretching

- Stretching of muscles to be used in the session (hold each stretch for ~5-6s)

Aerobic Exercise Session

- 20-30 minute's aerobic exercise at a mild to moderate intensity (RPE Scale ~ 11-13)

Gentle Aerobic Cool-down

- Gentle walk/cycle to gradually decrease your heart rate (RPE ~10-11)

Physiotherapy Exercises

- Carry out any symptom specific physio exercises now that the muscles and body are nice and warm

Light Stretching

- Stretching of muscles used in the session (hold each stretch for ~5-6s)

- *Remember exercises should not be painful.*
- *The amount and intensity of the exercise may need to be adjusted depending on how you feel on the day.*
- *If you have any significant time away from exercise, remember you will need to start slowly and gradually build back-up.*

Intensity - Borg's RPE Scale	
6	
7	Very, very light
8	
9	Very light
10	
11	Fairly Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard

Exercise Goals

Example Exercise Sessions

Short-Term

- Ideally exercise 4x week, but always at least 2
- Combinations of Yoga/swimming/walking/gym

Long-Term

- Maintain and further improve fitness
- Lose more weight
- Maybe start running

1. Gym (SHU) or private

- Warm-up: 10-min Treadmill (Hill profile, 3.3mph), stretching
- Session - Rower (1000m, 5-6 min), 10-min bike
- Ball Work
- Cool down: 10-min recumbant bike, stretching

2. Swimming

- 20-30 minutes (20-30 lengths)

3. Walking/bike ride

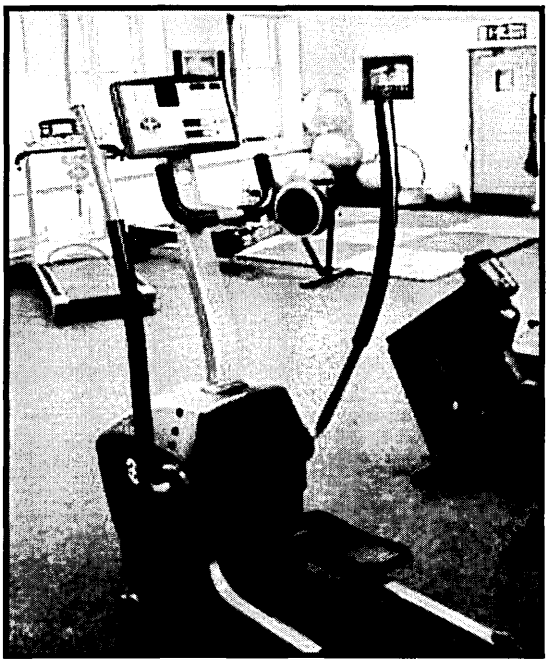
- 30min - 1hr

Physiotherapy Exercises

- Ball work - sit-ups, roll-outs, back raises, twists x10

Multiple Sclerosis and Exercise:

Advice Leaflet



The information provided in this leaflet is designed to be used in conjunction with the MS and exercise intervention research taking place at Sheffield Hallam University and is to be used alongside the individual exercise advice provided by the project team.

Sheffield Hallam University
SHARPENS YOUR THINKING

MS Multiple Sclerosis Society

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

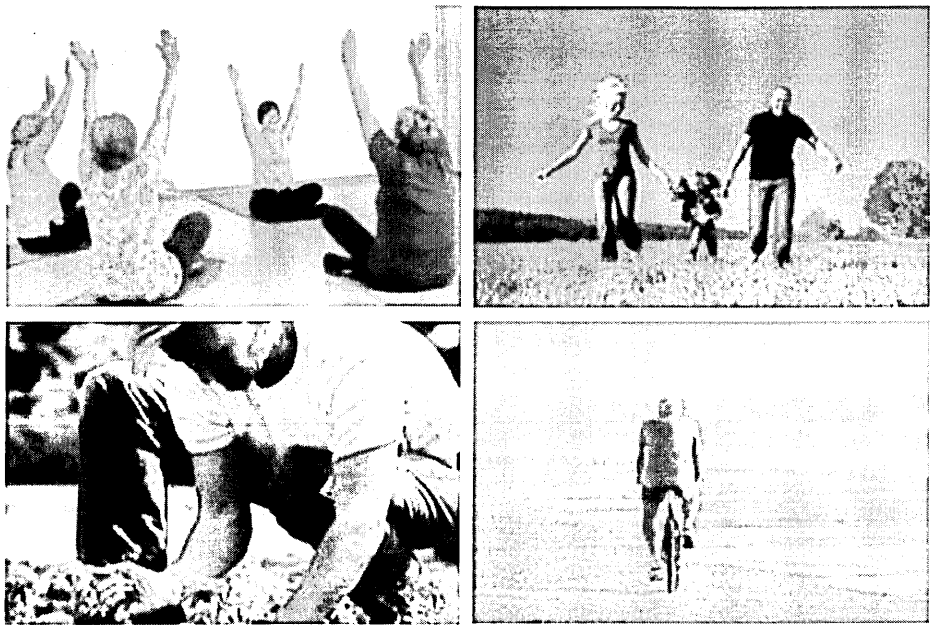
Benefits of Exercise

Being physically active can improve both your physical and mental health and reduce your risk of suffering from health problems such as; cardiovascular disease, stress, obesity, diabetes, some cancers, osteoporosis, high cholesterol and high blood pressure.

In addition, regular appropriate exercise can have a positive impact on living with MS, helping you to stay mobile and manage your symptoms better. There is no evidence that exercise makes your MS worse or that it increases the number of relapses.

Research has shown that regular aerobic exercise for people with mild to moderate MS can improve;

- Strength
- Stamina (aerobic capacity)
- Mobility (walking/balance)
- Mood state (anxiety/depression)
- Quality of life
- Fatigue



Choosing Physical Activity?

There are many types of physical activity to choose from. The most appropriate one's for you will depend on your symptoms and may vary over time and from day to day.

For example if you suffer from balance problems, spasticity or joint stiffness you might benefit more from activities such as Yoga or Pilates, whilst if you suffer from fatigue, research suggests that aerobic activities such as brisk walking may actually effectively reduce your fatigue.

Physical activity does not have to mean sport or exercise in a gym, just being more activity in your daily life, by using the stairs more or cleaning the car all counts.

Getting Started

When starting to increase your physical activity levels think about the type of exercise that you would like to do, what you would enjoy and what fits into your current lifestyle.

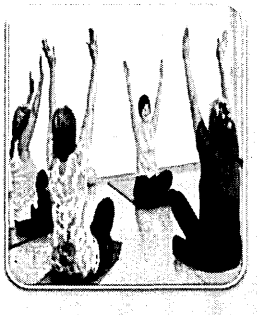
The type, amount and intensity of the exercise recommended will depend on your current level of fitness, symptoms and preferences.

Even small increases in physical activity could benefit your physical and mental health.

Exercise Type

Aerobic exercises include activities such as brisk walking, swimming and cycling that use large muscle groups for a reasonable length of time. These exercises work the heart and the lungs and will improve your stamina.

Strength exercises include resistance type exercises aimed at strengthening specific muscle groups and/or improving posture. These may include lifting small weights, using your own body weight or pulling against resistance bands.



Flexibility exercises should be done as a warm-up and cool down before aerobic and strength exercise, but can also be beneficial on their own for increasing range of motion.

Water-based activity reduces the strain on the body, supporting the body and reducing your risk of falling. If you are heat sensitive it may be good to check the temperature of the water before you go in.

Exercise Recommendations

- How much exercise and at what intensity?
  - 2-3 aerobic sessions a week, for 20-30 minutes, at mild/moderate intensity is suitable for people with mild to moderate MS.
  - Remember even if you can only manage a few minutes initially, something is better than nothing, just build up gradually.

- What is moderate activity and how is it monitored?
  - Moderate intensity can be described as;

    'an aerobic activity that noticeably increases your heart rate and breathing rate. You may sweat, but you are still able to hold a conversation, but you can't sing'.

  - The intensity of your exercise can also be monitored by taking your heart rate, or by monitoring your rating of perceived exertion (RPE) using a scale (see diagram opposite). The exercise should feel fairly light to somewhat hard on this scale (green portion).

- Exercise Progression
  - To improve fitness you need to work your body above the level that it is used to.
  - To progress you need to gradually increase the amount, duration or intensity of the physical activity that you are doing.
  - Remember you must give your body the time to adapt to being more physically active, before trying to progress further.

RPE Scale

6	
7	Very, Very Light - Rest
8	
9	Very Light - Gentle Walk
10	
11	Fairly Light
12	
13	Somewhat Hard
14	
15	Hard
16	
17	Very Hard
18	
19	Very, Very Hard
20	

Borg Rating of Perceived Exertion Scale, 1998

Exercise Safety

Exercise is safe for people with MS providing you take things slowly and follow some simple guidelines;

Wear appropriate clothing and footwear: If cycling use a helmet, reflective clothing and lights at night.

Chose a safe environment: When walking avoid being alone at night and keep to well lit areas.

Adapt exercises depending on your symptoms: If your balance is affected you may want to consider using gym equipment, such as a treadmill with a hand rail, or a stationary cycle.

Start slowly and gradually build-up: Splitting exercise into short bouts of mild/moderate exercise with rest periods can help you to manage more (and still gives you benefit).

Listen to your body: Don't try to do too much

- Learn your limits and stop before you get too tired
- If you feel pain, dizziness or discomfort, stop and seek advice
- If you are unwell or have a fever don't exercise
- Don't exercise during an acute relapse and take advice from a specialist before starting again. Remember start again slowly

Be flexible: If you are having a bad day, reduce the amount of exercise that you had planned, or re-schedule.

Warm-up and cool-down: This will help guard against injury and prevent existing muscle problems getting worse.

- Start aerobic sessions slowly, gradually increasing your heart rate
- Gently stretch muscles being used both before and after the session

Keep well hydrated

- When exercising you will need to drink more, particularly if exercising in the heat

- Drinking cool water may help to keep body temperature down

Consult your GP: If you have any other health issues, such as heart conditions or asthma, consult your GP before starting on an exercise programme.

Exercise and Fatigue

Fatigue is one of the most common symptoms for people with MS. Feeling tired can often put you off starting an exercise programme. However, research has shown that exercise can be a good thing, increasing your stamina and reducing muscle weakness.

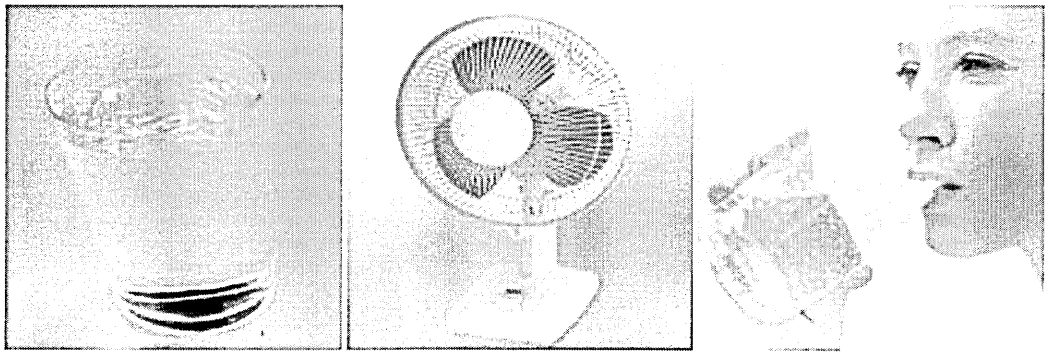
When starting an exercise programme you may feel more tired initially. However, these affects can be minimised by starting at an appropriate level and building up slowly.

Exercise and Heat Sensitivity

People with MS can suffer from heat sensitivity. This means that during and immediately after exercise when your body temperature has been increased your symptoms may feel worse. However, this effect is temporary and as the body cools down again your symptoms will return to normal. This should not be a reason to avoid exercise, but trying to keep cool when doing so may help.

Tips for keeping cool

- Drink cool fluids during and after exercise
- Exercise at a cooler time of day or in a well ventilated space (a fan may help)
- Wear appropriate clothing for the conditions
- Consider interval training (alternating short bouts of activity with rest to prevent your body getting too warm)
- Use cooling vests or caps
- Use wipes to cool your skin or take a cool shower after exercise
- Exercise at a mild to moderate intensity



CSES
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Contact Details

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Appendix 8.14 - Effect Sizes for Main Study Outcomes

OUTCOME	3-Months Follow-up			6-months Follow-up		
	Effect Size	Lower 95% limit	Upper 95% limit	Effect Size	Lower 95% limit	Upper 95% limit
Clinical Measurements						
EDSS	-0.08	-0.28	0.12	-0.09	-0.30	0.11
Systolic BP	-0.08	-0.27	0.12	0.01	-0.18	0.20
Diastolic BP	-0.11	-0.30	0.09	-0.20	-0.39	-0.01
Resting Heart Rate	0.19	-0.00	0.38	0.11	-0.08	0.30
Weight	0.06	-0.13	0.25	0.02	-0.18	0.21
BMI	0.06	-0.13	0.26	0.08	-0.11	0.28
Waist	-0.18	-0.37	0.01	-0.22	-0.41	-0.03
Hip	-0.21	-0.41	-0.02	-0.10	-0.29	0.09
Waist:Hip	-0.03	-0.23	0.16	-0.16	-0.36	0.03
Physical Activity - Godin/IPAQ						
Godin	0.25	0.05	0.46	0.18	-0.02	0.39
Vigorous MET hrs/wk	0.12	-0.09	0.32	-0.04	-0.25	0.17
Moderate MET hrs/wk	0.04	-016	0.25	0.09	-0.13	0.30
Walking MET hrs/wk	0.17	-0.03	037	-0.33	-0.55	-0.12
Total MET hrs/wk	0.17	-0.03	0.37	-0.15	-0.36	0.06
Sitting time hrs/day	-0.02	-0.17	0.13	0.06	-0.15	0.27
Physical Activity - Accelerometry						
Vertical	0.20	-0.08	0.39	0.01	-0.19	0.22
Horizontal	0.12	0.07	0.31	-0.12	-0.32	0.09
Step Count	0.26	-0.65	0.46	-0.01	-0.21	0.20
Physical Fitness						
6MWT	0.13	-0.06	0.33	0.14	-0.07	0.34
Fatigue - MFIS						
Physical	-0.45	-0.65	-0.26	-0.13	-0.33	0.08
Cognitive	-0.39	-0.58	-0.19	-0.15	-0.35	0.05
Psychosocial	-0.45	-0.64	-0.26	-0.10	-0.30	0.11
Total MFIS	-0.50	-0.69	-0.30	-0.16	-0.36	0.04
MS Functional Composite						
25ft walk	-0.17	-0.36	0.03	0.06	-0.15	0.26
9-hole peg test DH	-0.11	-0.31	0.08	-0.19	-0.40	0.01
9-hole peg test NDH	-0.10	-0.30	0.09	-0.13	-0.33	0.07
PASAT	-0.14	-0.34	0.06	0.17	-0.03	0.38
Quality of Life - MSQOL54						
Physical Health	0.33	0.14	0.53	0.13	-0.07	0.33
Role Physical	0.16	-0.04	0.35	-0.02	-0.22	0.19
Role Emotional	0.12	-0.08	0.32	0.08	-0.13	0.28
Pain	0.22	-0.02	0.41	0.04	-0.16	0.24
Emotional Wellbeing	0.37	0.18	0.57	0.26	0.05	0.46
Energy	0.56	0.36	0.75	0.11	-0.09	0.32
Health Perceptions	0.39	0.19	0.58	-0.05	-0.26	0.15
Social Function	0.37	0.18	0.57	0.30	0.09	0.50
Cognitive Function	0.19	-0.01	0.39	0.04	-0.16	0.25
Health Distress	0.46	0.26	0.65	0.05	-0.16	0.25
Sexual Function	0.25	0.04	0.45	0.13	-0.09	0.35
Change in Health	0.51	0.32	0.71	0.09	-0.11	0.29
Sexual Satisfaction	0.26	0.06	0.47	0.01	-0.21	0.22
Overall QoL	0.54	0.35	0.74	0.34	0.13	0.54
Quality of Life - EQ5D						
EQ5D	0.42	0.23	0.62	0.09	-0.11	0.30

Appendix 8.15

Cost effectiveness of a pragmatic exercise intervention (EXIMS) for people with multiple sclerosis: economic evaluation of a randomised controlled trial

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1.1 Abstract

Background: Exercise is a safe, non-pharmacological adjunctive treatment for people with multiple sclerosis but cost-effective approaches to implementing exercise within health care settings are needed.

Objective: The objective of this paper is to assess the cost effectiveness of a pragmatic exercise intervention in conjunction with usual care compared to usual care only in people with mild to moderate multiple sclerosis.

Methods: A cost-utility analysis of a pragmatic randomised controlled trial over nine months of follow-up was conducted. A total of 120 people with multiple sclerosis were randomised (1:1) to the intervention or usual care. Exercising participants received 18 supervised and 18 home exercise sessions over 12 weeks. The primary outcome for the cost utility analysis was the incremental cost per quality-adjusted life year (QALY) gained, calculated using utilities measured by the EQ-5D questionnaire.

Results: The incremental cost per QALY of the intervention was £10,137 per QALY gained compared to usual care. The probability of being cost effective at a £20,000 per QALY threshold was 0.75, rising to 0.78 at a £30,000 per QALY threshold.

Conclusion: The pragmatic exercise intervention is highly likely to be cost effective at current established thresholds, and there is scope for it to be tailored to particular sub-groups of patients or services to reduce its cost impact.

1.2 Introduction

Exercise is a safe, non-pharmacological treatment strategy for people with multiple sclerosis (PwMS) that can bring many health benefits, including improvements in muscle power, physical and psychosocial functioning, fatigue symptoms and quality of life [1–3] A major challenge, however, is to develop pragmatic and cost-effective interventions that can engage PwMS in exercise and have a long-lasting impact on physical activity behaviour. Ensuring that an intervention is both comprehensive and guided, but also pragmatic in terms of delivery and resource requirements, is a challenge that needs to be addressed so that health resources are appropriately utilised.

To date, cost-effectiveness analyses, aimed at comparing the costs and health benefits of exercise interventions for PwMS, are lacking. However, evidence to suggest that an exercise intervention provides health benefits at an acceptable cost may aid in the decision to implement new services. We recently undertook a parallel-arm, randomised controlled trial that investigated the effects of a pragmatic Exercise Intervention for people with MS (EXIMS) on a range of important health outcomes. The exercise intervention increased self-reported physical activity, improved fatigue symptoms and led to a sustained enhancement of health-related quality of life (HRQoL) [Epub ahead of print; 10.1177/1352458513519354]. Using a National Health Service (NHS) and societal perspective, we also undertook an economic evaluation to estimate the cost and cost effectiveness of the pragmatic exercise intervention in conjunction with usual care, in comparison with usual care alone for PwMS. The results of this economic evaluation are reported here.

1.3 Materials and Methods

1.3.1 Randomised controlled trial

Details of the randomised controlled trial have been published elsewhere.[4] Briefly, 120 PwMS were randomised (1:1) to a pragmatic exercise intervention (EXIMS) plus usual care group, or usual care only. Participants in the intervention group undertook a 12-week programme of exercise. During weeks 1–6, participants attended two supervised sessions per week at a university exercise facility close to the hospital and engaged in one additional self-directed exercise session in their home environment. During weeks 7–12, participants attended the centre once per week and completed two additional self-directed exercise sessions in their home environment. EXIMS also incorporated cognitive-behavioural techniques (e.g. goal setting, finding social support, understanding the costs/benefits of exercise, etc.) to promote long-term participation in physical activity. The study was approved by the South Yorkshire Research Ethics Committee and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from participants before entering the study.

1.3.2 Economic evaluation

The primary analysis examined intervention and NHS care costs up to nine months' post-randomisation. Other analyses included wider costs such as patient costs and productivity losses. Patient and productivity costs were excluded from the primary analysis as they do not fall on the budget of a health service payer.

1.3.3 Resource use

Data collected were NHS and Personal Social Services (PSS) resources, personal costs incurred by participants and lost productivity due to time off work. A questionnaire was used to report MS-related NHS contact with primary and secondary care services. We also asked participants to report any personally incurred expenditure due to their condition or treatment, as well as any private therapies and complementary and alternative medicines (CAMs). Participants were asked if they had received assistance from social care staff and if they had taken time off work because of their MS or their treatment for MS. Secondly, the NHS medical records for all participants were cross-checked for secondary consultations with MS consultants and nurses. These data were checked against the patient questionnaire to avoid double-counting of events. Accident and emergency (A&E) attendances and inpatient hospitalisations were extracted from NHS medical records. Finally, the number of prescribed exercise sessions completed by each patient in the intervention arm (out of a possible 18 sessions) was recorded by the exercise specialist who led the intervention.

1.3.4 Costs

Unit costs for each of the resources used are presented in Table 1.1. Three broad groups of costs were estimated: intervention costs, NHS costs, and personal costs. An estimate of the cost of the group exercise programme was an aggregation of staff costs, equipment costs and facility overheads. Staff costs were estimated using NHS physiotherapists and exercise specialists,[5] and weighted by the amount of time each staff member spent setting up and delivering the sessions. Equipment costs were estimated using retail prices for

each piece of exercise equipment, and annuitized for its life expectancy as judged by exercise experts on the research team. In an NHS setting, it was judged that the sessions would be delivered in a physiotherapy department. Overhead costs for a physiotherapy department were used from the published Unit Costs of Health and Social Care[5] and composed of management, non-staff and capital overheads. It was assumed that there were no costs associated with prescribing the home exercise sessions, as this was undertaken during the supervised exercise sessions.

Table 1.1. Cost of the intervention.

Resource use	Unit cost (£) – 2011 unless specified	Source
Intervention costs		
Staff	18.38 per session per patient	PSSRU Curtiis. 2011[5]
Equipment	3.31 per session per patient	Microcosted estimate. Retail prices, annuitized
Overheads	0.82 per session per patient	PSSRU Curtiis. 2011[5]
Intervention cost (2012 prices)	22.52 (per session per patient) 408 per patient –18 sessions 1216 per programme for three patients	
NHS costs		
GP appointment	36	PSSRU Curtiis. 2011[5]
Neurology outpatient visit	214	2011 Reference costs
NHS community health visit	£42	PSSRU Curtiis. 2011[5]
Social care visit	25	PSSRU Curtiis. 2011[5]
Neurology inpatient visit	144	2011 Reference costs
Hospitalisation	463	2011 Reference costs
Accident and emergency visit	55	PSSRU Curtiis. 2011[5]
Personal costs		
Time off work	13.11 (male), 11.91 (female), per hour	Annual Survey of Hours and earnings (ONS, 2011)

GP: general practitioner; NHS: National Health Service; ONS: Office for National Statistics.

NHS costs were provided by national published unit cost and reference cost sources. The cost of an A&E visit was estimated using a published figure for an A&E visit with no resulting hospital admission. If a patient experienced a hospitalisation, a daily unit cost was estimated based on a neurology inpatient hospitalisation (£2235 average cost for a 4.82-day-long stay). Personal costs

included any personal expenses reported by the patient, as well as any time off work. The human capital approach was used to estimate the productivity loss.[6] Office for National Statistics (ONS) sources were used to estimate the hourly rate per male and per female.

1.3.5 Cost-utility analyses

For the cost-utility analyses, health benefits were measured in terms of quality-adjusted life years (QALYs) using EQ-5D HRQoL values.[7] QALYs were calculated using the trapezium rule to estimate the area under the curve. As an alternative HRQoL measure, we used SF-6D utilities by extracting the SF-36 items from the Multiple Sclerosis Quality of Life-54 (MSQOL-54) instrument and applying the SF-6D algorithm.[8] The EQ-5D and MSQOL-54 scores were measured at baseline, three months and nine months. In the primary analysis, only NHS costs were included. Personal and societal costs were included in a sensitivity analysis. All analyses were conducted using STATA© 12 and Microsoft Excel© 2010.

1.3.6 Statistical analysis

All comparisons of costs and effects were performed at the end of the nine-month randomisation period. It was not necessary to discount costs and outcomes because of the nine-month time horizon. Mean costs and mean QALYs were estimated separately. An ordinary least squares (OLS) regression was applied to control the estimated QALYs for baseline level of utility. Mean differences between both groups are presented with their bootstrapped 95% confidence intervals (CIs). An incremental analysis was undertaken by dividing

the mean incremental costs by the mean incremental QALYs to produce an incremental cost effectiveness ratio (ICER). This can be interpreted as the additional cost per QALY gained for the exercise intervention. Uncertainty in the ICER was parameterised by bootstrapping 5000 replications of each ratio (replicated ICERs). The uncertainty was visualised in two ways: firstly with each replicate of costs and QALYs plotted on a two-dimensional cost-effectiveness plane, and secondly with the probability of cost effectiveness at a range of thresholds plotted on a cost-effectiveness acceptability curve.[9,10] We also estimated the net monetary benefit gained from adopting the intervention for given values of cost per QALY that society might be willing to pay (£20,000 and £30,000),[11] and the probability that the net monetary benefit is positive using these values.

1.3.7 Sensitivity analysis

The robustness of the results was examined in a series of scenario analyses. Firstly, the delivery of the intervention in private gyms or by third-party providers was costed and included as a sensitivity analysis. Secondly, personal costs and time off work were included to expand the analysis to a societal perspective. Thirdly, a priori sub-groups were defined by defining clinically meaningful patient sub-populations. The Expanded Disability Status Scale (EDSS) clinical measure of disability in people with MS was used to classify participants as EDSS $\leq$ 3.5 (mild disability) and 3.5 < EDSS $\leq$ 6.5 (moderate disability). The baseline Godin Leisure Time Exercise Questionnaire (GLTEQ) measure of physical activity was used to classify participants as GLTEQ < 14 (insufficiently active) and GLTEQ $\geq$ 14 (moderately active). The cost-utility analysis was conducted for all four sub-groups. Fourthly, there are numerous generic

preference-based measures of HRQoL, and although the EQ-5D is recommended in the United Kingdom (UK) for cost-utility analyses,[11] the SF-6D values were used in a scenario analysis to evaluate the uncertainty regarding the estimates of change in QALYs.

1.4 Results

A total of 120 PwMS were randomised into the two groups (N=60 participants in each group). The two groups had similar demographic, anthropometric and MS disease characteristics at baseline (Table 1.2). A total of 21 (17.5%) participants withdrew from the trial, and 27 (22.5%) participants were not a complete case (resource use questionnaire data missing from 17 (14%) and EQ-5D follow-up data missing from 27 (22.5%)). Where complete case data were missing, multiple imputation methods using the multiple imputation (MI) command in STATA© were used to impute missing values for costs and missing domains for EQ-5D. MI is a method by which each missing datum case is replaced by a set of plausible estimates, based on predictors (sex, age, baseline EDSS and baseline EQ-5D domains). The process is repeated using different estimates and then the results are combined using Rubin's rule.[12]

Table 1.2. Baseline characteristics of participants allocated to usual care only or usual care plus EXIMS. Values are numbers (percentages) or mean ± SD.

Characteristics	Usual care (*n*=60)	EXIMS (*n*=60)
Age (years)	46.0 ± 8.4	45.7 ± 9.1
Female	43 (71.7%)	43 (71.7%)
White	57 (95%)	54 (90%)
Married or cohabiting	46 (77%)	48 (80%)
Educated to A level or beyond	39 (65%)	41 (68%)
Employed full time	16 (27%)	9 (15%)
Employed part time	14 (23%)	17 (28%)
Time since MS diagnosis (years)	9.2 ± 7.9	8.4 ± 7.4
EDSS score subgroup	3.8 ± 1.5	3.8 ± 1.5
0–3.5	28 (47%)	29 (48%)
4.5–6.5	32 (53%)	31 (52%)
Mean score	3.8 ± 1.5	3.8 ± 1.5
MS subtype		
Relapsing–remitting	47 (78%)	51 (85%)
Secondary progressive	11 (18%)	7 (12%)
Primary progressive	2 (3%)	2 (3%)
Anthropometric variables		
Height (m)	1.68 ± 0.07	1.68 ± 0.08
Body mass (kg)	76.4 ± 15.5	79.4 ± 17.8
BMI (kg/m^2)	27.1 ± 5.8	28.0 ± 5.4

EXIMS: EXercise Intervention for people with MS; MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; BMI: body mass index.

1.4.1 Resource use

NHS and PSS resource use is shown in Table 1.3. The mean number of contacts was higher in the usual care control group compared to the exercise group, although variability in the estimates is too large to draw reliable conclusions about a difference in them. The number of outpatient, general practitioner (GP) visits, A&E visits and inpatient stays was small for both groups. Community visits and social care contact was not utilised by the majority of either group; however, the mean estimate of social care contact is heavily skewed because of a few patients requiring high levels of contact. Of the 60 participants allocated to receive the exercise intervention, six (10%) did not use the service at all, and 24 (40%) used the full allocation of 18 sessions.

Table 1.3. NHS and PSS resource use by allocation group.

	Usual care		EXIMS	
	n	%	*n*	%
Outpatient visits				
Missing values	13	21.7%	12	20.0%
0	12	20.0%	16	26.7%
1	14	23.3%	15	25.0%
2	9	15.0%	7	11.7%
3	1	1.7%	4	6.7%
4+	11	18.3%	6	10.0%
Total	60	100.0%	60	100.0%
Mean (SD)		2.0 (2.2)		1.4 (1.4)
Median (IQR)		1 (0–2)		1 (0–2)
GP visits				
Missing values	13	21.7%	12	20.0%
0	22	36.7%	28	46.7%
1	11	18.3%	9	15.0%
2	7	11.7%	2	3.3%
3	4	6.7%	1	1.7%
4+	3	5.0%	8	13.3%
Total	60	100.0%	60	100.0%
Mean (SD)		1.4 (2.6)		1.3 (2.3)
Median (IQR)		1 (0–2)		0 (0–1)
Community visits				
Missing values	13	21.7%	12	20.0%
0	34	56.7%	34	56.7%
1	3	5.0%	5	8.3%
2	3	5.0%	4	6.7%
3	2	3.3%	3	5.0%
4+	5	8.3%	2	3.3%
Total	60	100.0%	60	100.0%
Mean (SD)		1.3 (3.2)		0.7 (1.5)
Median (IQR)		0 (0–1)		0 (0–1)
Social care hours				
Missing values	13	21.7%	12	20.0%
0	42	70.0%	45	75.0%
1–20	1	1.7%	0	0.0%
21–40	0	0.0%	1	1.7%
41–60	0	0.0%	0	0.0%
61+	4	6.7%	2	3.3%
Total	60	100.0%	60	100.0%
Mean (SD)		15.6 (57.8)		10.8 (51.5)
Median (IQR)		0 (0–0)		0 (0–0)
Inpatient hospitalisations				
Missing values	0	0.0%	0	0.0%
0	60	100.0%	56	93.3%
1–5 nights	0	0.0%	1	1.7%
5 nights+	0	0.0%	3	5.0%
Total	60	100.0%	60	100.0%
Mean (SD)		0.0 (0.0)		0.78 (3.61)
Median (IQR)		0 (0–0)		0 (0–0)
A&E visits				
Missing values	0	0.0%	0	20.0%
0	59	70.0%	56	75.0%
1	1	1.7%	4	0.0%
Total	60	100.0%	60	100.0%
Mean (SD)		0.02 (0.13)		0.07 (0.25)
Median (IQR)		0 (0–0)		0 (0–0)
Exercise intervention (sessions)				
Missing values			1	1.7%
0			6	10.0%
1–6			0	0.0%
7–12			5	8.3%
13–17			25	41.7%
18			23	38.3%
Total			60	100.0%
Mean (SD)				14.6 (5.5)
Median (IQR)				17 (14–18)

NHS: National Health Service; PSS: Personal Social Services; IQR: inter-quartile range; EXIMS: Exercise intervention for people with multiple sclerosis; GP: general practitioner; SD: standard deviation.

1. 4.2 Cost-utility analyses

The average intervention cost per participant was £375 in the exercise group. There was a small increase in the wider NHS and PSS costs in the exercise group compared to the usual care control group (Table 1.4), which when combined with the exercise intervention cost resulted in a mean additional cost to the NHS and PSS of £466 (CI: –£273 to £1310) compared to the usual care control group. At the end of the follow-up period, PwMS who were randomised to the exercise group experienced 0.538 QALYs compared with 0.492 QALYs for patients in the usual care control group, indicating no significant difference in health benefit (difference 0.046, –0.022 to 0.115). Although the point estimates in difference in costs and QALYs were not statistically significant, they suggest that the EXIMS intervention may be more beneficial in providing QALYs but also more expensive. The ICER which relates increased costs to a gain in QALYs was £10,137 per QALY gained (£466/0.046). This indicates that each QALY gained by providing exercise to PwMS will cost the NHS £10,137. The EQ-5D scores for the control and intervention group at each assessment point are reported in Table 1.5. The probability of being cost effective at £20,000 per QALY is 0.70, and 0.78 if the threshold is £30,000 per QALY. Figure 1.1 plots the 5000 replicated cost and QALY pairs (generated using bootstrap methods), together with two threshold lines at £20,000 and £30,000 per QALY. The figure shows that 11% of replicates suggest that the pragmatic exercise intervention generates health benefits at lower cost (intervention dominates usual care). Figure 1.2 provides a cost-effectiveness curve, which indicates the probability of the intervention being cost effective for a range of maximum acceptable ICERs (MAICERs).

Table 1.4. Cost-utility analysis.

	Usual care n=60		EXIMS n=60		Difference (95% CI)
	Mean	(SD)	Mean	(SD)	
Intervention cost	–	–	375	7	375 (360 to 388)
Outpatient costs	437	67	290	42	−146 (−306 to 7)
Primary care costs	50	14	46	12	−4 (−40 to 30)
Community care costs	57	19	30	9	−26 (−69 to 13)
Social care costs	389	210	270	184	−119 (−677 to 426)
Hospitalisation costs	–	–	392	265	392 (−321 to 1780)
A&E costs	1	1	3	2	2 (−2 to 7)
TOTAL cost (£)	**932**	**225**	**1398**	**337**	**466 (−273 to 1310)**
QALYs	**0.492**	**0.028**	**0.538**	**0.021**	**0.046 (−0.022 to 0.115)**
ICER, cost per QALY gained					**£10,137**
Net monetary benefit (probability > 0)					
Willingness to pay (λ) = £20,000 per QALY				£453	0.75
Willingness to pay (λ) = £30,000 per QALY				£913	0.78

EXIMS: Exercise intervention for people with multiple sclerosis; SD: standard deviation; CI: confidence interval; A&E: accident and emergency; QALY: quality-adjusted life year; ICER: incremental cost effectiveness ratio.

Table 1.5. EQ-5D scores.

	Baseline			12 Weeks' post-baseline			Six months' post-baseline		
	Usual care	Intervention	Difference	Usual care	Intervention	Difference	Usual care	Intervention	Difference
Mean	0.642	0.634	−0.008	0.684	0.744	0.060	0.734	0.739	0.005
SD	0.255	0.279	0.024	0.263	0.204	−0.059	0.252	0.249	−0.003
Minimum	−0.016	−0.181	−0.165	−0.016	−0.016	0.000	−0.016	−0.181	−0.165
Lower quartile	0.587	0.516	−0.071	0.587	0.656	0.069	0.656	0.656	0.000
Median	0.717	0.725	0.009	0.727	0.727	0.000	0.727	0.727	0.000
Upper quartile	0.796	0.779	−0.017	0.850	0.919	0.069	0.919	0.919	0.000
Maximum	1.000	1.000	0.000	1.000	1.000	0.000	1.000	1.000	0.000

SD: standard deviation.

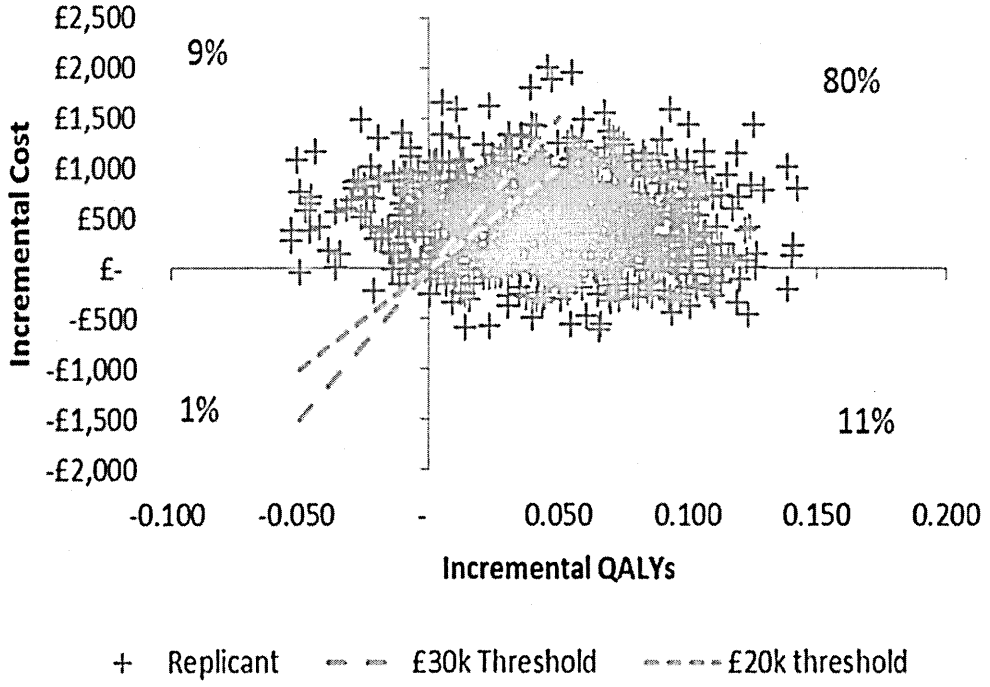

Figure 1.1. Cost-effectiveness plane.

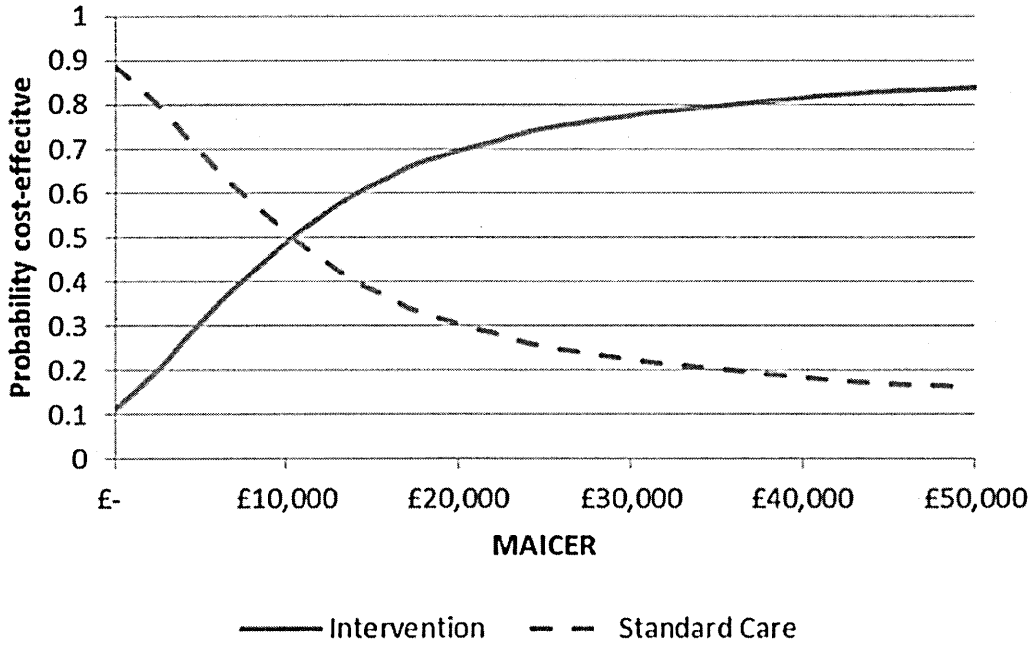

Figure 1.2. Cost-effectiveness acceptability curve.

Table 1.6. Scenario analysis results

Scenario 1: Stratified by EDSS score	Control		Intervention		ICER	Willingness to pay	
	Costs (£)	QALYs	Costs (£)	QALYs		£20,000 per QALY	£30,000 per QALY
EDSS < 4.0	434	0.592	1153	0.588	Dominated	−794 (0.18)	−832 (0.25)
EDSS ≥ 4.0	1378	0.406	1726	0.474	£5092	1017 (0.80)	1699 (0.84)
Scenario 2: Stratified by GLTEQ score	**Control**		**Intervention**		**ICER**	**Willingness to pay**	
GLTEQ ≥ 14	839	0.504	1253	0.548	£9558	£453 (0.65)	£886 (0.72)
GLTEQ < 14	1155	0.464	1766	0.517	£11,470	£454 (0.63)	£987 (0.70)
Scenario 3: Societal perspective	**Control**		**Intervention**		**ICER**	**Willingness to pay**	
	1660	0.492	2804	0.538	£24,897	−£225 (0.43)	£235 (0.58)
Scenario 4: Private provision (£495 per patient per programme)	**Control**		**Intervention**		**ICER**	**Willingness to pay**	
	932	0.492	1481	0.538	£11,938	£371 (0.67)	£830 (0.76)
Scenario 5: SF-6D utility scores	**Control**		**Intervention**		**ICER**	**Willingness to pay**	
	932	0.449	1398	0.473	£19,783	£5 (0.50)	£241 (0.63)

EDSS: Expanded Disability Status Scale; QALYs: quality-adjusted life years; GLTEQ: Godin Leisure Time Exercise Questionnaire; ICER: incremental cost effectiveness ratio.

1.4.3 Scenario analysis

The results of the scenario analyses are shown in Table 1.6. Two sub-group analyses were undertaken, splitting the trial participants by disease severity (EDSS < 4.0 (control n = 22, intervention n = 20) and EDSS ≥ 4.0 (control n = 38, intervention n = 40)), and by level of physical functioning (GLTEQ ≥ 14 (control n = 35, intervention n = 34) and GLTEQ < 14 (control n= 25, intervention n = 26)). In the less severe disease activity group (EDSS < 4·0), the intervention was more expensive and generated less QALYs (dominated). In the more severe disease activity group (EDSS ≥ 4.0), the intervention was more costly (+£348) and more effective (+0.068 QALYs), resulting in an ICER of £5092 per QALY gained. These results suggest a clear difference in the cost effectiveness of the intervention when comparing these two patient sub-groups.

Likewise, in the more physically active sub-group (GLTEQ ≥ 14), the intervention was more costly (+£414) and more effective (+0.044 QALYs), resulting in an ICER of £9558 per QALY gained. In the less physical active sub-

group (GLTEQ < 14), the intervention was more effective (+0.053 QALYs) and more costly (+£611), resulting in an ICER of £11,470. These results do not suggest that it is possible to define a more cost-effective subgroup of PwMS based on their baseline GLTEQ score.

A scenario analysis with a societal perspective was undertaken. Personal costs, as well as time-off-work productivity costs were included. This saw an increase in costs in both trial groups, with the exercise group more costly compared to the usual care control group (+£1144), and a resulting ICER of £24,897 per QALY gained.

A scenario analysis was undertaken with an alternative intervention cost. In the basecase analysis, the cost of £408 per patient per programme was derived using NHS facilities. An alternative option for providing the service is via private facilities and third-sector providers. An estimate of the cost of private provision from two local gyms was obtained resulting in an approximate estimate of £495 per patient per programme. As expected, the cost of the intervention group increased, resulting in an ICER of £11,938 per QALY gained compared to the control group.

Finally, to assess sensitivity in the measure of HRQoL, the SF-6D was used. The analysis was robust, with the intervention continuing to provide more QALYs (+0.024 QALYs). The ICER for the intervention when using the SF-6D was £19,783 per QALY gained compared to the usual care control group.

1.5 Discussion

In this economic evaluation, the exercise intervention appeared to be both more effective and more expensive than usual care alone; however, the differences in costs and benefits between the treatment groups were mostly small and not significant after nine months. The ICERs remained well below the generally accepted standard of £20,000 per QALY gained, with the intervention having a high probability of being cost effective. Therefore the intervention may be regarded as potentially cost effective for PwMS. The low amount of uncertainty relating to the cost-effectiveness results, as highlighted by the high probability of exercise being cost effective, seems counterintuitive in the face of non-statistically significant cost and QALY differences. However, this is due to the purpose of the analysis being to compare against a positive ratio of incremental costs and effects (typically set at £20,000 per QALY), rather than tests of no-difference in effects.[13]

As is common with economic evaluations conducted alongside clinical trials, the accuracy of the resource use data may limit the usefulness of the results. There is a debate in the literature regarding the appropriateness of methods to collect resource use data in trial participants.[14,15] Because of the finite resources for conducting this clinical trial, a pragmatic method was chosen, with participants asked to complete questionnaires with a three-month recall period. This method can lead to inaccurate results, as well as incomplete data. The questionnaire was also used to ask participants about any personal expenditure due to MS, and any time off work they had in the previous three months. Only a few participants reported any personal expense or time off work, which lead to skewed and uncertain estimates of cost effectiveness for the analysis with a societal perspective.

The costing of the intervention is potentially limited because of the variation in options for implementation of the service. Micro-costing for NHS provision was undertaken because the service does not fit within current NHS tariffs. The micro-costing approach uses national average data and may not be an accurate reflection of the true cost to the NHS if the service was commissioned. Alternatively, the service could be provided privately, and the cost estimates included in the scenario analysis for this option use Sheffield UK prices in terms of staff and local gym hire. If local gyms were to be used, the suitability and convenience for PwMS is important and staff would have to be appropriately trained to deliver the intervention. The scenario analysis undertaken found that the cost-effectiveness results were generally robust to changes in the cost of the EXIMS intervention.

This analysis only assessed the cost effectiveness of the EXIMS intervention across nine months. Because the intervention costs are borne up front, if results were to be extrapolated, the intervention would become even more cost effective, even if the effects diminished over time. In this respect, the analysis is a conservative estimate of cost effectiveness and the long-term benefits of the intervention have not been fully explored. Furthermore, the sub-group analyses highlighted that in less-active participants, and in more severely affected PwMS, the intervention is likely to be most cost effective, and potentially cost saving. In these sub-groups, the cost may be offset by a reduction in the substantial NHS and PSS resources that these participants require.

In conclusion, the results of this study suggest that this pragmatic exercise intervention could feasibly be provided by the NHS for PwMS and has a high probability of being cost effective. The results are generally robust to whether EXIMS is provided by the NHS or provided privately. Although the long-term

health impact of EXIMS has not been established, a more active lifestyle and the confidence to undertake home-based exercise are likely to lead to improved fatigue management, HRQoL benefits and potential cost benefits for the NHS.

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