TRIAL PROTOCOL

Balance Right in Multiple Sclerosis (BRiMS)

A guided self-management programme to reduce falls and improve quality of life, balance and mobility in people with secondary progressive Multiple Sclerosis: a feasibility randomised controlled trial

Version 4.0
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Chief Investigator:
Dr Jenny Freeman
Faculty of Health and Human Science
Peninsula Allied Health Centre
Derriford Road
Plymouth
PL6 8BH

Trial Sponsor:
Plymouth Hospitals NHS Trust
Research Office
Level 2, MSCP
Bircham Park Offices
1 Roscoff Rise
Derriford
Plymouth
PL6 8FP

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted, and that the Chief Investigator (JF) agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the department of health research governance regulations, GCP guidelines and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Plymouth University.

We also confirm that we will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay, that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Date:

Name (please print):

Chief Investigator:

Signature: Date:

Name (please print):

Statistician:

Signature: Date:

Name (please print):

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIAL SUPPORT
National Institute for Health Research Central Commissioning Facility Grange House, 15 Church Street Twickenham TW1 3NL Tel: 0208843 8000 Fax: 020 8843 8001 info@nihr-ccf.org.uk Web: www.ccf.nihr.ac.uk	The NIHR provides full financial support for all research aspects of this grant
Pauline McGlone Deputy Chief Operating Officer NIHR Clinical Research Network: South West The Knowledge Spa Royal Cornwall Hospitals NHS Trust Truro, Cornwall, TR1 3HD Tel: 01872256430; Mobile: 07766705508 pauline.mcglone@nhs.net	The Clinical Research Network (CRN) negotiates excess treatment costs for all participating sites with Clinical Commissioning Groups. The CRN also provides support costs for identification of patients, consent and recruitment.

KEY TRIAL CONTACTS

Chief Investigator	Dr Jenny Freeman Associate Professor (Reader) in Physiotherapy and Rehabilitation Faculty of Health and Human Science Peninsula Allied Health Centre Derriford Rd, Derriford Plymouth PL6 8BH jenny.freeman@plymouth.ac.uk Tel: 01752 588835
Trial Co-ordinator	Dr Hilary Gunn Lecturer in Physiotherapy Faculty of Health and Human Science Peninsula Allied Health Centre Derriford Rd, Derriford Plymouth PL6 8BH hilary.gunn100@plymouth.ac.uk Tel: 01752 588825
Sponsor	Research and Development Manager Plymouth Hospitals NHS Trust Research Office Level 2, MSCP Bircham Park Offices 1 Roscoff Rise Plymouth PL6 8FP Tel: 01752 431776 Fax: 01752 430919

Finances	Mrs Corinna Mossop Plymouth Hospitals NHS Trust Research Office Level 2, MSCP Bircham Park Offices 1 Roscoff Rise Plymouth PL6 FP Tel: 01752 431046 corinna.mossop@nhs.net
Clinical Trials Unit	Peninsula Clinical Trials Unit at Plymouth University (PenCTU) Room N16 ITTC Building Plymouth Science Park Plymouth PL6 8BX CTU Registration Number: 31 www.plymouth.ac.uk/penctu penctu@plymouth.ac.uk Tel: 01752 439831
Key Protocol Contributors	Chief investigator, CTU, trial co-ordinator, trial statistician and: - Prof Lorna Paul Professor of Allied Health Science Glasgow Caledonian University Cowcaddens Road, Glasgow, G4 0BA Tel : 0141 331 8108 Lorna.Paul@gcu.ac.uk Prof Jackie Andrade Professor of Psychology B232 Portland Square Building Drake Circus Campus Plymouth PL4 8AA Tel: 01752 584807 Jackie.andrade@plymouth.ac.uk Mr Andy Barton Associate Professor Peninsula Schools of Medicine & Dentistry ITTC Building Plymouth Science Park Plymouth, PL6 8BX Tel: 01752 439098 andy.barton@plymouth.ac.uk Prof Jonathan Marsden Professor of Rehabilitation Faculty of Health and Human Science Peninsula Allied Health Centre Derriford Rd, Derriford Plymouth PL6 8BH Tel: 01752 587590 jonathan.marsden@plymouth.ac.uk

	Prof Colin Green Professor of Health Economics University of Exeter Health Economics Group, University of Exeter Medical School South Cloisters, St Lukes Campus Exeter, Devon, EX1 2LU Tel: 01392 722283 c.green@exeter.ac.uk Ms Linda Renfrew Consultant Physiotherapist in MS, NHS Ayrshire and Arran Douglas Grant Rehabilitation Unit Ayrshire Central Hospital Kilwinning Rd Irvine KA12 8SS Tel: 01294 323057 linda.renfrew@aapct.scot.nhs.uk Mr Ben Marshall (Lay member) 67 Charlestown Rd St Austell Cornwall PL25 3NL Tel: 01726 61532 benmarshall0@gmail.com Prof John Zajicek Professor of Medicine/ Clinical Neurologist University of St Andrews School of Medicine, Medical and Biological Sciences Building North Haugh St Andrews, Scotland, KY169TF Tel: 01334 463560 jz45@st-andrews.ac.uk Prof Paul Ewings Director, NIHR Research Design Service (South West) Musgrove Park Hospital Taunton TA1 5DA Tel : 01823 342796 paul.ewings@tst.nhs.uk
Statistician	Mrs Siobhan Creanor University of Plymouth Centre for Health Statistics, Peninsula Schools of Medicine & Dentistry Plymouth Science Park 1 Davy Rd Derriford, Plymouth, PL6 8BX Tel: 01752 764434 siobhan.creanor@plymouth.ac.uk

TRIAL SUMMARY

Trial Title	Balance Right in Multiple Sclerosis (BRiMS): A guided self-management programme to reduce falls and improve quality of life, balance and mobility in people with secondary progressive Multiple Sclerosis: a feasibility randomised controlled trial
Acronym	BRiMS
Short Title	Balance Right in Multiple Sclerosis
Chief Investigator	Dr Jenny Freeman
Clinical Phase	Feasibility Testing
Trial Design	Pragmatic multi-centre feasibility randomised controlled trial with blinded assessment
Trial Aim	To provide the necessary data to inform the conduct and finalise the design of a definitive trial. The eventual aim is to assess the clinical and cost effectiveness of BRiMS in an appropriately powered, multi-centre, assessor-blinded RCT. However there are a number of uncertainties about the optimal parameters for this future trial; this trial will test the feasibility of such a trial.
Trial Objectives	i. utility and acceptability of the trial procedures ii. suitability of eligibility criteria iii. estimate numbers of eligible participants from the target population iv. willingness of clinicians to recruit patients v. willingness of patients to be randomised vi. recruitment and retention rates vii. optimising delivery of BRiMS programme viii. intervention fidelity and application between sites ix. acceptability of and adherence to the 13 week BRiMS programme x. completion and performance of proposed outcome measures xi. baseline factors most strongly associated with outcomes xii. data to guide sample size calculation required for a fully powered RCT xiii. cost of delivery xiv. development of a framework for cost effectiveness analyses (for future RCT) xv. data to inform the total resource required for a full trial
Trial Participants	Inclusion criteria: • Confirmed diagnosis of multiple sclerosis as has been determined by a neurologist; and in the secondary progressive phase as confirmed by an MS Specialist clinician • Aged 18 years or older. • Willing and able to understand/comply with all trial activities • Expanded Disability Status Scale (EDSS) ≥ 4.0 ≤ 7.0 • Self-report two or more falls in the past six months • Willing and able to travel to and participate in BRiMS group sessions in local sites and to commit to undertaking their individualised home-based programme • Access to a computer or tablet and to the internet. Exclusion Criteria: • Patient report of relapse or having received steroid treatment within the last month • Any recent changes in disease modifying therapies. More specifically patients will be excluded if: - They have ever had previous treatment with Alemtuzemab (Lemtrada / Campath); or: - Ceased Nataluzimab (Tysabri) in the last six months; or - Within three months of ceasing any other MS disease modifying drug • Participated in a falls management programme (e.g. for older people) within the past six months • Co-morbidities which may influence the ability of individuals to participate safely in the programme or likely to impact on the trial (e.g. uncontrolled epilepsy). • Participation in a concurrent interventional study

Sample Size	60	
Treatment Duration	13 weeks	
Follow up Duration	14weeks(+/- 1 week) after the end of the intervention period	
Trial Duration	20 months	
Outcome set	Outcomes	Objective Number(s)
Primary Outcomes	MS Walking Scale-12 vs2.0 EuroQoL EQ5D-5L MS Impact Scale-29 vs2.0	i, x, xi
Secondary Outcomes	Falls frequency and injury rates Physical Activity (accelerometry) - activPAL 2 Minute Walk Test Mini-Balance Evaluation Systems Test Functional Reach (forwards and lateral) Falls Efficacy Scale (International) Community Participation Indicators	i, x, xi
Measures of adherence	Attendance at face-to-face sessions Home exercise diary completion Web-based programme log-in sessions	vi-ix
Economic Evaluation	Economic Evaluation Intervention Report Form (Contact sheet) Participant Resource Use Questionnaire	xiii- xiv
Adverse Events	Daily participant diary and therapist records	
Process Evaluation	Intervention description and standardisation Fidelity testing	viii
Qualitative Evaluation	Qualitative telephone interviews with MS participants (individual) and Treating Therapists (focus group)	vii, ix

KEY WORDS:

Secondary Progressive Multiple Sclerosis; Exercise; Self-management; Mobility; Accidental falls; Balance; Cost-effectiveness; Quality of life

ROLE OF TRIAL SPONSOR AND FUNDER

The role of the Sponsor is to assume overall responsibility for the initiation and management of the trial in terms of governance issues and in accordance with ICH GCP.

The role of the Funder is to provide financial support for the research costs of this trial.

Neither the Sponsor nor the Funder will have a final decision over the trial design, conduct, data analyses and interpretation, manuscript writing, or dissemination of results.

ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES

There are three committees involved in the setup and management of this trial: The Trial Management Group, the Trial Steering Committee and the Data Monitoring Committee.

Trial Management Group (TMG)

Make up: Most members of the TMG were involved in the development of the grant application. It includes representation from the CTU (trial management), the sponsor and a person with MS.
Frequency of meetings: The TMG will meet approximately monthly (via face-to-face, webinar or telephone conference) over the course of the trial.
Responsibilities: Development of the protocol and other essential documentation, monitor progress, troubleshoot problems, report to TSC, funder, REC. The responsibility of this group is to ensure all practical details of the trial are progressing well and working well, and everyone within the trial understands them. This will include, for instance, monitoring adverse events, recruitment and attrition rates, the project timeline and finances. It will also include responsibility for the release of the trial results and publications.
Degree of independence from Sponsor and Investigators: the sponsor is represented on this group
Minutes of meetings will be sent to all members and the sponsor, and retained in the trial master file.

Trial Steering Committee (TSC)

Make up: the TSC comprises a group of experienced trialists with majority independent representation (chair (independent), external statistician (independent), CI, and a lay member (independent).
Frequency of meetings: the TSC will meet before the start of the trial and subsequently at least annually during the course of the trial. In addition, the TSC will receive a quarterly report of adverse events, and a telephone conference/additional face-to-face meeting will be instigated by the chair or the CI should any issues need to be discussed.
Responsibilities: The responsibility for calling and organising the TSC meetings lies with the CTU in association with the Chair.
Degree of independence from Sponsor and Investigators: Confirmation that independent members of the TSC are unconnected to either the trial sponsor or investigators will be made through the completion of Conflict of Interests documents by all TSC members.
Minutes of meetings will be sent to all members, the sponsor, and the funder and be retained in the trial master file.

Data Monitoring Committee (DMC)

Make up: The group comprises an independent statistician and two experienced methodologists, one of whom will be the chair.
Frequency of meetings: It is anticipated that the members will meet (via face-to-face, webinar or telephone conference) once to agree terms of reference and at a schedule to be agreed with the TSC
Responsibilities: The DMC will maintain the interests of trial participants, with particular reference to safety.
Degree of independence from Sponsor and Investigators: This committee will be independent of the study organisers and the TSC. The TSC and the DMC will meet independently of each other.

ORGANISATION OF THE TRIAL

There are two regions involved in this trial: South West England and Ayrshire

- The South West based research team will comprise: Dr J Freeman (CI), Dr H Gunn (BRiMS Trial Co-ordinator and Research Therapist for the region), C Green (Health Economist), Prof J Marsden, A Barton, and S Creanor (Trial Statistician).
- The Ayrshire based research team will comprise: Dr L Paul (Regional Co-ordinator), L Renfrew

Trial Management will be undertaken by the following individuals:

BRiMS Trial Co-ordinator: will lead the implementation of the trial, including recruitment and co-ordination of sites in the South West, awareness raising for potential participants, therapist training and monitoring implementation of the BRiMS intervention.

Peninsula Clinical Trials Unit (PenCTU): provides document design and control; day to day trial management; REC and HRA submissions; randomisation; trial database build; data management; safety monitoring; periodic reporting and more.

Research Therapists: There are two Research Therapists for this trial- one for the Ayrshire region and the second for the South West. They will undertake screening (in collaboration with the CRN (South West), consent and blinded assessments.

Treating therapists: There will be one Treating Therapist for each site within the trial (total of four). They will deliver the BRiMS programme.

ROLES AND RESPONSIBILITIES OF INDIVIDUALS

Protocol Contributors

Dr Jenny Freeman (Associate Professor Physiotherapy and Rehabilitation) is the Chief Investigator and has overall responsibility for the implementation of this trial. She has lead responsibility for writing the ethics and HRA submissions, developing training materials, recruitment, preparing periodic reports and will be supported in this by the BRiMS Trial Co-ordinator and CTU staff. Also responsible for analyses, the trial website, writing articles and reports. **TMG Chair and TSC member*.

Dr Hilary Gunn (Lecturer in Physiotherapy) is the BRiMS Trial Co-ordinator and South West Research Therapist. She will work closely with the CTU; raise study awareness across the South West, consent patients; train staff on the BRiMS intervention; undertake the blinded assessments for the South West (SW) participants and lead the qualitative analysis and process evaluation. She will undertake the telephone interviews with the Ayrshire participants for the qualitative component of this trial. **TMG member.*

Professor Lorna Paul (Professor of Allied Health Science) will lead the co-ordination of BRiMS in Ayrshire, including leading on the telephone interviews with the SW participants for the qualitative component of this trial. **TMG member.*

Professor Jackie Andrade (Professor in Psychology) will help to refine the intervention manual, advise on the psychological elements of the trial, train staff on the BRiMS intervention and monitor treatment fidelity throughout the trial. **TMG member.*

Siobhan Creanor (Associate Professor in Health Statistics), trial statistician, will assist with development of the trial protocol, be responsible for all elements of the statistical analyses, including supervising a junior statistician. **TMG member and TSC observer*.

Professor Paul Ewings (RDS South West Director) will provide expert methodological / statistical advice. **TMG member and TSC observer*

Professor Colin Green (Professor of Health Economics) will lead and supervise the junior statistician on all aspects of the economic component of the trial. He will also lead in the development of data collection forms for the economic aspects of the trial **TMG member.*

Mr Ben Marshall, who has progressive MS, has been actively involved in providing PPI input into the development of the BRiMS programme. He will provide input into the qualitative analysis, including developing the interview schedule and interpreting the results. **TMG member.*

Jane Vickery (Pen CTU Senior Trial Manager) will lead the CTU trial and data management teams. **TMG member.*

Andy Barton (RDS Advisor) provides methodological and management advice for this and the anticipated main trial. **TMG member.*

Professor Jonathan Marsden (Professor of Rehabilitation) will assist with interpretation/write-up.

Linda Renfrew (Consultant Physiotherapist in MS in NHS Ayrshire and Arran) will participate in the fidelity testing of the SW groups and will be Principal Investigator for Ayrshire. **TMG member.*

Professor John Zajicek (Professor of Medicine / Clinical Neurologist) will provide mentorship for the TMG and comment on interpretation/ write-up

LIST OF CONTENTS

ABBREVIATIONS

2MWT	Two Minute Walk Test
AE	Adverse Event
CI	Chief Investigator
CPI	Community Participation Indicators
CRF	Case Report Form
CRN	Clinical Research Network
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
FESi	Falls Efficacy Scale (International)
FFRT/ LFRT	Functional Reach Test forwards / lateral
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
IDEAL	Idea, Development, Exploration. Assessment, Long-term Follow-up
IMSFPRN	International MS Falls Prevention Research Network
ISRCTN	International Standard Randomised Controlled Trials Number
MiniBEST	Mini Balance Evaluation Systems Test
MRC	Medical Research Council
MS	Multiple Sclerosis
MSIS-29vs2.00	MS Impact Scale (29 item) version 2
MSWS-12vs2.00	MS Walking Scale (12 item) version 2
NHS	National Health Service
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QoL	Quality of Life
QALY	Quality of Life Adjusted Years
R&D	Research and Development Department
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSI	Site Specific Information
TMG	Trial Management Group
TSC	Trial Steering Committee

RECRUITMENT PATHWAY

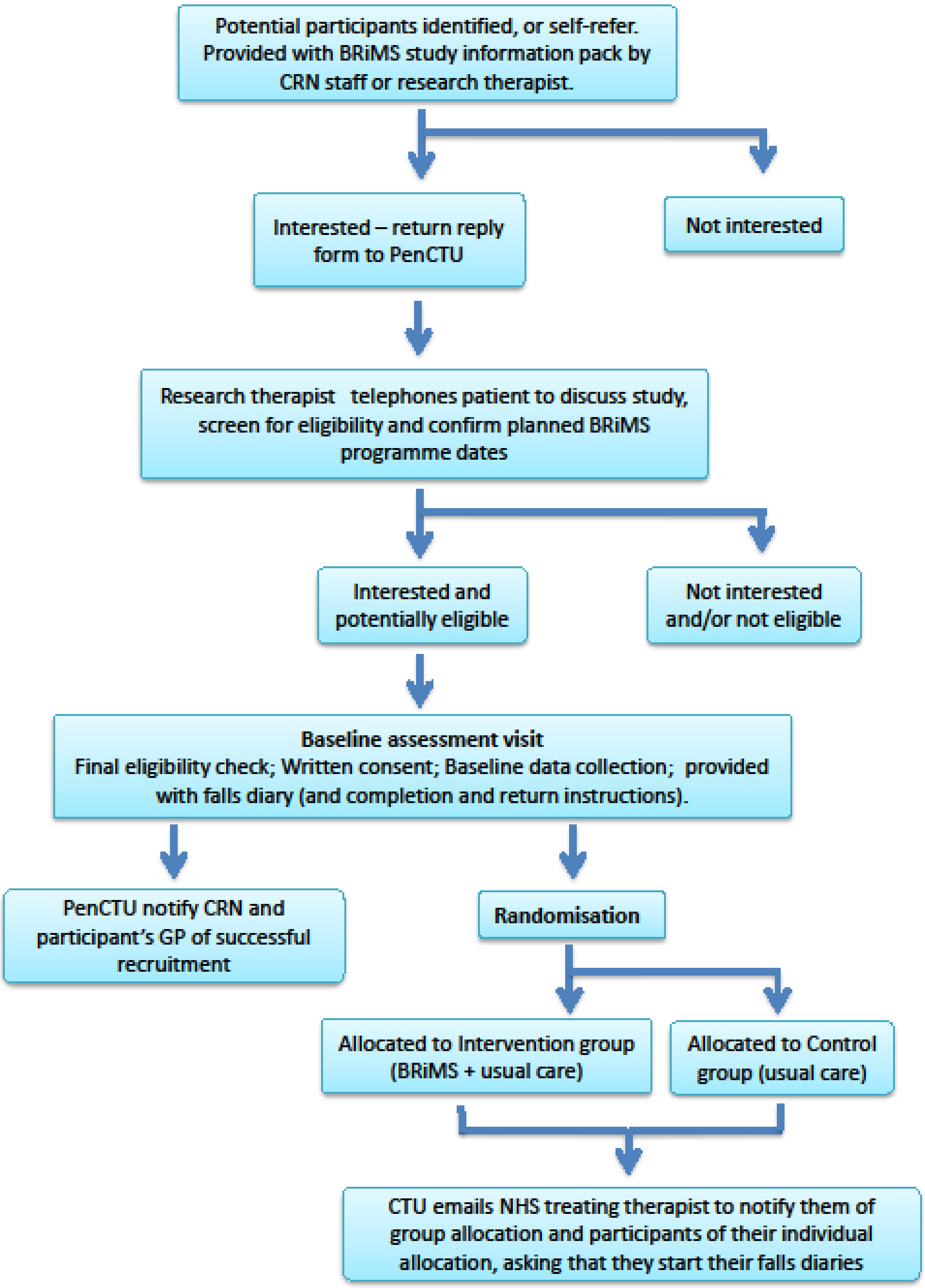

Figure 1: Recruitment Pathway

PARTICIPANT PATHWAY

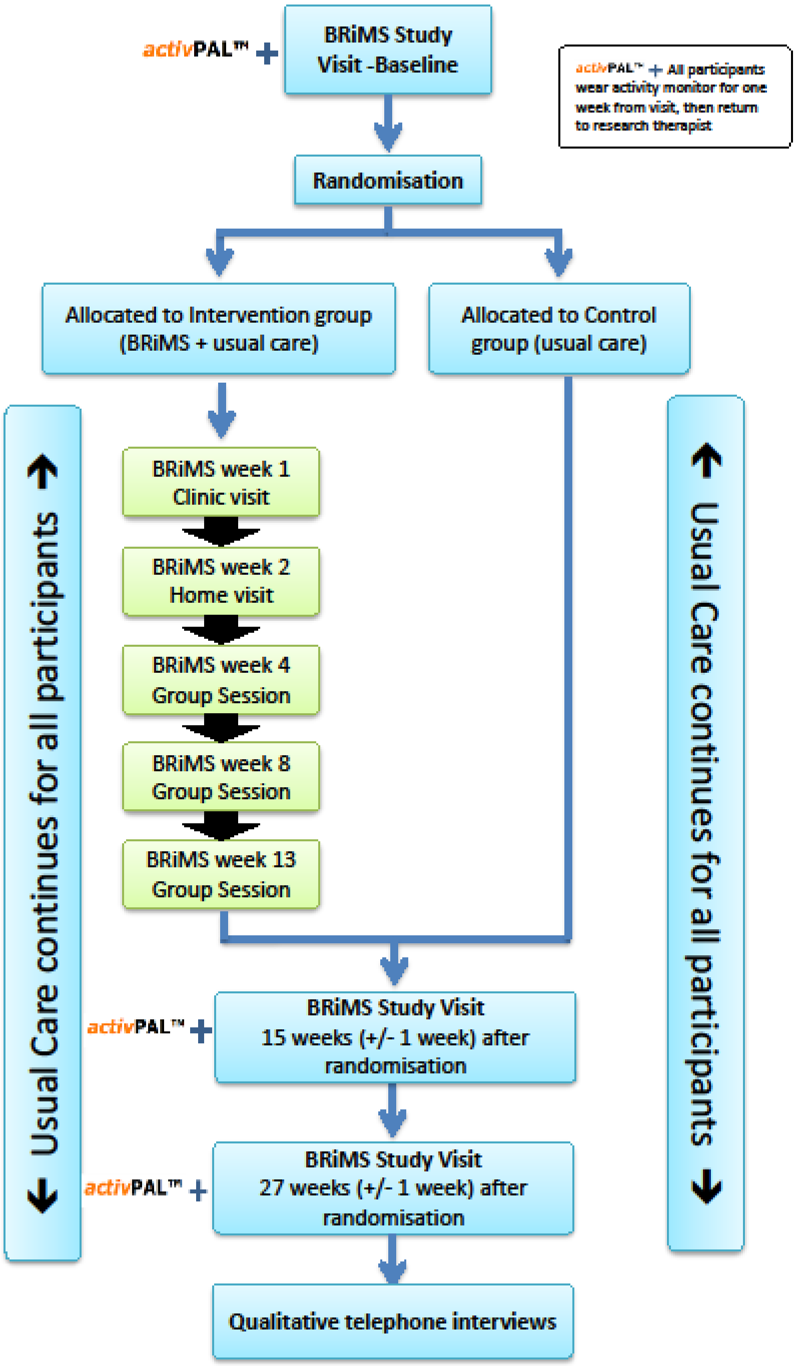

Figure 2: Participant pathway

1 BACKGROUND AND RATIONALE

1.1 Background

Multiple Sclerosis (MS) affects approximately 100,000 people in the UK[1], with an estimated cost of £1.4 billion/annum to the NHS and society[2]. Although most people start with a relapsing-remitting (RR) disease course, approximately two-thirds move to a progressive phase within eight years[3]. At this point, medical interventions are limited and progression is inevitable[4]. It is people who have entered the secondary progressive (SPMS) phase that are the target group for this trial. People in this phase, the majority of whom have limited mobility, are often excluded from clinical trials, which tend to focus on the RR stage[5].

Surveys of people with MS (pwMS) consistently rank mobility as their highest priority[6] and most important yet most challenging daily function. Eighty-five percent of pwMS report gait disturbance as their main problem[7]. Within approximately 15 years of diagnosis, 50% of people are unable to walk unaided, and over time 25% are dependent on a wheelchair[8]. Impaired balance and falls are common issues for people with SPMS and are an important contributory factor to mobility impairment[910]. The evidence shows that approximately 70% of pwMS fall regularly[11,12], at a rate of >26 falls/person/year in SPMS[13]. More than 10% of these falls lead to injuries[14] and pwMS are three times more likely to sustain a fracture than the general population[15].

Falling and fear of falling have a profound impact on individuals, leading to activity curtailment, social isolation and a downward spiral of immobility, deconditioning and disability accumulation[16]. There are also substantial economic and social costs related to increasing immobility, impaired balance and falls in pwMS[17]. Costs of health and social care have been shown to increase steeply with increasing disease severity/immobility, underlining the importance of optimising safe mobility for as long as possible[18]. This is particularly relevant given recent evidence that pwMS are living longer, leading to a rising population living with the disease[19]. This has important implications for resource provision, as highlighted in a national audit of neurological services[20].

The importance of mobility and falls is emphasised by their consistent prominence in recent policy documents for long term neurological conditions[7]. Work suggests that falls may be an early marker of mobility deterioration associated with disease progression in SPMS[11,12]. Rehabilitation interventions which improve balance and physical activity and decrease the risk of falls may slow this deterioration, providing a persuasive argument to prioritise provision of effective physical management strategies. However, there is currently minimal evidence-based guidance to inform optimal mobility management and none to inform falls management in pwMS. This paucity of evidence is highlighted by NICE Guidelines which nominated the rehabilitation of mobility as one of the five key research recommendations[7]. While evidence is available for older people and other neurological conditions, research suggests that translating existing interventions to pwMS is likely to be ineffective[21,22]. Small, limited duration studies have evaluated single elements of MS balance and falls interventions, individually demonstrating short term improvements in mobility, balance or falls awareness[23–25], but these elements have not yet been implemented or evaluated collectively. Moreover, no studies have been confined to people with SPMS. This feasibility trial begins to address all of these issues.

1.2 The BRiMS programme

Healthcare policy prioritises the need to empower and support patients to self-manage[26]. ‘Balance Right in MS’ (BRiMS); an innovative evidence-based, user-focused, self-management exercise and education programme, is designed to improve safe mobility and reduce falls for pwMS. The programme’s underlying philosophy is based on the premise that interventions must promote lifestyle behavioural change, be community based and focus on prevention and self-care; an approach which is in line with the future direction of the NHS[27]. Recent evidence[11,28] highlights that those in the progressive phase of MS are a target population for BRiMS, based on the extent of mobility impairment and falls in these people.

The BRiMS programme is delivered as a 13 week therapy-led personalised education and exercise intervention, structured to maximise the development of self-efficacy and support participant engagement. BRiMS addresses modifiable fall risk factors such as poor balance and mobility and enables self-management by the use of individualised mobility, safety and falls risk management strategies.

BRiMS includes a strong focus on home-based activities, supported by online resources and three group sessions interspersed over the duration of the programme. The programme also includes two ‘one to one’ sessions to enable individualised assessment, goal planning and development of exercise plans. A home-based online work package overarches the programme, supporting both educational and exercise components and enabling participants to personalise the programme and apply the activities in their daily lives from the outset. Developing and supporting motivation is addressed throughout using new functional imagery training techniques[29] to supplement established motivational techniques. The delivery of the BRiMS programme is supported by a manual, however the programme is structured to enable the components to be tailored to meet the needs of individual participants within the parameters of the manual.

The BRiMS education component aims to improve exercise self-efficacy and the development of individualised falls prevention and management practices through the acquisition and application of relevant knowledge and skills[30]. It is delivered through a mix of home and group activities embedded throughout the course of the programme. It utilises group brainstorming, problem-solving and action planning[31]. It also applies the principles of cognitive behavioural therapy (CBT) to facilitate self-efficacy enhancement. In group sessions, BRiMS utilises peer modelling, vicarious learning, social persuasion, and guided mastery to boost self-efficacy[32] and encourages the setting and imagery of short-term exercise goals to boost desire to achieve them[33]. Images of failure are ‘rescripted’ in the same way that thoughts of failure can be changed in conventional CBT[34].

The BRiMS exercise component is designed to achieve a minimum of 120 minutes of individualised, progressive, gait, balance and functional training per week. The BRiMS exercise component has been designed to be predominantly home-based, with exercise planning and progression undertaken in partnership between the participant and the programme leader. The group sessions include exercise activities to encourage peer support and problem solving. Additionally, BRiMS integrates an online exercise prescription resource[35] to support and guide participants’ home-based practice (www.webbasedphysio.com). The platform contains over 100 different MS relevant exercises presented in video, audio and text format. The resource can be customised to the participant’s individual exercise prescription, and remotely amended during the programme to maintain an appropriate level of challenge. These include setting goals and planning exercise sessions, providing feedback and monitoring and offering MS specific information and advice, which are known to be effective in terms of promoting and maintaining adherence to exercise programmes.

1.3 The Trial

The development of BRiMS has been based on the MRC framework for the development and evaluation of complex interventions[36] and supplementary guidance identifying specific tasks to be undertaken in the development process[37]. It has been informed by input from a number of internationally recognised experts[38] and a programme of research to identify potentially modifiable risk factors for falls in pwMS[39,40], to evaluate potential management approaches[41] and to clarify the key operational issues which could impact on the successful engagement with BRiMS and implementation and sustainability within the NHS[42]. Having now optimally developed BRiMS, it is critical to assess the delivery of this programme and proposed evaluation methods prior to undertaking a definitive trial to assess its effectiveness and cost effectiveness.

Following MRC Guidelines[28] and IDEAL Framework principles[43], this feasibility trial will aid the planning of an anticipated multi-centre RCT which will compare BRiMS plus usual care with usual care alone in improving mobility and QoL and reducing falls in people with SPMS. This feasibility trial will provide the necessary data and operational experience to inform the conduct and finalise the design of a definitive trial so that it can be successfully delivered with confidence. Ultimately this will add significantly to the present evidence by reporting results of a robust RCT of a manualised, complex intervention. The papers produced would make a significant contribution to relevant clinical reviews and guidelines. If demonstrated to be clinically and cost effective, BRIMS could be delivered in clinical and community settings throughout the UK and in other countries with similar health care systems.

2 OBJECTIVES AND OUTCOME MEASURES

2.1 Trial Aim

The aim of this feasibility trial is to obtain the necessary data and operational experience to finalise the planning of an intended future definitive multi-centre RCT to compare a manualised 13-week education and exercise programme (BRiMS) plus usual care with usual care alone in improving mobility and QoL and reducing falls in people with SPMS, so that the definitive trial can be successfully delivered with confidence.

2.2 Trial Objectives

The objectives of this feasibility trial are to determine:

i. feasibility, utility and acceptability of the trial procedures
ii. suitability and feasibility of eligibility criteria
iii. numbers of eligible participants from the target population
iv. willingness of clinicians to recruit patients
v. willingness of patients to be randomised
vi. likely recruitment and retention rates as participants move through the trial
vii. the optimum way of delivering the BRiMS programme
viii. intervention fidelity and application between sites
ix. acceptability of and adherence to the 13 week BRiMS programme
x. the completion and performance of proposed outcome measures, including: rates of outcome measure completion, baseline scores, distributional properties and standard deviations of outcome measures, and responsiveness to inform selection of primary outcome (and refine the number of secondary outcomes) for a definitive trial
xi. baseline factors most strongly associated with outcomes, as potential stratification factors in a definitive trial
xii. the sample size required for a fully powered RCT to evaluate the effectiveness of the BRiMS intervention
xiii. estimates of resource use and related costs associated with delivery of the BRiMS intervention
xiv. a framework (protocol) for assessing the cost effectiveness of the BRiMS intervention in a future economic evaluation alongside a full trial
xv. the total resource required for a full trial.

To meet these aims and objectives, this trial will use the same general research approach, design and methods as intended in the anticipated definitive RCT. In brief, a pragmatic multi-centre feasibility RCT with blinded outcome assessment will be undertaken. Participants will be randomised to a manualised 13-week education and exercise programme (BRiMS) plus usual care or usual care alone.

2.3 Trial Outcome Measures

Unless otherwise specified, standardised, validated clinician-rated and patient self-reported clinical outcomes will be measured at baseline, immediately post intervention (week 15 post randomisation +/- 1 week) and follow-up (week 27 post randomisation +/- 1 week). The Research Therapist will undertake all assessments in separate visits independently of treatment and away from the participant’s home. Participants will be asked not to discuss their exercises or activities. The outcome measures to be used are summarised below, with further information in Appendix 2 .

A. Primary Outcomes (objectives i, x, xi):

i. Walking

Multiple Sclerosis Walking Scale – 12 item (MSWS-12) Version 2.0[44]

The MSWS-12vs2.O is a widely used, patient-reported questionnaire that assesses the impact of MS on walking ability on 12 aspects of walking function and quality (walking, running, climbing stairs, standing, balance, distance, effort, support needed indoors, support needed outdoors, speed, smoothness, and concentration needed to walk).

ii. Measure of Health Related Quality of life

Two measures of disease specific health related QoL will be used:

1. EuroQoL [EQ5D-5L][45]

The EQ-5D (5L) is a standardised self-report measure of health status across five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

2. The 29-item Multiple Sclerosis Impact Scale [MSIS-29] Version 2.0[46]

The MSIS-29vs 2.0 is a 29-item condition specific, self-report measure of health-related QoL. The data can be used to derive a MS specific preference based measure, the MSIS-8D[47,48], which may be used in the assessment of cost effectiveness.

B. Secondary Outcomes (objectives i, x, xi)

i. Falls Frequency and Injury Rates

Falls will be defined as: “an unexpected event in which you come to rest on the floor or ground or lower level”[49]. In line with best practice guidance the number of falls, injurious falls and associated use of medical services will be recorded prospectively using a patient completed daily diary. All participants will be asked to start recording falls from the day after randomisation onwards and to return each completed diary on a fortnightly basis[50] to PenCTU using a FREEPOST envelope. The diary returns will be checked and data entered on receipt by PenCTU. Participants will be contacted by e-mail by the CTU to prompt them to continue completing the diaries, and remind them whenever any returns fall behind schedule.

ii. Activity Level

The level of physical activity will be objectively measured for a seven day period following each blinded assessment using an activity monitor (activPAL™, Paltechnologies Ltd, Glasgow)[51]. The activity monitor will be fitted to the participant at each assessment session and participants instructed to remove the device after seven days and post it back to the research team in the FREEPOST padded enveloped provided[52].

iii. Walking Capacity

To complement the self-report MSWS-12, an objective clinician-rated measure of walking capacity; the two-minute walk test (2MWT) will be undertaken. This determines the longest distance an individual can walk (using walking aids if required) over two minutes on a hard, flat surface[53].

iv. Balance

Poor balance is a key modifiable risk factor for falls in MS[12] and is one of the primary targets of the BRiMS exercise component. Balance will be evaluated using the following two measures:

> 1. The Mini-Balance Evaluation Systems Test (Mini-BEST) is a 14-item clinician rated balance assessment tool that aims to target and identify the contributions of six different balance control systems to functional stability: anticipatory postural adjustments, reactive postural correction, and dynamic balance during gait (including cognitive effects)[54].
>
> 2. The Functional Reach Test (FRT, forwards and lateral), is a clinician-rated measure of standing balance in which the person stands adjacent to a wall with shoulder flexed (forwards reach) or abducted (lateral reach) to 90 degrees, and leans forward (or laterally) as far as possible without stepping, thus testing the limits of stability[55–57].

v. Fear of Falling

Fear of falling (FoF) will be measured with the 16-item self-report Falls Efficacy Scale (International) (FESi)[58].

vi. Community Integration

Participation will be measured using the self-report Community Participation Indicators (CPI)[59] which evaluates participation using three key indicators: engagement, involvement in life situations and control over participation.

C. Measures of Adherence to the BRiMS Programme (objective vi-ix)

Attendance at the five face to face sessions (two individual and three group-based) will be monitored and recorded.

Participants are also advised to undertake a minimum of 120 minutes of home-based exercise per week for a minimum of 12 weeks, utilising a web-based physiotherapy programme; completing an exercise diary each time. Engagement in the home-based programme will be monitored based on the number of web-based log-in sessions and the exercise diary data recorded by the participant over the 12-week exercise programme; the adherence to each element will be calculated as a percentage.

D. Economic Evaluation (objective xiii-xiv)

Resource use and cost associated with delivery of the BRiMS intervention will be estimated. Economic evaluation methods will be developed and tested on the collection of resource use, cost, and outcome data. Data on resource use associated with the set-up and delivery of the BRiMS intervention (exclusive of time spent on research elements, e.g. reading the protocol and SOPS) will be collected via within trial reporting, including participant level contact and non-contact time for staffing input on delivery, equipment and consumable costs, training and supervision for delivery staff. Treating Therapists will complete contact sheets to capture time spent on each participant contact (including BRiMS visits and regular online reviews).Data on health and social care resource use will be collected at participant level using a participant resource use (RU) questionnaire, developed for this trial[60].The EQ-5D-5L will be used to inform the primary economic endpoint of cost per QALY. The MSIS-29vs2.0 data collected within the trial will be used to estimate health state values (QALYs) via the MS specific preference based MSIS-8D[47,48], for use in sensitivity analyses. In any future economic evaluation, the primary perspective of analyses will be that of the Third Party Payer (NHS), but a broader perspective will be considered, using data collected within trial, in sensitivity analyses.

E. Process Evaluation (objective viii)

The following elements of process evaluation are included in this feasibility trial, guided by the MRC Process Evaluation of Complex Interventions Guidelines[61] and the National Institute of Health Behaviour Change Consortium framework[62].

i. Intervention Description and Standardisation:

The BRiMS programme has been manualised to provide a detailed description of the intervention and to ensure consistency of content, approach and delivery of sessions across time, region and groups. The manual includes identification of the critical elements of each part of the programme, key objectives of each session and detailed guidance for programme leaders along with accompanying participant resources. The intervention groups will be conducted by NHS physiotherapists who will be trained by the BRiMS Trial Co-ordinator and the BRiMS Psychologist.

ii. BRiMS Programme Fidelity Testing:

With the participants' permission, all face to face sessions within the BRiMS programme will be audio recorded. The recorded sessions will be used alongside the data from participants' online programme logs to evaluate the quality of the intervention delivery and the degree of concordance between the BRiMS manual and the actual programme delivery. A random sample of a minimum of 25% of the audio recordings will be assessed. This sample will include at least two recordings of each session type (1:1 assessment, home visit and group sessions), and at least one session from each treating therapist. The recordings will be scored against a checklist based on the Dreyfus system for assessing skill acquisition[63] and an adaptation of the Motivational Interviewing Treatment Integrity scale[64].Comparison of scoring between two reviewers will be undertaken to refine the checklist and to develop consensus on its application in preparation for the definitive trial. No patient identifiable information will be recorded on the fidelity checklist, and the audio recordings will be destroyed at the earliest opportunity after the checklist has been completed.

F. Qualitative Evaluation (objective vii and ix)

As recommended by the MRC guidance[61], the quantitative fidelity checking data will be supplemented by qualitative data gained through one-to-one telephone interviews with trial participants and a telephone focus group[63] with Treating Therapists at the completion of the programme. The aims of this part of the evaluation are to:

- Assess the acceptability of the trial methods (across trial arms)
- Evaluate the acceptability of the intervention and identify possible adaptations
- Identify the components of the intervention perceived to be effective

A purposive sample of 10 participants will include people from different regions and BRiMS intervention groups plus a sample of control arm participants. Participants will be contacted and a mutually convenient time agreed to undertake a telephone interview within two weeks of the completion of their final trial visit.

All Treating Therapists (likely maximum = 4) will be invited to participate in the telephone focus group to be convened within one month of the completion of the final BRiMS programme delivery. This will be facilitated by the BRiMS Trial Co-ordinator. All interviews will be digitally recorded and transcribed verbatim by the research therapists conducting the interviews.

Outcome Group	**Outcome Measure**	**Objective**	**Evaluation Time point(s)**
Primary Outcomes	MS Walking Scale-12vs2.0, EuroQoL EQ5D-5L MS Impact Scale-29vs2.0	i, x, xi	Assessment by blinded research therapist at day 0; 15 weeks after randomisation(+/- 1 week) and 27 weeks after randomisation (+/- 1 week)
Secondary Outcomes	Falls frequency and injury rates, Physical Activity (activPAL), 2 Minute Walk Test, Mini-Balance Evaluation Systems Test, Functional Reach-forwards and lateral, Falls Efficacy Scale (international), Community Participation Indicators.	i, x, xi	Assessment by blinded research therapist at day 0; 15 weeks after randomisation(+/- 1 week) and 27 weeks after randomisation (+/- 1 week)
Measures of Adherence	Attendance at face-to-face sessions, Online exercise diary completion, Web-based programme log-in sessions.	vi-ix	Participants allocated to the intervention group will record adherence with the intervention (frequency, duration, progression) throughout the 27 week trial timeline
Evaluation of trial/ intervention feasibility and acceptability	Participant telephone Interviews Treating Therapist telephone focus group	vii, ix	A purposive sample of trial participants will be interviewed at the end of their involvement with the trial All treating therapists will be invited to attend a telephone focus group at the completion of all the trial intervention groups

Table 1: Summary of outcome measures

3 TRIAL DESIGN

This is a pragmatic multi-centre feasibility RCT with blinded outcome assessment. Sixty participants will be randomised in a 1:1 ratio either to a manualised 13-week education and exercise programme (BRiMS) plus usual care (Intervention) or to usual care alone (Control).

4 TRIAL SETTINGS

The sites involved are based in two geographical regions of the UK: South West (Devon/Cornwall) and Ayrshire.

Research activity will take place at these sites:

- Plymouth
- Exeter
- Cornwall
- Ayrshire and Arran

All sites will implement the trial protocol in the same manner. Physiotherapists (Treating Therapists) from each of these sites will perform the interventions (as part of their NHS role), and two BRiMS Research Therapists (employed specifically for the trial) will undertake the blinded assessments.

5 ELIGIBILITY CRITERIA

5.1 Inclusion criteria:

- Confirmed diagnosis of multiple sclerosis as has been determined by a neurologist; and in the secondary progressive phase as confirmed by an MS Specialist clinician.
- Aged 18 years or older.
- Willing and able to understand/comply with all trial activities
- Expanded Disability Status Scale (EDSS) ≥ 4.0 ≤ 7.0
- Self-report two or more falls in the past six months
- Willing and able to travel to and participate in BRiMS group sessions in local sites and to commit to undertaking their individualised home-based programme
- Access to a computer or tablet and to the internet.

5.2 Exclusion Criteria:

- Patient report of relapse or having received steroid treatment within the last month (patient reported relapse is 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")
- Any recent changes in disease modifying therapies. More specifically patients will be excluded if:
    - They have ever had previous treatment with alemtuzemab (Lemtrada / Campath); or
    - Ceased nataluzimab (Tysabri) in the last six months; or
    - Within three months of ceasing any other MS disease modifying drug
- Participated in a falls management programme (e.g. for older people) within the past six months
- Co-morbidities which may influence the ability of individuals to participate safely in the programme or likely to impact on the trial (e.g. uncontrolled epilepsy).
- Participation in a concurrent interventional study.

6 SCREENING AND RECRUITMENT

6.1 Recruitment Strategy

A multi-faceted recruitment approach will be undertaken to recruitment using both national and local routes.

This feasibility trial will only recruit from the South West and Ayrshire Regions, but the possibility of a future national trial will be made clear.

Nationally, recruitment will be promoted via a number of sources.

i. The UK MS Register via their quarterly newsletter and social networking sites
ii. Promotion through the MS charitable bodies' regular open access newsletters (i.e. MS Trust "Open Door" and MS Society "Research Matters").
iii. Promotion through the MS Society online resources which alerts pwMS to studies they may be interested in participating.
iv. Promotion through the Therapists in MS (TiMS) web-site.
v. Promotion and support from the NIHR CRN and national Speciality Lead for Neurology.
vi. The trial's web-site which will include generic email contact details.

All promotional materials will include information inviting people to make contact via the trial's generic email address. Emails to the trial email address will be monitored by PenCTU, who will triage enquiries and redirect them to the appropriate CRN staff or Research Therapist. PwMS who express an interest in participating will then be sent a BRiMS trial information pack by the CRN staff or Research Therapists at the appropriate site. The pack will consist of a letter of invitation; the participant information sheet (PIS); a list of local pre-scheduled BRiMS Programme dates and venues; a reply form and a Freepost envelope.

Locally, recruitment will also be via a number of routes, which include: -

vii. This trial will be adopted onto the UK CRN Portfolio; the local Clinical Research Speciality Lead will also promote the trial through existing clinical networks.
viii. Through the caseloads of neurologists, MS Specialist Nurses and NHS Therapists who could discuss the trial with interested patients, or write to potential participants with a letter of invitation
ix. Leaflets and posters will be placed in relevant outpatient clinics of the participating health establishments.
x. Promotion through local initiatives where they exist, for example the South West Impact of MS (SWIMS) project[64].
xi. Local MS Centres and MS Society Branches, via posters, newsletters and personal contact with the regional and branch leaders.

PwMS who are identified through the neurologists, CRN research staff, MS Specialist nurses and NHS Therapists will be sent a BRiMS trial information pack which will consist of a letter of invitation; the participant information sheet (PIS); a list of local pre-scheduled BRiMS Programme dates and venues; a reply form and a Freepost envelope. Where packs are distributed through direct contact (either face-to-face or by telephone), potential participants will be given the option to be contacted by the local Research Therapist to verbally discuss the project and answer any questions. If the potential participant opts in to this option, the member of staff will pass the person's name and contact details (email address or telephone number) Patients will be asked to read the PIS and return the reply form to indicate their interest, to confirm they feel they are eligible, and to give consent for the screeners to contact their treating team to confirm their diagnosis of SPMS. This will give the CRN staff or Research Therapists permission to contact them to establish fully whether they meet the trial's eligibility criteria. Screening Process

On receipt of the completed reply form the Research Therapists or CRN staff involved in the initial contact will telephone the person with MS to answer any further questions and to screen them for eligibility using a pre-formatted screening checklist based on the eligibility criteria. This will include determining their disability level using a telephone version of the EDSS[65]. During this screening telephone call, the participant's preferred contact details will be confirmed and the planned dates of the BRiMS programme discussed, in order to ensure that they will be able to attend should they be allocated to the BRiMS group. Screen failures (i.e. patients who do not meet eligibility criteria at time of screening) may be eligible for re-screening at a later date. The CRN staff or Research Therapists will rearrange the screening call for a suitable date.

CRN staff and Research Therapists will maintain a screening log of potential participants who made contact with the research team to be considered for entry to the trial. Anonymised data from the screening log will be transferred to PenCTU as required for the purpose of monitoring recruitment. These data will include the reason not eligible for trial participation, if they are eligible but declined, and their reason(s) for declining if they are happy to divulge this. Furthermore, a record will be kept of all participants who were sent invitation letters to determine the proportion of people who expressed an interest in the trial.

Once eligibility is confirmed, the participant's details will be passed to the Research Therapist (if screening was undertaken by CRN staff) and an appointment letter for the baseline assessment will be sent by the Research Therapist. The baseline assessment will be undertaken 2 weeks (+/- 1 week) before the participant commences the pre-scheduled BRiMS programme, should they subsequently be allocated to the intervention group. To minimise travel costs and burden on the participants, this baseline assessment will be undertaken at a local healthcare establishment. Reasonable travel expenses will be reimbursed for all visits additional to normal care, namely for the three assessments at the local health care establishments at day 0, 15 weeks(+/- 1 week) (after randomisation) and 27 weeks (+/- 1 week) (after randomisation). All participants will be reminded that allocation to either intervention or control arm of the trial will be informed by chance and will occur after baseline assessment.

6.2 Consent

In line with Good Clinical Practice (GCP) the Principal Investigator (PI) at each site will have overall responsibility for the informed consent of participants at their site. The PI will take responsibility for ensuring that all vulnerable subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

The Research Therapists at each site, together with members of the research team, may be delegated responsibility to undertake the informed consent process.

There will be three layers of consent to this trial.

i) Permission to be screened:

PwMS interested in participating will be invited to contact the research team as described in section 7.1. They will then be sent the BRiMS Trial information pack and asked to return the form giving permission for the CRN staff/ Research Therapist to undertake the telephone screening process.

ii) Consent to be recruited to the trial:

Written informed consent will be obtained by the Research Therapist at the baseline assessment session prior to any data collection. Prior to providing consent, patients will have at least 24 hours to review the information sheet and discuss with family and friends before responding to the study team. During this time, they will also have the opportunity to ask questions via the telephone, generic trial e-mail account (details listed in the PIS), or face-to-face. Consent will also be sought to contact patients' GPs to inform them of the patient's participation in the trial.

For those participants who are unable to provide written consent (for example due to severe upper limb impairment), a witness will be permitted to sign or date on the participant's behalf. There are no special arrangements made for participants who are unable to adequately understand verbal and/or written English. There is no intention to exclude patients, therefore, if they have regular access to a friend or family member who is able to translate for them they would be able to participate.

iii) Consent to participate in the post-trial qualitative interviews

Participants will be informed of the post-trial qualitative interviews within the PIS, and consent will be included within the pre-baseline informed consent processes. During the final trial assessment, consent to participate in the interviews will be reviewed and confirmed by the Research Therapist. Finally, verbal confirmation of ongoing consent will be obtained by the Research Therapist undertaking the interview prior to commencement.

In order to avoid any potential threats to the reliability of the data from this part of the trial, interviews with participants from the South West will be undertaken by the Scottish Research Team and vice versa. Therefore, the consent to participate in this element of the trial will include agreement that the participant's name and telephone number can be passed to the researcher carrying out the interviews by the local Research Therapist to facilitate contact to arrange the interview.

7 RANDOMISATION AND CONCEALMENT

7.1 Randomisation

The inclusion of group-based elements as part of the intervention necessitates the confirmed participation of a sufficient number of participants within a recruiting site before randomisation occurs. There are four sites where the intervention will be delivered. Once recruited, participants will ideally be randomised in blocks of 10, but the process can accommodate some flexibility within the limits 8-12 participants in each block. Randomisation will be undertaken when a sufficient number of individuals from a recruiting site have consented, indicated that they are able to attend the same BRiMS group (location, timing, should they be randomised to receive it), and complete baseline data has been collected. The decision to declare a block complete will be made by the Research Therapist in collaboration with the Trial Co-ordinator, CI and CTU. Randomisation will be undertaken a minimum of three and a maximum of seven working days prior to the commencement of the BRiMS programme delivery (for each block).

7.2 Method of Implementing the Allocation Sequence

When the block size from a recruiting site consists of 8 – 12 participants, the participants will be randomised to the intervention or control group, using block simultaneous randomisation. The randomisation will be 1:1 when the block consists of an even number of participants and when the block consists of an odd number of participants the allocation ratio will be in favour of the intervention group in order to maximise recruitment potential and learning opportunities in this feasibility trial. Participants in a block will be numbered in the order in which they were first entered onto the trial website. The randomisation process will follow a strict and auditable protocol. Randomisation will take place after all baseline assessments have been carried out; the Research Therapist will input relevant participant details into the study web-site and randomisation will subsequently be conducted by the CTU Trial Manager via the secure web-based system. The randomised allocations will be computer-generated by the CTU in conjunction with an independent statistician, in accordance with the CTU's standard operating procedure. The randomisation list and the program that generated it will be stored in a secure network location within the CTU, accessible only to those responsible for provision of the randomisation system.

After randomisation has taken place, an automatic email will be sent by the CTU to the NHS Therapist leading the BRiMS Programme locally and to the relevant PI to notify them of each participant's allocated group. Notification that randomisation has taken place (but NO details regarding individual participant's allocated group) will also be sent to the relevant Research Therapist and to the CI.

Access to the randomisation code and allocation list will be confined to the PenCTU data programmer; no-one else in the trial team will be aware of allocated trial arms until formal randomisation is completed, hence maintaining effective concealment. Following randomisation, only appropriate members of the trial team will be aware of participants' allocations to intervention or control group; the blinded Research Therapists will NOT have access to treatment allocation.

7.3 Blinding

The trial participants are unable to be blinded in this trial due to the nature of the intervention. Similarly, the NHS treating physiotherapists and health care providers are unable to be blinded. However, the Research Therapists who are undertaking the outcome assessments will be blinded to participants' allocated group. The initial baseline assessment will be undertaken prior to randomisation. All assessments will be undertaken in visits which are arranged independently of any intervention sessions, and away from the participant's home. Every effort will be made throughout to ensure these assessments are blinded, for example by reminding participants not to discuss their exercises/physiotherapy with the Research Therapist.

At each assessment time point, the blinded Research Therapists will be asked to record on the CRF whether or not they were un-blinded to group allocation. If this occurred, they will be asked to provide details as to how this un-blinding happened. Regardless of whether or not they had been un-blinded, they will also be asked to make a judgement as to which group the participant had been allocated.

7.4 Unblinding

Final unblinding of the research team (including the trial statistician) will be after the creation of a locked analysis data set and analysis has been undertaken.

8 TRIAL VISITS

8.1 Trial assessments

All participants will attend for three trial assessment visits undertaken by the blinded Research Therapists which are scheduled relative to the timing of randomisation (see Figure 2, page 15).

	Baseline		15 weeks post-randomisation (+/- 1 week)	27 weeks post-randomisation (+/- 1 week)
Consent	x	Randomisation to intervention or control		
Demographics & history	x			
Provide falls diaries	x			
EDSS	x			
MSWS-12vs2.0	x		x	x
MSIS-29vs2.0	x		x	x
EQ-5D-5L	x		x	x
Falls frequency	x		x	x
ActivPAL	x		x	x
2MWT	x		x	x
Mini-BEST	x		x	x
Functional Reach Test	x		x	x
Falls Efficacy Scale	x		x	x
Community Participation Indicators	x		x	x
Adverse events			x	x
Participant Resource use	x		x	x
Qualitative interviews				x

Table 2: Trial Assessments

8.1.1 Baseline Data

Baseline data will be collected at the baseline assessment visit during which eligibility is confirmed and once informed consent is obtained. The baseline assessment visit should take place 2 weeks (+/- 1 week) before the start of the BRiMS programme delivery date that each participant has committed to attend should they be allocated to the intervention group. In addition to the outcome measures detailed above, the following baseline data will be collected on all participants by the same Research Therapists who will be undertaking the blinded assessments. They will be recorded on a trial specific CRF:

- Demographic data: gender, age, ethnicity, home circumstances (place of residence and who they live with) and employment status (as indications of socio-economic status).
- Diagnostic data: EDSS score (a commonly used scale of disease severity in pwMS), year of diagnosis of MS, time since last relapse.
- Baseline characteristics: working memory and attention; self reported urinary continence; self reported mood.
- Medications and Co-morbid conditions: all current prescribed medications and their dose will be listed and coded (and any amendments will be noted at subsequent assessments).
- Mobility data: falls history over the past three months, walking aidsand assistive devices, wheelchair use.

8.1.2 Follow up assessments

Follow up assessments by the blinded Research Therapist will be scheduled for all participants at two further time points: 15 weeks after randomisation (+/- 1 week) and 27 weeks after randomisation (+/-1 week).

8.1.3 Other assessments

i) *Adherence* to the BRiMS exercise programme (for intervention group participants) will be measured using the online exercise diary completed by the participant to record adherence with the intervention (frequency, duration), together with the opportunity to comment on why exercises were undertaken or not. In addition, attendance at BRiMS face-to-face sessions and number of log-ins to the online exercise resource will also be monitored as described previously.

ii) Identification of how participants are 'lost to follow-up'

The blinded Research Therapists will identify participants lost to follow up and the reasons as to why they have been lost to follow-up.

iii) Measures taken to obtain the information if visits or data collection time-points are missed

If an assessment visit is missed, then the Research Therapist will book another appointment, preferably within one week of the original date. In some circumstances this may not be possible and so another assessment session will be scheduled for as close to possible to the original scheduled date, ideally within +/- two weeks of the relevant trial timepoint, with any non-compliances noted.

iv) Outcome data that will be recorded from protocol non-adherers

As far as is possible, all outcome data will be collected for all participants, regardless as to whether or not they have adhered to the protocol.

8.2 Qualitative assessments

The aim of this qualitative component is to explore the “real-life” experiences of people’s participation in this trial. This will help to further elucidate the acceptability of the BRiMS intervention and the trial procedures from the perspective of pwMS and Treating Therapists.

(i) Trial Participants

A purposive sample of 10 participants will include people from different regions, different BRiMS intervention groups, plus a sample of control arm participants. At the completion of the final trial assessment, the Research Therapist will confirm the participant’s ongoing consent to be involved in the interviews. Once the final trial assessments for each geographical group of participants have been completed and unblinding of the Research Therapist is possible, PenCTU will provide an unblinded list of participants to the Research Therapist, together with basic demographic data to enable the development of the purposive sample. Individuals will be formally approached by the Research Therapist conducting the interviews to invite them to participate, and arrange a convenient time for the telephone interview. Each interview will be guided by an interview guide (Appendix 3). Ongoing consent will also be confirmed verbally at the commencement of the telephone interview.

(ii) Treating Therapists

All NHS Treating Therapists (likely maximum = 4) will be invited to participate in a telephone focus group. They will be given an Information Sheet and asked to sign a consent form before taking part in the Focus Group. All interviews and focus groups will be guided by an interview guide (Appendix 3) and will be digitally recorded, pseudo-anomyised and transcribed verbatim.

(iii) Reasons for withdrawal

Should any participant withdraw from the trial, at the point of their withdrawal, they will be asked if they would be willing and able to provide the reason for their withdrawal.

9 WITHDRAWALS

Each participant has the right to voluntarily withdraw from the trial at any time, without repercussions. This is distinct from participants in the intervention group terminating their involvement in the BRiMS programme.

9.1 Discontinuation of the intervention

Participants in the intervention group may choose to discontinue the BRiMS programme, or may do so on the recommendation of a health professional, for example following an adverse event. Where appropriate, such participants will be asked to continue to attend blinded assessments as per protocol if this is feasible.

9.2 Withdrawal from the trial

Any participant may at any time after they have consented decide that they no longer wish to be part of the trial. This may be through personal choice (i.e. they withdraw their consent) or in consultation with a health professional, for example where it becomes impossible to provide outcome data or comply with any other trial procedures for whatever reason. In addition, the Research Therapist, NHS treating physiotherapist or neurologist responsible for the participant may suggest withdrawal following a significant protocol deviation. One such protocol deviation is a patient randomized in error, having discovered later that they were in fact ineligible. In this event, the decision as to whether they should be removed from the trial completely or retained on an intention to treat (ITT) basis will be made through an independent adjudication by the TSC who are blinded to group allocation[68].

In line with CONSORT Guidelines the reasons for withdrawal will be recorded. In the case of the participant requesting withdrawal, they will be asked if their data collected so far can still be used. Because of the nature of the randomisation and the scheduling of visits in this study it will not be possible to replace participants that withdraw, unless they do so before their group randomisation is conducted.

10 THE INTERVENTIONS

10.1 Intervention Arm

The BRiMS programme is delivered over 13 weeks and includes a mix of home-based activities and attended sessions (see Figure 3). The dates for all attended BRiMS sessions are pre-identified to potential trial participants in recruitment materials, and ability to attend the nominated sessions (should the participant be allocated to the intervention arm) will be confirmed by the CRN staff/ Research Therapists during screening and baseline assessments. On randomisation, intervention arm participants will be contacted by the Treating Therapist to arrange specific times for the one-to-one sessions and to confirm dates for the three group sessions. During the programme, participants will also be reminded about upcoming group sessions by email.

In week one, participants attend a one-to-one assessment session with the Treating Therapist to undertake assessment and goal setting activities, provide the BRiMS manual and to aid the development of an individualised exercise plan. In week two the therapist will undertake a home visit to set up and instruct the participant in their personalised exercise programme (including risk assessment and management activities), and to support engagement with the online elements of the programme. Three group sessions are interspersed over the duration of the programme (weeks four, eight and thirteen). These include exercise and education activities facilitated by the Treating Therapist but with a heavy emphasis on peer learning with fellow BRiMS participants.

In addition to the attended sessions, participants will undertake home-based exercise throughout the programme supported by the online exercise resource. This is customised to the individual participant and reviewed periodically by the Treating Therapist, amending the programme as required. There are also a series of self-completed online home packages, which include a range of falls prevention learning activities as well as resources to support exercise adherence and facilitate behaviour change. All online activities are accessed using secure login via the BRiMS website (www.brims.org.uk) and are supported by the BRiMS manual. Participants are able to undertake the various packages at their own pace, and will be supported by the Treating Therapist should any difficulties arise.

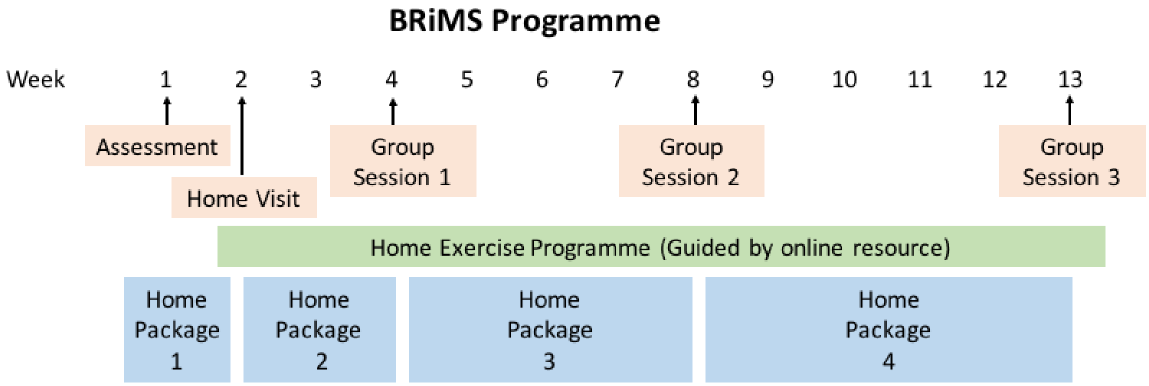

Figure 3: BRiMS programme activities

10.2 Control Arm (Usual Care)

All participants allocated to this group will continue to receive their usual clinical care; thus, with the exception of the trial assessments they will not be asked to attend any additional visits or sessions. Whilst usual care varies across the country[66] it rarely involves regular ongoing physiotherapy intervention within the community or as an outpatient, either on an individual or group basis. As a general rule, in those with SPMS, physiotherapy input is provided when an event has caused a significant deterioration in the person's ability to function (e.g. a respiratory infection or an injurious fall). The standard physiotherapy care pathway usually comprises short intermittent episodes of face-to-face intervention which are generally limited to a few sessions. The typical approach and content of these sessions is one wherein presenting problems are managed (e.g. providing mobility aids, a written home exercise programme and advice) rather than focusing on the promotion of long-term self-management strategies. Specifically, 'usual' care can be broken down as follows for the regions involved in this study:

Cornwall - MS therapy services are supplied as part of the county-wide neurological physiotherapy specialty team. Patients can be referred to the team for assessment, advice and management for specific issues. This typically involves an assessment and a small number of short term reviews to follow up.

East Devon - MS services are provided by the local healthcare trust who provide short episodes of physiotherapy either in peoples' homes or on an out-patient basis. Patients can be referred to the team for assessment, advice and management for specific issues. This typically involves an assessment and a small number of short term reviews to follow up. Patients may also be admitted to a rehabilitation ward for more intense rehabilitation (although this is uncommon), or they may also be admitted to an acute ward due to an acute episode during the period of the study, which may or may not be related to MS.

Plymouth - MS services are provided by the local healthcare trust who provide short episodes of physiotherapy either in peoples' homes or on an out-patient basis. Patients can be referred to the team for assessment, advice and management for specific issues. This typically involves an assessment and a small number of short term reviews to follow up. In addition, a weekly specialist MS physiotherapy clinic is provided; referrals are from the Plymouth-based neurologists or MS clinical specialist nurses. This is for assessment, and typically a one-off advice and onward referral when appropriate. Patients may also be admitted to a rehabilitation ward for more intense rehabilitation (although this is uncommon), or they may also be admitted to an acute ward due to an acute episode during the period of the study, which may or may not be related to MS.

Ayrshire and Arran: In addition to the usual description (above), provision can include more extended rehabilitation (up to around 8 sessions) if felt to be appropriate. Patients may also be admitted to a rehabilitation ward for more intense rehabilitation, or they may also be admitted to an acute ward due to an acute episode during the period of the study, which may or may not be related to MS.

For people with mobility impairment who are at risk of falling, physiotherapy regimes typically consist of gait re-education and the provision of a written home exercise programme which is aimed at strengthening muscles and/or optimising balance. In line with recent NICE Guidelines (2014)[7], in individuals with mild to moderate disability, advice may also be given to enhance cardiovascular fitness since this has been demonstrated to optimise general physical and emotional well-being and minimise deconditioning. For individuals whose mobility is more severely impaired, advice and information to support the carer in terms of facilitating movement (e.g. manual handling advice to enhance the safety of assisted transfers) may be given.

Usual care may also involve appointments with a variety of other health professionals (for example occupational therapist, general practitioner, MS nurse specialist, neurologist, rehabilitation consultant). As with physiotherapy, multi-disciplinary interventions are usually short term since resource restrictions limit the provision of long-term maintenance therapy

Falls programmes for older people exist in most locations across the UK, however, these are seldom accessed by pwMS. Some programmes specifically exclude those with neurological conditions from attending, and have lower minimum age restrictions which present further barriers.

This trial will record the content of usual care on the participant resource use questionnaire at the follow up assessments.

11 END OF TRIAL

The end of trial is the date of the last visit / last data item collected of the last participant. The following criteria will be used to prematurely stop the research

1. A decision made by the TSC, DMC and TMG on the grounds of safety issues, such as an unacceptable number of adverse events.
2. An evaluation via a fully powered RCT of a similar balance and falls program in people with progressive MS. Note that there are currently (last assessed 27/04/16) no similar trials registered with clinicaltrials.gov

12 SAFETY AND MANAGEMENT OF RISK

12.1 Participant Safety

Throughout the trial, all possible precautions will be taken to ensure participant safety and wellbeing. Experienced physiotherapists will undertake the initial assessment of the person with MS and will prescribe the participant's personalised exercise prescription in accordance with the BRiMS therapist manual. To standardise and optimise implementation of the intervention, and to further ensure the safety and wellbeing of our research participants, the Treating Therapists will attend a BRiMS training session run by the developers of BRiMS.

Risk assessment and development of an individual exercise safety and fall action plan are core activities within the BRiMS exercise package and will be undertaken prior to the participant commencing their exercise plan. This includes discussion of issues relating to fatigue and heat sensitivity which are common for pwMS. The participant will be introduced to their exercise programme in an individual home visit, giving time to explain the programme and seek necessary clarification. In addition, participants will be provided with a link to the BRiMS web-site which will include instructional videos demonstrating exercise safety principles, frequently asked questions, examples of how to intensify the programme using case scenarios, and links to the participant's personalised exercise prescription. This will complement and support the knowledge and skills of the physiotherapists who will be implementing the BRiMS programme, and the participants who will engage with the programme within their homes.

The exercise prescription will be individualised, and gradually progressed over the programme. The progression of exercises will be supported by weekly reviews (with modification where necessary) of the online exercise logs by the Treating Therapist over the first month, and then bi-weekly thereafter to optimise motivation and minimise adverse events. Additionally, the participants will keep a diary of their exercise experiences which will assist them in monitoring their progress and any adverse events, and to act as a prompt for the discussions with the Treating Therapist and fellow participants at group sessions. Participants will be advised to contact the Treating Therapist should any adverse events occur in order that they can advise re management of these issues. All adverse events will be recorded (See section 13).

The research assessments themselves may cause transient fatigue. The battery of measures has been carefully chosen in collaboration with pwMS/carers to ensure acceptability and relevance, and proven psychometric properties. The testing procedure has been developed to minimise unnecessary energy expenditure through changes in position, and to enable participants to rest between activities. Similarly, the assessment elements have been scheduled to vary the type of activity that participants undertake, which will also reduce potential fatigue. Trials of the assessment protocol demonstrate it will take approximately 60 minutes. This is the typical duration for NHS physiotherapy assessments for complex neurological conditions and within the 90-minute maximum that users have told us is acceptable. Rest breaks will be offered to participants to minimise fatigue.

A decision protocol has been formulated for withdrawing a participant on medical or other (at risk) grounds (See flowchart Appendix 4, page 57).

Adverse events reported to therapists, PI's or the research team will be reported according to a work instruction. Those reported in the daily diaries will be reviewed on their fortnightly return by the PenCTU.

12.2 Therapist Safety

For the home visit which is required as part of the BRiMS programme, the Treating Therapists will comply with their employing organisation's lone working policy. All Treating Therapists will also comply with the standard health and safety procedures of their employing organisation. This will minimise the risk to the Treating Therapists.

12.3 Participant Burden

Participants will be reimbursed travel expenses for attendance at the local assessment centre for the blinded assessments. All those who are unable to drive / use public transport, will be offered the option of a taxi service if they are otherwise unable to participate in the trial. To ensure the trial is cost effective an upper limit of (£25) per round trip journey will normally be applied.

Whilst the group sessions are pre-scheduled, the individual sessions and research assessments will be arranged at a time that is mutually convenient for the participant and assessor. In the case of the research assessments, wherever possible, flexible appointments will be made to help participants fit the trial commitments around their work and family life and fatigue/disability levels.

This trial is categorised as: Type A = No higher than the risk of standard medical care.

13 ADVERSE EVENTS

13.1 Adverse Events

An adverse event (AE) is defined as any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease that develops or worsens during the period of the trial, whether or not it is considered to be related to the trial intervention. The adverse event risks of taking part in this trial have been assessed to be low. AEs such as chest infections and urinary tract infections which are common in pwMS will NOT be monitored or recorded for any participants (intervention or usual care group). However, all participants will be asked to report any new or worsening problems which they perceive to be related to participation in activity and/or exercise, as well as any relapses and falls, in their diaries. These will be completed on a daily basis from the day of randomisation until the final (27 weeks following randomisation +/- 1week) assessment, and returned on a fortnightly basis to PenCTU (see page 19) for data entry. AEs may also be discovered by Treating or Research Therapists during questioning, physical examinations or other intervention. Should this be the case, the therapist will take any appropriate action and will ask the participant to record the AE in their diary to ensure its reporting as part of the trial data.

On receipt of the diary returns, any AEs will be recorded in the study database by PenCTU, with collated reports (of the whole group, i.e. not according to group allocation) presented to the monthly TMG meeting for review. The TMG will refer concerns to the TSC/DMC for further (unblinded) review if required.

AEs considered related to the trial intervention will be followed until resolution or the event is considered stable. In line with the “Decision Flowchart for Withdrawing a Participant on Medical Grounds” (Appendix 4, page 53), it will be left to the clinical care team’s judgment, in discussion with the CI, whether or not an AE is of sufficient severity to necessitate the participant to withdraw from the BRiMS intervention. The participant may also voluntarily stop participating in the intervention arm due to what he or she perceives as an intolerable AE.

13.2 Serious Adverse Events

A serious adverse event (SAE) is defined as 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; or
(f) is otherwise considered medically significant by the investigator.

It is not anticipated that there will be any SAEs related to the trial. Any SAE, whether thought to be related to any trial intervention or not, must be reported to the CTU by the local PI or another member of the research team by telephone (01752 315256), fax (01752 315254) or email (penctudata@plymouth.ac.uk) within 24 hours of the research team becoming aware of it. Serious adverse events should be recorded from the time of the baseline assessment until the date the participant completes follow-up or withdraws from the study. SAEs may be volunteered by the participant or discovered by the Treating Therapist or Research Therapist through questioning, physical examination or other investigation, or as a result of direct reporting (e.g. by telephone) by the participant, independent clinician or other informant.

Within seven days of a local research team becoming aware of such an event, an SAE form must be completed, signed by the PI and returned to the CTU. Completion of the SAE form must include the PI’s assessment of causality i.e. whether there is a reasonable causal relationship between the SAE and the trial intervention. If incomplete information is available at the time of reporting, all appropriate information relating to the SAE should be forwarded to the CTU as soon as possible.

If the PI considers that the SAE is not, or is unlikely to be, related to the trial, the CTU will obtain a second assessment of causality either from the Scottish Regional Co-ordinator (for SAEs at the Plymouth site) or from the CI (for SAEs at other participating sites).

Serious adverse events which in the opinion of either adjudicator are possibly related to the trial intervention and unexpected will be reported by the CTU to the Research Ethics Committee within 15 days of the local research team having become aware of the event, using the SAE report form for research other than clinical trials of investigational medicinal products (non-CTIMPs), published on the Health Research Authority (HRA) website. The report will be copied to the Sponsor and TSC.

All SAEs will be followed until resolution. The CTU will routinely notify the CI by email of all reported SAEs as they occur and will report organ system listings of all SAEs to the TSC and Sponsor on a quarterly basis. The CTU will be responsible for the preparation and submission of an annual safety report to the REC.

14 DATA ANALYSES

14.1 SAMPLE SIZE

As this proposal is for a feasibility trial, the more usual sample size calculation, based on considerations of power for detecting a between-group clinically meaningful difference in a primary clinical outcome, is not appropriate[67]. Instead, the aim is to provide robust estimates of the likely rates of recruitment and follow-up, as well as provide estimates of the variability of the proposed primary and secondary outcomes to inform sample size calculations for the planned definitive trial.

For this feasibility trial, we aim to recruit 60 participants across the two sites (40 in the South West and 20 in Ayrshire) over six months. This will mean we will run six intervention groups, each with approximately five participants. We anticipate that in order to recruit these 60 participants we will need to screen around 240 people, assuming that around 80% will agree to participate (n=190) of which approximately 35% (n=70) will be found to be ineligible after screening, leaving around 120 eligible people. Following this screening, we anticipate that approximately 50% of eligible people will consent to participate leaving around 60 participants to be randomised.

From other studies in similar settings, we believe that retention rates will be in the region of 80%[68,69]. With our intended sample size of 60 participants, we will be able to estimate the overall retention rate with precision of at least ±13%, and if the six-month follow-up rate is around 80%, with precision of around ±10%. Assuming a non-differential six-month follow-up rate of 80%, this should provide follow-up outcome data on a minimum of 24 participants in each of the allocated trial arms.

14.1.1 Planned Recruitment Rate

This feasibility trial will help to elucidate the recruitment rate for the planned definitive trial as we will record the sources of recruitment for all participants in this trial and ensure that the distribution is considered when extrapolating likely recruitment rates for the main trial.

The recruitment period is six months. Trial awareness raising activities are being undertaken during the four month set-up period, using the wide range of national and local fora described above (recruitment strategies i- vi, ix, xii page 26). A list of potential participants expressing an interest in participating in the trial will be screened as soon as ethical/R and D approvals are granted. As necessary, during the recruitment period we will complement this approach by utilising strategies vii, viii and xi. Our first priority will be to send out consultant invitation letters since this has been demonstrated to be a cost-effective strategy for recruitment in other MS rehabilitation trials[68–70].

14.2 Quantitative Analysis Plan

A detailed analysis plan will be developed prior to any statistical analysis. For the final analysis, the trial statistician will be presented with a database by the PenCTU containing a group code for each participant but not identifying which group is which; only after the primary analyses will the two groups be identified.

14.2.1 Summary of Baseline Data and Flow of Participants

A Consort-style diagram will provide detailed descriptions of numbers approached, meeting eligibility, having baseline data collected, being randomised, receiving the intervention and having follow-up data collected.

14.2.2 Outcome Analysis

The analyses of the quantitative data will be in two stages, with data summarised according to participants' allocated trial arm.

Stage One Analyses will summarise the feasibility outcomes: data from screening, recruitment and follow-up logs will be used to generate realistic estimates of eligibility, recruitment, consent and follow-up rates in the trial population (objectives i-vi). In addition, adherence data (e.g. session attendance and exercise adherence) will be used to contribute to the evaluation of the acceptability and concordance to the BRiMS programme (objective ix). Completion rates will be estimated for each of the patient-reported and clinical outcome measures at each time-point, including the health and social care resource use data (objective x). All such estimates will be accompanied by appropriate confidence intervals, to allow assumptions to be made in the planning of the definitive trial. The baseline characteristics of individuals lost to follow-up will be compared to those who complete the feasibility trial to identify any potential bias.

Stage Two Analyses will summarise the planned primary and secondary patient-reported and clinical outcomes including the health and social care resource use data, at each time point. As it is inappropriate to use feasibility trial data to formally test for between-group treatment effects, the statistical analyses will primarily be of a descriptive nature[67,71]. The CONSORT extension for reporting of pilot and feasibility studies[72] and the CONSORT extension for reporting of patient-reported outcomes[73] will be followed. Descriptive statistics of the proposed primary and secondary outcomes and the health and social care resource use data will be produced, as appropriate for each measure for each trial arm. Interval estimates of the potential intervention effects, relative to usual care only, will be produced in the form of a 95% confidence interval, to ensure that the effect size subsequently chosen for powering the definitive trial is plausible, but no formal hypothesis testing will be undertaken of the feasibility data[67] (objective xi- xii).

Interim analysis and criteria for the premature termination of the trial

There is no planned interim analysis for this trial; however, the TSC will receive a quarterly report of all AEs and SAEs which is blinded and unallocated to group for review. Should there be any safety concerns, the TSC will contact the chair of the DMC, to initiate a meeting to review this.

Due to the nature of the intervention it is not anticipated that new information will suggest termination of the trial, particularly given the evidence base for physical activity in this population. Hence, there are no planned stopping guidelines for this trial. However regular literature searches will be undertaken during the trial; should information suggest any changes be made, the research team will inform and request permission to do so from REC and the trial sponsor, Plymouth Hospitals NHS Trust.

14.2.3 Economic Evaluation Analyses

Economic evaluation methods will be developed and tested on the collection of resource use, cost, and outcome data. Data on resource use associated with the set-up and delivery of the BRiMS intervention will be collected via within trial reporting, including participant level contact and non-contact time for staffing input on delivery, equipment and consumable costs, training and supervision for delivery staff. Data on health and social care resource use will be collected at participant level using a participant resource use (RU) questionnaire, developed for this trial based on RU forms used successfully in prior studies in pwMS[74]. The primary economic endpoint (over 12-month follow-up) is the estimated cost per QALY, and EQ-5D data will be collected to inform this primary endpoint. In addition, given some debate and uncertainty over the appropriateness of the EQ-5D in pwMS the MSIS-29 data collected within the trial can be used in sensitivity analyses to estimate health state values (QALYs) via the MS specific preference based measure developed by Goodwin and Green[48].

14.3 Analysis of Qualitative Data

The qualitative analysis will be undertaken collaboratively by the BRiMS Trial Co-ordinator and Scottish Regional Co-ordinator. Analysis will employ a constructivist paradigm, described as an approach which allows the co-creation of understandings by respondent and researcher[75]. The qualitative data for analysis will include transcripts from one-to-one participant interviews, and the telephone focus group of staff involved in the delivery of BRiMS. Analysis will aim to achieve an in-depth investigation and critical analysis of the data to explore the underpinning concepts and emergent themes, rather than using the data as a simple representation of the phenomenon[76].

Initially, anonymised transcribed data will be entered into NVIVO software (QSR International, Southport, UK). A pragmatic process of data immersion, coding and generation of initial themes will then be undertaken[77]. Subsequently, refinement of these themes will be undertaken in discussion with other members of the research team with the aim of maximising credibility within the process[78]. Due to the variety of data included in the analysis, simple respondent validation is unlikely to be beneficial[79], however, interview and focus group participants will be invited to review an initial draft to ensure the analysis represents an accurate overview of participants' views, experiences and recommendations. Once this has been verified we will use the data to (where necessary) revise the BRiMS Operational Manual, and the Trial Procedures to optimise the success of the proposed future definitive trial

14.4 Determining Progression To The Full Trial Application

We shall progress to a full trial application if minimum success criteria are achieved in the key feasibility aims and objectives. These criteria will be finalised in discussion with the Trial Steering Committee, and so while it is difficult at this stage to precisely specify these, we suggest the criteria will include:

- a minimum of 80% recruitment of the intended 60 participants within our six month recruitment window
- a minimum of 80% of consented participants randomised to the intervention group engaging with and adhering to the 13 week BRiMS intervention
- a minimum of 80% completion rate of key outcome measures (including follow-up)
- that the total resource estimated to conduct the definitive trial is within a level that is likely to attract funding.

There are also likely to be grey areas which themselves are less than optimal but where our qualitative work and PPI team members will be able to indicate remedial action. Such action might be implemented within this feasibility study and/or be evident upon completion of the study; either way it will inform the feasibility, and optimum delivery, for the definitive trial

15 DATA MANAGEMENT

The PenCTU will be responsible for data management within this study.

15.1 Participant Numbering

Each participant will be allocated a unique trial number when they are registered on the data collection website by the CRN staff/ Research Therapists.

15.2 Data collection tools and source document identification

Case Report Form (CRF) entries will be considered source data. These will be printed on no-carbon-required (NCR) paper and collated into booklets. The baseline data and outcome measures that will be recorded are outlined in section 2, page 19, "Outcome measures" and page 52.

The Research Therapists will complete the CRFs for all participants. Completeness of data will be maximised by the Research Therapists, who will: -

- Check all forms at each assessment to ensure there are no missing items
- Wherever possible, arrange another assessment session, should the pre-scheduled session be cancelled/ not attended by the participants

PenCTU will prompt the participants should they fail to return their diaries (within 2 weeks of due date). In addition, periodic email reminders will be sent to all participants to maximise the completion of data within the diaries.

15.3 Data handling and record keeping

Completed CRFs will be checked and signed by the Research Therapists before sending the top copy to the Plymouth-based PenCTU on a patient-by-patient basis. On receipt of completed CRFs and falls diaries by PenCTU, all data will be double-entered onto a password-protected database. Double-entered data will be compared for discrepancies. Discrepant data will be verified using the original paper data sheets.

Contact sheets will be completed by the Treating Therapists following every contact they have with participants taking part in the BRiMS programme. These will be sent to PenCTU on completion of each BRiMS delivery for data entry as above.

Qualitative data in the form of telephone interview and focus group audio recordings will be transcribed and anonymised as soon as practicable; original recordings will be held securely until completion of the qualitative data analysis process, then deleted.

The research teams will ensure that participants' anonymity is maintained on all documents. Data will be collected and stored in accordance with the Data Protection Act 1998. All paper forms (including all original signed informed consent forms and copies of the CRF pages) will be archived by each site in a secure location for a minimum of five years after trial closure, in line with the sponsor's archiving requirements. These will be accessible for the purposes of monitoring, auditing, or at the request of regulatory bodies. Electronic records will be stored in a SQL Server database, stored on a restricted access, secure server maintained by the PenCTU. The data entry website will be encrypted using SSL.

Trial data will be analysed by S Creanor (trial statistician), the Trial Co-ordinator (Dr Hilary Gunn), Dr Jenny Freeman (CI), Prof Lorna Paul and Prof Colin Green (economic data).

15.4 Archiving

The Sponsor will be responsible for archiving the original study data (paper and electronic formats) and essential documentation (contents of Trial Master File) in a secure location for a minimum period of five years after the end of the trial. Archiving will be authorised by the Sponsor following submission of the end of study report. Each individual study site will be responsible for archiving copies of local study data (as applicable where copies exist) and essential documentation (contents of Investigator Site File) in a secure location for the same period. No essential documents should be destroyed unless or until the Sponsor gives authorisation to do so.

16 MONITORING, AUDIT AND INSPECTION

The CTU trial manager will devise a monitoring plan specific to the study, based upon an initial pre-trial risk assessment which will be updated as required throughout the study. The monitoring plan will include both central monitoring strategies and study site visits as appropriate and will be reviewed and agreed by the TMG. Monitoring will include oversight of processes relating to the safety of participants and the integrity/reliability of the study data, including adverse events reporting, participant enrolment, consent, eligibility, and allocation to trial groups, adherence to trial interventions and policies to promote the accuracy, and timeliness of data collection.

All study procedures will be conducted in accordance with the protocol and according to the principles of Good Clinical Practice. Procedures specifically conducted by the CTU team (e.g. randomisation, data management, trial management and study monitoring) will be conducted in compliance with CTU standard operating procedures (SOPs). As required, the PI's and the participating NHS Trusts will be required to permit the CTU trial manager or deputy to undertake trial-related monitoring to ensure compliance with the approved trial protocol and applicable SOPs, providing direct access to source data and documents as requested. Access to participants' study records and relevant health records at study sites may also be required for audit purposes, on request, by the study Sponsor.

Access to Data

Data generated as a result of this trial will be available for inspection on request by the participating research team, the University of Plymouth, Glasgow Caledonian University and University of Glasgow representatives, the REC, local R&D Departments and regulatory authorities.

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Research Ethics Committee (REC) Review and Reports

The trial will not be initiated before the protocol, informed consent forms, participant information sheets and other relevant documents (e.g. advertisements and GP information letters) have received approval from the Research Ethics Committee (REC), and the respective NHS R&D department.

Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and PIS (if appropriate) have been reviewed and received approval from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed. The PenCTU will be responsible for the overall management and implementation of these procedures.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

All correspondence with the REC will be retained in the Trial Master File/Investigator Site Files, for which the PenCTU/PIs will have responsibility respectively. An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended – this will be completed by Dr J Freeman (CI) in collaboration with the Trial Co-ordinator, Dr Hilary Gunn and the PenCTU.

PenCTU will notify the REC of the end of the trial. The REC will be notified if the trial is ended prematurely, including the reasons for the premature termination. Within one year after the end of the trial, Dr J Freeman in collaboration with Dr Gunn will submit a final report with the results, including any publications/abstracts, to the REC.

17.2 Protocol compliance

Any deviation from or non-compliance with the study protocol or GCP must be documented on the relevant study-specific form and reported to the CTU in accordance with written instructions provided. Deviations from the protocol which are found to recur frequently are not acceptable, will require immediate action and could potentially be classified as a serious breach. The CTU will review episodes of non-compliance with the CI/TMG (and Sponsor if appropriate) and every effort will be made to address any recurrent problems, including amendment of the study protocol if appropriate.

17.3 Notification of Serious Breaches to GCP and/or the protocol

A serious breach is a departure from the protocol and/or GCP during the trial conduct phase which is likely to affect to a significant degree:

a) the safety or physical or mental integrity of the trial participants; or

b) the scientific value of the trial

In the event of a serious breach occurring during the trial, the CTU will notify the CI and Sponsor immediately in writing and appropriate remedial action will be taken.

17.4 Data protection and patient confidentiality

17.4.1 Data Protection

All investigators and trial site staff will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles. Electronic trial records will be stored in a SQL server database, stored on a restricted access, secure server maintained by Plymouth University. Data will be entered into the database via a bespoke web-based data entry system encrypted using SSL.

Personal information will be collected, kept secure, and maintained so that:

- all CRF’s (source data) will be pseudo-anonymised by the use of unique participant identifying numbers
- the ID coded data and the linking code will be securely stored in separate locations using encrypted digital files within password protected folders and storage media
- only the research team will have access to the data

Confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators, as described in section 0, page 40.

The data will be stored by the sponsor for a minimum of five years following closure of the trial; Dr J Freeman (CI) is the data custodian.

17.4.2 Confidentiality

Individual participant medical data obtained as a result of this trial are considered confidential and disclosure to third parties is prohibited with the exceptions noted in section 16.

If information is disclosed during the trial that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

On all trial-specific documents, other than (a) the signed consent (b) the contact details form (providing the research team with contact detail information) the participant will be referred to by the trial participant number, not by name.

Qualitative telephone interviews and focus groups will be audio recorded on a digital audio recording device. On completion of the session, the data will be transferred to a University computer and erased from the device. On successful data transfer, the data on the audio recording device will be deleted.

17.5 Financial and other competing interests for the CI, PIs, TSC and DMC

At the time of writing the protocol it has been determined that there is no conflict of interest of any of the co-investigators or members of any of the trial committees in relation to:

- ownership interests related to the BRiMS programme
- commercial ties
- any non-commercial potential conflicts

17.6 Indemnity

The NHS indemnity scheme will meet the potential legal liability of the sponsor(s): -

- for harm to participants arising from the management of the research
- for harm to participants arising from the design of the research
- arising from harm to participants in the conduct of the research

This is an NHS-sponsored research trial. If an individual suffers negligent harm as a result of participating in the trial, the NHS indemnity scheme covers NHS staff and those people conducting the trial who have honorary contracts for research with the relevant Trust. Where organisations are non NHS then then this will be covered by the individual organisation’s relevant indemnity scheme. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but the normal NHS procedures for non-negligent harm will address this and an ex-gratia payment may be considered in the event of a claim.

17.7 Post-trial care

The Declaration of Helsinki 2013 states that “In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial”. This information will be disclosed to participants during the informed consent process. All individuals involved in the trial will continue to receive the usual care that they would receive once the trial is ceased. Participants in the intervention arm of the trial will continue to have access to the web-based resource, but they will not get any therapist feedback in the interactive elements.

17.8 Access to the final trial dataset

The research team will have access to the full dataset. After the end of the study, pseudo-anonymised information collected during the study will be made available to other researchers under an appropriate data sharing agreement, but it will not be possible to identify participants personally from any information shared.

18 DISSEMINATION POLICY

Results of this feasibility trial will inform the design of the anticipated definitive trial, rather than directly inform clinical decision making since clinical and cost effectiveness cannot be determined at this level. Hence dissemination, regardless of outcome, will focus on publication of the trial protocol, and related methodological issues, in an open access peer reviewed journal such as Pilot and Feasibility Studies. Conference proceedings describing the feasibility trial will be intended to engender enthusiasm for the potential future trial, as will trial summaries posted on to the websites/newsletters of the organisations who were involved in the recruitment process. In addition, all participants will be offered a lay summary of results and a clinically oriented summary will be provided to recruiting sites. A key output will be an application for funding for a definitive trial, if the results from this feasibility trial meets our criteria for progression.

18.1 Authorship eligibility guidelines and any intended use of professional writers

Authorship on the final trial report and future publications will, where appropriate be the named co-investigators and the Research Therapists involved in data collection.

19 PUBLIC AND PATIENT INVOLVEMENT

From the outset, our programme has been informed by people with SPMS. In 2010 this topic was identified by participants in our longitudinal trial evaluating mobility. A survey (n=116) asked for views about where our future research should focus: safe mobility and falls were priorities. Subsequently two discussion groups confirmed this and were used to focus research questions, determine acceptable trial designs and problem-solve implementation issues. People with SPMS have sat on advisory committees in our subsequent studies: the BRiMS programme is a direct output. People with SPMS have been intimately involved in the development of BRiMS through participation in the nominal group study (n=36, 50% pwMS), which was innovative in how it facilitated pwMS, health professionals, commissioners and the research team to work together. Dedicated training sessions (facilitated by the local NIHR User Involvement Group) supported pwMS to engage fully and confidently in the process. This high level of user engagement will continue throughout this feasibility trial: a person with MS is a co-applicant and will sit on the TMG. He will support the development of the qualitative interview schedule/evaluation/validation checks etc. An additional pwMS will sit on the TSC.

PwMS will be asked to provide advice on issues such as recruitment, and on participant materials such as the PIS, lay summary and publications designed for patient/general public consumption such as MS organisation newsletters. Participants from the nominal group phase, who helped us to design the BRiMS intervention, have given permission for us to involve them in related discussion groups; they will also be used as a sounding board for materials. Lay TSC members will be trained in elementary research design in-house; if further requirements become apparent during the trial, it will be provided. In line with INVOLVE guidance, lay members will be financially reimbursed to attend discussion groups/TSC/TMG meetings and the associated preparation time (included in the trial costs). The project team has a well-established relationship with the MS Trust and MS Society; both have been consulted about this application and are highly supportive.

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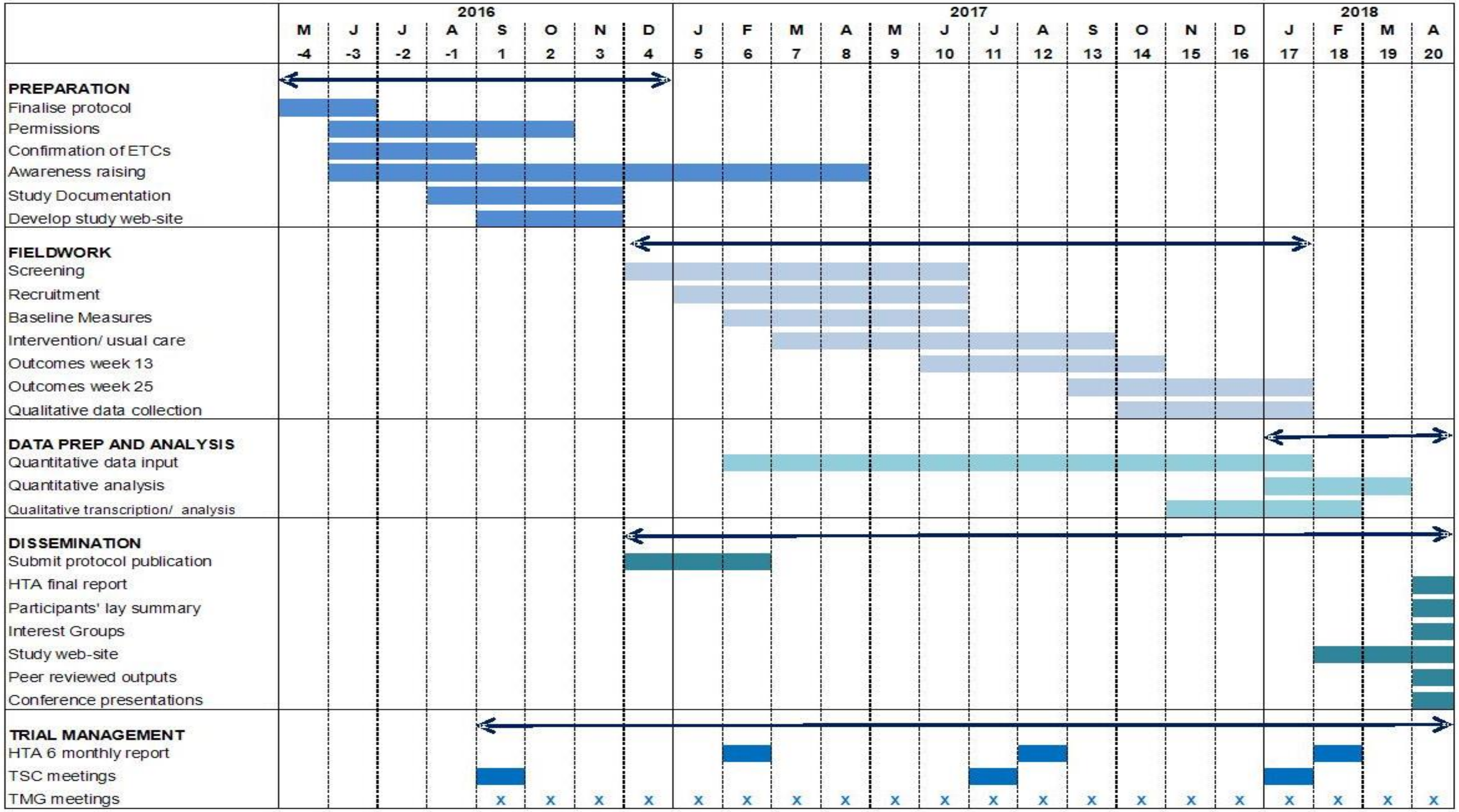
21 APPENDICES

Appendix 1 – Gantt Chart

BRiMS Trial Gannt Chart: HTA Project Ref No. 14/176/12



	2016								2017												2018			
	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A
	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
PREPARATION	←	─	─	─	─	─	─	→																
Finalise protocol	■	■																						
Permissions		■	■	■	■	■																		
Confirmation of ETCs		■	■	■																				
Awareness raising		■	■	■	■	■	■	■	■	■	■	■												
Study Documentation				■	■	■	■																	
Develop study web-site					■	■	■																	
FIELDWORK								←	─	─	─	─	─	─	─	─	─	─	─	─	→			
Screening								■	■	■	■	■	■	■										
Recruitment									■	■	■	■	■	■										
Baseline Measures										■	■	■	■	■										
Intervention/ usual care											■	■	■	■	■	■	■							
Outcomes week 13														■	■	■	■	■						
Outcomes week 25																	■	■	■	■	■			
Qualitative data collection																		■	■	■	■			
DATA PREP AND ANALYSIS																					←	─	─	→
Quantitative data input										■	■	■	■	■	■	■	■	■	■	■	■			
Quantitative analysis																					■	■	■	
Qualitative transcription/ analysis																			■	■	■	■		
DISSEMINATION								←	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	→
Submit protocol publication								■	■	■														
HTA final report																								■
Participants' lay summary																								■
Interest Groups																								■
Study web-site																						■	■	■
Peer reviewed outputs																								■
Conference presentations																								■
TRIAL MANAGEMENT					←	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	→
HTA 6 monthly report										■						■						■		
TSC meetings					■										■						■			
TMG meetings					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 2 – Outcomes

A. Primary Outcomes (objectives i, x, xi):

i. Walking

Multiple Sclerosis Walking Scale – 12 item (MSWS-12) Version 2.0[41]

The MSWS-12 is a widely used, patient-reported questionnaire that assesses the impact of MS on walking ability from the patient's perspective. The impact on 12 aspects of walking function and quality (walking, running, climbing stairs, standing, balance, distance, effort, support needed indoors, support needed outdoors, speed, smoothness, and concentration needed to walk) is assessed. There is evidence to support its internal consistency, reproducibility, validity, and responsiveness in a range of rehabilitation[41,42,43] and pharmaceutical studies.[44] All items have five response categories numbered one ("not at all limited") to five ("extremely limited"). Item scores are summed giving a total score whose range (12–60) is transformed to 0–100 (minimum to maximum walking disability) to ease interpretation.

ii. Measure of Health Related Quality of life

Two measures of disease specific health related QoL will be used:

1. EuroQoL [EQ5D-5L][45]

The EQ-5D (5L) is a standardised self-report measure of health status, recommended for use in UK health technology appraisals and health policy decision-making.[46] Taking approximately five minutes to complete, the EQ-5D collects data across five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is scored by the participant as no problems, slight problems, moderate problems, severe problems or extreme problems.

2. The 29-item Multiple Sclerosis Impact Scale [MSIS-29] Version 2.0[47]

The MSIS-29vs2.0 is condition specific measure of health-related QoL. This widely used self-report questionnaire was devised specifically for pwMS, and was founded on interviews with pwMS about how the disease impacted on their QoL. It consists of 29 items which all have five response categories numbered one ("not at all limited") to five ("extremely limited"); a higher score indicates greater impact on the individual's life. The MSIS-29vs2.0 provides domain scores for health-related QoL and summary scales for physical and psychological elements. There is good evidence to support its internal consistency, reproducibility, validity, and responsiveness.[47,48,49,50] Also of interest is that the MSIS-29vs2.0 data can be used to derive a MS specific preference based measure, the MSIS-8D,[51,52] which may be used in the assessment of cost effectiveness.

B. Secondary Outcomes (objectives i, x, xi)

i. Falls frequency and injury rates

Evaluation of falls status is important since there is a known link between falls status and activity curtailment[28] which may in turn impact on mobility and QoL. Falls will be defined as: "an unexpected event in which you come to rest on the floor or ground or lower level"[53] Falls will be assessed by prospective direct measurement as it is widely acknowledged that other methods lack reliability and validity.[54,55] In line with best practice guidance and recommendations from the IMSFPRN network, participants will be asked to prospectively record the number of falls and the number of injurious falls using a daily diary and return each completed diary on a monthly basis throughout the duration of the trial.[56] In addition, participants will record any injuries and the related use of medical services. The diary returns will be checked by PenCTU and participants will be contacted to remind them whenever any returns fall behind schedule.

ii. Activity Level

The level of Physical Activity will be objectively measured over a seven-day period after each trial assessment using an activity monitor (activPAL™, Paltechnologies Ltd, Glasgow).[57] The activPAL™ is a tri-axial accelerometer, worn on the thigh, which can record data continuously for up to 21 days. It attaches securely to the skin. The activPAL™, and its accompanying manufacturer's software, classifies activity in terms of the time spent sitting or lying, standing, stepping, number of steps taken, cadence and the amount of sit-to-stand and stand-to-sit transitions.

To ensure data collected are a true representation of the individual's physical activity five consecutive days of data are required.[58] Thus to improve the likelihood of achieving five full days of data, participants will be asked to wear the monitor continuously (24 hours a day) for seven consecutive days and to undertake normal daily activity. The device is attached to the participant's thigh and is not removed during the data collection period unless for taking a bath or swimming. The time spent in each posture and the number of steps will be averaged over the number of completed days. The activity monitor will be fitted to the participant at each assessment session and participants instructed to remove the device after seven days and post it back to the research team in the freepost padded enveloped provided .[59]

iii. Walking capacity

To complement the self-report MSWS-12vs2.0, an objective clinician-rated measure of walking capacity; the two-minute walk test (2MWT) will be undertaken. This determines the longest distance an individual can walk (using walking aids if required) over two minutes on a hard, flat surface[60] and strongly correlates to community mobility levels.[61] There is evidence to support the reliability, validity, and responsiveness of the 2MWT in a range of rehabilitation studies and reference values are available regarding clinically meaningful improvement, according to disability level, in pwMS).[60,61,62,63] The 2MWT has been recommended as the timed walking measure of choice for evaluating rehabilitation interventions in pwMS who have moderate disability,[63] which reflect the characteristics of our intended trial sample.

iv. Balance

Poor balance is a key modifiable risk factor for falls in MS[12] and is one of the primary targets of the BRiMS exercise component. Balance will be evaluated using the following two measures:

1. The Mini-BESTest, a 14-item clinician rated balance assessment tool that aims to target and identify the contributions of six different balance control systems to functional stability: anticipatory postural adjustments, reactive postural correction, and dynamic balance during gait (including cognitive effects).[64] Each item is scored on a three level ordinal scale (0-2), with higher scores indicating better performance; the maximum possible score is 28 points. The MiniBESTest has established psychometric properties, including excellent internal consistency, reliability, validity and responsiveness.[65] It was recently recommended for inclusion as part of a core outcome set for measuring balance in adult populations;[66]

2. The Functional Reach Test (FRT, forwards and lateral), is a clinician-rated measure of standing balance which mirrors the everyday activity of reaching for objects beyond arm's length. The person stands adjacent to a wall with shoulder flexed (forwards reach) or abducted (lateral reach) to 90 degrees, and leans forward (or laterally) as far as possible without stepping, thus testing the limits of stability. Measurements are taken with a metre rule. The FRT's are considered to be psychometrically robust for use in neurological clinical practice[67] and have been used in a number of MS interventional studies evaluating the effect of exercise interventions on balance.[68,69]

v. Fear of Falling

Fear of falling (FoF) has been highlighted as a risk factor for falls[70] and is also associated with activity curtailment in MS.[28] A reduction in FoF is therefore a potentially important outcome of BRiMS, given the recognised association between physical activity levels and QoL.[71] FoF will be measured with the Falls Efficacy Scale (International) (FESi)[72] which has been recommended by the European Falls network ProFane due to the speed and simplicity of completion.[53] The FESi has also been validated for use in ambulant pwMS, demonstrating excellent internal reliability and construct validity.[73] The FESi produces a single score based on the summed total of the individual responses to the 16 questions; the maximum possible score is 64, with higher scores indicating a greater degree of anxiety.

vi. Community Integration

Participation will be measured using the Community Participation Indicators (CPI),[74] a self-report measure which evaluates participation using three key indicators: engagement (20 items), involvement in life situations (14 items) and control over participation (13 items). There is preliminary evidence supporting its validity. Whilst its use has been relatively small scale to date, it has been recommended in an expert review paper published by members of the IMSFPRN.[75]

C. Measures of adherence to the BRiMS programme (objective vi-ix)

Attendance at the five face to face sessions (two individual and three group-based) will be monitored and recorded.

Participants are also advised to undertake a minimum of 120 minutes of home-based exercise per week for a minimum of 12 weeks, utilising a web-based physiotherapy programme; completing an exercise diary each time. Engagement in the home-based programme will be monitored based on the number of web-based log-in sessions and the exercise diary data recorded by the participant over the 12-week exercise programme; the adherence to each element will be calculated as a percentage. For example, with regard to adherence to the requested time spent exercising, the optimum duration of exercise is 24 hours (two hours per week for 12 weeks); thus if a participant completes 18 hours they will have 75% adherence. In addition, the weekly adherence will be monitored over the 12-week exercise programme.

Appendix 3 – Qualitative interviews

1:1 Telephone Interview Schedule (Participants)

Opening

The aim of today is to discuss your experiences of participating in the BRiMS trial. You have already read about this part of the trial in the information sheet, had the opportunity to ask questions and agreed that you are happy to take part. However, please can you confirm that you still consent to participate, and that you are happy for our conversation to be recorded?

Introductory questions

Can you tell me which area you are from (check which research cluster/ BRiMS programme (if any) participant was involved in)

What motivated you to volunteer for this trial?

Feasibility of trial processes

Firstly, I would like to find out about your experiences of being involved in the trial itself (i.e. not the intervention/ control group). We would really like your feedback on how the process was for you:

> *Prompts: Screening and Recruitment, Consent and Baseline Assessment, Follow up assessments. Areas to consider- suitability, acceptability, burden, ideas for improvement.*

The trial asked you to complete daily falls diaries and post them back to us. How was this for you?

> *Prompts: ease of completion, clarity of form, burden of daily completion, convenience of postal format (any alternative suggestions). Did reminders and periodic emails help/ hinder- any suggestions to change?*

Did you participate in the BRiMS programme?

If Yes:	If No:
• How did you feel when you were randomised to the intervention group? • Can you tell me about your overall experience of the programme? *Was it useful, what changes did participants make/ notice,* • How did you find the attended sessions? *Prompts: 1:1 sessions, home visit, group sessions. Areas to consider- suitability, acceptability, burden, ideas for improvement* • What about the online packages and home programme? *Prompts: Exercise resources, home packages, website as a whole* • How was the input from the programme facilitator? • What part(s) of the programme did you find most/ least helpful? • Were there any aspects of the programme that you would change? • In an ideal world is there anything else we could have included in the BRiMS programme? *Prompts: Encourage blue sky thinking and generation of ideas.* • What other ideas and suggestions could you make?	• How did you feel when you were randomised to the control group? • Did being in the control group impact on your view of the study?

Is there anything you would like to say that you don't feel you have had the chance to in this interview?

Thank participants for taking time for the interview. Explain that if they have any follow up questions or comments they are welcome to call/ email the researcher.

Telephone Focus Group Topic Guide (Treating Therapists)

Opening

Explain the role of the researcher during session. Check everyone is happy for the session to be recorded and reiterate that the audio recording will be transcribed and pseudo-anonymised. Remind everyone to speak loudly and clearly for the audio recording.

Prompt: Does anyone have any questions before we begin?

Introductory questions

It would be really helpful for each of you to give a brief summary of the programme(s) you ran, and one or two highs and lows based on your experiences

Key questions

- Topic area: format of the programme

Prompts: suitability, acceptability, burden, ideas for improvement. Consider all elements of the programme: 1:1 sessions, home visit, group sessions, home packages and web-based exercise.

- Topic area: content of the programme

Prompts: suitability, acceptability, burden, ideas for improvement. Consider both exercise and education elements of the programme

- Topic area: feasibility of the programme in daily practice

Prompts: time, expertise, practicality of mixed model of delivery, ?need for >one person in group sessions

- Topic area: training and support

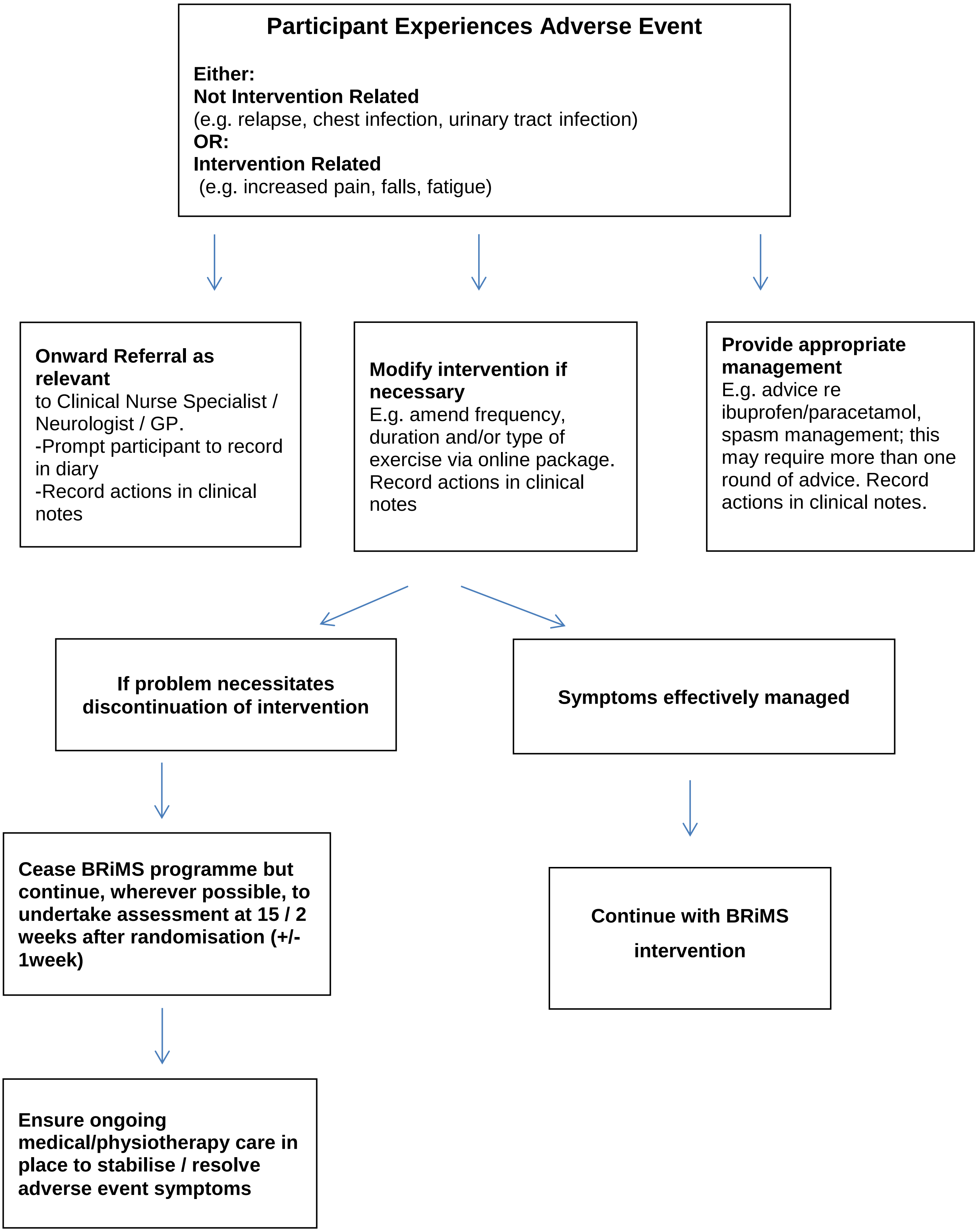
Prompts: time, content and delivery style, format and approach, suggestions for improvement

Ending questions

Is there anything anyone would like to talk more about? Have we missed anything?

Thank participants for taking time to join the focus group. Explain that if anyone has any follow up questions or comments they are welcome to call/ email the researcher.

Appendix 4 – Withdrawal Flowchart



Participant Experiences Adverse Event

Either:
Not Intervention Related
(e.g. relapse, chest infection, urinary tract infection)
OR:
Intervention Related
(e.g. increased pain, falls, fatigue)

Onward Referral as relevant to Clinical Nurse Specialist / Neurologist / GP.
-Prompt participant to record in diary
-Record actions in clinical notes

Modify intervention if necessary
E.g. amend frequency, duration and/or type of exercise via online package. Record actions in clinical notes

Provide appropriate management
E.g. advice re ibuprofen/paracetamol, spasm management; this may require more than one round of advice. Record actions in clinical notes.

If problem necessitates discontinuation of intervention

Symptoms effectively managed

Cease BRiMS programme but continue, wherever possible, to undertake assessment at 15 / 2 weeks after randomisation (+/- 1week)

Continue with BRiMS intervention

Ensure ongoing medical/physiotherapy care in place to stabilise / resolve adverse event symptoms

Appendix 5 – Amendment History

Details of all protocol amendments will be added here whenever a new version of the protocol is produced. All protocol amendments will be submitted to the Sponsor for approval prior to submission to the REC committee.

Previous Protocol version no/ date	Section	Details of changes made	Reason for change
Version 1_ 18AUG2016	8.2 ii and 8.2 iii	Qualitative assessments – addition of PIS and ICD to treating therapists focus group. Also removal of telephone call to withdrawing participants	Request of REC following meeting 01SEP2016
	10.2	Addition of site specific details to usual care section	
	Appendix 3	Removal of withdrawal participant questions	
Version2_11OCT2016	Pages 1, 3 and 4	Sponsor address has been updated	Required
	TRIAL SUMMARY Pages 6&7	Updated in accordance with other protocol changes	Consistency
	Trial Steering Committee page 8	Sentence removed	MS society declined
	2.3 Trial Outcome measures	Clarification of timing of outcome assessments in relation to randomisation	Following discussion between TMG and TSC
	2.3 Trial Outcome Measures (Bi) Fall Frequency	Clarification of process	Clarification
	2.3 Trial Outcome Measures (D) Economic Evaluation		

Previous Protocol version no/ date	Section	Details of changes made	Reason for change
Version2_11OCT2016	2.3 Trial Outcome Measures (Eii) Fidelity Testing	Clarification of process	Clarification
	Table 1: Summary of Outcome Measures	Clarification of timing of outcome assessments in relation to randomisation	Following discussion between TMG and TSC
	6.2 Screening Process (3rd paragraph)		Following discussion between TMG and TSC
	7.1 Randomisation & 7.2 Randomisation method	Both have been redrafted	Clarification
	8.1 Trial assessments and table 2	Clarification of timing of trial assessments in relation to randomisation	Following discussion between TMG and TSC
	8.1.1 baseline data, 8.1.2 Follow up assessments	Clarification of who is conducting trial assessments, when they are conducted and more precise description of the baseline data	Clarification
	8.2 (iii) and 9 Withdrawals	Clarification of process	Clarification
	13.1 Adverse Events		
	14.4 Determining Progression to the full trial	Addition for clarification	Following discussion with TSC
	15.3 Data handling and record keeping	Addition of a sentence to clarify collection of data from treating therapists	Clarification

Previous Protocol version no/ date	Section	Details of changes made	Reason for change
Version2_11OCT2016	Appendix 3	1:1 qualitative questions added again	Removed in error at previous protocol update
Version3_07DEC2016	Throughout	Substitution of the word ‘sites’ where ‘centres’ has been used	Consistency
	Throughout	Updated details of TMG member and protocol contributor Professor Lorna Paul	Change of title, contact details
	TRIAL SUMMARY Pages 6&7	Updated in accordance with other protocol changes	Consistency
	RECRUITMENT PATHWAY p16	Clarification of patient telephone contact to arrange Baseline visit and confirm eligibility	Clarification
	PARTICIPANT PATHWAY p17	Second group session – changed from “week 7” to “week 8”	Consistency
	5.1	Inclusion criteria amended: Confirmed diagnosis of ~~secondary progressive~~ multiple sclerosis as has been determined by a neurologist; (<u>additional text</u>) <u>and in the secondary progressive phase as confirmed by an MS Specialist clinician</u>	To reflect current practice in identifying diagnosis of disease progression
	6.1	Redrafted to clarify recruitment activities	Clarification