Study Short Title or Acronym

STIM MS

Full Study title

A randomised controlled feasibility study investigating surface neuromuscular **STIM**ulation as an exercise therapy versus usual care in people with multiple sclerosis **(MS)** to help improve lower limb strength, walking and fatigue (STIM-MS)

Protocol Version number and date

Version control: 1.2

Research Reference Numbers

IRAS Number:	341925
Sponsor Reference Number:	UoL001907
Funder Reference Number:	NIHR207134

Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

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

For and on behalf of the Study Sponsor:

Signature: **Date:**

……/……/……

……

Name (please print):

Mrs Karen Jennings-Wilding

Position:

Senior Clinical Research Governance Manager

Chief Investigator:

Signature: **Date:**

……/……/……

……

Name: (please print):

Dr Fraser Philp

Key Study Contacts

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Sponsor	The University of Liverpool is the research Sponsor for this Study. It is recognised that as an employee of the University the Chief Investigator has been delegated specific duties, as detailed in the Sponsorship Approval letter. For further information regarding the sponsorship conditions, please contact: Mrs Karen Jennings-Wilding Senior Clinical Research Governance Manager

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Study Summary

Study Design	A randomised controlled feasibility study with nested qualitative study
Study Participants	People with multiple sclerosis
Planned Size of Sample (if applicable)	68
Follow up duration (if applicable)	6 months
Planned Study Period	30 months 1st April 2025 to 30th September 2027
Research Question/Aim(s)	**Study aim** To determine the feasibility and acceptability of SNMES as an exercise therapy, for preventing muscle weakness, improving walking, fatigue and quality of life in people with MS to inform a future definitive trial of clinical and cost effectiveness. **Study objectives:** • Estimate screening, recruitment and attrition rates. • Determine the acceptability of the intervention and key aspects of study design including intervention • adherence rates, drawing on the Theoretical Framework of Acceptability (TFA) • Explore, via qualitative interviews, individuals' experiences of study participation (and where possible, reasons for non-participation) to gather feedback about the intervention, outcome measures and study procedures. • Inform primary outcome measure selection for a future trial. • Determine sample size for a future trial, informed by parameter estimates of outcomes. • Evaluate the acceptability and feasibility of health economics measures, including selection and ordering of questionnaires.

Funding and Support in Kind

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
NIHR - Research for Patient Benefit (RfPB) Programme: NIHR207134	£245,096.00

Protocol Contributors

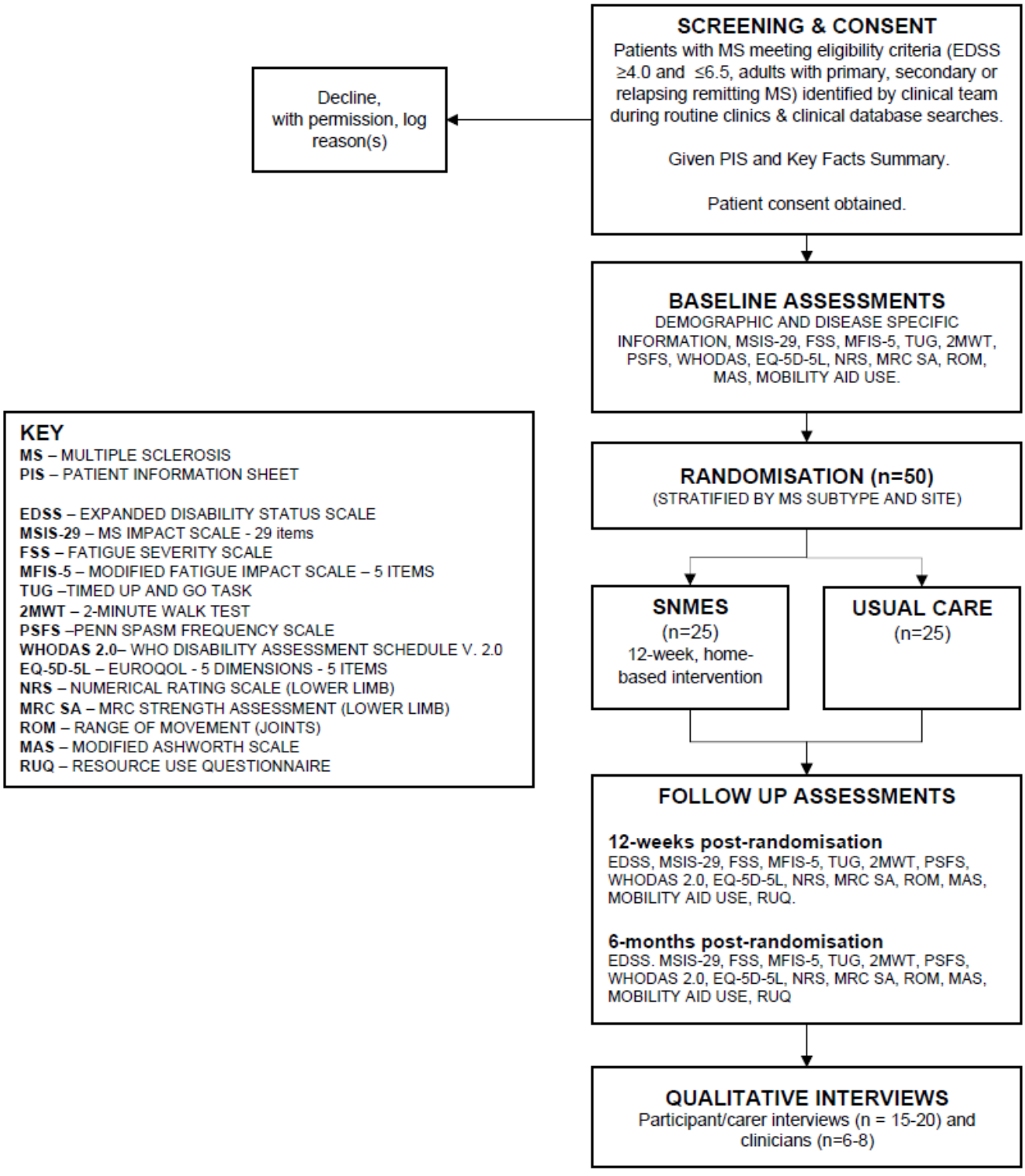
The Chief Investigator and all co-investigators have contributed to the development of the protocol.

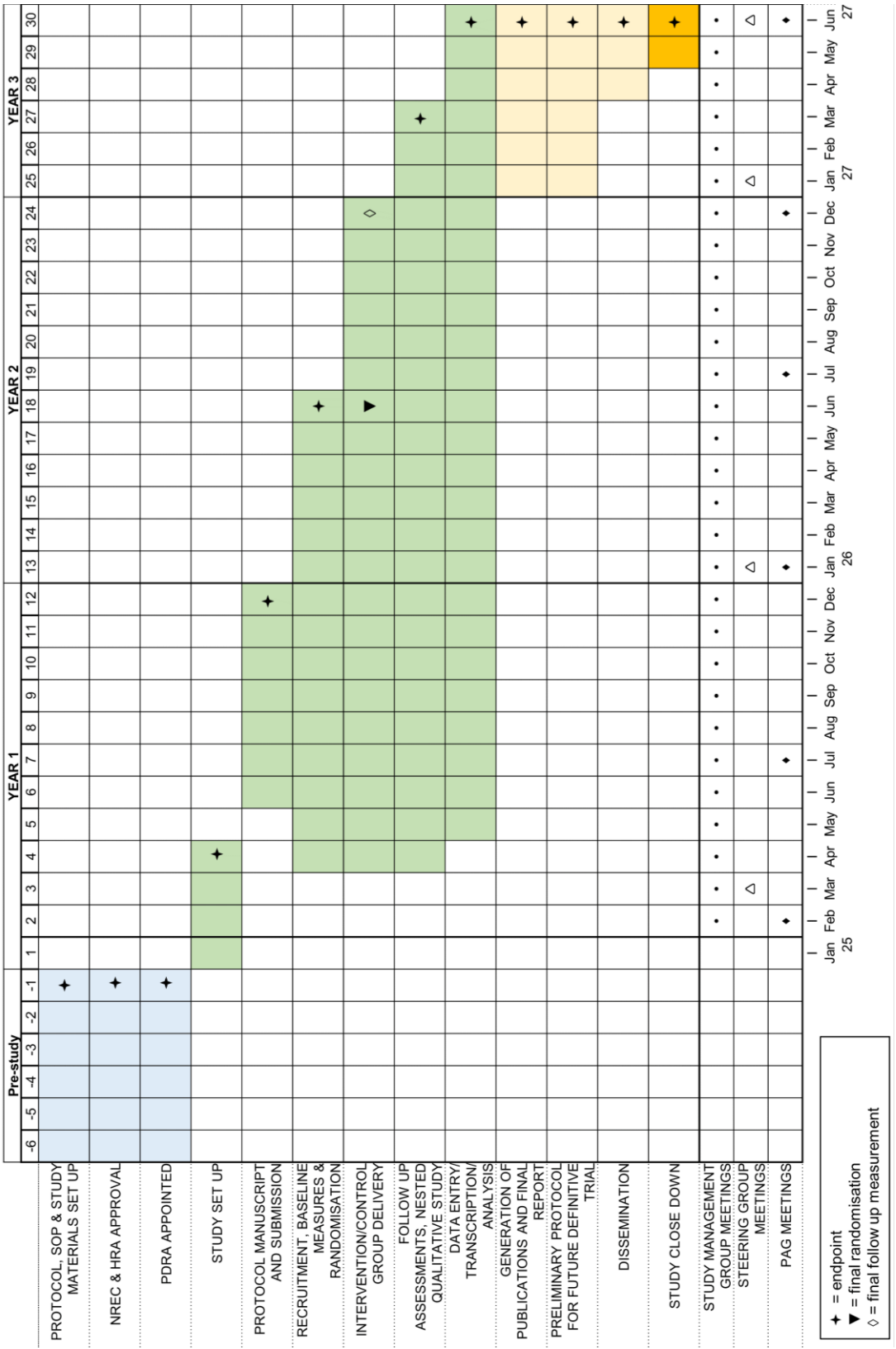
PPIE has contributed to the development of study materials and processes that are referenced in this document.

The sponsor has reviewed this document for approval.

Key Words: Multiple Sclerosis, Electrical stimulation, Rehabilitation, Randomised Controlled Trial

Study Flow Chart




Pre-study
YEAR 1
YEAR 2
YEAR 3
-6 -5 -4 -3 -2 -1 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec Jan Feb Mar Apr May Jun
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PROTOCOL, SOP & STUDY MATERIALS SET UP
NREC & HRA APPROVAL
PDRA APPOINTED
STUDY SET UP
PROTOCOL MANUSCRIPT AND SUBMISSION
RECRUITMENT, BASELINE MEASURES & RANDOMISATION
INTERVENTION/CONTROL GROUP DELIVERY
FOLLOW UP
ASSESSMENTS, NESTED QUALITATIVE STUDY
DATA ENTRY/ TRANSCRIPTION/ ANALYSIS
GENERATION OF PUBLICATIONS AND FINAL REPORT
PRELIMINARY PROTOCOL FOR FUTURE DEFINITIVE TRIAL
DISSEMINATION
STUDY CLOSE DOWN
STUDY MANAGEMENT GROUP MEETINGS
STEERING GROUP MEETINGS
PAG MEETINGS
✦ = endpoint
▶ = final randomisation
◊ = final follow up measurement

Glossary of Abbreviations

2MWT	Two-minute Walk test
6MWT	Six-minute Walk test
COM-B	Capability-Opportunity-Motivation-Behaviour
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
FSS	Fatigue Severity Scale
HRA	Health Research Authority
MAS	Modified Ashworth Scale
ModRUM	Modular resource use measure
MFIS-5	Modified Fatigue Impact Scale
MRC	Medical Research Council
MSIS 29	Multiple Sclerosis Impact Scale
MS	Multiple Sclerosis
NPRS	Numerical Pain Rating Scale
PPI	Public and patient involvement
PPIE	Public and patient involvement and engagement
PSFS	Penn Spasm Frequency Scale
REC	Research Ethics Committee
ROM	Range of Movement
SNMES	Surface Neuromuscular electrical stimulation
TFA	Theoretical framework of acceptability
WHODAS	WHO Disability Assessment Schedule

Contents

1 INTRODUCTION

This protocol describes a randomised controlled feasibility study investigating surface neuromuscular STIMulation as an exercise therapy versus usual care in people with multiple sclerosis (MS) to help improve lower limb strength, walking and fatigue (STIM-MS) and provides information about procedures for entering participants, study procedures, safety reporting and governance requirements. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study following receipt of required approvals.

Queries relating to this Study should be referred, in the first instance, to Dr Fraser Philp. This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and the UK GDPR as amended from time to time and any successor legislation in the UK and any other directly applicable regulation relating to data protection and privacy as well as any other regulatory requirements as appropriate.

2 BACKGROUND

Maintaining the ability to walk is the most important thing to people with MS.[1] Nearly half of all people with MS report difficulties with mobility one month after receiving a formal diagnosis.[2,3] At 10-years, 25% to 60% of people with MS are unable to walk without walking aids and 8% to 20% will be restricted to using a wheelchair or bed.[4] Walking ability is strongly linked to physical activity levels, long term management and ability to cope with MS, self-efficacy, employment status, care needs, fall risks and quality of life.[3] The annual economic impact of MS is approximately £1.4 billion.[5] Direct and indirect medical costs are 2 to 4 times higher in those with affected levels of mobility (<£1,000/person vs £2,000 to £4,000/person).[5]

Changes in walking ability, which correspond to Expanded Disability Status Scale (EDSS) categories, are associated with increased healthcare costs.[5-7] The EDSS score is a way of measuring how much someone is affected by MS and looks mainly at walking ability and other body functions such as muscle weakness, balance, tremors, eye movements and vision, swallowing, speech, sensory changes, bladder and bowel control, cognition, and memory. As people move from being independently mobile with no restrictions (EDSS 0 to ≤4) to needing

walking aids and having limited mobility (EDSS groups >4 to ≤7.5) mean costs in € (purchasing power parity (PPP)) increase from approximately €22,800 to €37,100 respectively. Once people become restricted to a bed or wheelchair (EDSS groups ≥8), care costs further increase to €57,500.[7] Worsening mobility and EDSS scores are associated with increased non-medical costs related to hospital attendances (inpatient, outpatient and emergency department), rehabilitation at home, aids and orthotics, modifications to people's homes and indirect costs to both people with MS and their caregivers.[6]

There are limited exercise-based rehabilitation options for people with MS and mobility issues (EDSS ≤4), particularly those with more progressive or higher levels of disability.[8-10] Current "usual" therapies have limited value as most people with MS are unable to participate at the required exercise intensity levels for improving or maintaining leg strength for walking[11] and achieving secondary health benefits. This may be due to severe fatigue, pain, spasms, low mood and depression, cognition, heat sensitivity, restricted joint movements (limb deformities) and spasticity.[12,13]

2.1 HOW DOES THE EXISTING LITERATURE SUPPORT THIS PROJECT?

Active exercise for MS is the primary method to prevent deterioration in both muscle structure and function (strength and fatigue).[9,10,14] However, people with MS who struggle to walk independently or without walking aids, may be unlikely to engage in exercise at an intensity that prevents progressive muscle wasting and deterioration in function. This could explain the small effect sizes associated with traditional exercise treatments.[14]

There are no phase III studies investigating the use of SNMES in people with MS.[15] Preliminary studies suggest that it can preserve or improve muscle structure and function, fatigue and potentially increase engagement with exercise-based interventions. However, existing studies are limited by small sample sizes and high drop-out rates.[16-20] Several studies have evaluated the broader use of electrical stimulation in MS; however, these have focused on functional electrical stimulation (FES) or assisted cycling, which are used in a distinctively different way to SNMES. FES can address impairments in walking, at a single joint e.g. lifting the foot up, but is not effective for strengthening and slowing down progressive changes in the lower-limb.[21] Cycling with electrical stimulation may increase leg strength and cardiovascular fitness but is not practical for all people with MS and settings, as it requires specialist and expensive equipment.[17,19]

2.2 EVIDENCE FOR SNMES IN DIFFERENT CLINICAL POPULATIONS

SNMES can help people whose conditions or symptoms prevent them engaging with conventional exercises at the required intensity for improving muscle strength and function. SNMES has been used to increase muscle strength and function in healthy individuals[22] and in multiple clinical conditions including stroke,[23,24] chronic obstructive pulmonary disease,[25,26] advanced coronary heart disease, thoracic cancer, older adults,[27] musculoskeletal and orthopaedic injuries,[22] dysphagia,[28] urinary incontinence[29] and hospitalised adults in ICU and non-ICU settings.[30] However, the majority of reviews conclude that the overall quality of evidence in support of SNMES is low-quality and further research of higher methodological quality is needed.

A 2023 systematic review concluded that SNMES combined with exercise significantly increases lower-limb muscle strength and power in both healthy individuals and those with musculoskeletal and orthopaedic injuries.[22] A 2018 Cochrane review in chronic obstructive pulmonary disease identified low quality evidence that SNMES in isolation increased muscle force, endurance, and walking performance (distance walked in 6-minutes) and time to symptom onset whilst decreasing reported leg fatigue.[25] When combined with exercise, SNMES increased walking performance and reduced time confined to a hospital bed (5 days) but evidence was low or very low quality. Evidence for combined SNMES and exercise on muscle force and quadriceps endurance was uncertain and of very low quality.[25] A more recent 2022 systematic review, based on similar studies identified low and very low quality evidence that SNMES increases exercise capacity and muscle strength in chronic obstructive pulmonary disease.[26] A 2016 Cochrane review reported SNMES improved quadriceps strength, muscle mass, and walking performance in advanced diseases including coronary heart disease, thoracic cancers and chronic obstructive pulmonary disease, although evidence was low quality.[15] A 2023 systematic review identified that SNMES improved walking performance in non-ICU hospital patients and muscle strength in ICU and non-ICU settings hospital settings.[30] A 2017 systematic review identified improvements in leg strength and balance in the older adults using SNMES.[27]

SNMES for the upper limb has been shown to have a moderate effect on functional activities of daily living, with only a trend observed in the lower-limb.[23] However, there are limited studies investigating use of SNMES in the lower-limb for stroke.[23] SNMES is recommended for strengthening muscles required for function in current clinical stroke guidelines for upper-limb

rehabilitation[24] and NICE guidelines for adults with dysphagia[28] and stress urinary incontinence.[29]

2.3 PREVIOUS PILOT WORK

We have demonstrated that SNMES is acceptable to and feasible for unimpaired and older adults.[31] Preliminary results suggest SNMES may increase lower-limb strength and muscle hypertrophy, particularly in those who have a previous history of exercising.[31] Our upper limb neurorehabilitation SNMES research in people affected by stroke has shown it to be acceptable and feasible,[32] with an evaluation in patients and therapists of barriers and facilitators to its use, which have been used to inform this study.[33] We have conducted phase I and II randomised controlled trials investigating if upper limb SNMES can be used to prevent complications (pain and contractures) associated with disuse in stroke survivors.[34-37] Disuse in both stroke and MS causes muscle wasting and decreased strength which is reversible with SNMES. Prolonged disuse can cause irreversible changes to the muscle resulting in contractures and limb deformities, which limits exercise ability and subsequent treatment effectiveness. SNMES may prevent these occurring.

3 RATIONALE FOR CURRENT STUDY

Mobility loss is considered one of the most disabling and visible consequence of MS.[38] This application addresses five priorities for MS from the James Lind Alliance i.e. evaluating which treatments are effective to slow, stop or reverse the accumulation of disability (priority-1), help fatigue (priority-3), support self-management (priority-4), improve mobility (priority-7) and evaluate physiotherapy's effectiveness in reducing disability (priority-10).[39]

SNMES has been used to make the muscles of people with MS contract in a similar way to resistance training, achieving the levels required to preserve or improve muscle structure and function needed to help with mobility and walking.[16-20] SNMES could address existing barriers to exercise experienced by people with MS, such as access to exercise facilities, expensive equipment and fatigue.[40,41] This would enhance individuals' ability and opportunities (key components of the COM-B (Capability-Opportunity-Motivation-Behaviour) model), for engagement in exercise-based rehabilitation, potentially increasing independence and quality of life, whilst also decreasing years lost to disability.[11]

If people with MS maintain or improve their leg strength this can keep them walking for longer and prevent a downward spiral of reduced exercise tolerance, progressive muscle wasting and leg weakness, worsening fatigue and sequelae associated with physical deconditioning e.g. joint contractures and cardiovascular complications. Ultimately this could reduce the care burden experienced by people with MS, their carers and the services used in the management of their condition.

4 THEORECTICAL FRAMEWORKS

This project will draw on several theoretical frameworks as identified below.

SNMES intervention

The delivery and rationale for the intervention is informed by the COM-B (Capability-Opportunity-Motivation-Behaviour) model (figure 1).[11] The SNMES intervention addresses components related to capability and opportunity. SNMES could address existing barriers to exercise experienced by people with MS, such as access to exercise facilities, expensive equipment and fatigue.[40,41]

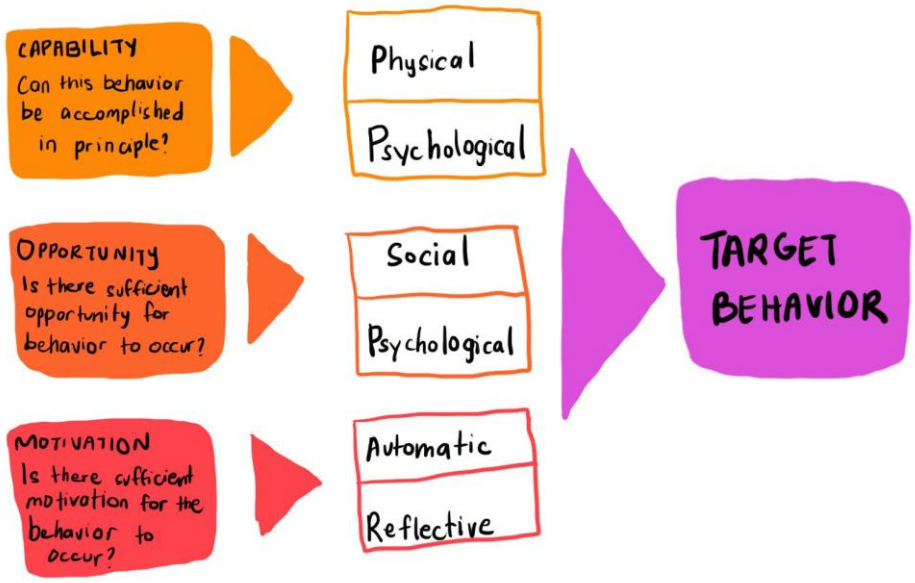


Figure 1. Outline of the COM-B model

Image taken from The decision lab - *https://thedecisionlab.com/reference-guide/organizational-behavior/the-com-b-model-for-behavior-change*

To facilitate engagement and compliance with the intervention, the following health behaviour strategies will be used in line with the COM-B model. During the intervention participants will

- Be provided with education of SNMES use and expectations. These will be delivered verbally and in accessible written and audio/ video formats. During the education sessions people will be instructed how to perform the behaviour and provide background information, discuss goal setting, problem solving and commitment.

- These will be supported by a resource provided to participants for goal setting alongside logging their use of the device, identifying aspects of their care and for facilitating compliance and retention.
- Undertake graded increments of SNMES use and intensity to facilitate a sense of achievement.
- Participants will be contacted after the first week and at 6-weeks to see how they are getting on (behavioural monitoring with feedback).
- Participants will also be provided with technical support contact details (social support practical).

Recruitment and retention

To facilitate recruitment and mitigate against drop out we will draw on behavioural interventions and a combined strategy approach (figure 2).[42] This will be applicable to people involved in running the study and participants.

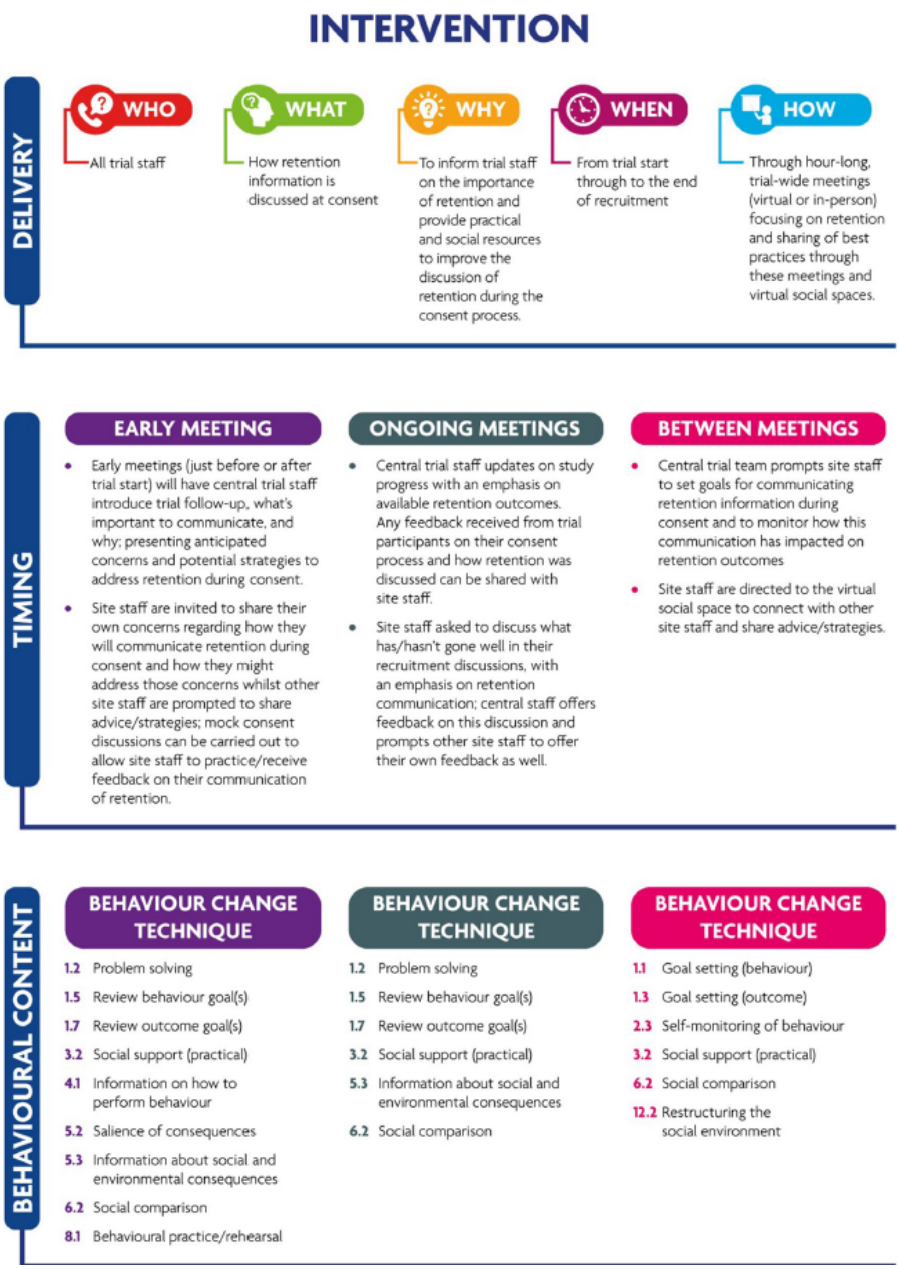


Figure 2. Overview of the behavioural strategy intervention to facilitate retention. Image taken from Coffey et al 2023 *https://doi.org/10.1186/s13063-023-07268-2*

Development of topic guides and analysis of study findings

The nested qualitative study will draw on the Theoretical Framework of Acceptability (TFA)[43] for development of the topic guides and mapping of the qualitative findings from the semi-structured interviews for participants and people involved in delivering the study (figure 3).

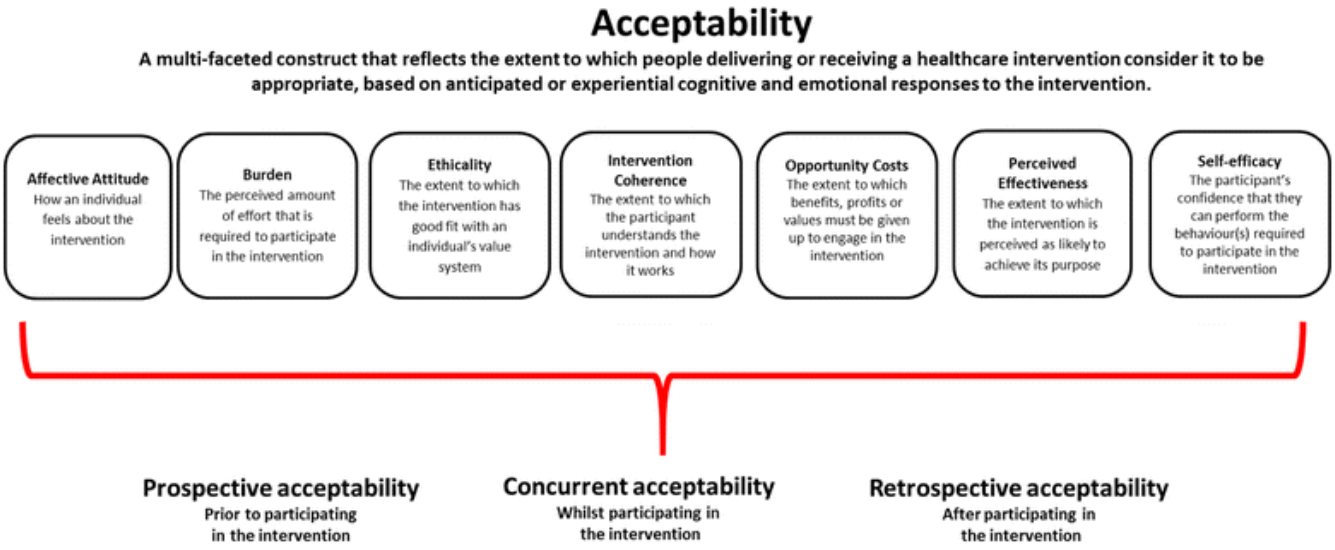


Figure 3. The theoretical framework of acceptability. Image taken from Sekhon et al 2022

https://doi.org/10.1186/s12913-022-07577-3

5 RESEARCH QUESTION/AIM(S)

Study aim

To determine the feasibility and acceptability of SNMES as an exercise therapy, for preventing muscle weakness, improving walking, fatigue and quality of life in people with MS to inform a future definitive trial of clinical and cost effectiveness.

5.1 OBJECTIVES

Study objectives:

- Estimate screening, recruitment and attrition rates.
- Determine the acceptability of the intervention and key aspects of study design including intervention adherence rates, drawing on the Theoretical Framework of Acceptability (TFA).[43]
- Explore, via qualitative interviews, individuals' experiences of study participation (and where possible, reasons for non-participation) to gather feedback about the intervention, outcome measures and study procedures.
- Inform primary outcome measure selection for a future trial.
- Determine sample size for a future trial, informed by parameter estimates of outcomes.
- Evaluate the acceptability and feasibility of health economics measures, including selection and ordering of questionnaires.

5.2 OUTCOME

To determine if a future definitive trial exploring the effectiveness and cost effectiveness of SNMES is feasible and warranted, and identify any requirements for improving recruitment, retention and delivery of the intervention.

6 STUDY SETTING

Multiple sclerosis services based at the Walton Centre, Liverpool and the Royal Wolverhampton NHS Trust. Activities across both sites will be the same. SNMES will be used at home with baseline and follow up appointments at the hospital sites.

7 SAMPLE AND RECRUITMENT PARTICIPANT ENTRY

7.1 ELIGIBILITY CRITERIA

7.1.1 For people with MS involved in the randomised controlled trial

7.1.1.1 Inclusion Criteria

- Adults with primary progressive, secondary progressive or relapsing remitting MS.
- Expanded disability status scale score ≥4.0 and ≤6.5.
    - 4= Significant disability, self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m.
    - 6.5= Requires two walking aids to walk about 20m without resting)

7.1.2 Exclusion Criteria

- Clinically isolated syndrome.
- People with MS in an active relapse or <8-weeks since a relapse.
- Lower-limb peripheral nerve injury.
- Fixed lower-limb contractures.
- Contraindications to SNMES.
    - Pregnancy
    - Uncontrolled Epilepsy
    - Any of the following in the lower limbs
        - Peripheral nerve injury
        - Unstable fractures or orthopaedic condition affecting the lower limb
        - Cancer (malignancy) in the areas of the electrode placement
        - Skin infection / devitalised skin at the electrode placement site

- Unable to apply and control SNMES device or braces independently or with carer assistance.
- Other co-morbidities that could affect mobility/additional underlying condition e.g. stroke.

Cardiac pacemaker/history of cardiac problems will not be a reason for exclusion, but recruitment will be subject to cardiologist approval.

7.1.3 Nested qualitative studies (semi-structured interviews)

Inclusion criteria for people with MS

- People with MS who were eligible for and took part in either arm of the randomised controlled trial will be eligible for the nested qualitative study

Exclusion criteria for people with MS

- People with MS who were not eligible for and did not take part in either arm of the randomised controlled trial will be eligible for the nested qualitative study

Inclusion criteria for carers of people with MS who were involved in the study

- Carers or people who help look after people with MS that were involved in the study.
    - This includes provision of informal or formal care, assistance with activities related to the study including attendance of hospital visits, use of the SNMES device, recording of information related to healthcare visits, physical activity or exercise.

Exclusion criteria for carers of people with MS who were involved in the study

- Carers or people who help look after people with MS but were not involved in the study will not be eligible.

Inclusion criteria for healthcare practitioners and staff involved in the study

- Healthcare practitioners and staff (clinical and non-clinical) who were involved in the set up or delivery of the study.

Exclusion criteria for healthcare practitioners and staff involved in the study

- Healthcare practitioners and staff (clinical and non-clinical) who were not involved in the set up or delivery of the study.

7.2 RECRUITMENT

7.2.1 Screening

7.2.2 Recruitment for people with MS and the randomised controlled trial

Potential participants will be identified and screened by a researcher or a member of their care team via

- attendance at routine MS clinic appointments and
- searching of respective unit patient databases.

People with MS who meet the eligibility criteria will be provided with verbal and written information (study related documents and a Key Facts sheet).

They will be given as much time as they need to decide whether to take part and will have opportunities to ask questions. Participants who express an interest in the study will be followed up by their local research team or the research assistant (minimum 24 hours after being informed about the study) by telephone to discuss the study in more detail.

We will use purposive sampling across people with MS, people with MS and carer dyads to ensure diversity in characteristics of treatment allocation (intervention vs usual care), high versus low engagement/adherence with the SNMES intervention, study recruitment site and patient demographics/protected characteristics. We will also collect reasons for declining participation or stopping the intervention in the study (where possible). All people with MS in the study will be informed about the interview and consistent with the principles of purposive sampling be recruited based on personal and study characteristics.
People with MS and their carers will be recruited in dyads but interviewed separately.

7.2.3 Recruitment for carers of people with MS who were involved in the study

Carers of people with MS who were involved in the study will be recruited alongside recruitment of people with MS during

- attendance at routine MS clinic appointments
- during attendance at any of the hospital visits for the clinical measurements

Carers of people with MS will also be provided with verbal and written information (study related

documents and a Key Facts sheet). They will be given as much time as they need to decide whether to take part and will have opportunities to ask questions. Participants who express an interest in the study will be followed by their local research team or the research assistant (minimum 24 hours after being informed about the study) by telephone to discuss the study in more detail.

7.2.4 Recruitment for healthcare practitioners and staff involved in the study

Healthcare practitioners and staff involved in the study will be recruited from sites involved in the set-up, running and delivery of the study. Participants will be recruited during the processes related to site initiation, regular updates and study site close meetings. We will also use our regular study update newsletter to help with recruitment of healthcare practitioners and staff involved in the study.

Healthcare practitioners and staff who meet the eligibility criteria will be provided with verbal and written information. They will be given as much time as they need to decide whether to take part and will have opportunities to ask questions. Participants who express an interest in the study will be followed by a member of the Liverpool research team (minimum 24 hours after being informed about the study) by telephone to discuss the study in more detail.

7.3 INFORMED CONSENT

Three different consent forms have been developed. These are

- a combined consent form for people with MS in the randomised controlled trial and nested qualitative study
- a consent form for carers of people with MS who were involved in the randomised controlled trial
- a consent form for healthcare practitioners and staff involved in the study

Our PPI group has reviewed both the consent forms and accompanying information sheets to provide feedback on the overall readability, clarity and accessibility for people with MS. Based on their feedback we have made changes to the consent forms. This includes

- use of a single rather than multiple consent forms for people with MS in the randomised controlled trial and nested qualitative study.

- We have also received feedback regarding the information sheets and consent forms from our clinical partners.

Participants who express an interest in the study will be followed by their local research team or the research assistant (minimum 24 hours after being informed about the study) by telephone to discuss the study in more detail. A member of the research team will spend time discussing the research with participant and carer to ensure that all their questions and concerns are addressed.

Conversations during the consenting process have been identified as an important part of our recruitment and retention strategy. In combination with the information sheets and study materials, conversations at the consent stage will ensure that participants are fully informed of the study including:

- Time commitments, intervention and control group processes, are clear in relation to study duration
- Expectations of participants
- Understand importance of completing all relevant study outcomes / questionnaires and impact of drop out or non-engagement.

Consent will be obtained at the baseline measures visit for people with MS in the randomised controlled trial and nested qualitative study. During the visit, the participants and their carer will be provided with an additional opportunity to ask questions. Once that is completed, the researcher will provide the consent form to the participant and their carer and will explain the purpose of the appropriate consent form.

For carers of people with MS who were involved in the randomised controlled trial

Consent will be gained prior to the semi-structured interviews. Prior to the interview they will be provided with an additional opportunity to ask questions. Once that is completed, the researcher will provide the consent form to the participant and explain the purpose of the appropriate consent form.

For criteria for healthcare practitioners and staff involved in the study

Consent will be gained prior to the semi-structured interviews. Prior to the interview they will be

provided with an additional opportunity to ask questions. Once that is completed, the researcher will provide the consent form to the participant and explain the purpose of the appropriate consent form.

7.4 STUDY DESIGN AND METHODS OF DATA COLLECTION

7.4.1 Study design

A randomised controlled feasibility study comparing SNMES plus usual care versus usual care only with a nested qualitative study.

This will involve

1) A randomised controlled trial comparing SNMES plus usual care (n=25) versus usual care only (n=25). Total of 50 participants.
2) A nested qualitative study using semi-structured interviews for people with MS who took part in either arm of the randomised controlled trial and their carers (n=15-20).
3) A nested qualitative study using semi-structured interviews for healthcare practitioners and staff who were involved in the set up or delivery of the study and intervention (n-6-8).

7.4.2 Data collection

A study flowchart through has been provided under the heading "Study flowchart". Participants will be required to attend the hospital a total of 3 times for the

- Baseline
- 3-month and
- 6-month timepoints. This is for clinical measures and collection of patients reported outcome measurements.

At each timepoint the relevant outcomes and clinical measures as identified in table 1 will be collected. Questionnaires may be sent out to participants (via email or post depending on their preference) prior to their attendance of the hospital visits. Instructions for collection of the

clinical measures and outcomes are outlined below.

An overview of the outcome measures to be collected and associated timepoints are provided below in table 1

Some participants and their carers will also have a qualitative interview after the 3-month or 6-month time points.

Table 1 – Overview of outcomes and timepoints for the study

Outcome	Description	Screening	Baseline	12 weeks*	6 months
Expanded Disability Status Scale (EDSS) [44]	Level of functional disability	✓		✓	✓
Demographic & disease characteristics	Patient information and disease classification		✓		
Timed up and Go (TUG)+ [45,46]	Muscle function / balance		✓	✓	✓
2 minute walk test (2MWT) [47]	Exercise tolerance		✓	✓	✓
Penn Spasm Frequency Scale (PSFS) [48]	Spasm frequency		✓	✓	✓
Multiple Sclerosis Impact Scale (MSIS-29v2) [86]	Quality of life measure		✓	✓	✓
Fatigue Severity scale (FSS) [49+]	Energy and drive (fatigue)		✓	✓	✓
5 -item Modified fatigue impact scale (MFIS-5) +	Impact of fatigue on cognitive, physical and psychosocial function		✓	✓	✓
World Health Organisation Disability Assessment Schedule (WHODAS 2.0) [50]	Measure of disability		✓	✓	✓
EQ-5D-5L [51]	Health related quality of life		✓	✓	✓
Resource use questionnaire (ModRUM) [52,53]	Health resources used and accessed			✓	✓
Numerical rating scale (Lower-limbs)	Pain		✓	✓	✓
MRC strength assessment (Lower-limbs)	Clinical scale of strength		✓	✓	✓
Joint range of movement (Lower-limbs)	Movement at the joints		✓	✓	✓
Modified Ashworth Scale[54]	Measure of muscle stiffness		✓	✓	✓
Level of impairment (Walking aids)	Type and number of		✓	✓	✓

	walking aids used				

** (Primary endpoint); ⁺measures of MS in exercise core set[34]*

7.4.3 Protocols for the completion of the clinical measures and outcome measures

7.4.4 Demographic and disease characteristics

7.4.4.1 Expanded disability status scale (EDSS)

The expanded disability subscale score is to be determined during screening, at 12 weeks and 6 months. Grey shaded EDSS scores indicate eligibility criteria at baseline for involvement in study.

EDSS Score	Descriptor	Select
0	Normal neurological exam, no disability in any FS	
1.0	No disability, minimal signs in one FS	
1.5	No disability, minimal signs in more than one FS	
2.0	Minimal disability in one FS	
2.5	Mild disability in one FS or minimal disability in two FS	
3.0	Moderate disability in one FS, or mild disability in three or four FS. No impairment to walking	
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking	
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m	
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m	
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m	

5.5	Disability severe enough to preclude full daily activities. Able to walk without aid or rest for 100m	
6.0	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting	
6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting	
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to wheelchair; though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 hours a day	
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorised wheelchair	
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally has effective use of arms	
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions	
9.0	Confined to bed. Can still communicate and eat	
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow	
10.0	Death due to MS	

7.4.4.2 Demographic characteristics

The following demographic characteristics will be recorded at baseline

- Date of birth
- Age at visit
- Sex assigned at birth
- Ethnicity
- Height
- Weight
- MS subtype
- Years since diagnosis
- Annual relapse rate[1] [55]
- Number of previous relapses

f

7.4.4.3 Relapses

A relapse is defined as "a *new symptoms or worsening of existing symptoms, causing neurological dysfunction for a minimum of 24 hours without any signs of infection or fever"*.[55] Exacerbation must be preceded by a stable 4-week period. In these cases, these will be noted by the study team. In the case of relapses, the study neurologist will be consulted and a time for return to the intervention will be agreed by them. Relapses will be confirmed in medical records and by a neurologist.

At each relevant time point e.g. follow up calls (Weeks 1 and 6), 12-weeks and 6-months post randomisation measurements, we will also ask and note if participants had any fluctuations in symptoms or medically confirmed relapses since enrolling on the study. We will additionally review the medical records of participants at the final follow up measure timepoint to identify if they have had any relapses.

[1] Annual relapse rate is calculated for each patient by dividing 365 days with the number of days in the study and multiplying by the number of relapses in the study period

7.4.4.4 Level of impairment (Walking aids)

Researcher to identify walking aids used

Walking aid	Tick
Independently mobile - no walking aids	
1 x walking stick (Fisher stick / cane)	
1 x elbow crutch	
2 x walking sticks (canes)	
2 x elbow crutches	
Rollator frame	
Zimmer frame	
Wheeled zimmer frame	
Ankle & foot orthosis (AFO) - single leg	
Ankle & foot orthosis (AFO) - bilaterally	
Functional electrical stimulation (FES) - single leg	
Functional electrical stimulation (FES) - bilaterally	
3 wheeled walker	
Gutter frame	
Gutter rollator frame	
Other (please state)	

7.4.5 Outcome measures related to MS symptoms and healthcare resource use

7.4.5.1 Multiple Sclerosis Impact Scale (MSIS- 29v2)

Based on Hobart et al 2001 [56] and Hobart et al 2009 [86]

Self-reported questionnaire – see outcome measure sheet

7.4.5.2 Fatigue severity scale (FSS)

Based on Krupp et al 1989 [57]

Self-reported questionnaire – see outcome measure sheet

7.4.5.3 Modified Fatigue Impact Scale – 5-item version (MFIS-5)

Based on D'Souza et al 2016 [49]

Self-reported questionnaire – see outcome measure sheet

7.4.5.4 World Health Organization Disability Assessment Schedule 2.0 - 36 version (WHODAS 2.0)

Based on Young et al 2023 [50]

Self-reported questionnaire – see outcome measure sheet

7.4.5.5 European Quality of Life 5 Dimensions 5 Level Version (EQ-5D-5L)

Based on Balestroni et al 2012 [51]

Self-reported questionnaire – see outcome measure sheet

7.4.5.6 Modular resource-use measure (ModRUM)

Key references Thorn et al 2018[52], Garfield et al 2021[58], Garflied et al 2023[53]

Self-reported questionnaire – see outcome measure sheet

7.4.5.7 Numerical rating scale (Lower limbs)

Based on The British Pain Society 2019 [59]

The Numerical Rating Scale (NPRS-11) is an 11-point scale for self-report of pain.

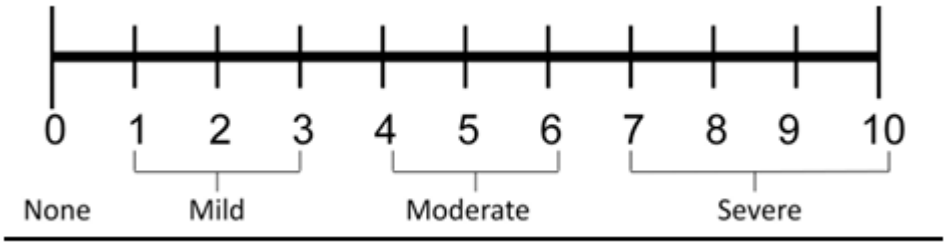
The respondent selects a whole number (integers 0–10) that best reflects the intensity (or other quality if requested of their leg pain.

- Legs scored together

Instructions for carrying out the test

The NPRS can be administered verbally (therefore also by telephone) or graphically for self-completion.

How intense was your pain on average last week (7 days) on a scale of 0 (no pain) to 10 (worst pain imaginable)



No pain Worst pain imaginable

7.4.5.8 Penn spasm frequency scale (PSFS)

Key references Priebe et al 1996 [60] and Penn et al 1985 [61]

Self-reported measure that assesses an individual's perception of spasticity frequency and severity.

- Legs scored together

Scoring: The Penn Spasm frequency Scale is comprised of two parts:

- Part 1 - spasm frequency and
- Part 2 - spasm severity.

Instructions for carrying out the test

Self-reported outcome measure. See outcome measure sheet for instructions and criteria.

A score is awarded based on the criteria below

Part 1 – Spasm frequency

Level	Description
0	No spasms
1	Mild spasms induced by stimulation
2	Infrequent full spasms occurring less than once per hour
3	Spasms occurring more than once per hour
4	Spasms occurring more than 10 times per hour

Part 2 – Spasm severity

Level	Description
1	Mild
2	Moderate
3	Severe

7.4.6 Clinical measures and exercise testing

7.4.6.1 Lower limb range of movement ROM (Knee and ankle)

Instructions adapted from Tidy's physiotherapy 2003 – Musculoskeletal assessment – Chapter 11 [62]

Required equipment (clinician)

- Goniometer
- In some cases visual estimation maybe used e.g.
    - Where the position of the limb is at easily recognizable range of movements such as fully extended = 0°, bent to 90° etc
    - where the range of movement for active is the same as the passive range of movement visual estimation maybe used

Instructions for carrying out the test

- These may be conducted with the participant sitting.
- If a plinth, bed or appropriate piece of equipment is present that allows the participant to lie down in a suitable position for carrying out the measurements.
- The test may be done for up to maximum of 3 times for each movement.
- Active range of movement is completed by the participant moving the joint as much as possible using their own muscles.
- Passive range of movement is completed by the researcher or practitioner moving the joint of the participant as much as possible.

7.4.6.2 Assessing knee ROM

Active range of motion

- The **axis** of the goniometer should be positioned over the lateral femoral condyle.
- The **static arm** should be parallel with the long axis of the femur towards the greater trochanter.
- The **dynamic arm** should be positioned parallel to the long axis of the fibula and lateral malleolus
- Measurements to be conducted for
    - Extension

- Flexion

- If the participant can hyper extend this should be reported as a negative value e.g. -5°

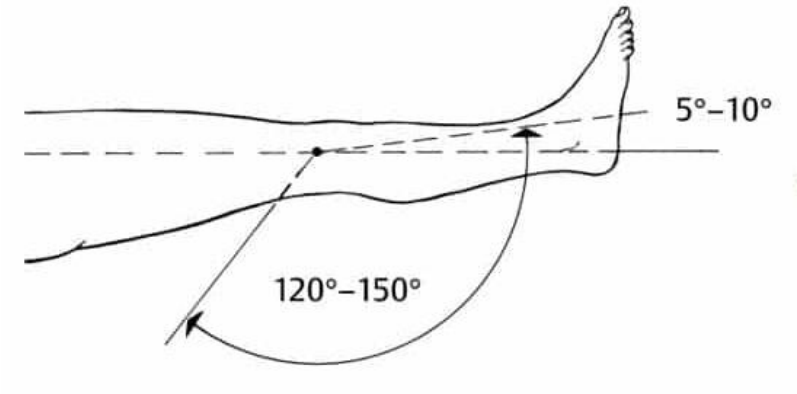


Image taken from OrthoFixar.com

Passive range of motion

- For each of the respective movement the limb should be taken to the end of its available range.
- Using the same axis and arm locations above measure the passive range of movement.
- Measurements to be conducted for
  - Extension
  - Flexion

7.4.6.3 Assessing ankle ROM

- The **axis** of the goniometer is placed just inferior to the lateral malleolus.
- The **static arm** should be parallel to the fibula.
- The **dynamic arm** should be parallel to the long axis of the fifth metatarsal
- Measurements to be conducted for
    - Plantarflexion
    - Dorsiflexion

- The neutral or 0° position of the ankle is determined with the ankle in an orthogonal or 90° to the shank participant
- Values for plantar flexion and dorsiflexion are reported as positive i.e. 10°

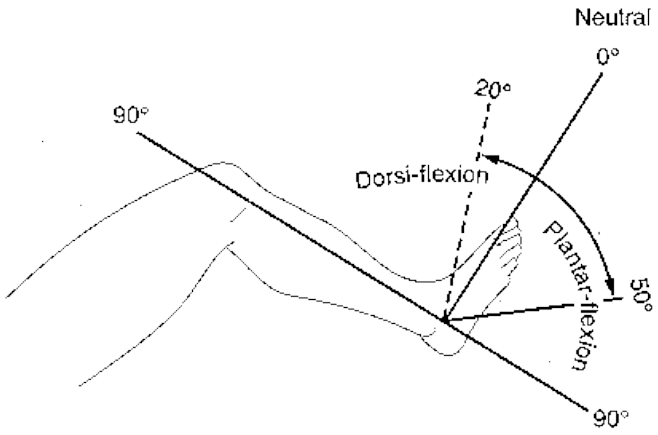


Image adapted from Luttgens & Hamilton, 1997 [63]

Passive range of motion

- For each of the respective movement the limb should be taken to the end of its available range.
- Using the same axis and arm locations above measure the passive range of movement.
- Measurements to be conducted for
    - Plantarflexion
    - Dorsiflexion

7.4.6.4 MRC Oxford strength assessment (Knee and ankle)

- The Oxford Scale is a quick method of assessing and grading muscle power.
- The Oxford Scale is a 0-5 scale which is then recorded as 0/5 or 2/5.
- Only whole numbers should be used for the assessment e.g. **no** use of + or - sign qualifiers should be used.
- The researcher should position the participant in the appropriate posture to allow accurate assessment and allow good vision and palpation of the appropriate structures.
- The muscles will be tested isometrically, usually in their mid-range and **NOT** through range.
- The movements being evaluated are
    - Knee extension strength
    - Knee flexion strength
    - Ankle dorsiflexion strength
    - Ankle plantarflexion strength
- This is achieved by positioning
    - Ankle joint in neutral (foot orthogonal to the shank)
    - Knee in 90° of flexion.
- The position of the limb may be adjusted to elicit a better contraction from the muscle group being tested.
- Instruct the participant that you are going to apply some resistance to the limb and that you want them to resist you.
- Verbal encouragement is allowed.
- A maximum of up to three tests are allowed, with the highest value being recorded.
- A score is awarded based on the criteria below

Level	Description
0	No contraction at all
1	Flicker of contraction only (visible/palpable muscle contraction), movement of the joint does not occur
2	movement is possible only with gravity and the weight of the limb counterbalanced
3	Movement against gravity only

4	Movement against gravity with some resistance
5	Movement against gravity with full resistance

7.4.6.5 Modified Ashworth test (MAS)

The modified Ashworth test will be used to assess the stiffness of the flexors and extensors of the knee and ankle joints.

- Legs and joints scored independently

Instructions for carrying out the test

- These may be conducted with the participant sitting.
- If a plinth, bed or appropriate piece of equipment is present that allows the participant to lie down in supine.
- The participant should be relaxed during the testing.
- The test may be done for a maximum of 3 times for each muscle group.

- When testing a muscle that primarily flexes a joint, place the joint in a maximally flexed position and move to a position of maximal extension over one second (count “one thousand one”).
- When testing a muscle that primarily extends a joint, place the joint in a maximally extended position and move to a position of maximal flexion over one second (count “one thousand one”).

The muscle groups to be assessed are for both the left and right legs are

- Knee joint through flexion– from fully extended to flexed
    - assessing knee extensors (quads)
- Knee through extension – from fully flexed to extended
    - assessing knee flexors – (hamstrings)
- Ankle joint through plantar flexion – from fully dorsiflexed to plantar flexed
    - ankle dorsiflexors (tib ant and toe extensors)
- Ankle joint through dorsi flexion - from fully plantar flexed to dorsi flexed
    - ankle plantar flexors (triceps surae and toe flexors)

A score is awarded based on the criteria below

Score	Descriptor
0	No increase in muscle tone
1	Slight increase in muscle tone, with a catch and release or minimal resistance at the end of the range of motion when an affected part(s) is moved in flexion or extension
1+	Slight increase in muscle tone, manifested as a catch, followed by minimal resistance through the remainder (less than half) of the range of motion
2	A marked increase in muscle tone throughout most of the range of motion, but affected part(s) are still easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) rigid in flexion or extension

7.4.6.6 Common equipment needed for Timed up and Go and 2MWT (clinical measures)

Required equipment (clinician)

- stopwatch
- two small cones to mark the turnaround points
- worksheets on a clipboard
- a measuring wheel
- telephone
- a source of oxygen
- sphygmomanometer
- automated electronic defibrillator

Required equipment (participant)

- Participants should use their usual walking aids during the test (cane, walker, etc.).

Safety considerations

1. Testing should be performed in a location where appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the person supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The researcher collecting the measurements should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support. A certified individual should be readily available to respond if needed.
4. Medical doctors are not required to be present during the test. The Principal Investigator after consultation with the wider research team may decide whether attendance by a medical doctor at a specific test is required.
5. If a participant is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed in their medical care plan.

Reasons for immediately stopping a TUG or 2MWT include the following:

1. chest pain,
2. intolerable dyspnea,
3. leg cramps,
4. staggering,
5. diaphoresis (excessive or abnormal sweating for no apparent reason) and
6. pale or ashen appearance.

The researcher must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the participant should sit or lie supine as appropriate depending on the severity or the event and the researcher's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

7.4.6.7 Timed up and Go (clinical measure)

Adapted from Podsialdo and Richardson 1991 [45]

Required equipment (clinician)

- stopwatch
- a chair that can be easily moved along the walking course
- 3.5 m hallway
- 30 m walkway

Location

- The Timed up and Go should be performed indoors, along a long, flat, straight, enclosed space with a hard surface. For the test, avoid corridors or spaces that are busy, used by lots of other people and have a high volume of footfall.
- Place a standard height chair at the beginning of the walkway

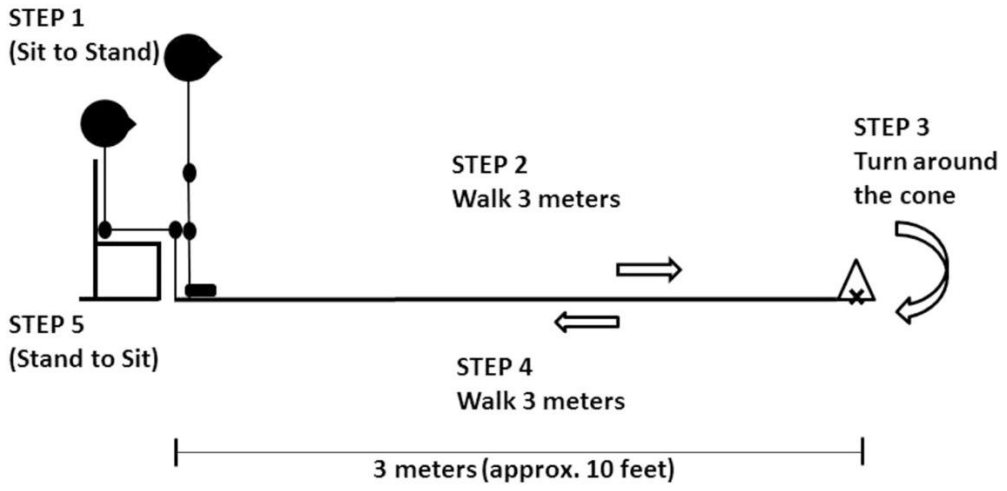


Image taken from Emerson Sebastião et al 2016 [46]

Measurement (carrying out the test)

- A "warm-up" period before the test is not required.
- A practice round may be performed if required but ensure that the participant has adequate time after this to recover.
- The participant should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.
- During this time make sure that clothing and shoes are appropriate.

Instructions for carrying out the test

1. The participant should sit on a standard armchair, placing their back against the chair and resting their arms chair's arms.
2. The upper extremities should not be on the assistive device (if used for walking), but it should be nearby.
3. Regular footwear and customary walking aids should be used.
4. Instruct the participant as follows:

- *The aim of this test is to assess the way you walk and balance.*
- *The test will start when I say Go.*
- *From sitting you will stand up, walk to the line/ cone that is 3 meters way, turn around at the line/cone walk back to the chair and sit down.*
- *I will stop the timer when your buttocks touch the seat*
- *The aim of the test is to see how fast you can do this but "You should walk at a comfortable and safe walking speed."*

5. Demonstrate the test to the participant.
6. A stopwatch should be used to time the test (in seconds).
7. When the participant is ready say

"Go"

8. Start the stopwatch

9. Do not talk to anyone during the walk. Use an even tone of voice if required to instruct the participant.

7.4.6.8 Two-minute walk test (2MWT) (clinical measure)

Instructions adapted from the ATS statement: guidelines for the six-minute walk test.[64]

Required equipment (clinician)

- countdown timer (or stopwatch)
- mechanical lap counter
- a chair that can be easily moved along the walking course
- 30.5 m hallway.
- 30 m walkway
- markings on floor

Location

- The 2MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface. For the test, avoid corridors or spaces that are busy, used by lots of other people and have a high volume of footfall.
- The walking course must be 30 m in length. A 30.5 m hallway is, therefore, required.
    - In relation to the 6MWT from which the 2MWT is adapted, most 6MWT studies have used a 30-m corridor [65], but some have used 20- or 50-m corridors.[66,67]
    - A multicenter study found no significant effect of the length of straight courses ranging from 15 to 50m, but patients walked farther on continuous (oval) tracks (mean 92m farther).[68]

- The length of the corridor should be marked every 3 m.
- The turnaround points should be marked with a cone (such as an orange traffic cone).
- A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly coloured tape.

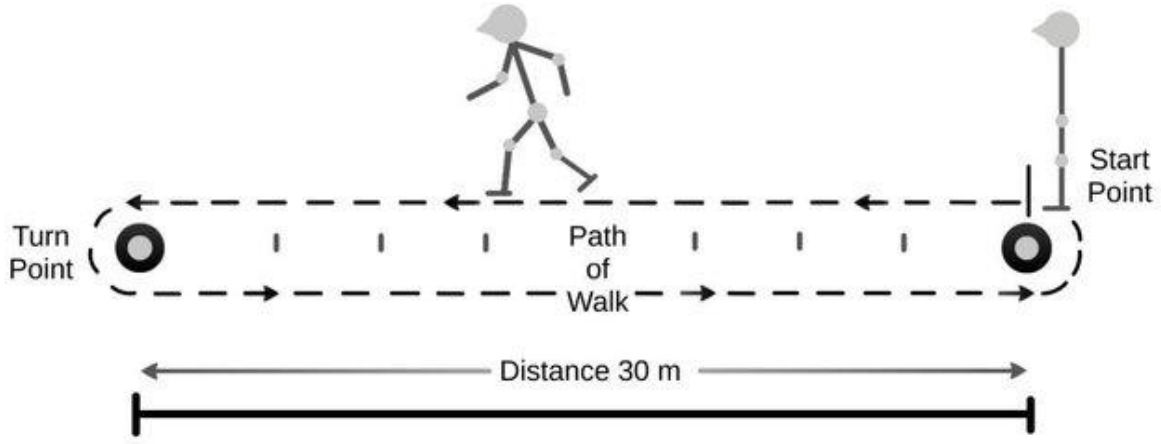


Image taken from Benavent-Caballer (2016) [69]

Measurement (carrying out the test)

- A "warm-up" period before the test should not be performed.
- Participants are allowed to stop and rest during the test.
- The participant should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.
- During this time, researcher may adjust the space for the setup of the 2MWT.

After the test

1. Record the time taken to complete the timed up and Go.
2. Congratulate the participant on good effort and offer a drink of water.

Instructions for carrying out the test

1. Set the lap counter to zero and the timer to 2 minutes.
2. Assemble all necessary equipment (lap counter, timer, clipboard, worksheet) and move to the starting point.
3. Instruct the participant as follows:

- *"The object of this test is to walk as far as possible for 2 minutes.*
- *Walk continuously, if possible, but do not be concerned if you need to slow down or stop to rest.*
- *The goal is to feel at the end of the test that more ground could not have been covered in the 2 minutes.*
- *You may lean against the wall while resting or we can provide a chair if required but resume walking as soon as you are able.*
- *You will be walking back and forth around the cones.*

- ***Now I'm going to show you. Please watch the way I turn without hesitation."***
    - *Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.*

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

- *Start now, or whenever you are ready."*

4. Position the participant at the starting line. You should also stand near the starting line during the test. Do not walk with the participant unless support is required. As soon as the participant starts to walk, start the timer.
5. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases

of encouragement. Watch the participant. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

- After the first minute, tell the participant the following (in even tones):

"You are doing well. You have 1 minute to go."

- When the timer shows only 30 seconds remaining, tell the participant:

"You are doing well. You have only 30 seconds to go."

- Do not use other words of encouragement (or body language to speed up).
- When the timer is 15 seconds from completion, say this:

"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

- When the timer rings (or buzzes), say this:

"Stop!"

- Walk over to the participant. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

After the test

3. Post-test: ask this:

"What, if anything, kept you from walking farther?"

4. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
5. Record the number of laps from the counter (or tick marks on the CRF).
6. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the CRF.
7. Congratulate the participant on good effort and offer a drink of water.

7.4.7 Randomisation

Randomisation lists will be generated using block randomisation with random variable block length, stratified by site and MS type, and a 1:1 randomisation ratio.

Lists will be produced by an independent statistician at Liverpool Clinical Trials Centre (LCTC).

Participant allocations will be irrevocably generated upon completion of the web-based randomisation form by a delegated member of the trial research team. Allocation concealment will be ensured as the service will not release the randomisation code until the participant has been recruited into the trial; this takes place after completion of all baseline measurements.

7.4.8 Intervention arm - SNMES plus usual care

Participants in the SNMES intervention arm will be provided with

- SNMES equipment needed
    - 1 x SNMES device
    - 2 x knee braces
    - 2 x ankle foot orthoses
    - 4 x big electrode pads
    - 4 x small electrode pads
    - 1 x spare 9v battery
- Supporting documentation
    - 1 x SNMES instruction and activity workbook including diary.
    - 1 x Moving more with MS booklet
    - 1 x Chartered Society of Physiotherapy – 6 exercises for staying steady booklet

Participants will be provided with the SNMES device and instructed how to use it. This includes a demonstration and acclimatization session, in which the researcher will go through set up and a series of SNMES cycles on each of the relevant muscle groups with the participant. The session will include instructions on placement of the stimulation pads, fitting the braces and selecting the correct program using the stimulator. The SNMES program will be set up on the device for the participant to use and saved

as a customized setting. The researcher will also discuss how the intervention may be adapted for use at home to ensure intervention fidelity is maintained and participants use the device safely. This will include precautions for using the device and indications for stopping as per instruction manual and workbook. The researcher will show the participant the workbook and signpost them to the section regarding instructions on using the device, study timeline and key dates to help with planning, importance of completing the measures and recording information related to device use, other physical activity and health resources used and support contact information. They will be advised to continue with their normal exercise and physical activity routines and will continue to receive their usual care.

Participants will be encouraged to set individual goals, self-monitor progress and undertake graded increases in SNMES intensity.

Participant set up for use of the SNMES device and maintaining intervention fidelity

The therapeutic effects of SNMES are achieved by the muscle contracting against resistance with the proximal and distal segments orientated at roughly 90 degrees to each other so that the muscle is in its's middle range. For clinical purposes this would be

- Knee joint flexed to 90°
- Ankle joint in neutral or 0°

* For pragmatic purposes a tolerance of up to 30 degrees (in either direction) is permissible at the knee joint and 15 degrees is permissible at the ankle joint i.e.

- Knee joint within 60 to 120 degrees of flexion.
- Ankle joint within 15 degrees of plantar or dorsiflexion

Contractions should be isometric, but it is recognized that some small movement within a constrained range of motion may occur.

It is anticipated that the SNMES program will be carried out with the participant in sitting, however some participants carry out the SNMES program in half or full lying. It is not recommended that participants carry out the SNMES program in standing for safety reasons and risk of falling.

To maintain the joint during the contraction, participants will be provided with knee and ankle braces. In some cases, participants may choose to not use the braces for all exercises, as long as the position of the joint is maintained during contraction.

If participants can sit and rest their feet on the floor, it is likely that the knee braces will not be required. If the participant can progress to an intensity at which the leg moves, despite resting on the floor, then a knee brace should be used.

Assuming the limbs of the participants are contracting against a comfortable and sufficiently soft surface that

1. does not compromise the integrity of the skin,
2. pose a risk of falls or
3. result in excessive movements

adaptations to the participants position should be allowed. Some examples of acceptable modifications to the participant position include:

Lying

Bilateral example

- Participant supine, knees flexed between 60° to 120° with pillows under knee joint, heels supported (either with or without brace)
    - hamstrings contract pulling heels into bed or brace
    - quads contract pulling quads against brace / heavy duvet / blanket over feet
- Participant supine (bed or floor), ankles in neutral, feet flat against surface/ wall (either with or without brace)
    - SNMES causing calves to contract pushing against surface

Seated

Bilateral example

- Participant sitting in chair, with knees flexed to 90° and lower legs against the chair (no brace fitted)
    - hamstrings contracting pulling heels into chair

- Participant sitting in chair, with ankle in neutral, pushing down on both knees or with weight on knees
    - claves to contracting pushing toes into floor

Unilateral examples (lying and sitting)

- In cases where legs are stimulated unilaterally, resistance may be offered by using the other limb. E.g. crossing the non-stimulated leg over or under e.g. quads or hamstring contractions respectively or pushing against the bottoms of the non-stimulated leg e.g. dorsiflexion contraction

Other modifications

In some cases, participants may have access to exercise facilities or equipment which may be used around the ankles or feet to provide resistance to the movement caused by the SNMES e.g. ankle weights.

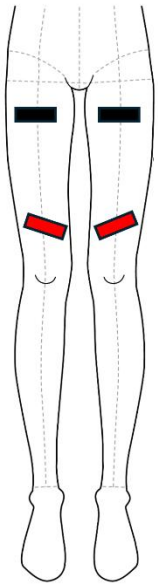
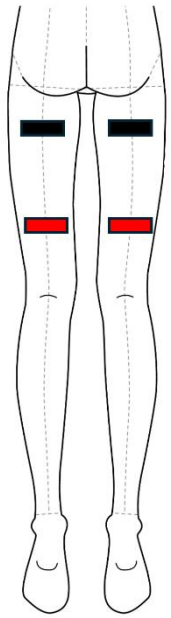
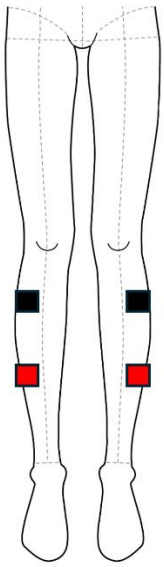
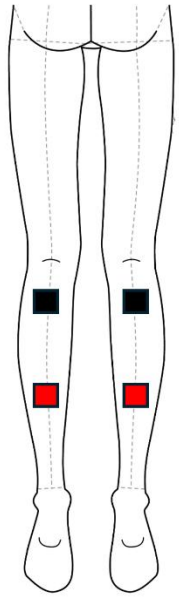
In some cases, the weight of the limb, particularly for knee extension exercises may be sufficient for the resistance required.

The underlying principles regarding Frequency, Intensity, Time and Type are listed in table 2

Table 2 – overview of FITT principles re interventions

Frequency	Participants should aim to stimulate each muscle group at least twice per week. This may be done over 3 to 4 sessions
Intensity	Parameters for the muscle stimulation are: • Pulse frequency: 50Hz • Pulse duration: 450μs • ON:OFF time 5:10 secs • Intensity: maximum tolerated (ma) • Total number of contractions = 45
Time	Each muscle group will take approximately 12 minutes to stimulate. Participants are advised to stimulate 2 muscle groups per session equating to approximately 30 minutes including set up time
Type	Isometric resistance training

The bilateral thigh (quadriceps and hamstrings) and shank (triceps surae and tibialis anterior) muscles will be stimulated. An outline of the pad placements has been provided below.

FRONT THIGH MUSCLES Large stimulation pads	BACK THIGH MUSLES Large stimulation pads
	
FRONT LOWER LEG MUSCLES Smaller stimulation pads	BACKLOWER LEG MUSCLES Smaller stimulation pads
	

As per the activities outlined in the workbook, participants will be encouraged to set individual goals, self-

monitor progress and undertake graded increases in SNMES intensity.

Participants will progressively work towards 3 to 4 -sessions per week over a 12-week period with a maximum of 36-sessions in total. The researcher will suggest to participants that they start with aiming for a total of 15 minutes per day so that they get comfortable with the machine and get a sense of achievement.

A suggested program has been identified as per below.

Day 1	Thigh workout • 15 mins bilateral thighs • 15 mins bilateral quads
Day 2	Lower leg workout • 15 mins bilateral tibialis anterior • 15 mins bilateral triceps surae
Day 3	
Day 4	Thigh workout • 15 mins bilateral thighs • 15 mins bilateral quads
Day 5	Lower leg workout • 15 mins bilateral tibialis anterior • 15 mins bilateral triceps surae
Day 6	
Day 7	

However, participants may choose to vary the program to suit their activities and symptoms.
Modifications may include stimulating

- Alternating front and back leg muscles e.g. quads and tib ant one day then hamstrings and triceps surae muscles another
- Stimulating their legs unilaterally e.g. stimulating their left quads and hamstrings together followed by tibialis anterior triceps surae in the same day (co-contractions). They would do the alternative leg the next day and repeat both legs later in the week.

Participants will be contacted after

- the first week and at
- 6-weeks to see how they are getting.

7.4.9 Control arm – usual care only

Participants in the control group will be provided with

- Documents
    - 1 x usual care information booklet and recording diary.
    - 1 x Moving more with MS booklet
    - 1 x Chartered Society of Physiotherapy – 6 exercises for staying steady booklet

Participants in the control group will continue to receive their usual care provided by their MS team. Participants will attend the clinic for baseline measurements and will complete the same outcome measures and assessments at equivalent timepoints to those in the SNMES arm.

The researcher will show the participant the information booklet and signpost them to the sections regarding the study timeline and key dates to help with planning, importance of completing the measures and recording information related to device use, other physical activity and health resources used and support contact information. They will be advised to continue with their normal exercise and physical activity routines and will continue to receive their usual care.

Consistent with the retention strategy of the study the researcher will discuss the importance of the control arm and implications for drop out.

7.4.10 Nested qualitative studies (semi structured interviews)

7.4.10.1 People with MS and carers

Semi-structured interviews will be conducted via telephone on online depending on the participants preference. Interviews will be exploratory and conversational, guided by flexible topic guides which have been developed with our PPI group.

The topic guides draw upon the Theoretical Framework of Acceptability (TFA)[43] and include questions related to experiences of study participation decisions, recruitment and randomisation processes, study arm allocation, perceptions of what outcomes are important, feedback on study information/materials and how to improve them, barriers and facilitators to engaging with the intervention, and any concerns. Interview formats will be considerate of individuals' needs e.g. provision of prior materials in different user-friendly formats, accommodative of fatigue levels (e.g. incorporating a rest break, if desired). Prior to the interviews we will also send people with MS a copy of the questions from the topic guide. The topic guides have been developed with our PPIE group to ensure they are appropriate and accessible to people with MS.

Interviews will be conducted by the research assistant who will be supported by a qualitative researcher on the study team.

Interviews, conducted in a timely manner after the 12-week end-point, were chosen rather than focus groups to minimise recall bias, help engage those who dislike group discussions and facilitate ease of scheduling around participants' availability.

7.4.10.2 Healthcare practitioners and staff involved in the study

Acceptability evaluation will be supplemented by interviews with healthcare practitioners and staff who were involved in the set up and delivery of the study.

Interviews will be conducted by a qualitative researcher from the University of Liverpool. Interviews, conducted in a timely manner during and after recruitment period of the study.

Separate topic guides have been developed, that are similar to those used for people with MS and their carers but also include additional questions related to the practicality of delivering the intervention across settings and recommendations for a future definitive trial. The topic guides have been developed with our PPIE group and clinical partners.

For all groups

All interviews will be audio-recorded using an encrypted Dictaphone, transcribed, anonymised and checked.

8 ADVERSE EVENTS

8.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject, including unfavourable and unintended signs, including abnormal laboratory results, symptoms or a disease associated with treatment.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Potential adverse event for this study

- Falls resulting from use of the SNMES machine or associated equipment.
- Muscle or joint injury requiring hospitalisation or attendance at a hospital/ GP or community-based services.

Previous research has identified no adverse events associated with SNMES in MS.[70]

Adverse reactions

Adverse reactions are derived mainly from those associated with exercise interventions in MS. As the SNMES is intended to replicate physiological demands consistent with exercise these have been included here.

- joint pain
- muscle pain or delayed onset muscle soreness
- sprains
- strains
- local muscle fatigue
- central fatigue
- wounds
- illness

Unexpected

The following events have been reported in the literature

- blood pressure spike (n=1 participant) - osteoarthritis population [71]
- Orthostatic events MS (n=2 participants) [72]
- superficial burn due to improper configuration (n=1 participant) [73] [74]

8.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

8.2.1 Non-serious Adverse Events (AEs)

Adverse Events (AEs) are any untoward medical occurrence in a patient or clinical study subject, including unfavourable and unintended signs, including abnormal laboratory results, symptoms or a disease associated with treatment.

All such events, whether expected or not, should be recorded. All adverse Events will be recorded for your study. These are usually always be recorded on a Case Report Form (CRF) and in the patient's medical notes.

8.2.2 Serious Adverse Events (SAEs)

Upon identification of an SAE the Principal Investigator should complete a study specific SAE form and sent to the Chief Investigator/Study Team within 24 hours. Relapse and death due to Multiple Sclerosis, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

Contact details for reporting SAEs

Please send SAE forms to: sponsor@liverpool.ac.uk and f.philp@livepool.ac.uk

Tel: 07717 863747 (study sponsor) (Mon to Fri 09.00 – 17.00)

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

- **'related'**, i.e. resulted from the administration of any of the research procedures; and
- **'unexpected'**, i.e. an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the HRA Non-CTIMP safety report to REC form. The Chief Investigator must also notify the Sponsor of all SAEs.

For NHS REC approved studies please refer to https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/ - (Scroll to Safety reporting for non-CTIMP studies).

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLING

9.1.1 Sample Size

Quantitative sample size

As this is a feasibility study, no formal sample size calculation for comparative estimates has been carried out. The aims are to provide robust estimates of rates of consent, retention, and adherence to the intervention and to gain estimates of the outcome event rates to accurately inform power calculations for a future definitive trial. We aim to recruit 50 participants across two sites over a 15-month period. Allowing for 20% loss to follow up, data will be available for 40 participants. A sample size has been chosen to ensure the objectives of the study can be met.

If we identify 100 eligible patients, we will be able to estimate a consent rate of 50% to within a confidence interval of +/-10%. If 50 patients are recruited, we will be able to estimate a retention rate of 80% to within a confidence interval of +/-11%. If we obtain complete data on 40 participants, we will be able to estimate an adherence rate of 60% to within a confidence interval of +/-15%.

Nested qualitative study

We will conduct semi-structured interviews with people with MS and their carers (n=15-20), and separate interviews with clinicians (n=6-8) who supervised/delivered the intervention. Sample size is informed by the information power concept, taking account of the study's well-defined aim, focused data gathering, preparation and ongoing review to enable informative dialogue during interviews and use of case analysis in combination with previous research.[75]

9.1.2 Sampling Technique

Randomised controlled trial

Potential participants will be identified and screened by a researcher via attendance at routine MS clinic appointments and searching of respective unit patient databases. People with MS who meet the eligibility criteria will be provided with verbal and written information.

Nested qualitative study

We will use purposive sampling to ensure diversity in characteristics of treatment allocation (intervention vs usual care), high versus low engagement/adherence with exercise, study recruitment site and patient demographics/protected characteristics. We will also collect reasons for declining participation or stopping the intervention in the study (where possible).

9.2 DATA ANALYSIS

9.2.1 Quantitative analysis

Descriptive statistics will be used to summarise data in respect to study objectives and outcome measures as outlined below.

- Estimating screening, recruitment and attrition rates.
- Collecting data on candidate outcome measures to determine the primary outcome for the future trial and enable sample size calculations based on this.
- Determining intervention acceptability.
- Evaluating the feasibility and acceptability of health economics measures.

Feasibility progression criteria

Programme criteria using a traffic light system, along with outcome measures and qualitative data will guide decisions about whether a future definitive trial is feasible and warranted and identify any required amendments.[76]

Outcome	**Green: feasible with minimal or no modifications**	**Amber: feasible with moderate modifications**	**Red: major modifications required/ limited feasibility.**
Consent rates	>50%	30-50%	<30%

(of eligible people)			
Retention at 6 months	>80%	60%-80%	<60%
Intervention adherence	≈ 22 sessions or more	≈ 10-21 sessions	≈ 9 sessions or fewer

Health economic component

The aim of the future trial will be to determine the effectiveness and cost-effectiveness of SNMES. This study will provide preliminary data for a descriptive analysis of quality-of-life measures, main cost drivers and differences between groups. It will inform preparatory work regarding rudimentary cost-effectiveness or value of information analysis and data collection methods for resource use and economic evaluation in the definitive trial. Overall levels of data completeness will also be evaluated.

9.2.2 Qualitative analysis

Analysis will be informed by Braun and Clarke's reflective thematic analysis, drawing on inductive and deductive approaches which link to previous research in people with MS, long-term diseases and use of qualitative research for informing trials. [77-80]

All interviews will be audio-recorded using an encrypted Dictaphone, transcribed, anonymised and checked. Data will be transcribed using University approved transcription services who are compliant with GDPR and checked by the research team to ensure transcripts are anonymised. Anonymised transcripts will be blindly coded and the data investigated by two research team members. Coding will be open and inductive. Themes and subthemes will be produced iteratively and independently. Preliminary themes will be discussed with the wider project and clinical teams for review.

Analysis may be carried out using NVivo qualitative data analysis software.

Data from people with MS, carers and healthcare staff will be analysed separately and where appropriate, we will synthesise experiences, ensuring the recognition of the respective group voices. Findings will be mapped to the TFA and be used to inform study strategies for facilitating recruitment, retention, adherence and communication in a future trial.[80]

Qualitative and quantitative data will be used in combination to inform the future definitive trial design. In

addition to the frameworks above, the intervention and methodology will also be iteratively mapped to the TIDieR checklist, APPEASE framework and Health Inequalities Assessment toolkit.[11,81,82]

Qualitative data from the interviews will be transferred from encrypted Dictaphone to a password protected computer for onward transfer to a centralised SharePoint site specific to the study and housed under the governance structure of the Sponsor. Only the relevant members of the research team will have access to the site.

Audio-recordings will be deleted from the recording device or computer as soon as they have been uploaded to the relevant site.

Archiving

Dr Fraser Philp will have overall responsibility for study management including regular contact with the Walton and Wolverhampton research departments, study sponsor, site PIs and wider team. Walton will be the host organisation and University of Liverpool will be the sponsor. Walton will provide centralised study communications, data tracking, monitoring, and management. This is to ensure timely set up and co-ordinated running of the study, facilitated by effective communication across sites and study teams, monitoring of study process and deliverables against study milestones and outcomes. The Walton centre has a track record of recruiting and coordinating national multicentre studies in Multiple Sclerosis.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period, consistent with the Data will be stored for 10-years in accordance with University of Liverpool Research Data Management policy (https://www.liverpool.ac.uk/csd/records-management/retention-schedule/), the UK Research and Innovation Data Policy, Data Protection Act 2018 and GDPR 2018 (unless otherwise directed by the funder/sponsor/regulatory bodies). Case report forms will be stored in locked filing cabinets at study trust sites. The anonymised study database will be managed through REDCap. After that period all hard copy material will be reviewed, and approval for destruction from the sponsor will be sought.

10 REGULATORY ISSUES

10.1 ETHICS APPROVAL

Before the start of the study, a favourable opinion will be sought from the UK Health Departments Research Ethics Service NHS REC for the study protocol, informed consent forms and other relevant documents e.g. activity workbook. Health Research Authority (HRA) approval will be obtained.

The chief investigator will ensure that REC approval is obtained prior to recruitment of any participants in the study. Before any site can enrol participants into the study, the Chief Investigator will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the Chief Investigator, in agreement with the sponsor will submit information to the appropriate body for them to issue approval for the amendment. The Chief Investigator will work with sites so they can put the necessary arrangements in place to implement the amendment and to confirm their support for the study as amended. Substantial amendments that require review by NHS REC will not be implemented until that review is in place and HRA approval obtained for the amendment.

All correspondence with the REC will be retained. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC. The Chief Investigator will notify the REC of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

The study will be submitted to each proposed research site for Confirmation of Capacity and Capability. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

10.2 PEER REVIEW

This study has been peer reviewed as part of the NIHR application process.

The following stages (as per below) have been taken to address the ethical consideration.

Measurement burden

PPIE has been involved at every stage of the project to ensure that the measurement burden on participants is appropriate. This includes

- Selection of outcome measures
- Methods or outcome distribution i.e. paper, electronic, accessible formats and easily understood by participants
- Ensuring time and support is available for people with MS to complete the outcomes e.g. during the sessions or over the phone
- Location of outcome measure collection and clinical tests
- Reimbursement of participants travel expenses and vouchers in recognition of their time
- Appropriate spacing of study timepoints
- Use of online or telephone interviews around times that best suit participants

Not receiving the SNMES device in the control arm

Throughout the participant information leaflet we have explained, with help from our PPIE group why the control group is important and why we are unable to provide them with an SNMES device.

Based on their input we have provided people in the control group with information that outlines the main components of usual care (determined across both of our sites). This includes information and resources regarding physical activity, exercise, management of MS symptoms and further information regarding MS services from national charities.

Exclusion of people with higher levels of disability and EDSS scores i.e. > 6.5

The research team recognise that this is an important ethical issue and one that was considered at length by our team and PPIE group in the development of this application. We have provided our justification below for excluding individuals with an EDSS score >6.5. We do not wish to unduly exclude an underrepresented subgroup of people with MS from our study.

Our decision to exclude people with and EDSS score of > 6.5 was based on the following:

The rationale for the use of SNMES is that it has the potential to slow down the deterioration of walking function and be cost effective. This is also consistent with the justification used in disease modifying therapies.

- SNMES for achieving the muscle strength required for walking is unlikely to be effective in people who have already lost the ability to walk given the negative and possibly irreversible changes to muscle structure such as contractures that occur with immobility.
- People with MS and a score of >6.5 on the EDSS will require wheelchairs and therefore be more likely to have developed fixed lower limb contractures which is an exclusion criterion of our study.
- For people with an EDSS score of ≥6.5 (6.5 to 8) standing frames have been shown to be beneficial for improving motor function in domains of functional activity most readily achievable by people in those sub groups e.g. rolling in bed, sit to stand, sitting and standing balance.[83]
- People with EDSS scores >6.5 may also be unable to partake in all the activity outcome measures identified in our study (particularly in a single measurement session) given their more limited functional capacity (unable to walk more than 5 metres) such as the Timed up and Go, 2-Minute Walk Test and strength assessments.

This may negatively impact data completeness for the outcomes and result in high drop out for the follow up outcome measures.

SNMES may potentially be beneficial for people with MS and higher EDSS scores in other outcomes, for example, spasms or quality of life. However, if in a future trial SNMES demonstrates a positive effect in the wider or secondary group of outcomes, SNMES could potentially be extended to people with MS and EDSS scores >6.5.

Inclusion of people included who have an EDSS score of ≥7.0 would also likely have an impact on our data completeness, retention and compliance rates, and our feasibility progression criteria.

An increase in the EDSS score to a score of 7.0 would reflect.

- **7.0** essentially you must use a wheelchair but are active all day. You can't walk more than 5 metres even with an aid

A score of 7.5 has very limited levels of mobility

- **7.5** you can only take a few steps. You use a wheelchair and may need help getting in and out of it. You may need a motorised wheelchair

Inclusion of people with an EDSS score of >6.5 may constitute a different study. Some of our selected outcomes may not be appropriate for higher subgroups in light of the points raised above.

10.3 PUBLIC AND PATIENT INVOVLEMENT

PPI members helped in the writing of our application. PPI helped with study methods and the overall intervention have been developed with our PPI group to facilitate recruitment
and retention. These include:

- appropriate measurement burden (length of follow up, number and type of outcomes, allowing
- enough time and spacing for completion, mitigating physical and cognitive fatigue),
- selection of data collection locations and methods (hospital based),
- individualising to participant needs (online, phone, in person),
- reimbursement of travel costs and
- introduction of monetary incentives for completion of outcome measures at follow up timepoints (£15
- for 12-week and 6-month timepoints).

PPI members helped with confirming the willingness of participants to attend hospital clinics for clinical measures, and how (face-to-face, paper based, online) outcome measures should be collected including selection and spacing of outcomes. They helped decide on study outcome measures for fatigue, strength, and walking (2-minute versus 6- minute walk test). Based on the discussions, frequency of spasms was identified as an important outcome and has been included. Considerations and changes to the intervention were identified to address the needs of people with MS e.g. practicalities around length of intervention sessions, initial support for use, times of the day and fitting it into their daily lives. They also provided useful strategies to help with recruitment and retention e.g. checking in with someone, involvement of family members/carers as needed, assurance regarding levels of discomfort and affordability of the technology outside of a research context. Their involvement was integral in helping us communicate the study and intervention more clearly for this application e.g. SNMES as an exercise therapy.

Since the application, PPI members have also helped in developing the study materials i.e. key fact sheet, information sheets, workbooks. They have helped in the design and in making decisions about what should and should not be included e.g. not duplicating information between the information sheets for people with MS and the information sheets for the carers of people with MS. They have also made sure the information is accessible and understandable for people with MS. Based on their feedback we have made the language simpler, used alternative phrases e.g. physical exercise rather than workouts (“sounds too hard”) and

changed the order and structure of how things are presented to people in the study such as use of a single rather than multiple consent sheets. They have also been involved in helping to sense check our recruitment and retention strategy, ensuring that it is appropriate for people with MS e.g. emphasis on needing to stay in the study was clear and not too forceful.

PPIE also helped us in developing the intervention and control arm components of the study.

Control arm

PPIE suggested better standardising the resources that are normally included as a part of usual care. This was also identified as being an important part of our retention strategy. PPIE expressed that even if participants were aware that they might not get the SNMES they would more likely drop out if they didn't receive anything as a part of the study. This was discussed in the PPI discussion in development of the application, and it was identified that more information may be helpful to participants. However, participants felt the potential for drop out after being randomised to the control group would not be offset by providing more information or further expanding on why we could not give everyone in the study a device either later in the study. The PPI group suggested resources that they have been given as a part of their usual care and this was also checked with the usual care given at the study sites

SNMES arm

Participants helped us to make the SNMES programme simpler for people to follow. PPI identified it would be good to give participants a rough plan to follow that could then be adapted based on how they felt. They also suggested keeping it simple, for example thigh muscles one day and then lower leg muscles the next. Previously participants would have been required to rotate different muscles between the thigh and lower leg. We have had to increase the overall number of days from 3 to 4, however the total number of times and duration for each muscle that needs to be stimulated has remained the same.

10.4 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will abide by the Data Protection Act 2018 and the UK GDPR as amended from time to time and any successor legislation in the

UK and any other directly applicable regulation relating to data protection and privacy.

10.5 DATA COLLECTION TOOLS AND SOURCE DOCUMENT IDENTIFICATION

All documents and information are confidential and will be handled and safeguarded in the manner that ensures privacy and confidentiality of participant's personal information, in compliance with Data Protection Act (2018).

All documents and forms containing participants' personal information will be safeguarded and stored on-site at either the Walton centre or the Royal Wolverhampton trust. Only authorised individuals involved in this study will have the right to access these documents and information. Any electronic participants' information and/or data will only be stored in an NHS secured laptop, with two-factor authentication access. Only anonymised data will be transferred to an encrypted university laptop or centralised study databases.

10.6 DATA HANDLING AND RECORD KEEPING

This data management plan was developed ensure that data of this research is managed and shared in a robust and professional manner. The plan was formulated with adherence to University of Liverpool Research Data Management, the United Kingdom Research and Innovation Data Policy, local NHS Trust Data Protection, Data Protection Act 2018 and General Data Protection Regulation 2018[2]. All forms, documents, and templates will be stored at the local research sites in lockable filing cabinets. Building and room access restricted by a reception desk and lockable or electronic passkey access doors.

The research team will only have access to the participant NHS records once the participant has been consented for the study. University of Liverpool, as a sponsor, will only have access to anonymised data. Any published materials related to this project will be shared with University of Liverpool.

Once the study is concluded, all appropriate paper-based forms of participants will be moved and stored

[2] Available at, respectively: https://www.liverpool.ac.uk/intranet/legal/data-protection-foi-staff/dataprotectiongdpr/ ; https://www.liverpool.ac.uk/library/research-data-management/essentials/ ; https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted; https://ico.org.uk/for-organisations/guide-to-data-protection/guide-to-the-general-data-protection-regulation-gdpr/

in a locked cabinet at each of the respective sites for 10 years, then they will be destroyed after notifying University of Liverpool, as the study sponsor. Confidentiality and anonymity will be maintained for all participants. Any identifying information provided (e.g. names and addresses) will be held in the strictest confidence and stored in a confidential, password protected database accessible by only those with permission. All data used for analysis will be kept separate from participant personal data. Hard copy material (e.g. signed consent forms) will be stored securely for a minimum period of 10 years after the study has been completed. After that period all hard copy material will be reviewed, and approval for destruction from the sponsor will be sought. All study participants will be allocated a unique identification number, therefore, making it possible to anonymise research data. All sensitive datasets will be retained on a secure server and access restricted to the study team. Access to all research datasets is controlled by password protection and additional permissions specific to folders.

All confidentiality arrangements adhere to relevant regulations and guidelines (General Data Protection Regulation 2018, Data Protection Act 2018, General Medical Council (GMC), Medical Research Council (MRC), Research Governance Framework) and the chief investigator has a responsibility to ensure the integrity of the data and that all confidentiality procedures are followed

10.7 ACCESS TO THE DATA

Members of the both the care and research teams will have access to the participants personal data for the duration of the study. The principal investigators at each site are already part of the direct healthcare team on-site. Members of staff from the sponsor and/or regulatory bodies may also require access to study participant's data to carry out audits. All these staff work to robust data security procedures.

The raw data will be generated and stored electronically on an NHS-secured computer. Only anonymised data will be transferred to an encrypted university laptop or central study database. Paper-based data will be stored at the respective study sites in a locked cabinet. Electronic data will be stored on the sponsor and University of Liverpool Trust servers, which have restricted access by a two-way authentication procedure. Paper-based data will be kept on-site for 10 years and will be destroyed after University of Liverpool approval.

Dr Sacha Niven is the custodian of the data. They are the deputy medical director at the Walton centre which is the host organisation. University of Liverpool will have a copy of anonymised electronic data,

which will be stored at University of Liverpool safeguarded servers for 10 years. Accessibility to these data is governed by local NHS trust hospital policies and University of Liverpool IT Services' guidelines and procedures. University of Liverpool is the sponsor of this study, which makes it the owner of the data generated by this study, even though they are stored and safeguarded at local NHS hospital trusts. All of these guidelines are implemented to ensure these arrangements are in compliance with the Data Protection Act 2018, GDPR 2018 and Research Governance Framework.

10.8 DATA SHARING AGREEMENTS

If required, transferring data from local hospital sites or servers to University of Liverpool is to be done according to the guidelines of University of Liverpool Data Sharing policy, governed by the university IT services.

10.9 INDEMNITY

The University of Liverpool holds Indemnity and insurance cover with Newline Insurance Company, which apply to this study.

10.10 AUDITS

The study may be subject to inspection and audit by the University of Liverpool under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research (v3.2 10th October 2017).

11 END OF STUDY

The activity used to define the end of the study will be the end of the analysis for the quantitative and qualitative study work packages.

12 DISSEMINIATION POLICY

12.1 DISSEMINATION POLICY

University of Liverpool is the sponsor of this study, which makes it the owner of the data generated by this study. Responsibility for timely publication of findings within a peer-reviewed open access journal resides with the chief (principal) investigator in receipt of NIHR funds. Accountability resides with the sponsoring organisation.

On completion of the study, the data will be analysed and tabulated and a final study report prepared. This will be shared with the NIHR as the Funder of the study. A report will also be shared with REC per the conditions of favourable opinion.

The full study report will be available from the trial registry.

In keeping with the NIHR policy on clinical trial registration and disclosure of results[3]

- The initial protocol will be publicly available before the first participant receives an intervention or before commencement of data collection, unless otherwise agreed with the funding NIHR programme.
- Findings will be published in a peer-reviewed journal or platform within 24 months from primary study completion.
- Registries will be updated during the study and key outcomes and protocols will be made publicly available within 12 months from primary study completion.

[3] https://www.nihr.ac.uk/documents/nihr-policy-on-clinical-trial-registration-and-disclosure-of-results/12252

A requirement of the study is that the NIHR is named and acknowledged when submitting a paper or report for publication, as a funder of this research project. The following statement is required to be in any presentations, posters or papers.

STARTS

This project is funded by the National Institute for Health and Care Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHR207134). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

ENDS

The study sponsor will also be acknowledged where appropriate in any study outputs.

It will not be possible for participants to specifically request results from their PI.

Consistent with the NIHR policy on clinical trial registration and disclosure of results[4] the full study report, anonymised participant dataset and any statistical code for generating the results will be made publicly available.

The anonymised study dataset and any statistical code for generating results will be stored on the University of Liverpool data repository.[5] The dataset will be assigned a Digital object identifier and will be openly available.

Individual transcripts from the qualitative interviews will not be made publicly available as information disclosed throughout the interview may allow for identification of individual participants even after anonymisation.

Participants who wish to be notified about the outcomes of the study will be provided with a copy of the final publication and a study summary newsletter. Our dissemination strategy will be developed with our PPIE group.

[4] https://www.nihr.ac.uk/documents/nihr-policy-on-clinical-trial-registration-and-disclosure-of-results/12252
[5] http://datacat.liverpool.ac.uk/

12.2 AUTHORSHIP ELIGIBILITY GUIDELINES AND ANY INTENDED USE OF PROFESSIONAL WRITERS

Authorship will be determined as per the criteria outlined the International Committee of Medical Journal Editors.[84] The Contributor Role Taxonomy (CRediT) will also be used to ensure that the type of contribution for individual authors is recognised.[85]

13 ARCHIVING

Study related data will be stored as per local NHS trust hospital policies, which are compliant with the NHS Retention schedules reported in Records Management Code of Practice for Health and Social Care 2023.[6] Paper-based data will be kept on-site for 10 years and will be destroyed after University of Liverpool approval.

Dr Sacha Niven is the custodian of the data for the Walton Centre. They are the deputy medical director at the Walton centre which is the host organisation. University of Liverpool will have a copy of anonymised electronic data, which will be stored at University of Liverpool safeguarded servers for 10 years. Accessibility to these data is governed by local NHS trust hospital policies and University of Liverpool IT Services' guidelines and procedures. University of Liverpool is the sponsor of this study, which makes it the owner of the data generated by this study, even though they are stored and safeguarded at local NHS hospital trusts. All of these guidelines are implemented to ensure these arrangements are in compliance with the Data Protection Act 2018, GDPR 2018 and Research Governance Framework.

Dr Fraser Philp will have overall responsibility for study management including regular contact with the Walton and Wolverhampton research departments, study sponsor, site PIs and wider team. Walton will be the host organisation and University of Liverpool will be the sponsor. Walton will provide centralised study communications, data tracking, monitoring, and management. This is to ensure timely set up and co-ordinated running of the study, facilitated by effective communication across sites and study teams, monitoring of study process and deliverables against study milestones and outcomes. The Walton centre

[6] https://transform.england.nhs.uk/information-governance/guidance/records-management-code/updates-to-the-records-management-code-of-practice/

has a track record of recruiting and coordinating national multicentre studies in Multiple Sclerosis.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period, consistent with the Data will be stored for 10-years in accordance with University of Liverpool Research Data Management policy (https://www.liverpool.ac.uk/csd/records-management/retention-schedule/), the UK Research and Innovation Data Policy, Data Protection Act 2018 and GDPR 2018 (unless otherwise directed by the funder/sponsor/regulatory bodies). Case report forms will be stored in locked filing cabinets at study trust sites. The anonymised study database will be managed through REDCap. After that period all hard copy material will be reviewed, and approval for destruction from the sponsor will be sought.

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15 APPENDICES

15.1 APPENDIX 1- REQUIRED DOCUMENTATION

- Key facts sheet
- Participant information sheet – People with MS
- Participant information sheet – Carer of people with MS

- Consent form – People with MS
- Consent form – Carer of people with MS

- Workbook - SNMES group
- Usual care recording diary and further information sheet – Control group

- Study protocol
- Study outcome measure and clinical test pack

- CV's of the research team

15.2 APPENDIX 2 – SCHEDULE OF RESEARCH PROCEDURES (EXAMPLE)

Outcome	Screening	Baseline	Week 1	Week 6	3 months	>3 months < 6 months	6 months	> 6 months
Expanded Disability Status Scale (EDSS) [44]	✓				✓		✓	
Informed consent		✓						
Demographic & disease characteristics		✓						
Telephone calls			✓	✓				
Timed up and Go (TUG)+ [45,46]		✓			✓		✓	
2 minute walk test (2MWT) [47]		✓			✓		✓	
Penn Spasm Frequency Scale (PSFS) [48]		✓			✓		✓	
Multiple Sclerosis Impact Scale (MSIS-29v2) [86]		✓			✓		✓	
Fatigue Severity scale (FSS) [49+]		✓			✓		✓	
5 -item Modified fatigue impact scale (MFIS-5) +		✓			✓		✓	
World Health Organisation Disability Assessment Schedule (WHODAS 2.0) [50]		✓			✓		✓	
EQ-5D-5L [51]		✓			✓		✓	
Resource use questionnaire (ModRUM) [52,53]					✓		✓	
Numerical rating scale (Lower-limbs)		✓			✓		✓	

MRC strength assessment (Lower-limbs)		✓			✓		✓	
Joint range of movement (Lower-limbs)		✓			✓		✓	
Modified Ashworth Scale[54]		✓			✓		✓	
Level of impairment (Walking aids)		✓			✓		✓	
Semi-structured interviews (people with MS and carers)						✓		
Semi-structured interviews (clinicians)								✓

15.3 APPENDIX 3 – AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made