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Changing physical activity behaviour for people with multiple sclerosis: protocol of a randomised controlled feasibility trial (iStep-MS)

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ABSTRACT

Introduction Although physical activity may reduce disease burden, fatigue and disability, and improve quality of life among people with multiple sclerosis (MS), many people with MS are physically inactive and spend significant time in sedentary behaviour. Behaviour change interventions may assist people with MS to increase physical activity and reduce sedentary behaviour. However, few studies have investigated their effectiveness using objective measures of physical activity, particularly in the long term. Further, interventions that have proven effective in the short term may not be feasible in clinical practice because of the large amount of support provided. The iStep-MS trial aims to determine the safety, feasibility and acceptability of a behaviour change intervention to increase physical activity and reduce sedentary behaviour among people with MS.

Methods and analysis Sixty people with MS will be randomised (1:1 ratio) to receive a 12-week intervention or usual care only. The intervention consists of four physical activity consultations with a physiotherapist supported by a handbook and pedometer. Outcomes assessed at baseline, 12 weeks and 9 months are physical activity (ActiGraph wGT3X-BT accelerometer), sedentary behaviour (activPAL3µ), self-reported activity and sitting time, walking capability, fatigue, self-efficacy, participation, quality of life and health service use. The safety of the intervention will be determined by assessing change in pain and fatigue and the incidence of adverse events during the follow-up period. A parallel process evaluation will assess the feasibility and acceptability of the intervention through assessment of fidelity to the programme and semistructured interviews exploring participants' and therapists' experiences of the intervention. The feasibility of conducting an economic evaluation will be determined by collecting data on quality of life and resource use.

Ethics and dissemination Research ethics committee approval has been granted from Brunel University London. Results of the trial will be submitted for publication in journals and distributed to people with MS and physiotherapists.

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Strengths and limitations of this study

► The iStep-MS trial will investigate the feasibility of delivering a behaviour change intervention to increase physical activity and reduce sedentary behaviour as part of routine physiotherapy care.
► The feasibility of conducting a large randomised controlled trial of the clinical effectiveness and cost-effectiveness of the intervention, should the intervention prove feasible, will also be determined.
► Physical activity and sedentary behaviour will be assessed using objective measures. However, all other outcome measures are patient reported.
► Participants, physiotherapists and researchers collecting the data will not be blinded to group allocation.

INTRODUCTION

Multiple sclerosis (MS) is typically a progressive and unpredictable condition of the central nervous system that is a major cause of neurological disability among young adults.[1] As a consequence of MS, people experience disorders of mobility, balance, sensation, cognition and vision.[2] There is also consistent evidence that people with MS participate in low levels of physical activity and spend increased time in sedentary behaviour.[3–6] Increasing physical activity and reducing sedentary behaviour may have specific benefits for people with MS. Those who participate in high levels of physical activity and spend little time in sedentary behaviour have milder disability, better mental health, better social functioning, less fatigue and a lower rate of premature mortality than people who are inactive and sedentary.[7–10] Increases in physical activity over time may be associated with improvements in health-related quality of life and the stability of MS symptoms.[11 12]

Although the terms physical activity and exercise are often used interchangeably, there is an important distinction between them; exercise is a type of physical activity that is planned, structured and repetitive, whereas physical activity includes a broader range of activities that result in energy expenditure such as occupation-related physical activity, activities of daily living and travel-related physical activity.[13] Similarly, although sedentary behaviour and physical inactivity have historically been used synonymously, sedentary behaviour is 'any waking behaviour characterised by an energy expenditure ≤1.5 metabolic equivalents, while in a sitting, reclining or lying posture', whereas physical inactivity is defined as not meeting physical activity recommendations.[14]

There is substantial evidence that exercise interventions improve mobility, fatigue, strength, quality of life and cardiorespiratory fitness in people with MS[15–19] but little evidence regarding effective interventions to increase physical activity in this group. If physical activity is not maintained beyond the duration of an exercise intervention, the benefits of exercise are likely to be short-lived. At present, people with MS who want to increase physical activity report not receiving support to do so.[20]

Behaviour change interventions

Behaviour change interventions are a potential method of increasing physical activity and reducing sedentary behaviour in people with MS. Behaviour change interventions are 'coordinated sets of activities designed to change specified behaviour patterns'.[21] These are often complex interventions, involving multiple, interacting components. Such interventions are commonly used to increase physical activity and reduce sedentary behaviour in the general population.[22–24] Examples of established techniques that may be incorporated in interventions include goal setting, action planning, providing information on the consequences of the behaviour and providing feedback on performance of the behaviour.[25]

A recent meta-analysis indicated that behaviour change interventions of approximately 8 to 12 weeks' duration are effective at increasing physical activity in people with MS in the immediate period following the intervention.[26] While this suggests that physical activity may be increased in the short term, this finding must be interpreted with caution. Eight of the 11 studies were judged at being at high risk of bias.[26] Nine of the 11 studies assessed physical activity using self-reported measures, which are likely to result in biased estimations of the effect of the intervention given that activity is often overestimated or underestimated.[27 28] Further, self-reported physical activity may be subject to significant reporting bias when participants are not blinded to group allocation, as was the case in all included studies. While it is rarely possible to blind participants to group allocation when examining the effectiveness of complex interventions, an objective measure of physical activity will prevent recall bias. Of the

two studies that objectively measured physical activity,[29 30] one reported a significant increase in physical activity immediately after a 3-month intervention.[29] However, this increase was not sustained at 9 months. The second study reported no significant increase in objectively measured physical activity after a 6-month intervention despite improvements in self-reported physical activity.[30] Further, no study included in the review investigated the long-term effect of a behaviour change intervention on physical activity.

In addition to these methodological limitations, there is large variation in the volume (ie, duration and frequency) and mode of delivery of interventions across studies. The only intervention that resulted in a significant increase in objectively measured physical activity following a 3-month intervention included 20 exercise consultations, which incorporated behaviour change techniques, each lasting 60 min.[29] It may not be feasible or acceptable to deliver or receive such a large volume of exercise in clinical practice, therefore preventing the implementation of the intervention into routine care.

Although behaviour change interventions present as a potentially effective method of increasing physical activity and reducing sedentary behaviour in people with MS, the current evidence to support the use of these interventions for people with MS is limited.[26] More research is required to identify a feasible, acceptable, clinical-effectiveness and cost-effective intervention to help people with MS increase physical activity and reduce sedentary behaviour in the long term.

Study objective

The aim of the iStep-MS trial is to determine the safety, feasibility and acceptability of a behaviour-change intervention to increase physical activity and reduce sedentary behaviour for people with MS. Should the results of this study indicate that the intervention is safe, feasible and acceptable, it is proposed to investigate the effectiveness of the intervention in a larger phase 3 trial.

METHODS
Trial design

The iStep-MS trial is a single-centre randomised controlled trial with parallel process evaluation comparing a physiotherapist-led behaviour change intervention to increase physical activity and reduce sedentary behaviour in addition to usual care, with usual care only (figure 1).

METHODS AND ANALYSIS
Study setting

The study is based in the Berkshire MS Therapy Centre in Reading, South East UK.

Trial status

At the time of submission of this study protocol, recruitment to the trial is ongoing.
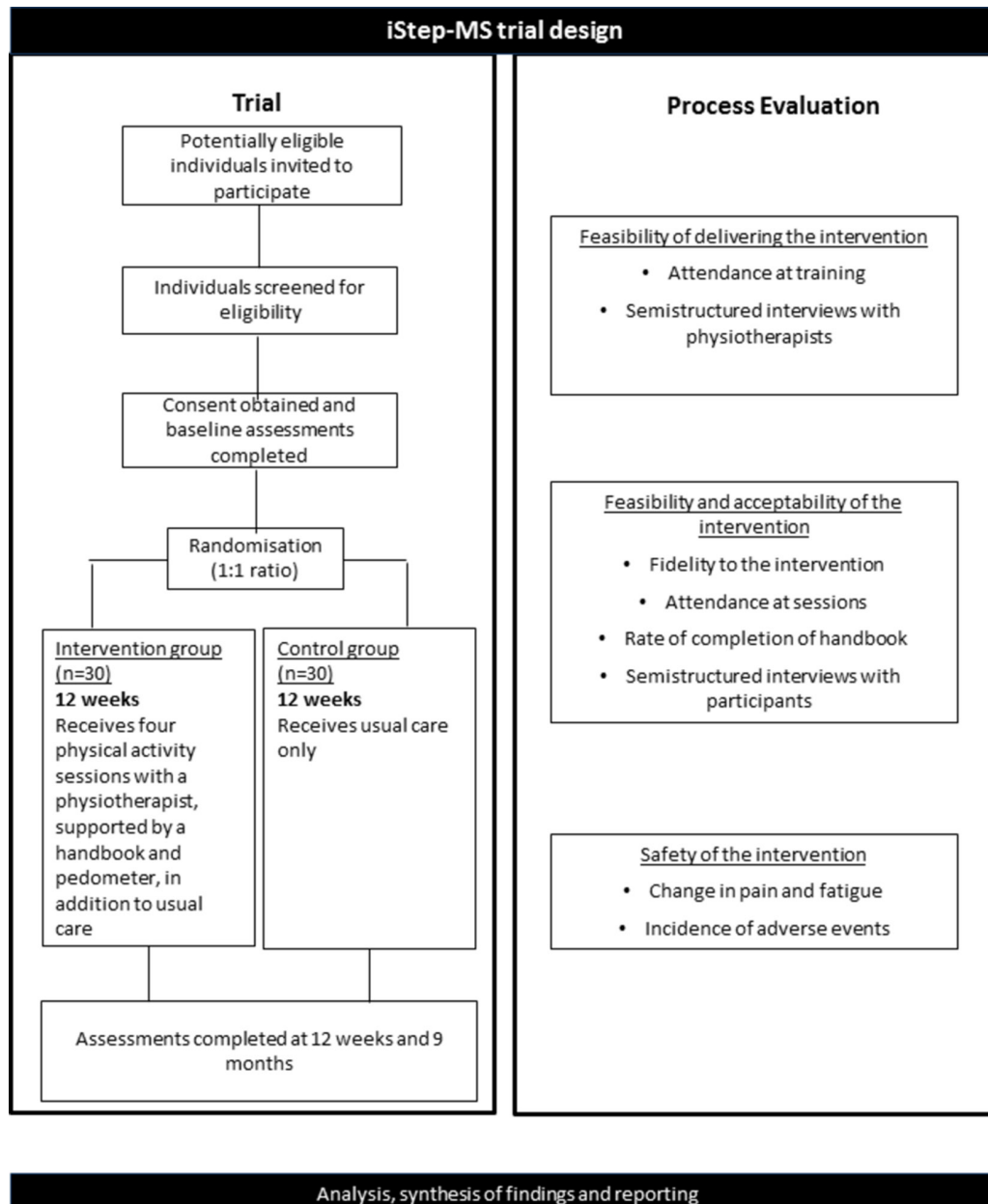
Figure 1 iStep-MS trial design.

Participants

Participants are eligible to be included in the trial if they meet the following inclusion criteria:

1. They have a self-reported diagnosis of MS; this method of identifying a diagnosis of MS is consistent with the method used in the MS Therapy Centre, which is the site for this trial.
2. They are relapse free for the past 3 months; a relapse will be defined as 'the appearance of new symptoms, or the return of old symptoms, for a period of 24 hours or more, in the absence of a change in core body temperature or infection'.[31]
3. They are independently ambulatory at a minimum within their home with or without a walking aid.
4. They are free of unstable medical conditions, for example, unstable angina.

5. They are able to travel to the Berkshire MS Therapy Centre for the intervention.
6. They are fluent in English to a standard sufficient for completion of the trial assessment and intervention.
7. They have an ability to comprehend and follow all instructions relating to participation in the study including providing informed consent, completing the outcome measures or participating in the intervention.

Potential participants will be excluded if they are pregnant. Those already participating in a clinical trial will also not be permitted to participate to minimise the impact of potential confounding variables on the study outcome. We have chosen not to limit the eligibility criteria to people who are physically inactive or people with a specific type of MS as the impact of these factors on

study outcomes will be determined following completion of this feasibility study. Our analysis of the impact of these factors on study outcomes will inform inclusion criteria and stratification factors in a definitive trial.

Sample size

Sixty participants will be recruited for this study. This is a pilot study and thus a sample size calculation has not been performed. There are currently 1200 people on the database of the Berkshire MS Therapy Centre. Recruitment rate to the study is estimated to be 10% based on previous physical activity studies that include an intervention to change physical activity behaviour.[32 33]

Recruitment

Participants will primarily be recruited from people with MS who are registered at the Berkshire MS Therapy Centre and meet the eligibility criteria. As it is not possible to screen the database at the Therapy Centre to identify potentially eligible participants, due to the type of data stored on the database, everyone on the database will be provided with an information pack by post or email. The information pack, sent by an administrator at the centre, includes a participant invite letter and a participant information sheet. People who receive information by post will also receive a questionnaire about their reasons for non-participation (described under the "reasons for non-participation" section) and a stamped addressed envelope. Participants who receive information by email will be directed to an online version of the questionnaire. If no response is received within 4 weeks of the first contact, the administrator will send a second invitation pack containing a new participant invite letter, participation information sheet, questionnaire and stamped addressed envelope (or link to the online version of the questionnaire). Information on the study will be shared through Berkshire MS Therapy Centre newsletter, blog and social media, and posters advertising the study will be displayed at the centre. In addition, the study will be advertised on the MS Society website. People who express an interest in participating in the trial will be contacted by a member of the research team who will provide them with more information about the study, screen for eligibility and answer questions.

Potential participants identified by the physiotherapy team during routine attendance at the MS Therapy Centre will also be approached by a member of the research team. A member of the physiotherapy team will obtain consent from the individual for the member of the research team to approach them before they do so. The researcher will introduce the study, ensure the person is eligible to participate and provide them with an information pack.

The study recruitment period will run from May 2017 to end January 2018. Over the 9-month recruitment period, we expect to recruit 60 participants with MS through the Berkshire MS Therapy Centre, which equates to approximately 1.5 participants per week. At the time of recruitment for this study, there will be no competing studies ongoing at the MS Therapy Centre.

Reasons for non-participation

A potential concern is that the people who are already physically active select to participate in the study. The broad inclusion criteria and various recruitment pathways aim to counteract this. In addition, the profile of participants and non-participants will be compared in order to identify potential selection bias. In order to identify the reasons why people refuse to participate in the study and to identify any differences in baseline characteristics between participants and non-participants, we will ask non-participants to complete an online or paper questionnaire. Individuals will be asked to provide information on sociodemographic factors, health and lifestyle factors, and physical activity, and provide reason(s) for non-participation. This survey will take approximately 5 min to complete. Completion of the survey will indicate consent. Non-participants will be incentivised to complete the questionnaire by being included in a raffle for a £50 gift voucher on completion of the questionnaire.

Randomisation

Following baseline assessments, participants will be randomly allocated to the intervention or usual care control group in a 1:1 ratio. Allocation will be performed by an individual independent to the study according to a computer-generated random schedule in permuted blocks of 2 or 4. The allocation sequence will be placed in sequentially numbered, opaque, sealed envelopes. Following each baseline assessment, an envelope will be drawn sequentially by a researcher who will inform the participant if they are in the intervention group or the control group.

Blinding

Participants and physiotherapists will not be blind to group allocation. Researchers conducting the assessments will also not be blind to group allocation. However, the questionnaires will be self-reported and participants will receive standardised instructions to mitigate against measurement bias. Assessment of objectively measured physical activity and sedentary behaviour is unlikely to be influenced by the assessor being aware of group allocation. To mitigate against observer bias during data processing and analysis, a person independent to the study will apply anonymous codes to all data sheets and physical activity data files before analysis to ensure that the research team and statistician are blinded to group allocation when processing and analysing the data.

Intervention

Participants in the intervention group will receive four physical activity sessions with a trained physiotherapist delivered over 3 months, supported by a handbook and pedometer, in addition to usual care. Participants will be provided with a handbook prior to session 1.

The handbook was developed to guide physiotherapists and participants through the four physical activity sessions. It was developed by cognitive-behavioural trainers with experience in training health professionals to use brief behaviour change techniques, the research team, people with MS and experienced neurological physiotherapists. The intervention handbook was adapted from the National Health Service (NHS) Health Trainer Handbook[34] and incorporated aspects from the Supportive Adjustment for Multiple Sclerosis (saMS) manual.[35] The NHS Health Trainer Handbook incorporates established, effective techniques that help people change behaviours that are known to cause ill-health. It does not focus on a specific theory of behaviour change but incorporates behaviourchange techniques that draw from several theories. At present, the NHS Health Trainer Handbook is not appropriate for use for the purpose of this study as it does not specifically focus on changing physical activity and sedentary behaviour and is designed for use in the general population. A modified version of the NHS Health Trainer Handbook delivered alongside four supporting consultations has proved effective at increasing physical activity in older adults.[36] The saMS manual was developed to guide a cognitive behavioural therapy programme aimed to help people with MS adjust to living with MS.[35] The specific aspects of the saMS manual that were adapted for use in the handbook were addressing the particular challenges of MS in relation to physical activity, identifying strategies for coping with MS-related problems in relation to physical activity and reducing 'symptom focusing'.

The handbook consists of seven sections. The content of each section is described in box. An independent group of people with MS and physiotherapists reviewed and revised each section in consultation with the research team. Briefly, the handbook consists of an introduction, a section dedicated to each of the four sessions and additional resources. The format of the sections dedicated to each session is: overview, pre-session reading and reflection, content specific to that session (eg, barriers and facilitators to physical activity), goal setting, and a diary to record and monitor goals. Key behaviour change techniques drawn from Michie *et al*'s taxonomy of behaviour change techniques[25] were incorporated into each session. These included 'goal setting (behaviour)', 'action planning', 'barrier identification/problem solving', 'set graded tasks', 'prompt review of behavioural goals', 'prompt self-monitoring of behaviour' and 'provide information on where and when to perform behaviour'. Physiotherapists were advised that they did not have to cover all aspects of the handbook but may focus on specific aspects depending on the needs of the individual. However, the participant must set a goal relating to step-count, general physical activity and sedentary behaviour, in consultation with the physiotherapist, at the end of sessions 1, 2 and 3.

Participants in the intervention arm will be provided with a Yamax SW-200 digiwalker pedometer at session 1. The Yamax SW-200 digiwalker has strong concurrent validity in adults with MS when compared with accelerometry.[37] Participants will be asked to wear the pedometer on their trousers or skirt at the right hip for all waking hours, except for swimming and bathing, for at least 7 days between each session. They will record their step-count and whether or not they achieved their physical activity and sedentary behaviour goal for at least 1 week between each session in the handbook. Participants will be advised that they may record this information for more than 1 week.

Session 1 (approximately 45 min duration) will be arranged within 10 days of the baseline assessment by the physiotherapist. Session 2 (approximately 30 min duration) will be scheduled by the physiotherapist for 2 weeks after session 1. Session 3 (approximately 45 min duration) will be scheduled by the physiotherapist for 4 weeks after session 2. Session 4 (approximately 30 min duration) will be scheduled by the physiotherapist for 4 weeks after session 3.

Training
The physiotherapists will be trained by a cognitive-behavioural trainer in the use of the handbook as guided self-help and will be provided with information regarding the behaviour change techniques included in each session. This training will comprise of four half days of training; two delivered prior to the intervention and two delivered during the intervention. Training will be experiential in nature. The physiotherapists will be guided through a sequence of learning activities to develop and refine their intervention delivery. Key skills such as pacing and timing of the sessions will be practised. An additional 3-hour session with the research team will cover all aspects of delivering the trial at the site including maintaining the study documentation and teaching participants to use the pedometer.

Control group
Participants allocated to the control group will receive ongoing usual care that could range from intensive physiotherapy to no treatment. Participants' use of physiotherapy services will be recorded as part of an assessment of their health service use as outlined in the "outcomes" section. Participants in both groups will be asked not to discuss the intervention with other participants in order to avoid participants in the usual care group integrating components of the intervention into their routine. The impact of allocation to the control group on the participant will be explored within the process evaluation.

Assessments
Assessments will be completed at baseline, 3 months post-randomisation and 9 months post-randomisation. Assessments will take place at the Berkshire MS Therapy Centre or in the participant's home with their permission. All participants will be requested to complete follow-up assessments, including those who withdrew or were

Box	Content of the iStep-MS handbook

Section 1: About multiple sclerosis (MS)
► An overview of MS and the associated symptoms
► The particular challenges of MS

Section 2: About the iStep-MS programme
► Overview of the programme
► About this handbook
► About the physical activity sessions
► After the programme

Section 3: Session 1—first steps
► Pre-session reading: definitions of physical activity and sedentary behaviour; examples of light, moderate and vigorous intensity activity; physical activity guidelines; possible ways to reduce sedentary behaviour and increase physical activity
► Pre-session reflection: identify personal examples of light, moderate and vigorous activity that you perform; identify ways to increase your physical activity safely; identify the most important values in your life
► About you: identify symptoms of MS that affect your ability to carry out physical activity; identify other health conditions that prevent you from doing more physical activity; identify other issues that may make increasing physical activity difficult
► Benefits of physical activity
► Common myths and facts about increasing physical activity with MS
► Personal thoughts, worries or emotions concerning increasing physical activity
► Summary of current subjectively and objectively measured levels of physical activity and sedentary behaviour
► Planning your overall physical activity target
► Goal setting: identifying small steps to reach your physical activity target

Section 4: Session 2—overcoming challenges overview
► Pre-session reading: the role of thoughts and feelings; coping with MS
► Pre-session reflection: identify personal strategies that support coping and improve quality of life; identify personal difficulties and factors than make it harder to cope; identify useful tips from pre-session reading regarding how to strengthen personal coping strategies
► Reviewing your goals
► Barriers and facilitators for physical activity
► Overcoming barriers to change—developing positive coping strategies
► Goal setting

Section 5: Session 3—keeping up the changes
► Pre-session reading: dealing with setbacks; reducing symptom focusing; reducing 'boom and bust' activity patterns
► Pre-session reflection: identify how you usually deal with setbacks; identify personal setbacks; identify useful tips from pre-session reading on coping with setbacks
► Reviewing your goals
► Strategies for coping with setbacks
► Pacing and prioritising
► Building 'if–then' plans
► Goal setting

Section 6: Session 4—building lasting habits
► Pre-session reading: reminder of the tips and techniques covered in the handbook
► Pre-session reflection: identify difficulties encountered during the programme; identify tips and techniques in the handbook that have proved helpful to overcome difficulties
► Reviewing your goals
► Reviewing progress so far
► Reflection on personal experience of programme
► Building habits
► Planning a new overall physical activity target

Section 7: Additional information and resources
► Confidence ruler
► Further examples of light, moderate and vigorous intensity activity
► Local resources for getting active

withdrawn from the intervention. If participants do not respond to the first request to complete a follow-up assessment, at least one further contact will be made by email or telephone. Assessments will take approximately 2 hours and participants will be allowed breaks during the assessment if required. A pilot assessment was conducted to determine the burden of assessment on individuals; amendments to the process were made to ensure that the burden was minimised.

The following information will be collected at baseline: (1) socioeconomic information including age, gender, ethnicity, employment status and marital status; (2) MS-specific information including year of diagnosis, type of MS, use of mobility aids, assistive devices such

as functional electrical stimulation and ankle and foot orthoses, and the MS Impact Scale[38]; (3) health problems and lifestyle factors including self-reported chronic diseases (eg, hypertension, type 2 diabetes mellitus), current medication use, alcohol intake and smoking history; and (4) anthropometric measures including height, weight, body mass index, waist circumference and hip circumference.

The practicality, quality of data, quantity of missing data and reasons for missing data associated with the data collection tools will be recorded as part of determining the feasibility of conducting a phase 3 trial.

Outcomes

Objectively measured physical activity and step-count

Physical activity and step-count will be objectively measured with the ActiGraph wGT3X-BT accelerometer. Inbuilt sensors detect the magnitude of a person's acceleration in each plane, which is expressed as accelerometer counts per unit time when downloaded for processing in the ActiLife 6 software. Participants will be asked to wear the accelerometer on their right side or least effected side in the case of significant asymmetry at the hip for 7 days at each assessment point. They will be instructed to wear the accelerometer during waking hours and remove it for swimming and bathing. They will be asked to complete a diary indicating the times that they wore the accelerometer. Data will be collected in 15 s epochs. Accelerometer counts from the vertical axis only will be used for data processing in line with the method used to derive a cut-point to classify moderate-to-vigorous physical activity in adults with MS.[39] Time spent in moderate-to-vigorous physical activity will be calculated using the cut-point of 1980 counts per minute derived in a group of adults with mild to moderate disability.[39] Mean counts per minute will be calculated to provide an indication of total physical activity.[40] The ActiGraph accelerometer has previously demonstrated excellent reliability for assessing both total activity counts and time in moderate-to-vigorous activity among among people with MS.[41] Average daily step-count will be calculated from raw activity data collected with the ActiGraph wGT3X-BT accelerometer. The ActiGraph accelerometer is a valid method of measuring step-count at all walking speeds in adults with MS.[42]

Objectively measured sedentary behaviour

Sedentary behaviour will be measured over 7 days using the activPAL3μ activity monitor. The activPAL3μ is a small, lightweight device that is worn on the anterior aspect of the person's thigh. It incorporates accelerometry and inclinometry data to provide information on the volume of time people spend in sedentary, upright and ambulatory activities. Participants will be asked to wear the activPAL3μ on their right thigh or least effected side. Data will be downloaded and processed using activPAL software to provide time in sedentary positions. The activPAL was 100% accurate for identifying time in sedentary positions versus time in an upright position in adults with mobility limitations.[43]

Self-reported physical activity and sitting

Self-reported time spent in moderate and vigorous activity, walking and sitting will be assessed using the International Physical Activity Questionnaire (IPAQ) short-form. The IPAQ short-form asks participants to recall the amount of time they spent in moderate activity, vigorous activity, walking and sitting in the past 7 days. The IPAQ short-form demonstrated acceptable validity and reliability in adults without MS.[44] It has also been successfully used to investigate the change in sedentary behaviour among people with MS following a behaviour change intervention.[45]

Walking capacity

Walking capability will be assessed using the 12-item MS Walking Scale (MSWS-12). The MSWS-12 is a self-report measure of the impact of MS on a person's walking capability over the past 2 weeks.[46] Individuals are asked to rate the impact of MS on 12 items relating to mobility on a scale of 1 to 5 (not at all to extremely) resulting in a total score out of 60, which is converted to a percentage. The MSWS-12 captures different aspects of walking capability including balance, use of support, speed, distance and automaticity. The MSWS-12 has demonstrated excellent validity and test–retest reliability, and high internal consistency among people with MS across a range of disability severities.[46 47] A higher score on the MSWS-12 indicates poorer walking capability.

Fatigue

Fatigue will be assessed using the Modified Fatigue Impact Scale (MFIS). The MFIS assesses the impact of fatigue on a person's activities. Individuals are asked to rate how often fatigue affected them in the past 4 weeks on 21 items. The items can be aggregated into three subscales (physical, cognitive and psychosocial). The MFIS demonstrated high internal consistency, excellent test–retest reliability and good construct validity among people with MS.[48 49] The total MFIS score can range from 0 to 84 with a higher score indicating a greater impact of fatigue on a person's activities.

Self-efficacy

Self-efficacy will be assessed using the Multiple Sclerosis Self-Efficacy Scale (MSSE). The MSSE assesses an individual's confidence in their ability to perform behaviours associated with engaging in activities of daily living and managing disease symptoms, reactions and impact on activities of daily living. Individuals rate their confidence for each item on a scale of 10 to 100 (very uncertain to very certain).[50] The MSSE demonstrates high internal consistency, good test–retest reliability and good construct validity.[50] A higher score on the MSSE indicates higher self-efficacy.

Participation

Participation will be assessed using the Impact on Participation and Autonomy Questionnaire (IPA). The IPA is a valid and reliable measure of participation and autonomy among adults with disability, including people with MS.[51 52] The IPA contains 32 items, which load on to five domains (autonomy indoors, family role, autonomy outdoors, social life and relationships, work and education). Each item is scored on a scale of 0 to 4 with higher scores representing poorer participation and autonomy. At least 75% of the domain needs to be completed in order to calculate a median score for each domain.

Quality of life

Quality of life will be assessed using the 5 level version of the EQ-5D (EQ-5D-5L). The EQ-5D-5L describes and values health defined in terms of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five response categories ranging from no problems to extreme problems. Participants are also asked to rate their overall health on the day of the interview on a visual analogue scale with values ranging from 0 to 100 (EQ-VAS). The EQ-5D-5L displayed good discriminatory capacity among people with MS.[53]

Health service use

Health service use will be assessed using a modified version of the Client Service Receipt Inventory (CSRI). The CSRI collects retrospective information on service utilisation, service-related issues and income.[54] The CSRI has been successfully used to estimate service use among adults with MS.[55]

Economic evaluation

The feasibility of conducting an economic evaluation as part of a phase 3 trial of the clinical and cost-effectiveness of the intervention will be determined by collecting data on quality of life and resource use. Specifically, the practicality of collecting data on quality of life and resource use, the quality of data and quantity of missing data will be recorded. Resource use data will include (a) training of physiotherapists, (b) sessions (eg, duration and frequency) provided by physiotherapists and (c) provision of handbooks and pedometers. Out-of-pocket expenses related to participation in physical activity (eg, equipment costs) and travel to and from the intervention sessions will also be collected as participation in physical activity interventions could increase the private costs of physical activity and impact on cost-effectiveness.[56 57] Data will be collected through key informant interviews (participants and physiotherapists), review of trial records, adapted client service receipt inventory and participants' questionnaires at baseline, 3 months and 9 months.

In a definitive trial, the cost-effectiveness analysis (from baseline to 9 months post-randomisation) of the intervention against usual care will take NHS, personal social services and participants' perspective.[58] Unit costs will be taken from the NHS reference costs (eg, DH 2015/16), standard unit costs (eg, PSSRU 2016) and published literature. The main outcome of the economic analysis will be an incremental cost per quality-adjusted life-year, based on EQ-5D-5L.

Process evaluation

A parallel process evaluation will be conducted alongside the randomised controlled trial in order to determine the feasibility and acceptability of the intervention.

The feasibility of delivering the intervention will be assessed through multiple mechanisms following the guidelines for fidelity in complex rehabilitation interventions.[59] Specifically, the feasibility of training physiotherapists to conduct the trial and perceived adequacy of training will be assessed by recording attendance at the training and gathering subjective data at the end of the study through semistructured interviews with all participating physiotherapists. Informed consent will be obtained from physiotherapists prior to conducting the interview.

The feasibility and acceptability of the intervention for people with MS will be assessed by evaluating fidelity to programme receipt through the assessment of attendance at sessions, evaluating fidelity to programme task through the assessment of rates of completion of the handbook and exploring the experience of participation through semistructured interviews with 15 participants from the intervention group and 10 participants from the control group at the end of the study period. Sampling of participants to participate in interviews will involve key criteria such as gender, age, type of MS and level of baseline walking ability to ascertain a range of views.

Fidelity

Fidelity to the programme will be assessed through fidelity to intervention content and delivery skills. The content parallels the main skills identified in the intervention itself. Skills relate to delivery skills of the therapists including empathic listening, partnership working and motivational interviewing, all part of the training delivered to the therapists. A fidelity tool has been developed by an expert panel consisting of experienced cognitive-behavioural trainers involved in intervention development. Prior to its use in the trial, the tool will be piloted by three raters (two members of the research team and a cognitive-behavioural trainer) independently rating four different recorded sessions. All therapists delivering the intervention will have each of the four sessions assessed with the specific sessions selected at random, ensuring a minimum of 10% of each therapists' sessions are assessed. Assessment will occur through audio-recordings of the sessions and no feedback will be given to the therapists .

Fidelity to intervention content will be achieved if 70% of appropriate content is covered either completely or partially within a session. This acknowledges that for some individuals, certain content may not be appropriate and

can therefore be removed from the assessment. Fidelity to delivery skills will be achieved if the therapist is scored at an adequate level or above in each of the designated skill categories.

Interviews

Interviews will be conducted in person or over the phone. In-person interviews will be held in a private room at the Berkshire MS Therapy Centre or in the participant's home. The interviews will be conducted by an experienced qualitative researcher following topic guides developed from relevant literature and the specific aims of the process evaluation.

Safety

The safety of the intervention will be determined by assessing pain and fatigue at baseline, 3 months and 9 months, and recording the incidence of adverse events (AEs), including falls and relapses from the time of baseline measures until the end of the trial for each participant. Pain will be assessed using the section relating to pain on the EQ-5D-5L. Fatigue will be assessed using the MFIS. At each assessment point, participants will be asked if they experienced a fall, a relapse or any AE since the last contact. Although this method of assessing falls relies on the recall ability of the participant, it accurately detects injurious falls in community-dwelling older adults.[60] Participants will also be advised to contact the research team if they experience an AE during the trial. An adverse event is considered serious if it results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation and results in persistent or significant disability or incapacity. All serious adverse events (SAEs) will be reported to the trial Sponsor and Research Ethics Committee within 48 hours of a member of the research team or the physiotherapy team at the MS Therapy Centre first becoming aware of the SAE. The Trial Steering Committee (TSC) will be notified of all AEs. Participants who experience a SAE will be withdrawn from the study.

A summary of all data collected and when these are collected is provided in table 1.

Data management

Personal data collected during the trial will be handled and stored in accordance with the 1998 Data Protection Act. All data will be stored securely to maintain confidentiality. To preserve the participant's anonymity, only their allocated trial number and initials will be recorded on any trial documentation except for the consent form and contact details. Documents with identifiable information will be stored separately to other study documents. Pseudonyms will be used when reporting findings from qualitative research. The use of the data from the study will be controlled by the Chief Investigator. All data and documentation related to the trial will be stored in accordance with applicable regulatory requirements and access to data will be restricted to authorised trial personnel.

Pseudonymised quantitative data will be made available in a public repository once the data have obtained validation through publication.

Service user involvement

People with MS have been involved in the development of the protocol and will be included in all stages of the study. The need for the study was highlighted through interviews with people with MS. A reference group of two people with MS and four experienced neurological physiotherapists was developed to advise the research team. The reference group contributed to the development of the intervention and assisted with piloting the intervention and creating materials for training physiotherapists. The reference group also reviewed the documentation developed for the trial, including participant information sheets, participant invite letters and questionnaires. A member of the reference group also assisted with piloting the assessment. The reference group will continue to advise the research team on recruitment, retention and dissemination of the results of the trial throughout the project.

Data analysis
Qualitative data

In order to determine the feasibility and acceptability of the intervention among both people with MS and physiotherapists, interviews from both groups (physiotherapists and people with MS) will be analysed independently through framework analysis.[61] This method of analysis provides a clear audit trail of the analytical process, which enhances transparency.[62] The technique involves five iterative stages of analysis: familiarisation, identifying thematic framework, labelling, charting, and mapping and interpretation,[62] following which significant themes can be presented. Further steps to enhance rigour in this process including peer debriefing will be put in place and reported. NVIVO will be used for interview data management.

Quantitative data

To determine fidelity to the intervention, descriptive statistics will be used to describe the number of sessions received by participants, the time between each session and the duration of each session. The percentage of participants who receive at least 70% of appropriate content, either completely or partially, within a session will be reported.

To determine acceptability of the intervention, descriptive statistics will be used to report attendance at physical activity consultations, completion rate of the handbook and completion of the physical activity diary.

To determine safety of the intervention, descriptive statistics will be used to report fatigue and pain at baseline, 3 months and 9 months, respectively. Linear mixed models will be used to assess differences in changes in pain and fatigue during follow-up between groups. Descriptive statistics will be used to report the number of adverse events,

Table 1 Data collected throughout the participant's involvement in the trial

	Baseline	During intervention	12 weeks	9 months	Other
Baseline information					
Socioeconomic information	✓				
MS-specific information	✓				
MS Impact Scale	✓				
Self-reported history of chronic disease and medication use	✓				
Self-reported history of lifestyle factors	✓				
Anthropometric measures	✓				
Outcomes (measures)					
Daily moderate-to-vigorous physical activity (ActiGraph GT3x-BT)	✓		✓	✓	
Total daily physical activity (ActiGraph GT3x-BT)	✓		✓	✓	
Daily step count (ActiGraph GT3x-BT)	✓		✓	✓	
Time in sedentary, upright and ambulatory activities (activPAL3µ)	✓		✓	✓	
Self-reported daily time in moderate-to-vigorous activity and walking (IPAQ short-form)	✓		✓	✓	
Self-reported daily time in sitting (IPAQ short-form)	✓		✓	✓	
Walking capability (12-item MS Walking Scale)	✓		✓	✓	
Fatigue (Modified Fatigue Impact Scale)	✓		✓	✓	
Self-efficacy (Multiple Sclerosis Self-Efficacy Scale)	✓		✓	✓	
Participation (Impact on Participation and Autonomy Questionnaire)	✓		✓	✓	
Quality of life (EQ-5D-5L)	✓		✓	✓	
Health service use (adapted Client Service Receipt Inventory)	✓		✓	✓	
Resource use		✓			
Out-of-pocket expenses related to participation in physical activity	✓		✓	✓	
Out-of-pocket expenses related to travel to and from the intervention sessions*			✓		
Process evaluation					
Physiotherapist attendance at training*					✓
Attendance at physical activity sessions		✓			
Rate of completion of handbook†		✓			
Fidelity to the intervention†		✓			
Incidence of adverse events (including falls and relapses)‡	✓		✓	✓	
Semistructured interviews with participants			✓		
Semistructured interviews with physiotherapists§					✓

*Data collected prior to start of intervention delivery.
†Assessed among participants in intervention group only.
‡Data collected throughout a participant's involvement in the trial (9 months) but participants only specifically questioned at these time points.
§Data collected after physiotherapists have completed delivery of intervention.
IPAQ, International Physical Activity Questionnaire; MS, multiple sclerosis.

including falls and relapses, in each group for the duration of the trial. A negative binomial model, which accounts for overdispersion in the outcome, will be used to investigate if the number of adverse events differ between groups. Participants with data recorded at at least one follow-up assessment will be included in the analysis. The type and severity of the adverse event will be described.

As this is a feasibility study, the efficacy of the intervention is not of primary interest. However, exploratory analysis will be conducted to examine how outcomes differ between the intervention and control group over time. A detailed statistical analysis plan will be made prior to the analysis. It is anticipated that linear mixed models, to account for within-participant correlation, will be used to

determine the difference in objectively measured moderate-to-vigorous activity, step-count, sedentary behaviour, walking capability, fatigue, self-efficacy and participation between groups at 3 months and 9 months. The baseline score for the relevant outcome will be included in the model as a covariate in order to improve precision of the effect estimate.

The primary analysis will be an intention-to-treat analysis. A secondary per-protocol analysis will be conducted using participants who attended at least 75% of the sessions and completed follow-up to 9 months. The amount and mechanism of missing data will be explored. If data are only missing in the outcome and the missingness mechanism is assumed to be MAR (missing at random), linear mixed models provide an unbiased and efficient estimate of the treatment effect.[63] Sensitivity analyses will be conducted to determine if the assumption of MAR is reasonable.[64]

All analyses will be conducted using Stata (StataCorp).

The following criteria are proposed to determine if the intervention warrants further investigation in a larger phase 3 trial: there is no evidence of a greater number of adverse events or a greater negative change in pain and fatigue in the intervention group in comparison to the control group; there is no indication of a dominant negative theme from interviews with participants and physiotherapists; and the attrition rate is less than 20%. In addition, if these criteria are met, data collected during interviews will be used to adapt the intervention in order to improve its acceptability for use in a definitive trial.

Timeline

The trial is funded for a period of 24 months and commenced in January 2017. This includes time to develop the intervention. Recruitment commenced in May 2017 and is projected to be completed by January 2018. The final follow-up assessment is projected to be completed by September 2018 with data analysis and report writing being conducted from month 21 onwards.

Ethics

The study is sponsored by Brunel University London. Any protocol modifications will be communicated to the Brunel University London Ethics Committee and consent will be reobtained from participants if the Research Ethics Committee deems it necessary. The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Medical Research Council Good Clinical Practice (GCP) guidelines. All researchers working on the trial will receive training in GCP guidelines. It will also comply with all applicable Brunel University Research integrity guidance.

Consent will be obtained from the manager of the Berkshire MS Therapy Centre to conduct the research at the centre. All participants will freely give their informed consent to participate in the trial. Additional informed consent will be obtained from individuals sampled to participate in semistructured interviews.

Monitoring

Due to the low risk nature of the intervention, we do not anticipate any potential harms and therefore there will be no Data Monitoring Committee, interim analyses or stopping rules.

Administrative structures

The trial will be run by the trial management group, which consists of the Chief Investigator, co-Chief Investigator, co-Investigators and two Research Fellows. The conduct of the trial will be supervised by a TSC.

Dissemination

A detailed dissemination plan will be developed in the early phases of the trial in collaboration with the TSC. The results will be disseminated to all participants and participating physiotherapists through study summary documents and presentations at the MS Therapy Centre. The results of the trial will also be published in a peer-reviewed journal and presented at National and International MS conferences. The trial will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement. Authorship will be based on the International Committee of Medical Journal Editors criteria.

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