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EFFECTS OF ACTUAL AND IMAGINED MUSIC-CUED GAIT TRAINING ON MOTOR FUNCTIONING AND BRAIN ACTIVITY IN PEOPLE WITH MULTIPLE SCLEROSIS: PROTOCOL OF A RANDOMISED PARALLEL MULTICENTRE TRIAL

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EFFECTS OF ACTUAL AND IMAGINED MUSIC-CUED GAIT TRAINING ON MOTOR FUNCTIONING AND BRAIN ACTIVITY IN PEOPLE WITH MULTIPLE SCLEROSIS: PROTOCOL OF A RANDOMISED PARALLEL MULTICENTRE TRIAL

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ABSTRACT

Introduction

Motor imagery (MI) refers to the mental rehearsal of a physical action without muscular activity. Our previous studies showed that MI combined with rhythmic-auditory cues improved walking, fatigue and quality of life (QoL) in people with multiple sclerosis (pwMS). Largest improvements were seen after music- and verbally cued MI. It is unclear whether actual cued gait training achieves similar effects on walking as cued MI in pwMS. Furthermore, in pwMS it is unknown whether any of these interventions leads to changes in brain activation. The purpose of this study is therefore to compare the effects of imagined and actual cued gait training and a combination thereof on walking, brain activation patterns, fatigue, cognitive and emotional functioning in pwMS.

Methods and analysis

A prospective double-blind randomised parallel multicentre trial will be conducted in 132 pwMS with mild to moderate disability. Randomised into three groups, each participant will receive music-, metronome- and verbal cueing, plus MI of walking (1), MI combined with actual gait training (2), or actual gait training (3) for 30 minutes, 4x per week for 4 weeks. Supported by weekly phone calls, participants will practise at home, guided by recorded instructions. Primary endpoints will be walking speed (Timed 25-Foot Walk) and distance (2-Minute Walk Test). Secondary endpoints will be brain activation patterns, fatigue, QoL, MI ability, anxiety, depression, cognitive functioning, music-induced motivation-to-move, pleasure, arousal and self-efficacy. Data collection will be performed at baseline, post-intervention and 3-month follow-up. MRI reference values will be generated using 15 matched healthy controls.

Ethics and dissemination

This study follows the SPIRIT-PRO Extension. Ethical approval was received from the Ethics Committees of the Medical Universities of Innsbruck (1347/2020) and Graz (33-056 ex 20/21), Austria. Study results will be disseminated via national and international conferences and published in peer-reviewed journals.

Trial registration number DRKS00023978.

Study protocol, first submission, 21.8.2021

Keywords: Multiple sclerosis, Music, Cues, Motor Imagery, Walking, Fatigue, Rehabilitation, fMRI.

ARTICLE SUMMARY

Strengths and limitations of this study

- The intervention of this study was developed based on previous study results and involvement of patients with multiple sclerosis (MS). Semi-structured telephone interviews will assist in gaining insight into participants' perspectives of the intervention.
- This is the first prospective double-blind randomised parallel multicentre trial to investigate the effects of imagined and actual gait training with music-, metronome- and verbal cueing versus a combination thereof in people with MS (pwMS).
- Subjective and objective assessments and functional magnetic resonance imaging will be used as outcome parameters.
- Study participants with MS will receive close individual telephone support of their home-based training to facilitate their motor learning.
- Study results can be generalised only to pwMS with mild to moderate disability, without cognitive impairment or higher levels of depression or anxiety.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system leading to disability accumulation. People with MS (pwMS) frequently have impairment in motor, sensory, visual and other functional systems.[1] Walking impairment and fatigue contribute to a limitation in quality of life (QoL).[2-4] Motor imagery (MI)[5] and rhythmic-auditory stimulation, or cueing[6-9] are specific physiotherapy interventions. Rhythmic-auditory cues facilitate cyclical movements, predominantly gait,[6] which can be provided either by a metronome or music beat,[7 8] a combination thereof,[9] or by rhythmic verbal cues.[10 11] Cued walking training has been found to improve walking in people with neurological diseases including MS.[12-16] The stimulation leads to interactions between sensory and motor processes, referred to as sensorimotor interaction.[17]

MI is the mental execution of a movement without its actual performance[18] and MI of walking activates brain areas similar to those in actual walking.[19 20] Different imagery models exist and include individual and group MI, with or without physical practice.[21] Jeannerod has distinguished between an internal and an external MI perspective.[22] Further, a visual and a kinaesthetic MI mode have been described.[23] Persons imagine watching themselves moving with visual MI, with the kinaesthetic mode, they feel themselves moving.[24]

Few small studies have explored rhythmic-cued gait training[15 16] or MI of walking[25 26] in pwMS, showing promising preliminary results. Results from our previous work showed superior effects of music- and verbally cued MI over non-cued MI on walking, fatigue and QoL.[27 28] So far, no studies have compared the effects of cued MI on walking and cued gait training or a combined cued MI and gait training in pwMS. Building on the promising results of our previous studies, we furthermore want to learn whether observed behavioural changes are reflected by changes in brain activation

patterns. Magnetic resonance imaging (MRI) has been suggested to contribute to the understanding of mechanisms behind motor deficits and functional recovery in pwMS.[29 30] So far, functional MRI studies on motor rehabilitation in pwMS are scarce and,[29 31] to our knowledge, brain activation changes due to specific walking training need to be further explored in pwMS. We expect that MI training may lead to similar neural reorganisation patterns to actual practice.[32]

Therefore, the purpose of this study is to explore the effects of actual and imagined rhythmic-cued gait training versus their combination on walking, cognitive and emotional functioning in pwMS. Further aims are to investigate to what extent any of these interventions lead to brain activation changes during a motor or MI task and which changes are specifically associated with behavioural improvements in gait function.

ALTERNATIVE HYPOTHESES

H1: All trainings are effective for walking, brain activations, fatigue, QoL, and emotional and cognitive functioning in pwMS.

H2: The effects of cued MI combined with cued gait training are superior to those of cued MI and cued gait training alone.

METHODS AND ANALYSES

Study design, setting and timeline

This study is designed as a multicentre, randomised, parallel, double-blind controlled trial in pwMS with mild to moderate disability and follows the SPIRIT 2013 and SPIRIT-PRO Extension Checklist (Supplemental File 1). Study results will be reported in accordance with the Consolidated Standards of Reporting Statement (CONSORT).[33] The study will be conducted at the Clinical Department of Neurology, Medical Universities of Innsbruck (Centre 1) and Graz (Centre 3) and Clinic for

Rehabilitation Muenster (Centre 2), Austria. The expected recruitment phase is from 01.02.2021 to 31.03.2023.

Patient and public involvement

The study intervention was developed based on previous study results and patient involvement. Semi-structured telephone interviews will be used to gain insight into patients' problems with and acceptability of the intervention. Patients' acceptance of the intervention is essential for adherence.

Sample size and participants

The sample size for this study was calculated using previous study data and Cohen´s d effect sizes of the walking distance endpoint, with 95% confidence interval (CI) and corrected estimates of pooled standard deviation. Based on 80% power (β=0.2), α=0.025 and conservative effect sizes of d=0.74,[27] a sample size of 37 participants per group is required to detect a between-group difference. Including 15% attrition and making the number divisible by 3, a total sample size of 132 participants results. Thereof, 36 patients will also undergo MRI scanning, while 15 healthy controls will be enrolled to provide reference values for the MRI analyses. Study procedures including screening for eligibility are presented in Supplemental Figure 1 (Flow Diagram).

Eligibility criteria for this study are listed in Table 1.

Table 1 Eligibility criteria

People with MS	**Inclusion criteria** • any MS phenotype according to the revised McDonald's criteria[34 35] • aged 18 years or older • any ethnicity

	• disability status score on the Expanded Disability Status Scale (EDSS)[36] of 2.0 to 5.0 • stable disease; no clinical evidence of disease activity • ability to speak and understand German language **Exclusion criteria** • significant concomitant diseases (such as malignant diseases, other neurological or psychiatric disorders, musculoskeletal problems affecting walking, pain, uncorrected visual or hearing impairment) • cognitive impairment as defined by a MoCA cut-off score of 26/30 (<26 = impaired cognition)[37] • anxiety or depression as signified by a HADS anxiety[38] or depression subscale score of 11/21[39] or suicidality as evaluated by a narrative screening[40] • pregnancy • relapse of MS within the last three months before the study • any medication initiation or change (including corticosteroids) or any physiotherapy change or inpatient rehabilitation within three months prior to the study • any change of symptomatic treatment affecting walking (medication or physiotherapy) or of disease modifying treatment during the study will lead to an exclusion of the participant from further analysis

Healthy controls	• age- and gender-matched • without any history of neurological, psychiatric, or orthopaedic disorders
MRI/fMRI contraindications	• metallic or electricity conducting implants or prostheses (cardiac pacemaker, insulin pump, middle-ear implants, heart valve or hip prostheses, artificial teeth, hearing aid etc.) in or on the body • non-removable metal parts (coil, braces etc.) or metal shrapnel in or on the body • tattoos in the head or neck area, nicotine plasters or cosmetic eye modifications • pregnancy • epilepsy • claustrophobia

EDSS, Expanded Disability Status Scale;[36] HADS, Hospital and Anxiety and Depression Scale;[41] MoCA, Montreal Cognitive Assessment;[42] MS, multiple sclerosis

Recruitment, randomisation and blinding

Information brochures and invitations for study participation will be displayed in the study Centres 1-3 and on the Austrian MS Society website, with pwMS notified about the study by clinical department staff. Written informed consent will be obtained from all participants. Healthy controls will be enrolled at Centre 3 only.

Patients fulfilling the eligibility criteria will be randomised into one of three groups with stratified blocked randomisation performed by an independent researcher at Centre 1 using an online software-based random number generator (Sealed Envelope, London, UK), blocks of prespecified size and 1:1:1 allocation. Stratification will be

performed according to relevant predictive factors for a change in walking i.e.,[43] age (<40, ≥40), gender (female, male) and disability (EDSS[36] 2.0–3.5, 4.0–5.0). Sequentially numbered sealed opaque envelopes including group allocation numbers for groups 1-3 will be fabricated for each stratum. Allocation concealment will be performed to avoid allocation bias, assessors blinded to participants' group allocation and participants unaware of the study hypotheses.

Intervention

Three intervention groups will receive home-based kinaesthetic MI and/or gait training with music-, metronome- and verbal cueing for a total of 30 minutes, 4 times per week, for 4 weeks. Participants will receive cued MI (Group 1), combined cued MI and gait training (Group 2) or cued gait training (Group 3).

An audio-mix has been created specifically for this study (Audacity®. Version 3.0.0)[44] for download on participants' electronic devices or available as study CDs (Group 1). Instrumental motivational music at a regular beat in a 2/4 or 4/4 metre and strong ON and OFF beat patterns (i.e., with every first or first and third music beats stressed) will be utilised.[6 45 46] Additionally, metronome cues will accentuate the music beat and tempo and support gait synchronisation with the beat. Verbal cueing will be employed as a reminder of the task to practise and aid participants' focus on the respective body parts e.g., the feet.

Suitable rhythmical sequences at 80-120 beats per minute will be cut and mixed with instructions on MI or gait training. Rhythmic-verbal cues will accentuate the cueing intermittently, for example using "step-step" or "toe-off",[47] with different walking tasks used. Familiarisation will occur individually with the rhythmic-cued MI and gait training as previously recommended.[21 48] The audio mix will be changed weekly to gradually increase the tempo and facilitate adherence. The PETTLEP approach to MI will be applied, involving the "**P**hysical, **E**nvironmental, **T**ask, **T**iming, **L**earning, **E**motional,

and **P**erspective" components of MI.[49] Using the template for intervention description and replication (TIDieR) checklist,[50] detailed information on the PETTLEP approach and intervention is provided in Supplemental Table 1. In Figure 1, key aspects of the intervention are presented.

Figure 1 around here

Figure 1 Key elements of the intervention in the three groups

Practice frequency will be noted in a diary with weekly reports on participants' practice frequency prepared. Weekly phone calls will be used in the homebased training support of all participants, additionally at 4-weeks post-intervention. Additional phone call support will be provided upon request by the intervention providers. The content of the semi-structured telephone interviews during and post-intervention is presented in Figure 2.

Figure 2 around here

Figure 2 Content of semi-structured interviews

Data collection

Demographic disease specific data will be collected as detailed in Table 2. Clinical data will be collected by trained and blinded assessors (physiotherapists, occupational therapists, sports scientists, and psychologists). A schedule of the study procedures is provided in Table 2.

Table 2 Schedule of study procedures

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			
	Screening		Baseline test Day 1	Post-intervention test Week 4	Follow-up phone call Week 8	Follow-up test Month 3
TIMEPOINT	$-T_1$	*0*	T_1	T_2	T_3	T_4
ENROLMENT						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS						
Music-cued MI group			←	→		
Music-cued MI and gait training group			←	→		
Music-cued gait training group			←	→		

OUTCOMES (ASSESSMENTS)						
Baseline variables						
Demographics (age, gender)	X					
Clinical characteristics (EDSS, MS phenotype, disease duration, disease modifying treatment[1])	X					
Global cognitive impairment (MoCA test)	X			X		X
Anxiety and depression (HADS)	X			X		X
Suicidality (narrative screening)	X			X		X
Primary outcomes						
Walking speed and distance (T25FW, 2MWT)			X	X		X
Secondary outcomes						
Brain activation patterns (fMRI)			X	X		
MS related fatigue (NFI-MS)			X	X		X
Health-related QoL (MusiQoL)			X	X		X
MI ability (KVIQ-10, mental chronometry test)			X	X		X
Cognitive functioning (SDMT)			X	X		X

Music-induced motivation in exercise (BMRI-II)			X	X		X
Music-induced pleasure & arousal (SAM)				X		
MS specific self-efficacy (USE-MS)						
Adverse events and adverse reactions (log)				X	X	X
Falls (log)				X	X	X
Acceptability of the intervention, adherence and coping (checklist, weekly semi-structured phone interviews)			←	→		
Self-report health status and feedback on the study intervention (follow-up semi-structured phone interviews)					X	

[1]Three categories of disease modifying treatment (DMT): (1) no DMTs; (2) lowly effective DMTs: interferon-b 1a and 1b, pegylated interferon-b 1a, glatiramer acetate, dimethyl fumarate, teriflunomide, azathioprine, intravenous immunoglobulins; (3) highly effective DMTs: alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, cyclophosphamide, mitoxantrone, rituximab.

BMRI-II, Brunel Music-Rating Inventory-II; EDSS, Expanded Disability Status Scale; fMRI, functional magnetic resonance imaging; HADS, Hospital Anxiety and Depression Scale; KVIQ-10, Kinaesthetic and Visual Imagery Questionnaire, short version; MI, motor imagery; MoCA, Montreal Cognitive Assessment; MS, multiple sclerosis; MusiQoL, Multiple Sclerosis International Quality of Life; NFI-

MS, Neurological Fatigue Index - Multiple Sclerosis; SAM, Self-Assessment Manikin; SDMT, Symbol Digit Modalities Test; T25FW, Timed 25-Foot Walk; USE-MS, Unidimensional Self-Efficacy Scale for Multiple Sclerosis; 2MWT, 2-Minute Walk Test.

Primary outcomes

Primary outcomes are walking speed as assessed by the Timed 25-Foot Walk (T25FW)[51] and walking distance as assessed by the 2-Minute Walk Test (2MWT).[52] [53] For the T25FW, patients will be asked to walk a marked distance of 25 feet (7.62 metres) as quickly as possible, though safely, with an assistive device as required.[54] Scoring is achieved by taking the average of two trials. Excellent psychometric properties of the T25FW have been demonstrated.[55] [56] A 20% change in the T25FW is interpreted as a clinically significant difference in walking speed.[57]

The 2MWT will be performed as outlined in the American Thoracic Society Guidelines, which were developed for the 6-Minute Walking Test[58] and adapted by international experts from the NIH Toolbox.[59] For the 2MWT, excellent validity[60] [52] and test-retest reliability have been found.[61] A 20% change represents a clinically significant difference in walking distance.[62]

Secondary outcomes

Brain activation patterns

MRI data will be acquired at T_1 and T_2 on a 3 Tesla scanner (Siemens PRISMA, Siemens Healthcare Erlangen) using a 20-channel head coil. The MRI protocol includes a high-resolution structural three-dimensional (3D) T1-weighted MPRAGE sequence with 1 mm isotropic resolution (repetition time (TR) = 1900 ms, echo time (TE) = 2.7 ms) and a T2-weighted sequence (1mm isotropic, TR = 2800 ms, TE = 405 ms). A 3D fluid-attenuated inversion recovery (FLAIR) sequence (1 mm isotropic, TR = 5000 ms, TE = 393 ms) is administered to assess hyperintense T2-lesion load in patients. Additionally, diffusion tensor imaging (DTI; 1.5 mm isotropic, TR = 3318 ms, 64 directions), task-related fMRI (2 mm isotropic; TR = 2500 ms; TE = 30; 198 volumes, field of view = 192 × 192 mm², acquisition time = 8.31 minutes) and resting-state fMRI (rsfMRI; 2 mm isotropic; TR = 1000 ms; TE = 35; field of view = 256 × 256

mm², acquisition time = 5.20 minutes) will be performed. The scans will take approximately 35 minutes in total.

Task-related fMRI: experimental stimuli and procedure

The block-fMRI task will comprise a music-cued bipedal ankle movement on a treadmill i.e., alternating dorsi- and plantarflexion of both feet [63], a corresponding music-cued MI, and a listen-to-music-only condition. Four instrumental music-excerpts were selected as cues based on the same criteria used in the interventions.[6] Pace is held constant at 110 BPM for all cues. Each condition is repeated four times, and presented in a pseudo-randomised order, so that no condition or music-cue occurs twice in a row, and identical music-cues never run successionally.

Before each condition, a coloured symbol cue appears in the centre of the screen for 2.5 seconds, indicating the subsequent condition (orange feet for movement, blue think bubble for MI, violet ear for music-only condition; Figure 3a). At the start of each condition, a fixation cross in the corresponding colour appears and the music starts. Participants are instructed to perform the ankle movement at the pace of the music, starting with the right foot, and concentrate on the music beat during the music-only condition. After 22.5 seconds, the fixation cross turns black, indicating a period of total rest for 15 seconds (Figure 3b).

Figure 3 around here

Figure 3 Schematic representation of the block fMRI-paradigm

Figure legend: a) Presentation of each condition (music-cued movement, music-cued motor imagery, music-only), the corresponding symbol cues and the treadmill used for the study. b) Timeline of the paradigm.

Prior to entering the scanner, participants will practice the paradigm. Throughout the whole paradigm, participants are instructed to fixate on the cross, not to move their heads, to relax their entire body, except their feet during the movement condition. To

decrease stimulus-correlated motion, participants' heads are fixed with foam-cushions and their knees flexed to approximately 135° using a soft roll and cushion beneath their knees (Figure 3a).[63] Vision is corrected with prism lenses if necessary. During the paradigm, participants are observed with correct and incorrect movements recorded. After the scan, participants are asked to complete a short questionnaire on whether they recognised the songs (yes/no), liked the music-cues and found them motivating to move (both items: 7-point Likert scales). Three items will ask about the MI conditions (7-point Likert scale): the perceived MI difficulty and the extent to which they have "seen" or "felt" the MI (similar to the KVIQ-10 response format).

Fatigue

The Neurological Fatigue Scale - Multiple Sclerosis (NFI-MS) will be used to assess fatigue, including subscales of physical and cognitive fatigue, relief through daytime sleep or rest and abnormal nighttime sleep and sleepiness.[64 65] A summary score of items 1-7, 9 and 11-12 is generated. A 4-point Likert scale is used, from 0 = 'strongly disagree' to 3 = 'strongly agree', where higher scores represent more severe fatigue. The NFI-MS displayed good validity[65] and reliability.[65]

Health-related quality of life

The 31-item Multiple Sclerosis International Quality of Life questionnaire (MusiQoL)[66 67] has been chosen to record patient-reported health-related QoL (HRQoL). Nine dimensions of HRQoL are assessed: everyday activities, psychological wellbeing, symptoms, relationships with friends, family and the health care system, emotional and sex life, coping and rejection. A 5-point Likert scale from 1 = 'never/not at all' to 5 = 'always/a lot' is used with reverse scoring of negatively worded items. Nine domain scores and the global index are standardised on a 0-100 scale, where 100 represents the best HRQoL. A good validity [68] and reliability have been shown for the MusiQoL.[66 67]

MI ability

MI ability should be assessed using at least two different approaches,[69] hence the Kinaesthetic and Visual Imagery questionnaire,[70 71] utilising a German short version (KVIQ-G-10) [70] and a mental chronometry (MC) test.[72-74]

The KVIQ-(G)10 is patient-reported and assessor-administered and measures visual and kinaesthetic MI ability in neurological patients using five items.[71] Scoring is achieved using a 5-point Likert scale from 1 = 'no image' to 5 = 'image as clear as seeing' (visual subscale) and from 1 = 'no sensation' to 5 = 'as intense as executing the action' (kinaesthetic subscale). The KVIQ-G-10 has excellent psychometric properties.[70]

MC tests are based on the theory of functional equivalence between MI and actual movement.[49 75 76] Excellent temporal equivalence has been found for corresponding imagined and real movements.[74 77] MC evaluation will be at a comfortable tempo on a marked 6-metre path.[72-74] The "index of deviation from isochrony" will be calculated to quantify the discrepancy between imagined and real walking: deviation index = absolute value (1−(MI/motor execution).[78] Values close to zero are indicative of high MI ability.[78]

Depression, anxiety, and suicidality

The German version[79] of the Hospital Anxiety and Depression Scale (HADS)[41] and narrative screening for suicidality[40] adapted from item 9 of the Beck Depression Inventory[80] and a suicidality screening checklist[81] will be employed for screening. The 14-item HADS assesses patient-reported anxiety and depression during the previous two weeks. Anxiety or depression will be signified by a HADS anxiety[38] or depression subscale score of 11/21 points[39] or suicidality as evaluated by a narrative screening [40]. Good validity, reliability[82] and a bifactorial structure has been shown for the German HADS.[79]

Overall cognitive impairment

Overall cognitive impairment (attention and concentration, executive functions, memory, language, visuo-constructive abilities, conceptual thinking, arithmetic and orientation) will be assessed using the German Montreal Cognitive Assessment (MoCA).[42 83] The highest possible score is 30 points; values ≥26 are considered normal,[37] with good psychometric properties demonstrated.[37 84 85]

Motivational qualities of music in exercise settings

The 6-item Brunel Music Rating Inventory-2 (BMRI-2)[86] has been chosen to assess the music-induced motivation to move on a 7-point Likert scale. Music pieces selected from the audio-mix will be played to participants (in relevant 90-second excerpts).[86] Motivational properties of the musical rhythm, style, melody, tempo, instrumentation and beat during physical exercise will be patient-rated. The BMRI-2 has shown good validity and reliability.[86 87]

Music-induced pleasure and arousal

The Self-Assessment Manikin (SAM) will be used to measure the emotional responses of pleasure and arousal to the music selected for the study intervention.[88 89] The SAM consists of two series of pictograms, each of which displays a dimension on a 9-point scale[88 89]. SAM validations have demonstrated good to excellent validity[89 90] and reliability[91].

Self-efficacy

The validated German version[92] of the Unidimensional Self-Efficacy Scale for MS (USE-MS)[93] will be used to assess self-efficacy. For this patient-reported 12-item questionnaire using a 4-point Likert scale, excellent psychometric properties have been seen.[92 93]

Cognitive function

Cognitive function including attention, visual scanning, working memory and psychomotor speed will be measured using the Symbol Digit Modalities Test (SDMT)[94]. Patients will be asked to assign the numbers 1 through 9 to nine different symbols within 90 seconds. The number of maximum possible substitutions is 110. Excellent construct,[95] predictive [96] and discriminatory validity[97] and test-retest reliability[98] for the SDMT is demonstrated in pwMS.

Falls, adherence, and acceptability of the intervention

Falls and adverse events will be recorded in structured logs, the relationship with the intervention evaluated and treatment provided if necessary. which is covered by an indemnity insurance policy. Semi-structured telephone interviews will gain information on adherence and acceptability. Adherence will be monitored using a self-report checklist (Figure 2).

Data management

As for confidentiality, the Austrian, Tyrolean and Styrian Data Protection Acts will be adhered to, and personal data codified by a participant ID. Only the research team will have access to the data. Data will be only used for the purposes for which they were collected and saved on a password-protected computer. Data will be digitised in double entry with double coding of interview data performed. Quality assurance measures such as spot checks of value ranges and field types and logical checks will be performed.

Data analyses

Statistical data analyses

All statistical analyses employ IBM SPSS software, release 27.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 9, San Diego, California. A two-tailed p-value <0.05 will signify statistical significance. Including all cases as originally allocated,

intention-to-treat analysis will be performed. Descriptive statistics will be used as appropriate and continuous data tested for normal distribution using the Shapiro Wilk test, Q-Q-plots and histograms. For between-group comparisons at baseline, One-Way Analysis of Variance (ANOVA), Kruskal Wallis and Chi square tests will be used.

Mixed Design ANOVA test assumptions will be tested for e.g., sphericity (Mauchly´s test) and homogeneity of variance (Levene´s test), and standard correction procedures applied where appropriate. For continuous variables (T25FW, 2MWT, MC and SDMT), a 2-Way Mixed Design ANOVA will be conducted, using time as within-subject factor and group as between-subject factor, and the three DMT categories as covariates (no DMT; lowly effective DMT; highly effective DMT). Post-hoc Bonferroni adjustment performed as appropriate. For categorical data (NFI-MS, MusiQoL, KVIQ-10, HADS, MoCA, BMRI-2, SAM, and USE-MS), calculation of differences between post-intervention and baseline values will be followed by Kruskal Wallis and Dunn's multiple comparisons tests.

Structural MRI analyses

Using the Statistical Parametric Mapping - Lesion segmentation toolbox, T2-lesion load (T2-LL) will be assessed on T2-FLAIR images by the lesion prediction algorithm[99] controlled by a single experienced rater. Individual binarised T2-LL masks will be registered to MNI and lesion probability mapping performed to identify the lesion locations, using FSL randomise. After lesion filling with the FSL lesion filling toolbox, brain volumes will be assessed from T1-weighted MPRAGE images using SIENAX.

Functional MRI analyses

Individual resting state and task-fMRI data will be pre-processed using FEAT (FMRIB's Expert Analysis Tool, v 6.0, part of FSL v 6.0.[100] Pre-processing includes:

motion correction using MCFLIRT, brain extraction, spatial smoothing using a Gaussian kernel of FWHM (full width at half maximum) of 5 mm,[101] high pass temporal filtering using a cut-off of 150 s (0.007 Hz), linear registration to main structural image (BBR) and nonlinear registration warp resolution of 10 mm. High-resolution T1 scans are used for image registration.

First-level task fMRI analyses will be performed for each participant, assessing activation patterns of the three conditions (movement, MI, music-only) and related contrasts. Higher-level analyses will be used to examine potential differences between intervention groups. Independent Component Analysis (ICA) will be performed for rs-fMRI data (FSL-MELODIC, v 3.12). The resulting denoised functional images will be resampled to standard space (MNI152 template 2 mm). Dual-regression analyses on the denoised, registered functional images of each subject will be performed to obtain individual spatial maps of the resting-state networks, focusing on the sensorimotor and salience network. Group functional connectivity maps for timepoints 1 and 2 and longitudinal change will be computed for each subject (using FSL Randomise).

Qualitative data analysis

A thematic analysis, understood as a 'method for identifying, analysing, and reporting patterns or themes within data'[102] of the interview material will be performed.[103 104] Semantic and latent themes will be identified, summarised and interpreted,[102] with data coded, segmented and extracted. From this data, broader themes will be developed. Themes will be reviewed, refined and validated in an iterative and reflexive process,[105] data recoded as appropriate, and subthemes identified. Subthemes or categories will be judged by the criteria of internal homogeneity (meaningful coherence within a category) and external heterogeneity (clear differences between categories).[106] The

consolidated criteria for reporting qualitative research (COREQ) will be followed to enhance rigour, credibility and reliability.[107]

DISCUSSION

This study will investigate the effects of three variants of home-based cued gait training interventions on walking, fatigue, emotional and cognitive function, and brain activation. Music will be included to both provide a temporal cueing to the real or imagined walking and potentially induce pleasure in practitioners. Pleasurable, motivating music is known to induce highly enjoyable emotions, motivation and arousal.[108] This may be relevant because studies have shown that depression[109] and cognitive or higher levels of motor impairment[110 111] reduce the MI ability in pwMS. Therefore, it seems relevant to include screening for anxiety, depression, and cognitive impairment in the planned study. It needs to be considered however, that our music-based intervention could impact on mood and cognition in study participants.[112 113] Moreover, other aspects, such as music-induced motivation, pleasure or arousal have not been previously measured in pwMS.

Functional MRI is a state-of-the-art method for assessing potential underlying mechanisms of motor impairment and rehabilitation. Extending the study by Tavazzi et al.,[29] who showed a reduction in brain activation following its expansion after gait rehabilitation in pwMS, we will assess potential changes in brain activation associated with cued MI and/or cued gait training. In line with previous studies, we expect that pwMS recruit similar brain areas during MI and actual movement, albeit sensorimotor regions might be activated to a lesser and premotor and parietal regions recruited to a higher extent during MI.[114 115] Additionally, cued MI training may lead to similar reorganisation patterns compared to training of the actual movement.[32]

Advantages of a home-based intervention are that pwMS can practise independently. Depending on the results from this study, the most effective music-cued gait intervention can easily be put into practice, provided that specifically trained physiotherapists guide patients' training.

DECLARATIONS

Ethics, licences and dissemination plan

The study will be conducted in accordance with the principles of the Declaration of Helsinki (1964; 2013) and ICH E6(R2) Guideline for Good Clinical Practice (2016). The study protocol was approved by the Ethics Committees of the Medical Universities of Innsbruck and Graz on the 22.12.2020 (references 1347/2020 and 33-056 ex 20/21). A licence was obtained for using the MoCA, SDMT and MusiQoL from MoCA Test Inc. (Greenfield Park, Quebec), Hogrefe Austria GmbH (Vienna, Austria) and Mapi Research Trust (Lyon, France). Results will be disseminated to participants via letters and to clinicians and researchers via conferences and peer-reviewed publications.

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Author Contributions

BS devised and designed the study, qualitative methodology and overall data analyses. FD, CB, CE and DP substantially contributed to the conception and design of the study. BS, DP and BH drafted the manuscript. DP, BH, SR and GR devised the MRI analyses. RE and HH provided substantial input on the study methodology. FD, CE and CB are study managers at their centres. All authors critically revised and approved the final manuscript.

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Competing interests

None declared.

Data sharing statement

Data generated by this research that support any publications will be made available upon reasonable request as soon as possible. It will be considered submitting these data to the Open Science initiative once future analyses related to this data set are completed. The informed consent form includes the consent to controlled data sharing.

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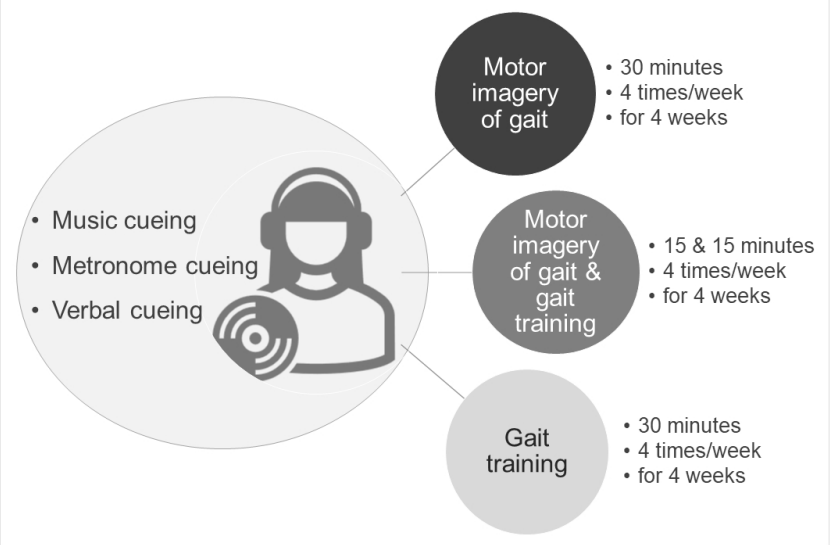

Figure 1

108x60mm (300 x 300 DPI)

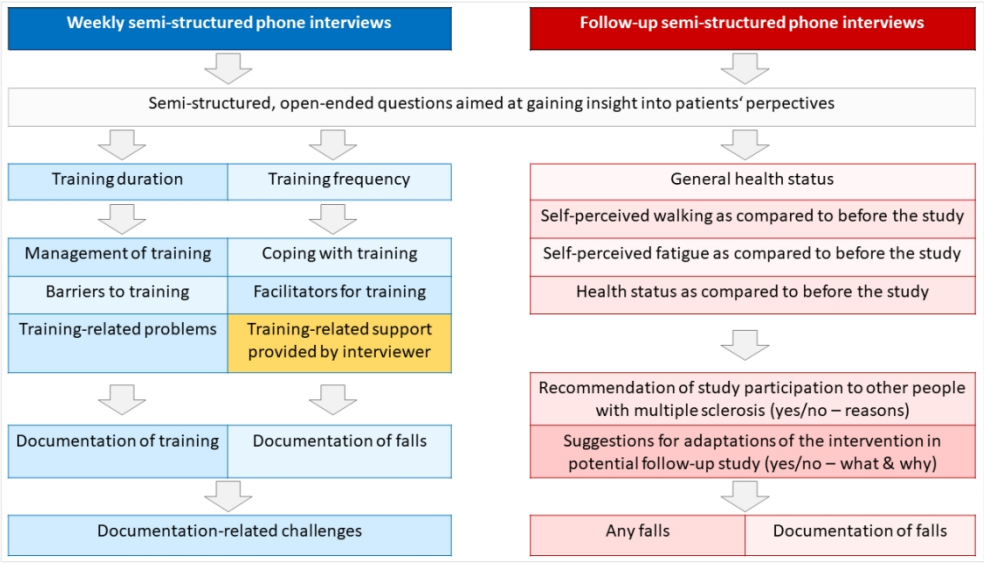

Figure 2

108x60mm (300 x 300 DPI)

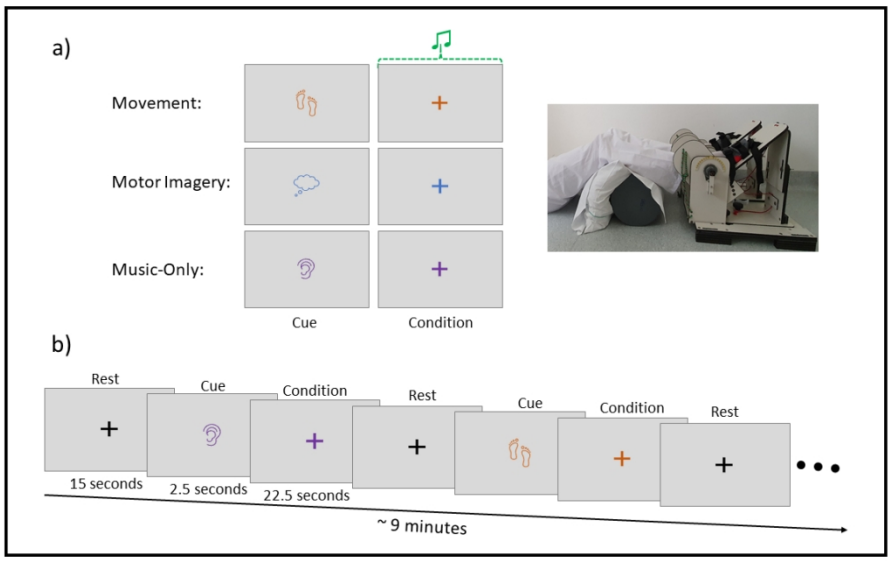

Figure 3

108x60mm (300 x 300 DPI)

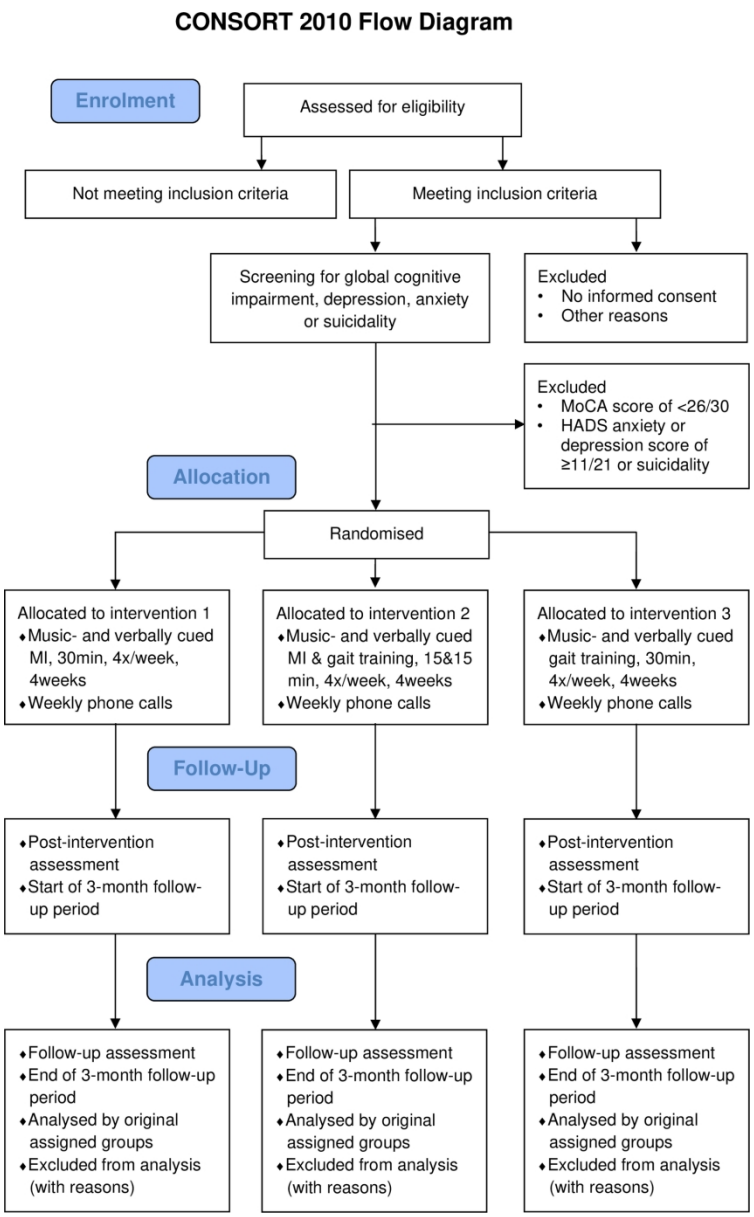

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Table 1 Intervention chart

ITEM NO	ITEM DESCRIPTION		
1 BRIEF NAME	**Group 1**	**Group 2**	**Group 3**
	Motor imagery (MI) with music-, metronome- and verbal cueing	MI and gait training with music-, metronome- and verbal cueing	Gait training with music-, metronome- and verbal cueing
	Music accentuated by metronome cues and intermittent concise verbal cueing		
2 WHY	- PETTLEP (Physical, Environment, Task, Timing, Learning, Emotion, Perspective) approach to MI (Holmes and Collins 2001)[1] - Rhythmic-auditory stimulation (cueing) for gait training (Thaut 2007)[2]		
3 WHAT MATERIALS	- Dropbox link including the audio mix and download to smartphone, laptop, tablet or MP3-player, or study CDs in group 1 - 4 sessions in each audiomix, one for each week - Headphones or earphones may be used if desired		
Audiomix Content	- Kinaesthetic MI instructions	- Kinaesthetic MI and gait training instructions	- Gait training instructions

	- Instrumental music in 2/4 or 4/4 metre - Beat-accentuating metronome cues - Intermittent verbal cueing (e.g., “toe-off” or “step-step”) - Weekly change of music titles - Gradual increase in tempo		
4 WHAT PROCEDURES	- Introduction to cued MI, familiarisation and training	- Introduction to MI and gait training with cueing, familiarisation and training	- Introduction to gait training with cueing, familiarisation and training
	- In lay language; description of the concept of MI; its application in sports and neurorehabilitation; MI perspectives (internal and external) and modes (visual, kinaesthetic). - Measurement of actual and imagined walking duration over a 6-metre distance to monitor the mental process - Performance feedback for participants and repeated training if desired		
		- In lay language; description of the concept of cued gait training and sensorimotor interaction; its application in sports and neurorehabilitation;	

		gait synchronisation with the music/metronome beat; musical tempo modulations. - Additional introduction to rhythmic auditory stimulation plus its use in neurorehabilitation - Rhythmic-cued MI familiarisation
	- Weekly phone calls for training support, adherence and adverse events reports - Phone calls at 4-week follow-up for feedback	
PETTLEP Elements		**Rhythmic-cued gait training**
Position (Physical)	- Practise at any time of the day when alert - Seated in an upright body position - Shoulders relaxed - Avoid tightening the muscles or moving - Eyes closed - Normal breathing	
		- Practice at any time of the day when alert - Use of headphones or earplugs if desired - Walking on a hallway (indoors) and/or familiar straight path (outdoors)

		- Adjusting one's steps with the music or metronome beat (every second music beat) - Use of walking sticks if required for reasons of safety - Avoid using walking sticks with balance related tasks if safe - Periods of rest as desired
Environment	- Practice in a quiet place at home - Imagine walking indoors (e.g., a long hallway) and walking outdoors (on a straight and familiar path)	
Tasks for all groups	- Take long/giant strides - Take extremely slow/small and quick strides - Touch the ground with your heels first - Roll your feet on the ground and feel your body weight on your soles - Toe-off - Raise your knees - Pace elegantly and upright like a queen/king - Place/feel your weight on your feet/legs - - Feel the swinging of your arms while walking/swing your arms during walking	

	- Stamp your feet while walking, walk forcefully and energetically - Walk effortlessly, feeling lightly - Take wide/narrow steps		
Timing of the MI and gait training	External timing is provided: “imagine yourself walking in time with the music or metronome and verbal cues”		
		External timing is provided: “walk in time with the music or metronome and verbal cues”	
	- Tempo (cadence) is between 80 and 120 steps/minute - Slow, medium and fast music pieces alternate, with a gradual progression in the tempo over the 4 weeks		
Learning	- See familiarisation - Weekly phone call support is provided		
Emotion related to the MI and gait training	- MI instructions include motivational and arousal enhancing aspects. See instructions under Tasks. - Motivational instrumental music is used with the MI		
		- Gait training instructions include motivational and arousal enhancing aspects. See instructions under Tasks. - Motivational instrumental music is used with the gait training	

Perspective	Kinaesthetic MI from an internal, first-person perspective	No MI
5 WHO PROVIDES	- The audiomix was created by the lead researcher (BS), an experienced neurological physiotherapist with 11 years of musical training and a PhD in physiotherapy. - The introduction, familiarisation and training is provided by neurological physiotherapists, occupational therapists and psychologists who received a structured and specific training by the lead researcher - All therapist researchers are supervised and supported by the lead researcher - Any intervention related processes are documented by the study team	
6 HOW – all delivery modes	- MI introduction, familiarisation and training: individually - Monitoring of mental process: individually	
		- Cued gait training introduction, familiarisation and training: individually - Monitoring of understanding of gait synchronisation with beat: individually
	- Weekly phone calls: individually	
7 WHERE	- MI introduction, familiarisation, training and monitoring of mental process: at Medical University of Innsbruck (Centre 1) or Graz (Centre 3), Clinical Department of Neurology or Rehab Centre Münster (Centre 2), Austria	

		- Cued gait training introduction, familiarisation and training: at Medical University of Innsbruck (Centre 1) or Graz (Centre 3), Clinical Department of Neurology or Rehab Centre Münster (Centre 2), Austria	
	- Cued MI practice: at participants' homes		
		Cued gait training: at participants' homes	
8 WHEN AND HOW MUCH	30 minutes, 6 times a week, for 4 weeks	15 & 15 minutes, 6 times a week, for 4 weeks	30 minutes, 6 times a week, for 4 weeks
9 TAILORING	Same intervention for all participants	Same intervention for all participants	Same intervention for all participants
10 MODIFICATIONS	No modifications	No modifications	No modifications
11 HOW WELL PLANNED	- Intervention adherence is assessed using a participant diary and also during weekly phone calls and at post-intervention - Support to intervention adherence is performed by the researchers who instruct participants (guidance and motivation) - Recording in structured support call logs is performed by the researchers who instruct participants - Recording in excel sheets is performed in excel sheets by the lead researcher		

12 HOW WELL **ACTUAL**	This is a study protocol and the adherence rates are not yet available.

References

1. Holmes PS, Collins DJ. The PETTLEP approach to motor imagery: A functional equivalence model for sport psychologists. *J Appl Sport Psychol* 2001;13(1):60-83.
2. Thaut MH. Rhythm, music and the brain. Scientific foundations and clinical applications. New York: Routledge 2007:272.

SPIRIT 2013 and SPIRIT-PRO Extension Checklist: Recommended Items to Address in a Clinical Trial Protocol

Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA : the journal of the American Medical Association 2018;319(5):483-94 doi: 10.1001/jama.2017.21903[published Online First: Epub Date])

Section/item	ItemNo	Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Addressed on Page No.
Administrative information					
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym			Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry			Abstract
	2b	All items from the World Health Organization Trial Registration Data Set			See below (pages 14-20)
Protocol version	3	Date and version identifier			Abstract
Funding	4	Sources and types of financial, material, and other support			25

Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors			25
	5b	Name and contact information for the trial sponsor	SPIRIT-5a-PRO Elaboration	Specify the individual(s) responsible for the PRO content of the trial protocol.	See Spirit Item 2B below
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities			See Spirit Item 2B below; 25
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)			9 and 21
Introduction					

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	SPIRIT-6a-PRO Extension	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	5-6
	6b	Explanation for choice of comparators			5-7
Objectives	7	Specific objectives or hypotheses	SPIRIT-7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)			Title, Abstract, 4 and 6
Methods: Participants, interventions, and outcomes					
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained			6 and 9

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	SPIRIT-10-PRO Extension	Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	7, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered			10-11, Figure 1, Supplemental Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)			21, Table 2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)			7, 10-11, 14, Figure 2
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial			Tables 1 and 2 including legends

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	SPIRIT-12-PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (eg, overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.	11-21, Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	SPIRIT-13-PRO Extension	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized.	6-7, Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	SPIRIT-14-PRO Extension	When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.	7

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size			9-10
Methods: Assignment of interventions (for controlled trials)					
Allocation:					
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions			9-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned			10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions			9-10

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how			10-11
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial			10-11
Methods: Data collection, management, and analysis					
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	SPIRIT-18a (i)-PRO Extension	Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.	2, 11-21, Table 2, Figure 2
			SPIRIT-18a (ii)-PRO Extension	Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other).	2, 4, 6-7, 10-11, Table 2

			SPIRIT-18a (iii)-PRO Extension	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	8, 19-20
			SPIRIT-18a (iv)-PRO Extension	When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available.	NA
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	SPIRIT-18b (i)-PRO Extension	Specify PRO data collection and management strategies for minimizing avoidable missing data.	7, 10, 21, Table 2
			SPIRIT-18b (ii)-PRO Elaboration	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	21
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol			21, 23

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	SPIRIT- 20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	21-23
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)			23
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	SPIRIT- 20c-PRO Elaboration	State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).	21
Methods: Monitoring					
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed			21, 25

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial			NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	SPIRIT- 22-PRO Extension	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; eg, in the participant information sheet and consent form.	Table 2, Figure 2, page 21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor			NA
Ethics and dissemination					
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval			3, 24-25

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)			NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)			9-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable			NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial			25
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site			25
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators			21

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation			21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions			25
	31b	Authorship eligibility guidelines and any intended use of professional writers			25
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code			25
Appendices					
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates			NA

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable			NA

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; PRO, patient-reported outcome.
*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license and is reproduced with permission.

Spirit Item 2B WHO Trial Registration Dataset

Data Category	Information
Primary registry and trial identifying number	German Clinical Trials Register https://www.drks.de/drks_web/ Trial ID: DRKS00023978
Date of registration in primary registry	28.12.2020
Secondary identifying numbers	Universal Trials Number (UTN): U1111-1263-1856 Ethics approval reference number: 1347/2020

Source(s) of monetary or material support	This study is an independent academic study, which is conducted with the financial support of Celgene, a company of Bristol Myers Squibb (NA-CL-MS-PI-13909_Seebacher: Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study). The people involved in decision-marking about this funding have no influence on the planning, conduct and publication of the study.
Primary sponsor	Medical University of Innsbruck, Austria
Secondary sponsor(s)	N/A
Contact for public queries	Dr Barbara Seebacher Phone: +435050482499 Email: barbara.seebacher@i-med.ac.at
Contact for scientific queries	Dr Barbara Seebacher Phone: +435050482499 Email: barbara.seebacher@i-med.ac.at

Public Title	Effects of actual and imagined music-stimulated gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study
Scientific Title	Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study
Countries of recruitment	Austria
Health condition(s) or problem(s) studied	Multiple sclerosis (MS)
Intervention(s)	Group 1: Motor imagery (MI) with music cueing; the music beat is accentuated using metronome cueing and intermittent verbal cueing; 30 min, 4x per week, for 4 weeks Group 2: MI with music cueing (the music beat is accentuated using metronome cueing and intermittent verbal cueing) plus gait training with music cueing; 15 & 15 min, 4x per week, for 4 weeks Group 3: Gait training alone with music cueing; the music beat is accentuated using metronome cueing and intermittent verbal cueing; 30 min, 4x per week, for 4 weeks

Key inclusion and exclusion criteria	Inclusion criteria: people with any MS phenotype according to the revised McDonald's criteria; aged 18 years or over; any ethnicity; disability status score on the EDSS of 2.0 to 5.0; stable disease; no evidence of disease activity; and able to speak and understand German language. Exclusion criteria: people with MS with concomitant diseases (such as malignant diseases, other neurological or psychiatric disorders, musculoskeletal problems affecting walking, pain, uncorrected visual or hearing impairment); cognitive impairment as defined by a MoCA cut-off score of 26/30 (<26 = impaired cognition; ≥26 = intact cognition); anxiety or depression as signified by a HADS anxiety subscale score of 11/21 or a depression subscale score of 11/21 or suicidality as evaluated by a narrative screening; pregnancy; a relapse of MS within the last three months; any medication initiation or change (including corticosteroids) or any physiotherapy change within three months prior to the study; any change of symptomatic treatment affecting walking (medication or physiotherapy) or of

	disease modifying treatment (DMT) during the study will lead to an exclusion of the participant from the further analysis. Any MRI/fMRI contraindications, e.g. implanted ferrous metal, heart pacemaker or claustrophobia. Healthy controls for the fMRI scanning: 15 age- and gender matched healthy controls without any history of neurological, psychiatric, orthopaedic or other disorder.
Study type	Prospective double-blind randomised parallel multicentre trial Allocation: stratified blocked randomisation with allocation concealment Intervention model: parallel assignment (1:1:1) Masking: assessor-blinded; patients blinded to the study hypotheses Primary study aim: to investigate whether there is a difference between the effects of accentuated music- and verbally cued MI, accentuated music- and verbally cued MI combined with gait training and accentuated music- and verbally cued gait training alone on walking in people with MS.
Date of first enrolment	09.02.2021

Target sample size	132 people with MS and 15 healthy controls (fMRT)
Recruitment status	Recruiting
Primary outcome(s)	• Walking speed as assessed by the Timed 25-Foot Walk (T25FW) • Walking distance as assessed by the 2-Minute Walk Test (2MWT)
Secondary outcomes	• Brain activation patterns as assessed by fMRI (and structural MRI); in addition to patients, healthy controls will be scanned at baseline and 4 weeks later, corresponding with the intervention period of this study • MS related fatigue as assessed by the validated German version of the Neurological Fatigue Index (NFI-MS) • MS related health-related QoL, HRQoL as assessed by the validated German version of the Multiple Sclerosis International Quality of Life (MusiQol) questionnaire • MI ability as measured by the validated German version KVIQ-G-10 of the Kinaesthetic and Visual Imagery Questionnaire, short version (KVIQ-10)

	• MI ability as measured by a mental chronometry test comparing the duration of imagined and real walking on a 6-metre walkway • Anxiety and depression as assessed by the German version of the HADS, complemented by additional narrative screening for suicidality • Global cognitive impairment as assessed by the German version of the Montreal Cognitive Assessment (MoCA) • Psychomotor speed, attention, visual scanning and tracking and working memory as assessed by the Symbol Digit Modalities Test (SDMT) • Music-induced motivation / the motivational qualities of music as assessed by the Brunel Music Rating Inventory-2 (BMRI-2) • Music-induced pleasure and arousal as assessed by the Pictorial Self-Assessment Manikin (SAM) • MS specific self-efficacy as assessed by the validated German version of the Unidimensional Self-Efficacy Scale for MS (USE-MS)

	• Number of falls in the intervention and follow-up periods (falls log, telephone interviews) • Home-based training management and coping, barriers to, facilitators of and problems with the training, documentation of the training frequency and duration (support will be provided) (weekly semi-structured telephone interviews during the intervention period) • Feedback on the general health status, walking, fatigue, training content and suggestions for adaptations of the intervention in a potential follow-up study, falls and documentation of falls (semi-structured telephone interview at 4-weeks follow-up)

BMJ Open

EFFECTS OF ACTUAL AND IMAGINED MUSIC-CUED GAIT TRAINING ON MOTOR FUNCTIONING AND BRAIN ACTIVITY IN PEOPLE WITH MULTIPLE SCLEROSIS: PROTOCOL OF A RANDOMISED PARALLEL MULTICENTRE TRIAL

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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Rehabilitation medicine, Neurology
Keywords:	Multiple sclerosis < NEUROLOGY, REHABILITATION MEDICINE, NEUROLOGY

EFFECTS OF ACTUAL AND IMAGINED MUSIC-CUED GAIT TRAINING ON MOTOR FUNCTIONING AND BRAIN ACTIVITY IN PEOPLE WITH MULTIPLE SCLEROSIS: PROTOCOL OF A RANDOMISED PARALLEL MULTICENTRE TRIAL

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ABSTRACT

Introduction

Motor imagery (MI) refers to the mental rehearsal of a physical action without muscular activity. Our previous studies showed that MI combined with rhythmic-auditory cues improved walking, fatigue and quality of life (QoL) in people with multiple sclerosis (pwMS). Largest improvements were seen after music- and verbally cued MI. It is unclear whether actual cued gait training achieves similar effects on walking as cued MI in pwMS. Furthermore, in pwMS it is unknown whether any of these interventions leads to changes in brain activation. The purpose of this study is therefore to compare the effects of imagined and actual cued gait training and a combination thereof on walking, brain activation patterns, fatigue, cognitive and emotional functioning in pwMS.

Methods and analysis

A prospective double-blind randomised parallel multicentre trial will be conducted in 132 pwMS with mild to moderate disability. Randomised into three groups, participants will receive music-, metronome- and verbal cueing, plus MI of walking (1), MI combined with actual gait training (2), or actual gait training (3) for 30 minutes, 4x per week for 4 weeks. Supported by weekly phone calls, participants will practise at home, guided by recorded instructions. Primary endpoints will be walking speed (Timed 25-Foot Walk) and distance (2-Minute Walk Test). Secondary endpoints will be brain activation patterns, fatigue, QoL, MI ability, anxiety, depression, cognitive functioning, music-induced motivation-to-move, pleasure, arousal and self-efficacy. Data will be collected at baseline, post-intervention and 3-month follow-up. MRI reference values will be generated using 15 matched healthy controls.

Ethics and dissemination

This study follows the SPIRIT-PRO Extension. Ethical approval was received from the Ethics Committees of the Medical Universities of Innsbruck (1347/2020) and Graz (33-056 ex 20/21), Austria. Results will be disseminated via national and international conferences and published in peer-reviewed journals.

Trial registration number German Clinical Trials Register, DRKS00023978.

Study protocol, first revision, 5.12.2021

Keywords: Multiple sclerosis, Music, Cues, Motor Imagery, Walking, Fatigue, Rehabilitation, fMRI.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first prospective double-blind randomised parallel multicentre trial to investigate the effects of imagined and actual gait training with music-, metronome- and verbal cueing versus a combination thereof in people with MS (pwMS).
- The intervention of this study was informed by previous study results and involvement of patients with multiple sclerosis (MS).
- Study participants with MS will receive close individual telephone support of their home-based training to facilitate their motor learning and adherence.
- Semi-structured telephone interviews will assist in gaining insight into participants' perspectives of the intervention.
- Subjective and objective assessments and functional magnetic resonance imaging will be used as outcome parameters.

INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system leading to disability accumulation. People with MS (pwMS) frequently have impairment in motor, sensory, visual and other functional systems.[1] Walking impairment and fatigue contribute to a limitation in quality of life (QoL).[2-4] Motor imagery (MI)[5] and rhythmic-auditory stimulation, or cueing[6-9] are specific physiotherapy interventions. Rhythmic-auditory cues facilitate cyclical movements, predominantly gait,[6] which can be provided either by a metronome or music beat,[7 8] a combination thereof,[9] or by rhythmic verbal cues.[10 11] Cued walking training has been found to improve walking in people with neurological diseases including MS.[12-16] The stimulation leads to interactions between sensory and motor processes, referred to as sensorimotor interaction.[17]

MI is the mental execution of a movement without its actual performance[18] and MI of walking activates brain areas similar to those in actual walking.[19 20] Different imagery models exist and include individual and group MI, with or without physical practice.[21] Jeannerod has distinguished between an internal and an external MI perspective.[22] Further, a visual and a kinaesthetic MI mode have been described.[23] Persons imagine watching themselves moving with visual MI, with the kinaesthetic mode, they feel themselves moving.[24]

Few small studies have explored rhythmic-cued gait training[15 16] or MI of walking[25 26] in pwMS, showing promising preliminary results. Results from our previous work showed superior effects of music- and verbally cued MI over non-cued MI on walking, fatigue and QoL.[27 28] So far, no studies have compared the effects of cued MI on walking and cued gait training or a combined cued MI and gait training in pwMS. Building on the promising results of our previous studies, we furthermore want to learn whether observed behavioural changes are reflected by changes in brain activation

patterns. Magnetic resonance imaging (MRI) has been suggested to contribute to the understanding of mechanisms behind motor deficits and functional recovery in pwMS.[29 30] So far, functional MRI studies on motor rehabilitation in pwMS are scarce and,[29 31] to our knowledge, brain activation changes due to specific walking training need to be further explored in pwMS. Extending the study by Tavazzi et al.,[29] who showed a reduced extent of the widespread brain activation during a motor task (plantar dorsiflexion) after gait rehabilitation in pwMS, we will assess potential changes in brain activation associated with cued MI and/or cued gait training. In line, beneficial training might be associated with an increased activation of the primary motor areas, along with decreased activation outside the sensorimotor network (e.g., frontal areas).[29 32 33] We expect that MI training leads to similar neural reorganisation patterns as actual practice.[34]

Therefore, the purpose of this study is to determine the effects of actual and imagined rhythmic-cued gait training versus their combination on walking, cognitive and emotional functioning in pwMS. Further aims are to compare brain activation changes during a motor or MI task between groups and determine which changes are specifically associated with improvements in gait function.

ALTERNATIVE HYPOTHESES

H1: All trainings will significantly improve walking, fatigue, QoL, emotional and cognitive functioning, and normalise brain activation (i.e., a more focal activation of the sensorimotor network as observed in healthy controls) in pwMS.

H2: The effects of cued MI combined with cued gait training are superior to those of cued MI and cued gait training alone.

METHODS AND ANALYSES

Study design, setting and timeline

This study is designed as a multicentre, randomised, parallel, double-blind trial in pwMS with mild to moderate disability and follows the SPIRIT 2013 and SPIRIT-PRO Extension Checklist (Supplemental File 1). Study results will be reported in accordance with the Consolidated Standards of Reporting Statement (CONSORT).[35] The study will be conducted at the Clinical Department of Neurology, Medical Universities of Innsbruck (Centre 1) and Graz (Centre 3) and Clinic for Rehabilitation Muenster (Centre 2), Austria. The expected recruitment phase is from 01.02.2021 to 31.03.2023.

Patient and public involvement

The study intervention was developed based on previous study results[27 28 36 37] and patient involvement. An MS advisory group was consulted to clarify any questions, for example, with respect to their music preference and suggestions for the duration of the imagined and actual gait training. Semi-structured telephone interviews will be used to gain insight into patients' problems with and acceptability of the intervention. Patients' acceptance of the intervention is essential for adherence.

Sample size and participants

The sample size for this study was calculated using previous study data[27] and Cohen´s d effect sizes of the walking distance endpoint, with 95% confidence interval (CI) and corrected estimates of pooled standard deviation. Based on 80% power (β=0.2), α=0.025 and conservative effect sizes of d=0.74, a sample size of 37 participants per group is required to detect a between-group difference. Including 15% attrition and making the number divisible by 3, a total sample size of 132 participants results. Thereof, 36 patients will also undergo MRI scanning, while 15 healthy controls will be enrolled to provide reference values for the MRI analyses. Study procedures including screening for eligibility are presented in Supplemental Figure 1 (Flow Diagram).

Eligibility criteria for this study are listed in Table 1.

Table 1 Eligibility criteria

People with MS	**Inclusion criteria** • any MS phenotype according to the revised McDonald's criteria[38 39] • aged 18 years or older • any ethnicity • disability status score on the Expanded Disability Status Scale (EDSS)[40] of 2.0 to 5.0 • stable disease; no clinical evidence of disease activity • ability to speak and understand German language **Exclusion criteria** • significant concomitant diseases (such as malignant diseases, other neurological or psychiatric disorders, musculoskeletal problems affecting walking, pain, uncorrected visual or hearing impairment) • cognitive impairment as defined by a MoCA cut-off score of 26/30 (<26 = impaired cognition)[41] • anxiety or depression as signified by a HADS anxiety[42] or depression subscale score of 11/21[43] or suicidality as evaluated by a narrative screening[44] • pregnancy • relapse of MS within the last three months before the study

	• any medication initiation or change (including corticosteroids) or any physiotherapy change or inpatient rehabilitation within three months prior to the study • any change of symptomatic treatment affecting walking (medication or physiotherapy) or of disease modifying treatment during the study will lead to an exclusion of the participant from further analysis
Healthy controls	• age- and gender-matched • without any history of neurological, psychiatric, or orthopaedic disorders
MRI/fMRI contraindications	• metallic or electricity conducting implants or prostheses (cardiac pacemaker, insulin pump, middle-ear implants, heart valve or hip prostheses, artificial teeth, hearing aid etc.) in or on the body • non-removable metal parts (coil, braces etc.) or metal shrapnel in or on the body • tattoos in the head or neck area, nicotine plasters or cosmetic eye modifications • pregnancy • epilepsy • claustrophobia

EDSS, Expanded Disability Status Scale;[40] HADS, Hospital and Anxiety and Depression Scale;[45] MoCA, Montreal Cognitive Assessment;[46] MS, multiple sclerosis

Recruitment, randomisation and blinding

Information brochures and invitations for study participation will be displayed in the study Centres 1-3 and on the Austrian MS Society website, with pwMS notified about the study by clinical department staff. Written informed consent will be obtained from all participants (see Supplemental File 2 for an English version of the patient information sheet and informed consent form). Healthy controls will be enrolled at Centre 3 only.

Patients fulfilling the eligibility criteria will be randomised into one of three groups with stratified blocked randomisation performed by an independent researcher at Centre 1 using an online software-based random number generator (Sealed Envelope, London, UK), blocks of prespecified size and 1:1:1 allocation. Stratification will be performed according to relevant predictive factors for a change in walking i.e.,[47] age (<40, ≥40), gender (female, male)[48 49] and disability (EDSS[40] 2.0–3.5, 4.0–5.0). Sequentially numbered sealed opaque envelopes including group allocation numbers for groups 1-3 will be fabricated for each stratum. Allocation concealment will be performed to avoid allocation bias, assessors blinded to participants' group allocation and participants unaware of the study hypotheses.

Intervention

Three intervention groups will receive home-based kinaesthetic MI and/or gait training with music-, metronome- and verbal cueing for a total of 30 minutes, 4 times per week, for 4 weeks. Participants will receive cued MI (Group 1), combined cued MI and gait training (Group 2) or cued gait training (Group 3).

An audio-mix has been created specifically for this study (Audacity®. Version 3.0.0)[50] for download on participants' electronic devices or available as study CDs (Group 1). Instrumental motivational music at a regular beat in a 2/4 or 4/4 metre and strong ON and OFF beat patterns (i.e., with every first or first and third music beats stressed) will be utilised.[6 51 52] Additionally, metronome cues will accentuate the music beat and

tempo and support gait synchronisation with the beat. Verbal cueing will be employed as a reminder of the task to practise and aid participants' focus on the respective body parts e.g., the feet.

Suitable rhythmical sequences at 80-120 beats per minute will be cut and mixed with instructions on MI or gait training. Rhythmic-verbal cues will accentuate the cueing intermittently, for example using "step-step" or "toe-off",[53] with different walking tasks used. Familiarisation will occur individually with the rhythmic-cued MI and gait training as previously recommended.[21 54] The audio mix will be changed weekly to gradually increase the tempo and facilitate adherence. The PETTLEP approach to MI will be applied, involving the "**P**hysical, **E**nvironmental, **T**ask, **T**iming, **L**earning, **E**motional, and **P**erspective" components of MI.[55] Using the template for intervention description and replication (TIDieR) checklist,[56] detailed information on the PETTLEP approach and intervention is provided in Supplemental Table 1. In Figure 1, key aspects of the intervention are presented.

Figure 1 around here

Figure 1 Key elements of the intervention in the three groups

Practice frequency will be noted in a diary with weekly reports on participants' practice frequency prepared. Weekly phone calls will be used in the homebased training support of all participants, additionally at 4-weeks post-intervention. Additional phone call support will be provided upon request by the intervention providers. The content of the semi-structured telephone interviews during and post-intervention is presented in Figure 2 and Supplemental File 3.

Figure 2 around here

Figure 2 Content of semi-structured interviews

Data collection

Demographic and disease specific data will be collected as detailed in Table 2. Three categories of disease modifying treatment (DMT) will be operationalised according to the disease activity and course (1) no DMTs; (2) moderately effective and (3) highly DMTs (active substances are detailed below Table 2). DMTs will be recorded and handled as a covariate in the data analysis because they may affect the primary and secondary outcomes. Clinical data will be collected by trained and blinded assessors (physiotherapists, occupational therapists, sports scientists, and psychologists), with the order of the patient-reported outcome measures being randomised for each participant and visit to minimise order effects. A schedule of the study procedures is provided in Table 2.

Table 2 Schedule of study procedures

	STUDY PERIOD					
	Enrolment	**Allocation**	**Post-allocation**			
	Screening		Baseline test Day 1	Post-intervention test Week 4	Follow-up phone call Week 8	Follow-up test Month 3
TIMEPOINT	$-T_1$	*0*	T_1	T_2	T_3	T_4
ENROLMENT						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS						
Music-cued MI group			←	→		
Music-cued MI and gait training group			←	→		
Music-cued gait training group			←	→		

OUTCOMES (ASSESSMENTS)						
Baseline variables						
Demographics (age, gender)	X					
Clinical characteristics (EDSS, MS phenotype, disease duration, disease modifying treatment[1])	X					
Global cognitive impairment (MoCA test)	X			X		X
Anxiety and depression (HADS)	X			X		X
Suicidality (narrative screening)	X			X		X
Primary outcomes						
Walking speed and distance (T25FW, 2MWT)			X	X		X
Secondary outcomes						
Brain activation patterns (fMRI)			X	X		
MS related fatigue (NFI-MS)			X	X		X
Health-related QoL (MusiQoL)			X	X		X
MI ability (KVIQ-10, mental chronometry test)			X	X		X
Cognitive functioning (SDMT)			X	X		X

Music-induced motivation in exercise (BMRI-II)			X	X		X
Music-induced pleasure & arousal (SAM)				X		
MS specific self-efficacy (USE-MS)						
Adverse events and adverse reactions (log)				X	X	X
Falls (log)				X	X	X
Acceptability of the intervention, adherence and coping (checklist, weekly semi-structured phone interviews)			←	→		
Self-report health status and feedback on the study intervention (follow-up semi-structured phone interviews)					X	

[1]Three categories of disease modifying treatment (DMT): (1) no DMTs; (2) moderately effective DMTs: interferon-b 1a and 1b, pegylated interferon-b 1a, glatiramer acetate, dimethyl fumarate, teriflunomide, azathioprine, intravenous immunoglobulins; (3) highly effective DMTs: alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, cyclophosphamide, mitoxantrone, rituximab, siponimod, ofatumumab, and ozanimod.[57]

BMRI-II, Brunel Music-Rating Inventory-II; EDSS, Expanded Disability Status Scale; fMRI, functional magnetic resonance imaging; HADS, Hospital Anxiety and Depression Scale; KVIQ-10, Kinaesthetic and Visual Imagery Questionnaire, short version; MI, motor imagery; MoCA, Montreal Cognitive Assessment; MS, multiple sclerosis; MusiQoL, Multiple Sclerosis International Quality of Life; NFI-

MS, Neurological Fatigue Index - Multiple Sclerosis; SAM, Self-Assessment Manikin; SDMT, Symbol Digit Modalities Test; T25FW, Timed 25-Foot Walk; USE-MS, Unidimensional Self-Efficacy Scale for Multiple Sclerosis; 2MWT, 2-Minute Walk Test.

Primary outcomes

Primary outcomes are walking speed as assessed by the Timed 25-Foot Walk (T25FW)[58] and walking distance as assessed by the 2-Minute Walk Test (2MWT).[59] [60] For the T25FW, patients will be asked to walk a marked distance of 25 feet (7.62 metres) as quickly as possible, though safely, with an assistive device as required.[61] Scoring is achieved by taking the average of two trials. Excellent psychometric properties of the T25FW have been demonstrated.[62] [63] A 20% change in the T25FW is interpreted as a clinically significant difference in walking speed.[64]

The 2MWT will be performed as outlined in the American Thoracic Society Guidelines, which were developed for the 6-Minute Walking Test[65] and adapted by international experts from the NIH Toolbox.[66] For the 2MWT, excellent validity[67] [59] and test-retest reliability have been found.[68] A 20% change represents a clinically significant difference in walking distance.[69]

Secondary outcomes

Brain activation patterns

MRI data will be acquired at T_1 and T_2 on a 3 Tesla scanner (Siemens PRISMA, Siemens Healthcare Erlangen) using a 20-channel head coil. The MRI protocol includes a high-resolution structural three-dimensional (3D) T1-weighted MPRAGE sequence with 1 mm isotropic resolution (repetition time (TR) = 1900 ms, echo time (TE) = 2.7 ms) and a T2-weighted sequence (1mm isotropic, TR = 2800 ms, TE = 405 ms). A 3D fluid-attenuated inversion recovery (FLAIR) sequence (1 mm isotropic, TR = 5000 ms, TE = 393 ms) is administered to assess hyperintense T2-lesion load in patients. Additionally, diffusion tensor imaging (DTI; 1.5 mm isotropic, TR = 3318 ms, 64 directions), task-related fMRI (2 mm isotropic; TR = 2500 ms; TE = 30; 198 volumes, field of view = 192 × 192 mm², acquisition time = 8.31 minutes) and resting-state fMRI (rsfMRI; 2 mm isotropic; TR = 1000 ms; TE = 35; field of view = 256 × 256

mm², acquisition time = 5.20 minutes) will be performed. The scans will take approximately 35 minutes in total.

Task-related fMRI: experimental stimuli and procedure

The block-fMRI task will comprise a music-cued bipedal ankle movement on a treadmill i.e., alternating dorsi- and plantarflexion of both feet [70], a corresponding music-cued MI, and a listen-to-music-only condition. Four instrumental music-excerpts were selected as cues based on the same criteria used in the interventions.[6] Pace is held constant at 110 BPM for all cues. Each condition is repeated four times, and presented in a pseudo-randomised order, so that no condition or music-cue occurs twice in a row, and identical music-cues never run successionally.

Before each condition, a coloured symbol cue appears in the centre of the screen for 2.5 seconds, indicating the subsequent condition (orange feet for movement, blue think bubble for MI, violet ear for music-only condition; Figure 3a). At the start of each condition, a fixation cross in the corresponding colour appears and the music starts. Participants are instructed to perform the ankle movement at the pace of the music, starting with the right foot, and concentrate on the music beat during the music-only condition. After 22.5 seconds, the fixation cross turns black, indicating a period of total rest for 15 seconds (Figure 3b).

Figure 3 around here

Figure 3 Schematic representation of the block fMRI-paradigm

Figure legend: a) Presentation of each condition (music-cued movement, music-cued motor imagery, music-only), the corresponding symbol cues and the treadmill used for the study. b) Timeline of the paradigm.

Prior to entering the scanner, participants will practice the paradigm. Throughout the whole paradigm, participants are instructed to fixate on the cross, not to move their heads, to relax their entire body, except their feet during the movement condition. To

decrease stimulus-correlated motion, participants' heads are fixed with foam-cushions and their knees flexed to approximately 135° using a soft roll and cushion beneath their knees (Figure 3a).[70] Vision is corrected with prism lenses if necessary. During the paradigm, participants are observed with correct and incorrect movements recorded. After the scan, participants are asked to complete a short questionnaire on whether they recognised the songs (yes/no), liked the music-cues and found them motivating to move (both items: 7-point Likert scales). Three items will ask about the MI conditions (7-point Likert scale): the perceived MI difficulty and the extent to which they have "seen" or "felt" the MI (similar to the KVIQ-10 response format).

Fatigue

The Neurological Fatigue Scale - Multiple Sclerosis (NFI-MS) will be used to assess fatigue, including subscales of physical and cognitive fatigue, relief through daytime sleep or rest and abnormal nighttime sleep and sleepiness.[71 72] A summary score of items 1-7, 9 and 11-12 is generated. A 4-point Likert scale is used, from 0 = 'strongly disagree' to 3 = 'strongly agree', where higher scores represent more severe fatigue. The NFI-MS displayed good validity[72] and reliability.[72]

Health-related quality of life

The 31-item Multiple Sclerosis International Quality of Life questionnaire (MusiQoL)[73 74] has been chosen to record patient-reported health-related QoL (HRQoL). Nine dimensions of HRQoL are assessed: everyday activities, psychological wellbeing, symptoms, relationships with friends, family and the health care system, emotional and sex life, coping and rejection. A 5-point Likert scale from 1 = 'never/not at all' to 5 = 'always/a lot' is used with reverse scoring of negatively worded items. Nine domain scores and the global index are standardised on a 0-100 scale, where 100 represents the best HRQoL. A good validity [75] and reliability have been shown for the MusiQoL.[73 74]

MI ability

MI ability should be assessed using at least two different approaches,[76] hence the Kinaesthetic and Visual Imagery questionnaire,[77 78] utilising a German short version (KVIQ-G-10) [77] and a mental chronometry (MC) test.[79-81]

The KVIQ-(G)10 is patient-reported and assessor-administered and measures visual and kinaesthetic MI ability in neurological patients using five items.[78] Scoring is achieved using a 5-point Likert scale from 1 = 'no image' to 5 = 'image as clear as seeing' (visual subscale) and from 1 = 'no sensation' to 5 = 'as intense as executing the action' (kinaesthetic subscale). The KVIQ-G-10 has excellent psychometric properties.[77]

MC tests are based on the theory of functional equivalence between MI and actual movement.[55 82 83] Excellent temporal equivalence has been found for corresponding imagined and real movements.[81 84] MC evaluation will be at a comfortable tempo on a marked 6-metre path.[79-81] The "index of deviation from isochrony" will be calculated to quantify the discrepancy between imagined and real walking: deviation index = absolute value (1−(MI/motor execution).[85] Values close to zero are indicative of high MI ability.[85]

Depression, anxiety, and suicidality

The German version[86] of the Hospital Anxiety and Depression Scale (HADS)[45] and narrative screening for suicidality[44] adapted from item 9 of the Beck Depression Inventory[87] and a suicidality screening checklist[88] will be employed for screening. The 14-item HADS assesses patient-reported anxiety and depression during the previous two weeks. Anxiety or depression will be signified by a HADS anxiety[42] or depression subscale score of 11/21 points[43] or suicidality as evaluated by a narrative screening [44]. Good validity, reliability[89] and a bifactorial structure has been shown for the German HADS.[86]

Overall cognitive impairment

Overall cognitive impairment (attention and concentration, executive functions, memory, language, visuo-constructive abilities, conceptual thinking, arithmetic and orientation) will be assessed using the German Montreal Cognitive Assessment (MoCA).[46 90] The highest possible score is 30 points; values ≥26 are considered normal,[41] with good psychometric properties demonstrated.[41 91 92]

Motivational qualities of music in exercise settings

The 6-item Brunel Music Rating Inventory-2 (BMRI-2)[93] has been chosen to assess the music-induced motivation to move on a 7-point Likert scale. Music pieces selected from the audio-mix will be played to participants (in relevant 90-second excerpts).[93] Motivational properties of the musical rhythm, style, melody, tempo, instrumentation and beat during physical exercise will be patient-rated. The BMRI-2 has shown good validity and reliability.[93 94]

Music-induced pleasure and arousal

The Self-Assessment Manikin (SAM) will be used to measure the emotional responses of pleasure and arousal to the music selected for the study intervention.[95 96] The SAM consists of two series of pictograms, each of which displays a dimension on a 9-point scale[95 96]. SAM validations have demonstrated good to excellent validity[96 97] and reliability[98].

Self-efficacy

The validated German version[99] of the Unidimensional Self-Efficacy Scale for MS (USE-MS)[100] will be used to assess self-efficacy. For this patient-reported 12-item questionnaire using a 4-point Likert scale, excellent psychometric properties have been seen.[99 100]

Cognitive function

Cognitive function including attention, visual scanning, working memory and psychomotor speed will be measured using the Symbol Digit Modalities Test (SDMT)[101]. Patients will be asked to assign the numbers 1 through 9 to nine different symbols within 90 seconds. The number of maximum possible substitutions is 110. Excellent construct,[102] predictive [103] and discriminatory validity[104] and test-retest reliability[105] for the SDMT is demonstrated in pwMS.

Falls, adherence, and acceptability of the intervention

Falls and adverse events will be recorded in structured logs, the relationship with the intervention evaluated and treatment provided if necessary, which is covered by an indemnity insurance policy. Semi-structured telephone interviews will gain information on adherence and acceptability. Adherence will be monitored using a self-report checklist (Figure 2).

Data management

As for confidentiality, the Austrian, Tyrolean and Styrian Data Protection Acts will be adhered to, and personal data codified by a participant ID. Only the research team will have access to the data. Data will be only used for the purposes for which they were collected and saved on a password-protected computer. Data will be digitised in double entry with double coding of interview data performed. Quality assurance measures such as spot checks of value ranges and field types and logical checks will be performed.

Data analyses

Statistical data analyses

All statistical analyses employ IBM SPSS software, release 27.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 9, San Diego, California. A two-tailed p-value <0.05 will signify statistical significance. Using Little's test of missing completely at random

(MCAR) the assumption of missing completely at random will be tested, signified by a p-value >0.05.[106] With data missing (completely) at random, multiple imputation will be used for handling missing data, or other strategies as appropriate.[107] Including all cases as originally allocated, intention-to-treat analysis will be performed. Descriptive statistics will be used as appropriate and continuous data tested for normal distribution using the Shapiro Wilk test, Q-Q-plots and histograms. For between-group comparisons at baseline, One-Way Analysis of Variance (ANOVA), Kruskal Wallis and Chi square tests will be used.

Mixed Design ANOVA test assumptions will be tested for e.g., sphericity (Mauchly´s test) and homogeneity of variance (Levene´s test), and standard correction procedures applied where appropriate. For continuous variables (T25FW, 2MWT, MC and SDMT), a 2-Way Mixed Design ANOVA will be conducted, using time as within-subject factor and group as between-subject factor, and the three DMT categories as covariates (no DMT; moderately effective DMT; highly effective DMT).[108] Post-hoc Bonferroni adjustment performed as appropriate. For categorical data (NFI-MS, MusiQoL, KVIQ-10, HADS, MoCA, BMRI-2, SAM, and USE-MS), calculation of differences between post-intervention and baseline values will be followed by Kruskal Wallis and Dunn's multiple comparisons tests.

Structural MRI analyses

Using the Statistical Parametric Mapping - Lesion segmentation toolbox, T2-lesion load (T2-LL) will be assessed on T2-FLAIR images by the lesion prediction algorithm[109] controlled by a single experienced rater. Individual binarised T2-LL masks will be registered to MNI and lesion probability mapping performed to identify the lesion locations, using FSL randomise. After lesion filling with the FSL lesion filling toolbox, brain volumes will be assessed from T1-weighted MPRAGE images using SIENAX.

Functional MRI analyses

Individual resting state and task-fMRI data will be pre-processed using FEAT (FMRIB's Expert Analysis Tool, v 6.0, part of FSL v 6.0.[110] Pre-processing includes: motion correction using MCFLIRT, brain extraction, spatial smoothing using a Gaussian kernel of FWHM (full width at half maximum) of 5 mm,[111] high pass temporal filtering using a cut-off of 150 s (0.007 Hz), linear registration to main structural image (BBR) and nonlinear registration warp resolution of 10 mm. High-resolution T1 scans are used for image registration.

First-level task fMRI analyses will be performed for each participant, assessing activation patterns of the three conditions (movement, MI, music-only) and related contrasts. Higher-level analyses will be used to examine potential differences between intervention groups. Independent Component Analysis (ICA) will be performed for rs-fMRI data (FSL-MELODIC, v 3.12). The resulting denoised functional images will be resampled to standard space (MNI152 template 2 mm). Dual-regression analyses on the denoised, registered functional images of each subject will be performed to obtain individual spatial maps of the resting-state networks, focusing on the sensorimotor and salience network. Group functional connectivity maps for timepoints 1 and 2 and longitudinal change will be computed for each subject (using FSL Randomise).

Qualitative data analysis

A thematic analysis, understood as a 'method for identifying, analysing, and reporting patterns or themes within data'[112] of the interview material will be performed.[113 114] Semantic and latent themes will be identified, summarised and interpreted,[112] with data coded, segmented and extracted. From this data, broader themes will be developed. Themes will be reviewed, refined and validated in an iterative and reflexive process,[115] data recoded as appropriate, and subthemes identified. Subthemes or categories will be judged by the criteria of internal homogeneity (meaningful coherence within a

category) and external heterogeneity (clear differences between categories).[116] The consolidated criteria for reporting qualitative research (COREQ) will be followed to enhance rigour, credibility and reliability.[117]

DISCUSSION

This study will investigate the effects of three variants of home-based cued gait training interventions on walking, fatigue, emotional and cognitive function, and brain activation. Music will be included to both provide a temporal cueing to the real or imagined walking and potentially induce pleasure in practitioners. Pleasurable, motivating music is known to induce highly enjoyable emotions, motivation and arousal.[118] Music-based interventions have been found to improve motor performance, mood and cognition in healthy people and patients with neurological disorders including MS.[119 120] This may be relevant because studies have further shown that depression[121] and cognitive or higher levels of motor impairment[122 123] reduce the MI ability in pwMS. Therefore, it seems relevant to include screening for anxiety, depression, and cognitive impairment in the planned study. Moreover, other aspects, such as music-induced motivation, pleasure or arousal have not been previously measured in pwMS.

Functional MRI is a state-of-the-art method for assessing potential underlying mechanisms of motor impairment and rehabilitation. Despite the paucity of recent literature, we expect a training-induced decrease of the widespread activation, leading to a more focal activation of the primary sensorimotor network during the motor tasks.[1–3] This would also be in line with previous research indicating a rehabilitation-induced “normalization” in brain activation, i.e. activation patterns more similar to those observed in healthy controls[3]. In accordance with previous studies, we expect that pwMS recruit similar brain areas during MI and actual movement, albeit sensorimotor regions might be activated to a lesser and premotor and parietal

regions recruited to a higher extent during MI.[124 125] Additionally, cued MI training may lead to similar reorganisation patterns compared to training of the actual movement.[34]

The absence of a physiotherapist during the homebased intervention could be a potential limitation of this study. Using a thorough familiarisation to the music-supported MI and gait training, as well as regular telephone support, this limitation should be overcome. A further limitation could be a lack of motivation and adherence in participants, which we aim to counterbalance using weekly support phone calls and further support calls upon request. A potential limitation in achieving the study objectives may be patients' hesitancy to undergo two extra MRI investigations at Centre 3. Patients will be explained that they will be provided with the examination results at their request, which their treating doctors may include in their consultation and treatment planning.

Advantages of a home-based intervention are that pwMS can practise independently, provided that specifically trained physiotherapists familiarise them with the programme and guide their initial training phases. Depending on the results from this study, the most effective music-cued gait intervention can easily be put into practice.

DECLARATIONS

Ethics, licences and dissemination plan

The study will be conducted in accordance with the principles of the Declaration of Helsinki (1964; 2013) and ICH E6(R2) Guideline for Good Clinical Practice (2016). The study protocol was approved by the Ethics Committees of the Medical Universities of Innsbruck and Graz on the 22.12.2020 (references 1347/2020 and 33-056 ex 20/21). A licence was obtained for using the MoCA, SDMT and MusiQoL from MoCA Test Inc. (Greenfield Park, Quebec), Hogrefe Austria GmbH (Vienna, Austria) and Mapi

Research Trust (Lyon, France). Results will be disseminated to participants via letters and to clinicians and researchers via conferences and peer-reviewed publications.

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Author Contributions

BS devised and designed the study, qualitative methodology and overall data analyses. FD, CB, CE and DP substantially contributed to the conception and design of the study. BS, DP and BH drafted the manuscript. DP, BH, SR and GR devised the MRI analyses. RE and HH provided substantial input on the study methodology. FD, CE and CB are study managers at their centres. All authors critically revised and approved the final manuscript.

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Competing interests

None declared.

Data sharing statement

Data generated by this research that support any publications will be made available upon reasonable request as soon as possible. It will be considered submitting these data to the Open Science initiative once future analyses related to this data set are completed. The informed consent form includes the consent to controlled data sharing.

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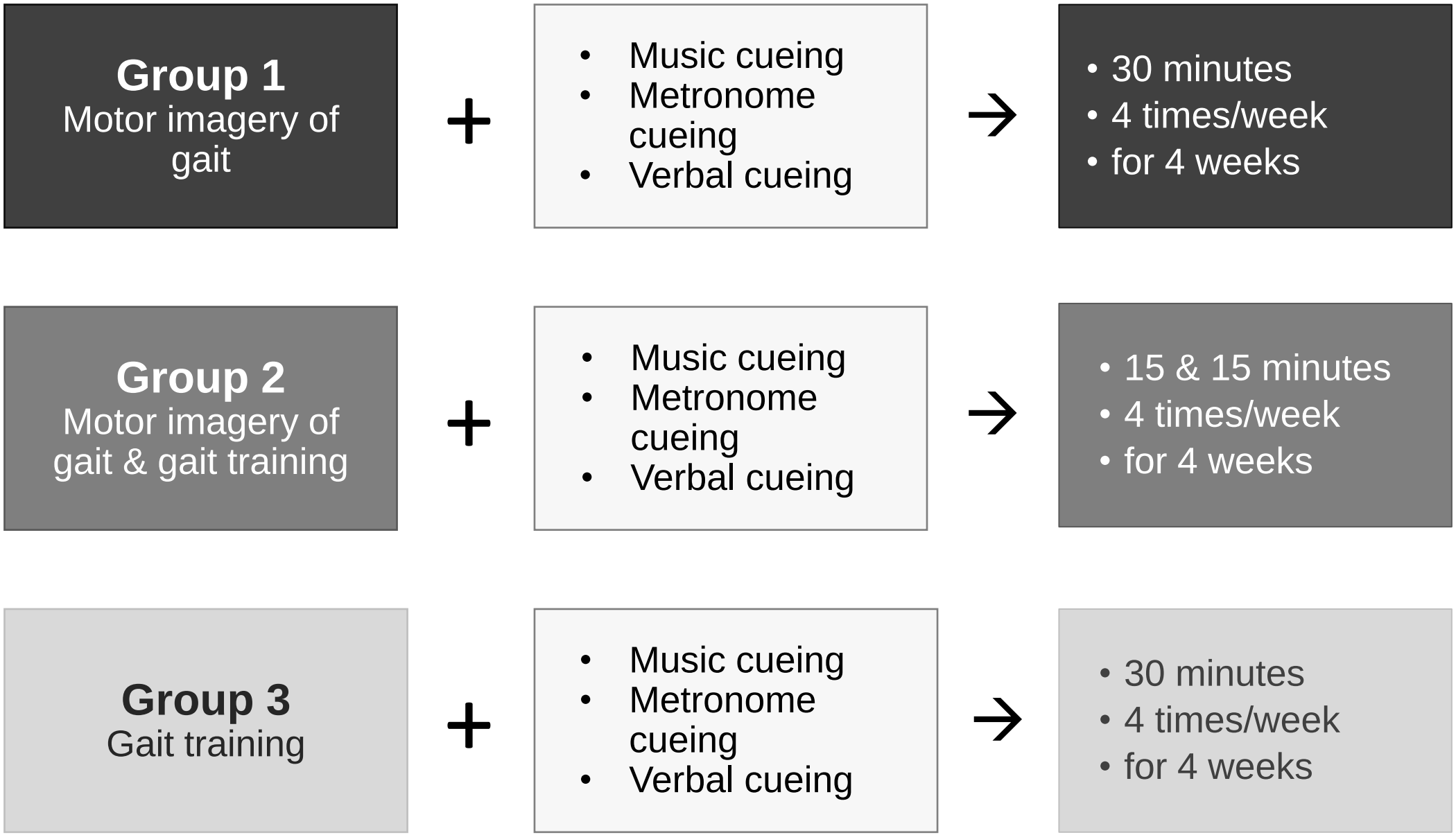

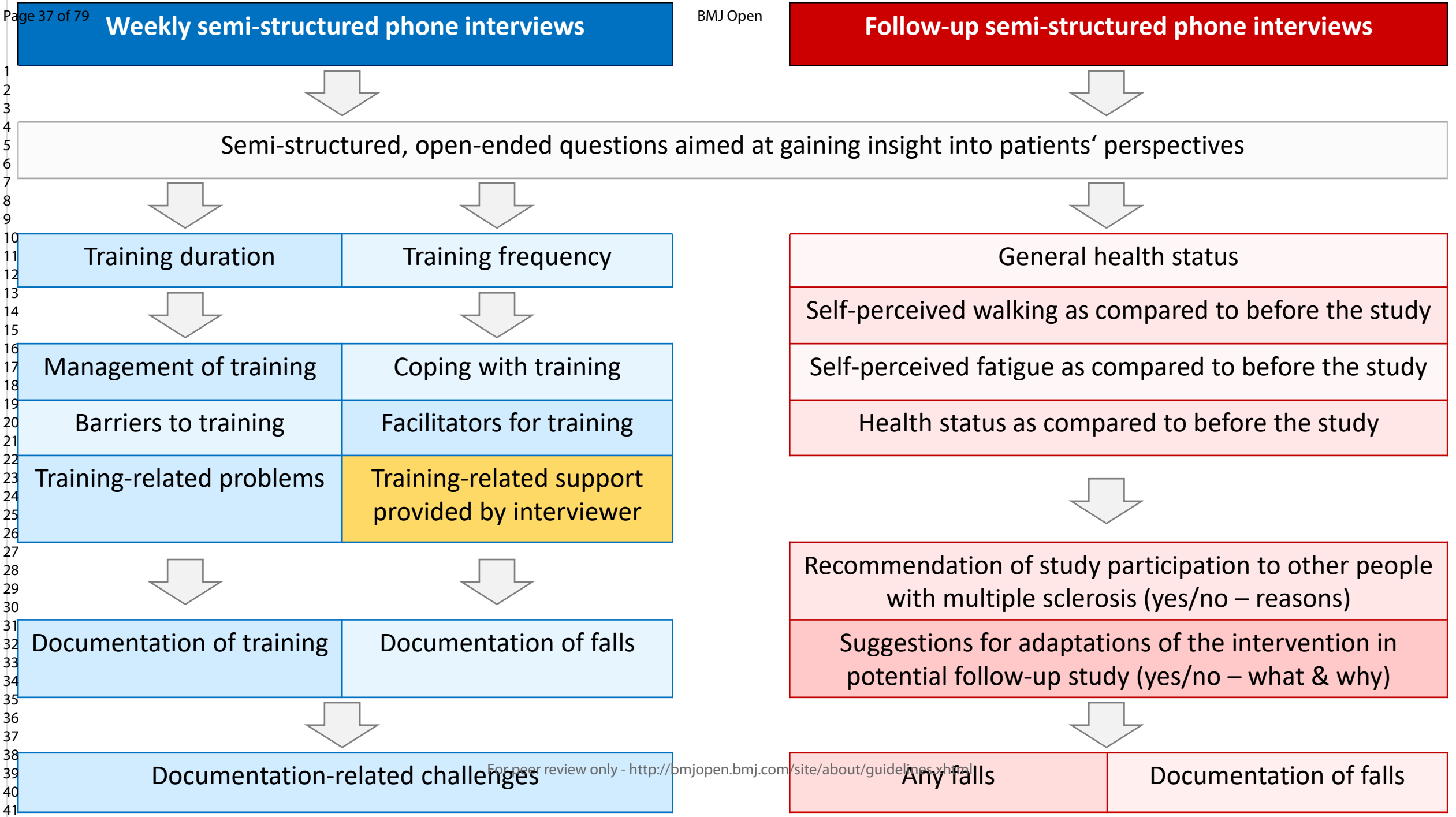

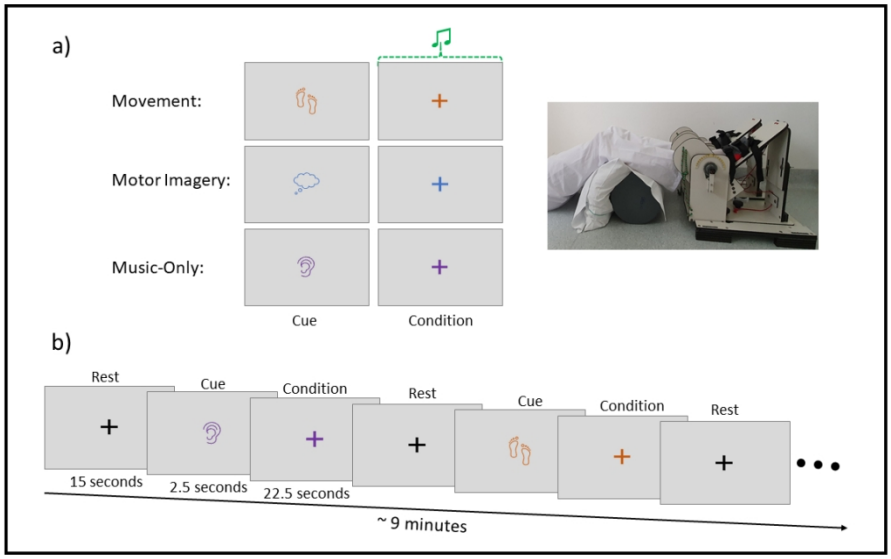

Figure 3

108x60mm (300 x 300 DPI)

CONSORT Flow Diagram (Extension to randomised pilot and feasibility trials; Eldridge et al., 2016)

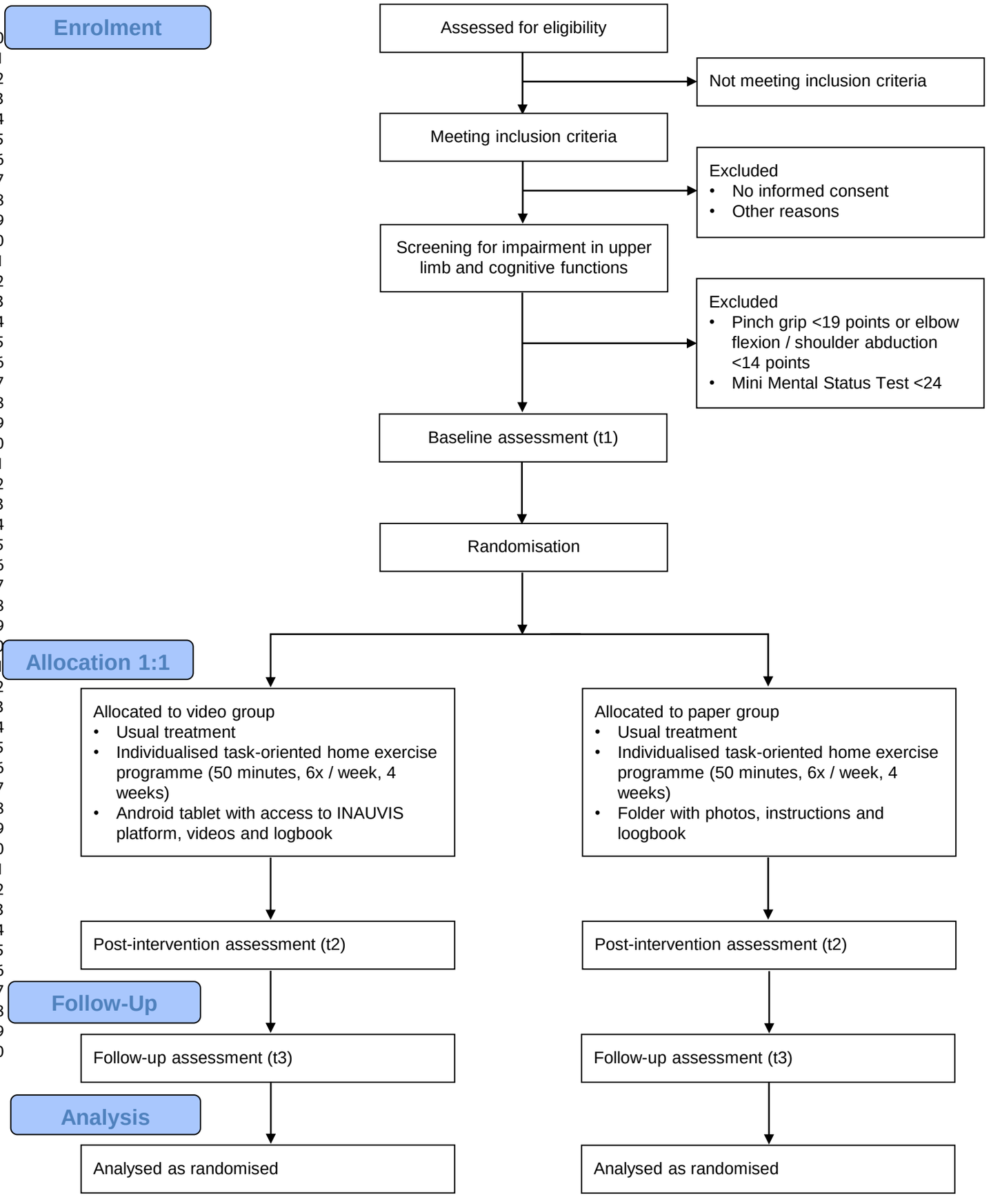

Table 1 Intervention chart

ITEM NO	ITEM DESCRIPTION		
1 BRIEF NAME	**Group 1**	**Group 2**	**Group 3**
	Motor imagery (MI) with music-, metronome- and verbal cueing	MI and gait training with music-, metronome- and verbal cueing	Gait training with music-, metronome- and verbal cueing
	Music accentuated by metronome cues and intermittent concise verbal cueing		
2 WHY	- PETTLEP (Physical, Environment, Task, Timing, Learning, Emotion, Perspective) approach to MI (Holmes and Collins 2001)[1] - Rhythmic-auditory stimulation (cueing) for gait training (Thaut 2007)[2]		
3 WHAT MATERIALS	- Dropbox link including the audio mix and download to smartphone, laptop, tablet or MP3-player, or study CDs in group 1 - 4 sessions in each audiomix, one for each week - Headphones or earphones may be used if desired		
Audiomix Content	- Kinaesthetic MI instructions	- Kinaesthetic MI and gait training instructions	- Gait training instructions

	- Instrumental music in 2/4 or 4/4 metre - Beat-accentuating metronome cues - Intermittent verbal cueing (e.g., “toe-off” or “step-step”) - Weekly change of music titles - Gradual increase in tempo		
4 WHAT PROCEDURES	- Introduction to cued MI, familiarisation and training	- Introduction to MI and gait training with cueing, familiarisation and training	- Introduction to gait training with cueing, familiarisation and training
	- In lay language; description of the concept of MI; its application in sports and neurorehabilitation; MI perspectives (internal and external) and modes (visual, kinaesthetic). - Measurement of actual and imagined walking duration over a 6-metre distance to monitor the mental process - Performance feedback for participants and repeated training if desired		
		- In lay language; description of the concept of cued gait training and sensorimotor interaction; its application in sports and neurorehabilitation;	

		gait synchronisation with the music/metronome beat; musical tempo modulations. - Additional introduction to rhythmic auditory stimulation plus its use in neurorehabilitation - Rhythmic-cued MI familiarisation
	- Weekly phone calls for training support, adherence and adverse events reports - Phone calls at 4-week follow-up for feedback	
PETTLEP Elements		**Rhythmic-cued gait training**
Position (Physical)	- Practise at any time of the day when alert - Seated in an upright body position - Shoulders relaxed - Avoid tightening the muscles or moving - Eyes closed - Normal breathing	
		- Practice at any time of the day when alert - Use of headphones or earplugs if desired - Walking on a hallway (indoors) and/or familiar straight path (outdoors)

		- Adjusting one's steps with the music or metronome beat (every second music beat) - Use of walking sticks if required for reasons of safety - Avoid using walking sticks with balance related tasks if safe - Periods of rest as desired
Environment	- Practice in a quiet place at home - Imagine walking indoors (e.g., a long hallway) and walking outdoors (on a straight and familiar path)	
Tasks for all groups	- Take long/giant strides - Take extremely slow/small and quick strides - Touch the ground with your heels first - Roll your feet on the ground and feel your body weight on your soles - Toe-off - Raise your knees - Pace elegantly and upright like a queen/king - Place/feel your weight on your feet/legs - - Feel the swinging of your arms while walking/swing your arms during walking	

	- Stamp your feet while walking, walk forcefully and energetically - Walk effortlessly, feeling lightly - Take wide/narrow steps	
Timing of the MI and gait training	External timing is provided: “imagine yourself walking in time with the music or metronome and verbal cues”	
		External timing is provided: “walk in time with the music or metronome and verbal cues”
	- Tempo (cadence) is between 80 and 120 steps/minute - Slow, medium and fast music pieces alternate, with a gradual progression in the tempo over the 4 weeks	
Learning	- See familiarisation - Weekly phone call support is provided	
Emotion related to the MI and gait training	- MI instructions include motivational and arousal enhancing aspects. See instructions under Tasks. - Motivational instrumental music is used with the MI	
		- Gait training instructions include motivational and arousal enhancing aspects. See instructions under Tasks. - Motivational instrumental music is used with the gait training

Perspective	Kinaesthetic MI from an internal, first-person perspective	No MI
5 WHO PROVIDES	- The audiomix was created by the lead researcher (BS), an experienced neurological physiotherapist with 11 years of musical training and a PhD in physiotherapy. - The introduction, familiarisation and training is provided by neurological physiotherapists, occupational therapists and psychologists who received a structured and specific training by the lead researcher - All therapist researchers are supervised and supported by the lead researcher - Any intervention related processes are documented by the study team	
6 HOW – all delivery modes	- MI introduction, familiarisation and training: individually - Monitoring of mental process: individually	
		- Cued gait training introduction, familiarisation and training: individually - Monitoring of understanding of gait synchronisation with beat: individually
	- Weekly phone calls: individually	
7 WHERE	- MI introduction, familiarisation, training and monitoring of mental process: at Medical University of Innsbruck (Centre 1) or Graz (Centre 3), Clinical Department of Neurology or Rehab Centre Münster (Centre 2), Austria	

		- Cued gait training introduction, familiarisation and training: at Medical University of Innsbruck (Centre 1) or Graz (Centre 3), Clinical Department of Neurology or Rehab Centre Münster (Centre 2), Austria	
	- Cued MI practice: at participants' homes		
		Cued gait training: at participants' homes	
8 WHEN AND HOW MUCH	30 minutes, 6 times a week, for 4 weeks	15 & 15 minutes, 6 times a week, for 4 weeks	30 minutes, 6 times a week, for 4 weeks
9 TAILORING	Same intervention for all participants	Same intervention for all participants	Same intervention for all participants
10 MODIFICATIONS	No modifications	No modifications	No modifications
11 HOW WELL PLANNED	- Intervention adherence is assessed using a participant diary and also during weekly phone calls and at post-intervention - Support to intervention adherence is performed by the researchers who instruct participants (guidance and motivation) - Recording in structured support call logs is performed by the researchers who instruct participants - Recording in excel sheets is performed in excel sheets by the lead researcher		

12 HOW WELL **ACTUAL**	This is a study protocol and the adherence rates are not yet available.

References

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SPIRIT 2013 and SPIRIT-PRO Extension Checklist: Recommended Items to Address in a Clinical Trial Protocol

Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA : the journal of the American Medical Association 2018;319(5):483-94 doi: 10.1001/jama.2017.21903[published Online First: Epub Date])

Section/item	ItemNo	Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Addressed on Page No.
Administrative information					
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym			Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry			Abstract
	2b	All items from the World Health Organization Trial Registration Data Set			See below (pages 14-20)
Protocol version	3	Date and version identifier			Abstract
Funding	4	Sources and types of financial, material, and other support			27

Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors			27
	5b	Name and contact information for the trial sponsor	SPIRIT-5a-PRO Elaboration	Specify the individual(s) responsible for the PRO content of the trial protocol.	See Spirit Item 2B below
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities			See Spirit Item 2B below; 27
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)			10 and 22
Introduction					

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	SPIRIT-6a-PRO Extension	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	5-6
	6b	Explanation for choice of comparators			5-6
Objectives	7	Specific objectives or hypotheses	SPIRIT-7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)			Title, Abstract, 4 and 7
Methods: Participants, interventions, and outcomes					
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained			6 and 10

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	SPIRIT-10-PRO Extension	Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	7, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered			10-11, Figure 1, Supplemental Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)			22, Table 2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)			7, 11, 15, Figure 2, Supplemental File 3
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial			Tables 1 and 2 including legends

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	SPIRIT-12-PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (eg, overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.	12-22, Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	SPIRIT-13-PRO Extension	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized.	10, Table 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	SPIRIT-14-PRO Extension	When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.	7

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size			10
Methods: Assignment of interventions (for controlled trials)					
Allocation:					
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions			10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned			10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions			10

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how			10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial			10
Methods: Data collection, management, and analysis					
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	SPIRIT-18a (i)-PRO Extension	Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.	2, 12-22, Table 2, Figure 2
			SPIRIT-18a (ii)-PRO Extension	Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other).	2, 4, 11, Table 2, Supplemental File 3

			SPIRIT-18a (iii)-PRO Extension	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	8, 20-21, 26-27
			SPIRIT-18a (iv)-PRO Extension	When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available.	NA
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	SPIRIT-18b (i)-PRO Extension	Specify PRO data collection and management strategies for minimizing avoidable missing data.	7, 11, 22, Table 2
			SPIRIT-18b (ii)-PRO Elaboration	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	22-23
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol			22, 24-25

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	SPIRIT- 20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	22-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)			24
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	SPIRIT- 20c-PRO Elaboration	State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).	22-23
Methods: Monitoring					
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed			21, 27

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial			NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	SPIRIT- 22-PRO Extension	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; eg, in the participant information sheet and consent form.	Table 2, Figure 2, page 22
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor			NA
Ethics and dissemination					
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval			3, 26

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)			NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)			10, Supplemental File 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable			NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial			27, Supplemental File 2
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site			27
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators			22

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation			22
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions			3, 27
	31b	Authorship eligibility guidelines and any intended use of professional writers			27
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code			27
Appendices					
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates			Supplemental File 2

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable			NA

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; PRO, patient-reported outcome.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license and is reproduced with permission.

Spirit Item 2B WHO Trial Registration Dataset

Data Category	Information
Primary registry and trial identifying number	German Clinical Trials Register https://www.drks.de/drks_web/ Trial ID: DRKS00023978
Date of registration in primary registry	28.12.2020
Secondary identifying numbers	Universal Trials Number (UTN): U1111-1263-1856 Ethics approval reference number: 1347/2020

Source(s) of monetary or material support	This study is an independent academic study, which is conducted with the financial support of Celgene, a company of Bristol Myers Squibb (NA-CL-MS-PI-13909_Seebacher: Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study). The people involved in decision-marking about this funding have no influence on the planning, conduct and publication of the study.
Primary sponsor	Medical University of Innsbruck, Austria
Secondary sponsor(s)	N/A
Contact for public queries	Dr Barbara Seebacher Phone: +435050482499 Email: barbara.seebacher@i-med.ac.at
Contact for scientific queries	Dr Barbara Seebacher Phone: +435050482499 Email: barbara.seebacher@i-med.ac.at

Public Title	Effects of actual and imagined music-stimulated gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study
Scientific Title	Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study
Countries of recruitment	Austria
Health condition(s) or problem(s) studied	Multiple sclerosis (MS)
Intervention(s)	Group 1: Motor imagery (MI) with music cueing; the music beat is accentuated using metronome cueing and intermittent verbal cueing; 30 min, 4x per week, for 4 weeks Group 2: MI with music cueing (the music beat is accentuated using metronome cueing and intermittent verbal cueing) plus gait training with music cueing; 15 & 15 min, 4x per week, for 4 weeks Group 3: Gait training alone with music cueing; the music beat is accentuated using metronome cueing and intermittent verbal cueing; 30 min, 4x per week, for 4 weeks

Key inclusion and exclusion criteria	Inclusion criteria: people with any MS phenotype according to the revised McDonald's criteria; aged 18 years or over; any ethnicity; disability status score on the EDSS of 2.0 to 5.0; stable disease; no evidence of disease activity; and able to speak and understand German language. Exclusion criteria: people with MS with concomitant diseases (such as malignant diseases, other neurological or psychiatric disorders, musculoskeletal problems affecting walking, pain, uncorrected visual or hearing impairment); cognitive impairment as defined by a MoCA cut-off score of 26/30 (<26 = impaired cognition; ≥26 = intact cognition); anxiety or depression as signified by a HADS anxiety subscale score of 11/21 or a depression subscale score of 11/21 or suicidality as evaluated by a narrative screening; pregnancy; a relapse of MS within the last three months; any medication initiation or change (including corticosteroids) or any physiotherapy change within three months prior to the study; any change of symptomatic treatment affecting walking (medication or physiotherapy) or of

	disease modifying treatment (DMT) during the study will lead to an exclusion of the participant from the further analysis. Any MRI/fMRI contraindications, e.g. implanted ferrous metal, heart pacemaker or claustrophobia. Healthy controls for the fMRI scanning: 15 age- and gender matched healthy controls without any history of neurological, psychiatric, orthopaedic or other disorder.
Study type	Prospective double-blind randomised parallel multicentre trial Allocation: stratified blocked randomisation with allocation concealment Intervention model: parallel assignment (1:1:1) Masking: assessor-blinded; patients blinded to the study hypotheses Primary study aim: to investigate whether there is a difference between the effects of accentuated music- and verbally cued MI, accentuated music- and verbally cued MI combined with gait training and accentuated music- and verbally cued gait training alone on walking in people with MS.
Date of first enrolment	09.02.2021

Target sample size	132 people with MS and 15 healthy controls (fMRT)
Recruitment status	Recruiting
Primary outcome(s)	• Walking speed as assessed by the Timed 25-Foot Walk (T25FW) • Walking distance as assessed by the 2-Minute Walk Test (2MWT)
Secondary outcomes	• Brain activation patterns as assessed by fMRI (and structural MRI); in addition to patients, healthy controls will be scanned at baseline and 4 weeks later, corresponding with the intervention period of this study • MS related fatigue as assessed by the validated German version of the Neurological Fatigue Index (NFI-MS) • MS related health-related QoL, HRQoL as assessed by the validated German version of the Multiple Sclerosis International Quality of Life (MusiQol) questionnaire • MI ability as measured by the validated German version KVIQ-G-10 of the Kinaesthetic and Visual Imagery Questionnaire, short version (KVIQ-10)

	• MI ability as measured by a mental chronometry test comparing the duration of imagined and real walking on a 6-metre walkway • Anxiety and depression as assessed by the German version of the HADS, complemented by additional narrative screening for suicidality • Global cognitive impairment as assessed by the German version of the Montreal Cognitive Assessment (MoCA) • Psychomotor speed, attention, visual scanning and tracking and working memory as assessed by the Symbol Digit Modalities Test (SDMT) • Music-induced motivation / the motivational qualities of music as assessed by the Brunel Music Rating Inventory-2 (BMRI-2) • Music-induced pleasure and arousal as assessed by the Pictorial Self-Assessment Manikin (SAM) • MS specific self-efficacy as assessed by the validated German version of the Unidimensional Self-Efficacy Scale for MS (USE-MS)

	• Number of falls in the intervention and follow-up periods (falls log, telephone interviews) • Home-based training management and coping, barriers to, facilitators of and problems with the training, documentation of the training frequency and duration (support will be provided) (weekly semi-structured telephone interviews during the intervention period) • Feedback on the general health status, walking, fatigue, training content and suggestions for adaptations of the intervention in a potential follow-up study, falls and documentation of falls (semi-structured telephone interview at 4-weeks follow-up)

Medizinische Universität Innsbruck
UNIVERSITÄTSKLINIK FÜR NEUROLOGIE

Karl Landsteiner Institut für interdisziplinäre Forschung
REHA ZENTRUM MÜNSTER

Steiermärkische Krankenanstalten Ges.m.b.H. Landeskrankenhaus - Universitätskliniken - Graz
UNIVERSITÄTSKLINIK FÜR NEUROLOGIE
MEDIZINISCHE UNIVERSITÄT GRAZ

Protocol RIGMUC, Version 1.1 of 28.11.2020

Patient Information Sheet and Informed Consent Form for participation in the clinical study

Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: protocol of a randomised parallel multicentre trial (RIGMUC)

Dear Patient,

We invite you to take part in the above mentioned clinical study. The patient information on the study details will take place as part of a medical consultation.

Your participation in this clinical study is entirely voluntary. You can withdraw from the study at any time without giving a reason. The refusal to participate or a withdrawal from this study will not have any negative consequences for your medical care.

Clinical studies are necessary for obtaining reliable new medical research results. An indispensable prerequisite for the conduct of a clinical study is that you provide written informed consent to participate in this clinical study. Please read the following text carefully - as a supplement to the consultation with your study physician - and do not hesitate to ask questions.

Please only provide written informed consent

- if you fully understand the type and process of the clinical trial,
- if you are ready to agree to participate and
- if you are aware of your rights as a participant in this clinical trial.

The responsible ethics committee issued a favourable opinion to this clinical study as well as on the patient information sheet and the informed consent form.

1. What is the purpose of this clinical study?

Rehabilitation is very important for people with multiple sclerosis (MS) in order to improve their independence in daily life. Physiotherapy serves to improve and maintain the ability to walk. Many novel physiotherapy approaches for people with MS have been developed in recent years. Among other things, the use of music was found to be helpful in training gait rhythm, walking speed and walking distance. The effectiveness of motor imagery on walking and fatigue in people with MS has also been demonstrated. However, some questions remain open: Is pure physical training superior to motor imagery, or is it the other way around? Does a combination of the two have a greater or lesser effect? Are there learning effects in the brain after such a therapy that can be detected with magnetic resonance imaging (MRI)? Which of the three approaches to physical therapy is most popular with people with MS at home? It is our aim to clarify these questions with a multicentre study. The purpose of the study is to examine the effectiveness of three different gait training types with music.

2. How does the clinical study work?

This clinical trial will be conducted at multiple locations and plans to enroll a total of 132 people with MS. Study centres are the Clinical Department of Neurology at the Medical Universities of Innsbruck and Graz and the Rehabilitation Centre in Münster.

The following measures will be carried out exclusively for study reasons:

Your therapy period within this study is expected to be 4 weeks. You can carry out your therapy at home with an electronic study file or CD and will be supported by your study therapist over the phone. A total of 3 examinations with a maximum duration of 90 minutes will take place: The first examination takes place before the 4-week therapy, the second examination takes place immediately after the 4-week therapy, and the third examination takes place 3 months after your last therapy takes place, so your participation in this clinical trial is expected to take 4 months.

You will be informed about the study in a detailed medical discussion and can calmly consider your participation and discuss it with relatives. If you are interested in participating, your suitability for the study will be examined with a questionnaire and a clinical test. In the event of suitability and after you have signed the informed consent form, information on your neurological history will be collected on the basis of existing medical records after your consent.

In the following you will be examined by a physiotherapist and occupational therapist and one of the three therapies will be randomly drawn. The examinations include walking tests, questionnaires and tests for motor imagery. You will then receive information about your therapy at home (4x per week, 30 minutes, for 4 weeks). The therapy groups include the following treatment: motor imagery with music stimulation (30 min, group 1); motor imagery with music stimulation plus gait training with music stimulation (15 & 15 min, group 2); gait training with music stimulation (30 min, group 3). You will also be informed how to use the electronic study files containing music and guidance. The file consists of 4 parts, so you will

receive new training instructions and a new motor imagery and/or gait with music every week. After each week you will receive a call from your therapist for support. If you have any questions or problems, you can also contact your therapist between these phone calls at any time. Four weeks after this therapy period, you will also receive a call from your therapist to ask how you are.

You will be asked to travel to the Clinical Department of Neurology at the Medical Universities of Innsbruck and Graz or the Rehabilitation Centre in Münster for a total of three visits. Adhering to appointments and instructions from the study physician is critical to the success of this clinical trial.

3. What are the benefits of participating in the clinical study?

Based on previous studies, it can be assumed that you will derive direct health benefits from participating in this clinical study. Since these are new therapy interventions, a direct benefit cannot be predicted with certainty. The purpose of this study is to compare three physiotherapy measures to determine whether there is any benefit to a particular therapy.

By participating in this study, you are helping to gain new knowledge about the targeted treatment of patients with MS.

4. Are there any risks, complaints and side effects?

Performing the examinations and home therapy can trigger adverse events and side effects. But this is very unlikely. A short-term increased tiredness can occur or pre-existing balance deficits can be intensified for a short time. It is assumed that falls can occur in rare cases, but that they can also occur outside of the study in daily life in MS patients with a physical impairment. In order to keep the risk of falling as low as possible, you will receive appropriate instructions from the study team.

The travel to the Medical University of Innsbruck or Graz or the Rehabilitation Centre Münster for the study visits, the physical examination and the collection of the assessment scores represent a small additional burden.

5. Additional medication intake?

Please discuss treatments and therapies outside of the study with your study investigator.

6. What should be done if symptoms, side effects and/or injuries occur?

Should any symptoms, side effects or injuries occur in the course of the clinical study, we ask you to inform your study doctor about them, in the case of serious side effects immediately, if necessary by telephone (telephone numbers and other contact details see below).

7. Insurance

As a participant in this clinical study, you have the legally required indemnity insurance coverage that covers all damage to your life or health that may be caused by the clinical

study measures, with the exception of damage due to changes in the genetic material in germline cells.

The insurance has been taken out for you at Zürich Versicherungs-Aktiengesellschaft, Schwarzenbergplatz 15, A-1010 Vienna, phone.: 0800 0808080, policy number 07225462-7. If you wish, you can inspect the insurance documents.

In the event of damage, you can contact the insurer directly and make your own claims. Austrian law applies to the insurance contract. Any insurance claims are enforceable in Austria.

You can also contact the patient representative for support.

In order to not endanger the insurance cover

- You may only undergo other medical treatment during your participation in this clinical study with the consent of your treating study doctor (with the exception of emergencies). This also applies to taking additional medication or participating in another study.

- you need to immediately notify the attending study doctor or the above-mentioned insurance company of any damage to your health occurs that could be a result of this clinical study.

- you need to do everything reasonable to clarify the cause, course and consequences of the insured event and to keep the damage to a minimum. This may also include authorising your treating doctor to provide information requested by the insurer.

Please note that the insurance does not provide cover for an accident that occurs to you on your way to and from the study.

8. When will the clinical trial be prematurely terminated?

You can revoke your willingness to participate and withdraw from the clinical study at any time without giving reasons, without incurring any disadvantages for your further medical care.

Your study doctor will inform you immediately of any new information that becomes known in relation to this clinical study and that could become material to you. On this basis, you can reconsider your decision to continue participating in this clinical study.

However, it is also possible that your study doctor may decide to terminate your participation in the clinical trial prematurely without first obtaining your consent. The reasons for this can be:

a) You cannot meet the requirements of the clinical study.

b) Your study doctor has the impression that your further participation in the clinical study is not in your interest.

9. Data protection

As part of this clinical study, data about you will be collected and processed. There is a fundamental distinction between

1) those personal data by which a person can be directly identified (e.g., name, date of birth, address, social security number, images, ...).

2) Pseudonymised personal data i.e., data in which all information is removed that allows directly draw conclusions about a specific person, or replaced by a code (e.g., a number) or made illegible (e.g., in the case of pictures). Despite compliance with these measures, it cannot be completely ruled out that inadmissible re-identification occurs.

3) Anonymised data that cannot be traced back to the specific person.

The study doctor and other employees of the study centre who are involved in the clinical study or your medical care have access to the data by which you can be directly identified (see point 1). In addition, authorised representatives of the sponsor Medical University of Innsbruck, as well as representatives of national and/or international health authorities and the respective responsible ethics committees can inspect these data insofar as this is necessary or prescribed for the verification of the proper conduct of the clinical study. All persons who have access to this data are subject to the respective applicable national data protection regulations and/or the EU Data Protection Law (DSGVO) when handling the data.

The code that enables the pseudonymised data to be assigned to you will only be stored at your study centre.

Only the pseudonymised or anonymised data will be used for any publications.

In the context of this clinical study, no data will be transferred to countries outside the EU (third countries).

Your consent form is the legal basis for the processing of your personal data. You can revoke your consent to the collection and processing of your data at any time without giving a reason. After your revocation, no further data will be collected about you. The data collected up to the point of revocation can, however, continue to be processed in the context of this clinical study.

According to the DSGVO, you have the right to information, correction, deletion, restriction of processing, data portability and objection, as long as this does not make the aims of the clinical study impossible or seriously impaired and unless other legal regulations contradict this.

The expected overall duration of the clinical study is 26 months. The duration of the storage of your data beyond the end or termination of the clinical study is regulated by legal provisions.

If you have any questions about the handling of your data in this clinical study, please contact your study doctor first. If necessary, they can forward your request to the persons responsible for data protection.

Contact details of the data protection officers of the institutions involved in this clinical study:

- Data protection officer of the Medical University of Innsbruck: datenschutzbeauftragter@i-med.ac.at

- Data protection officer of the Tirol Kliniken: datenschutzbeauftragte@tirol-kliniken.at

- Data protection officer of the Rehabilitation Centre Münster: datenschutz@reha-muenster.at

- Data protection officer of the Medical University of Graz: datenschutz@medunigraz.at, datenschutz@kages.at

- You have the right to lodge a complaint with the Austrian data protection authority about the handling of your data (www.dsb.gv.at; E-mail: dsb@dsb.gv.at

10. Are there any costs for the participants? Is there a reimbursement or compensation?

No additional costs will be incurred for you by participating in this clinical study. Unfortunately, we cannot reimburse you for any travel costs that may arise. You will not receive any financial compensation for your participation in this study.

11. Opportunity to discuss further questions

Your study doctor and his staff will answer any further questions you may have in connection with this clinical study. We will also answer any questions you may have about your rights as a patient and participant in this clinical study.

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Clinical Department of Neurology, Medical University of Innsbruck, [redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
Rehabilitation Centre Münster, [redacted]	
[redacted]	[redacted]

Department of Neurology, Medical University of Graz, [redacted]

[redacted]

If you have any questions about the informed consent, you can also contact the Tyrolean patient representative:

[redacted]

Tel.: [redacted]

Fax: [redacted]

Email: [redacted]

WWW: http://www.tirol.gv.at/patientenvertretung

12. Informed Consent Form

Name of the patient: ....

Date of birth: ....

I agree to take part in the clinical study „Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: protocol of a randomised parallel multicentre trial“ (short: RIGMUC). I have been informed that I can refuse participation without any negative consequences, in particular for my medical care.

I have been informed by Ms / Mr (MD) ..... in detail and understandably about the clinical study, possible burdens and risks, as well as about the type, meaning and scope of the clinical study and the requirements resulting for me. I have also read the text of this patient information and informed consent, which comprises a total of 8 [10] pages. Questions that arose were answered comprehensibly and satisfactorily by the study doctor. I had enough time to make up my mind. At the moment, I do not have any further questions.

I will comply with the medical instructions required to carry out the clinical study, but I reserve the right to terminate my voluntary participation at any time without incurring any disadvantages, in particular for my medical care.

I particularly agree that my data collected as part of this clinical study will be processed as described in the "Data Protection" section of this document. Should I withdraw or be excluded from the study, I agree that my data are continued to be stored and analysed as described in this information.

☐ Yes ☐ No

I have received a copy of this patient information and informed consent. The original remains with the study doctor.

....

(Date and signature of the patient)

....

(Date, name and signature of the responsible study doctor)

(The patient receives a signed copy of the patient information and informed consent, the original remains with the study doctor's folder.)

Protocol RIGMUC, Version 1.1 of 14.11.2020

Patient Information Sheet and Informed Consent Form for participation in the clinical study

Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: protocol of a randomised parallel multicentre trial (RIGMUC)

Additional information for Centre 3 only (Department of Neurology, Medical University of Graz)

Magnet Resonance Imaging (MRI)

MRI:

Idiopathic inflammatory, demyelinating diseases of the central nervous system (CNS), such as multiple sclerosis in particular, are caused by inflammation in the area of the nerve sheaths in the brain and spinal cord. Investigations such as magnetic resonance imaging (MRI) are needed to better understand the condition that you are suspected of having or have been diagnosed with. Multiple sclerosis is a disease in which there are foci of the disease at different times, in different places in the brain and spinal cord. MRI has been an examination method that has been used for years, which provides images of these changes in the brain and spinal cord without exposure to radiation. In the planned examinations using a 3-Tesla MRI device, the relatively new examination techniques, including functional MRI (fMRI), are to be used in order to obtain information about the function of the brain that goes beyond the nature and structure.

1. **A) How does the MRI investigation work?**

This clinical study will be carried out at the Department of Neurology, Medical University of Graz, and a total of 36 people with MS and 15 healthy people are expected to take part.

The examinations are carried out at the Department of Neuroradiology at the LKH University Hospital Graz. An MRI machine is an elongated tube that creates a magnetic field. The process uses **neither ionising radiation nor radioactive substances and is therefore not associated with any radiation exposure.** Rather, the images are created by signals from water particles in the body, which are generated with the help of a strong magnet and high-frequency pulses (radio waves).
This technology is used worldwide and, according to the current state of knowledge, is completely harmless to the human organism and free of biological risks.

During the investigation you lie on your back, whereby a special mirror device allows you to look out of the tube (e.g., at an image projection). We also have "eye contact" with you via a camera. Verbal communication can take place via an intercom. In addition, you will be given an alarm button ("signal ball") with which you can indicate that the examination should be stopped immediately if you feel uncomfortable for any reason. The examination itself is relatively loud, which is why we will protect your hearing with headphones. During the exam, you should keep your head as still as possible.

However, if you are known to suffer from claustrophobia, you should not participate in this study.

As part of the MRI examination, the structure and function (using functional magnetic resonance tomography (fMRI for short) of your brain are precisely recorded. With this study, we want to investigate the way in which the brain reacts to changes in tissue function, such as those in the context of your disease can occur, reacts or tries to limit their consequences.
During the fMRI examination you will be asked to perform certain movements, look at pictures or solve tasks. We will rehearse the processes that you are supposed to carry out during the fMRI examination together with you before the actual examination outside of the MRT machine.

With the help of this technology, we receive images on which parts of the brain “light up” that are activated during such tasks. However, do not expect to receive conventional radiological findings from this examination. **No contrast agent** is required for the fMRI examination. The total duration of the MRI examination is approx. 30 minutes.

3. Are there any risks, burdens and side effects?

If the following safety measures are observed, no harmful effects are to be expected:

Since a strong magnetic field is generated by the MRI machine, interference from pacemakers or heat build-up or relocation of metal parts in the body can occur. If one of these circumstances could apply (for example the presence of a pacemaker or metal parts in the body, such as metal clips after operations on the brain or after old injuries, especially in the eye area, etc.), you cannot participate in this study. This also applies to pregnancy. If you have any questions, we will of course be happy to answer any further questions you may have.

If you change your mind, you can of course revoke your consent at any time without giving reasons, without incurring any disadvantages.

Supplemental File 3

1. List of semi-structured questions for telephone support interviews once weekly during the intervention period

No	Question
1	Please tell me how often you practice music-supported walking / motor imagery per week. [If not 4x a week:] Who or what keeps you from attending the walking training programme? Who or what supports you in attending the walking training programme?
2	Tell me how long you practice music-supported walking / motor imagery per session? [If not 30 minutes per session:] Who or what keeps you from practicing for 30 minutes per session? Who or what would support you in practising 30 minutes per session?
3	Could you please share your experiences with the music-supported walking / motor imagery? [If the participant reports any problems:] Can you explain this in more detail for me? Can you give me reasons for that? What do you feel as the easiest part about the music-supported walking / motor imagery? What do you feel as the most difficult part about the music-supported walking / motor imagery?
4	Are you using the compliance checklist for documentation (practiced / not practiced)? [If not:] Can you give me reasons for that? Who or what could support you in completing the checklist?

5	Did you experience a fall within the study period? [If so:] How often did you fall? Could you please describe under what circumstances the fall(s) occurred? Are you using the fall protocol? [If not:] Can you give me reasons for that? Who or what could support you in completing the checklist?
Thank you for the interview!	

2. List of semi-structured questions for follow-up telephone interviews at 4-weeks post-intervention

No	Question
1	Could you please describe your health since the end of the music-supported walking / motor imagery practice?
2	Tell me about how your walking has been in the last few weeks compared to before the music-supported walking / motor imagery practice.
3	How did you experience your fatigue / tiredness in the last few weeks compared to before the music-supported walking / motor imagery practice?
4	Please describe your present health as compared to before the music-supported walking / motor imagery practice.
5	How should the homebased music-supported walking / motor imagery programme be for you to recommend it to others?
6	Can you please share your thoughts on how we could improve the music-supported walking / motor imagery programme?
7	What should the homebased music-supported walking / motor imagery programme be like that you would carry it out for a longer period of time?
8	Did you fall in the past 4 weeks?

	[If so:] How often did you fall? Could you please describe under what circumstances the fall(s) occurred? Are you using the fall protocol? [If not:] Can you give me reasons for that? Who or what could support you in completing the checklist?
Thank you for the interview!	