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A randomized controlled pilot and feasibility study of multimodal agility-based exercise training versus strength and endurance training to improve Multiple Sclerosis-related fatigue and fatigability during inpatient rehabilitation [ReFEx] – study protocol.

Akronym: ReFEx (Rehabilitation, Fatigue, and Exercise)

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Trial status: The first participant has been enrolled on 18 November 2021. At the time of submission, 9/24 participants have been recruited, 3/24 participants have finished the intervention period and completed the primary measurement time point one week after the end of the intervention period.

ABSTRACT

Introduction: Subjective fatigue and objectively assessed fatigability are common symptoms in persons with Multiple Sclerosis (pwMS). Recent work has suggested a positive effect of balance and motor control training (BMCT) in reducing fatigue. It is unclear whether this effect can also be attained during inpatient rehabilitation. This study will evaluate the feasibility of a randomized controlled trial comparing BMCT with added agility components (i.e., multimodal agility-based exercise training [MAT]) with strength and endurance training (SET) for the improvement of MS-related fatigue and fatigability in a German neurologic rehabilitation center. With the conductance of the ReFEx (Rehabilitation, Fatigue, and Exercise) project we plan to (I) translate existing evidence on BMCT in pwMS to the setting of inpatient rehabilitation, (II) introduce the framework of MAT, and (III) apply a clear focus on the treatment of fatigue as one of the most challenging symptoms in MS.

Methods and analysis: A total of 24 pwMS (Expanded Disability Status Scale ≤5.0, Fatigue Scale for Motor and Cognitive Functions ≥53) will be randomly assigned to either SET or land-based and water-based MAT for 4 to 6 weeks during inpatient rehabilitation. Assessments of subjective fatigue, motor and cognitive fatigability, cognitive and cardiorespiratory performance, and balance confidence will be performed at admission and discharge. Subjective fatigue will also be assessed 1, 4, and 12 weeks after discharge. Feasibility outcomes will include patients' acceptance of study procedures and interventions, recruitment rate, retention rate, time needed to complete baseline assessments, intervention adherence, and fidelity. A

total of 12 pwMS (6 per group) will be interviewed to gain insights into participants' experiences during study participation.

Ethics and dissemination: Ethical approval has been obtained from the Ethics Committee of the University of Bonn (reference number: 543/20). Dissemination of findings is planned via peer-reviewed journals, conferences, and media releases.

Trial registration: German Clinical Trials Register: DRKS00023943, date of registration: 23 September 2021

Keywords

multiple sclerosis, sports medicine, rehabilitation medicine

Strengths and limitations

- Comprehensive assessment of subjective fatigue, as well as objective cognitive and motor fatigability
- First application of agility-based exercise training to pwMS
- Mixed-methods approach to acquire patient perspective and acceptance
- Clinical inpatient setting will challenge standardization of study procedures

INTRODUCTION

Fatigue, described as 'a subjective sensation of lack of energy and exhaustion' (p. E79)[1], was reported as the most common symptom (58%) among 35,000 patients from the German multiple sclerosis (MS) register[2]. It is also reported as one of the most disabling symptoms[3] with high socioeconomic relevance as 25% of persons with MS (pwMS) have impaired working capacity because of 'invisible symptoms' such as fatigue and impaired cognition[4 5].

Data from the MS register also show that only 35% of fatigued pwMS receive any kind of treatment and among them only 15% receive pharmacological treatment to specifically handle fatigue symptoms[2]. No clear pathomechanisms for fatigue have been defined yet leading to the consequence of still limited pharmacotherapy options for the treatment of fatigue[6].

According to the established taxonomy by Kluger and colleagues[7] two concepts must be separated when considering fatigue: (I) the subjective experience of fatigue and (II) objective performance fatigability during motor or cognitive tasks. Whether improvements in fatigability also transfer to subjective fatigue is still unclear. Interestingly, the association between the two constructs seems to be relatively weak[8 9].

Next to distinguishing between 'fatigue' and 'fatigability', a further dichotomy exists with 'primary fatigue' resulting from pathophysiological processes of the disease itself (e.g., central nervous system, immunologic or endocrine changes) and 'secondary fatigue' resulting from mechanisms not directly related to the disease (e.g., sleep, depression, medication)[10].

To reduce subjective fatigue, exercise interventions have been studied as a non-pharmacological treatment option. However, several methodological issues exist. As fatigue is frequently assessed as a secondary outcome variable, subjects are often not pre-screened for fatigue symptoms at baseline and the intervention is not primarily designed to reduce fatigue[11 12]. Consequently, to date, there are few studies investigating the specific pathophysiological pathways of primary or secondary fatigue that are altered by exercise[10].

In a recent meta-analysis Moss-Morris and colleagues[11] performed a detailed review of exercise intervention studies, that specifically aimed at fatigue reduction. Here, the authors reported variance in the effects of different types of exercise. For example, endurance exercise has been frequently investigated, as it can be easily standardized, but was reported to have only small effects on fatigue outcomes measured with self-report questionnaires[13]. If combined with other modalities such as resistance exercise, effects might be greater (e.g., strength and

endurance training [SET]). Lastly, exercise types primarily consisting of stimuli targeting motor control (e.g., balance and motor control training [BMCT]) were described as promising[14-16].

In the special setting of inpatient rehabilitation, the number of exercise studies for subjective fatigue reduction is very limited. In their review, Moss-Morris and colleagues[11] identified only one study conducted in an inpatient rehabilitation setting. However, this trial was restricted from the meta-analysis because of methodological limitations, indicating the need for future systematic research on fatigue-specific therapy. This is also evident in the first German practice guideline for exercise therapy in pwMS, which highlights mobility rehabilitation but does not consider symptoms of fatigue or fatigability[17].

Therefore, the ReFEx (Rehabilitation, Fatigue, and Exercise) project aims to transfer BMCT, which is promising for subjective fatigue reduction, to inpatient rehabilitation and compare it with SET, which is considered the control group or 'usual care'. We also adapted the BMCT to be based on the agility framework described by Donath and colleagues[18]. Thus, the treatment manual will also include functional leg strength and agility-based exercises (i.e., multimodal agility-based exercise training [MAT]). This is the first study applying the agility framework to pwMS. In doing so, we not only expect to target subjective fatigue, but also other frequent MS-specific symptoms including performance fatigability as well as disturbed gait and balance. Applying the agility framework to BMCT could further provide an opportunity for combined motor and cognitive rehabilitation[19], that is fun, enjoyable, and social[18].

Referring to the pathophysiological framework by Langeskov-Christensen and colleagues[10] we hypothesize that the SET will improve secondary fatigue via improved aerobic capacity and motor function, while the MAT intervention will improve secondary fatigue via improved motor function and reduced cognitive effort in daily life (as hypothesized by Moss-Morris and colleagues[11] and others[14-16 20]). Based on the existing evidence, we expect greater benefits on

secondary fatigue parameters from MAT than for SET. Regarding performance fatigability, we hypothesize, that MAT will be superior to SET in improving motor and cognitive fatigability. In a first step, the pilot and feasibility study (PAFS) described in this protocol will be used to determine whether the adapted MAT and SET are feasible in the inpatient rehabilitation setting with a special emphasis on patients' acceptance. This will include both, a quantitative, and qualitative evaluation.

METHODS AND ANALYSIS

Study design

The PAFS will be conducted at the Neurological Rehabilitation Center (NRC) 'Godeshoehe' (Bonn; certified MS Rehabilitation Center). It will have a two-armed, parallel-group, randomized-controlled design with twelve weeks follow-up, following a mixed-methods approach. Measurement time points are provided in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure (Table 1).

Patient and public involvement

In our therapeutic work of several years in a specialized rehabilitation clinic for MS, the majority of pwMS report that fatigue is difficult to cope with and limits quality of life. These patient reports were the impetus for the conception of this study, especially as there are few evaluated therapy approaches. In the conception of this PAFS, it was important for us to appreciate the patient perspective and to include the affected persons as 'experts of their disease'. In particular, this takes the form of qualitative interviews, which we base on a constructivist paradigm that allows for the co-creation of knowledge by the participants and the researcher.

Table 1 SPIRIT figure depicting the schedule of enrollment, interventions and assessments for the pilot and feasibility study.

	STUDY PERIOD						
	Enrolment	**Allocation**	**Post-Allocation**				
TIMEPOINT	$-T_0$	**0**	T_0	T_1	T_2	T_3	T_4
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Stratified randomization		X					
INTERVENTIONS							
MAT			←	→			
SET			←	→			
ASSESSMENTS:							
Fatigue (WEIMuS)	X			X	X	X	X
Fatigue (FSMC)	X			X	X	X	X
Cognitive fatigability (TAP-Alert)			X	X			
Motor fatigability (6MWT)	X			X			
Cognitive performance (CVLT, SDMT)			X	X			
Cardiorespiratory fitness (GXT)			X	X			
Motor function (T25FW, SSST, FGA)	X			X			
Balance confidence (ABC)	X			X			
Depression (CES-D)			X	X			
Feasibility outcomes	←	—	—	—	→		
Interview 1 (Feasibility)				X			
Interview 2 (Fatigue responder)					X		

-T_0 = admission; *0* = after written informed consent; T_0 = post-randomization; T_1 = prior to discharge; T_2 = 1 - 2 weeks after discharge; T_3 = 4 weeks after discharge; T_4 = 12 weeks after discharge; *MAT* = Multimodal Agility-based exercise Training; *SET* = Strength and Endurance Training; *WEIMuS* = Würzburg Fatigue Inventory for Multiple Sclerosis; *FSMC* = Fatigue Scale for Motor and Cognitive Functions; *TAP-Alert* = Test Battery of Attention Performance – Alertness; *6MWT* = 6-Minute Walk Test; *CVLT* = California Verbal Learning Test; *SDMT* = Symbol Digit Modalities Test; *GXT* = Graded Exercise Test; *T25FW* = Timed 25-foot Walk Test; *SSST* = Six Spot Step Test; *FGA* = Functional Gait Assessment; *ABC* = Activities-Specific Balance Confidence Scale; *CES-D* Center for Epidemiological Studies Depression Scale (German version)

Screening and recruitment

Individuals admitted to the NRC will be screened for pwMS. All pwMS will then be scheduled for neuropsychological examination the day after admission, according to usual practice. Here, patients will be asked to complete the Fatigue Scale for Motor and Cognitive Functions (FSMC). If a patient is classified as, at least, 'moderately fatigued' and the patient fulfils all other eligibility criteria (Table 2), he or she will be informed about the study by his or her neuropsychologist (JN, JS, EH), verbally, and in written form.

Randomization

If patients provide the written informed consent to one of the study staff members within a maximum of three days, they will be randomly allocated (1:1) to the intervention or control group according to the minimization procedure[21] and stratified by Expanded Disability Status Scale (EDSS, ≤3 or ≥3.5), Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS, <38 or ≥38), age (<45 or ≥45), and MS disease course (relapsing-remitting or secondary-

progressive). Randomization will be provided by an independent researcher from the German Sport University Cologne using RITA ('Randomization-In-Treatment-Arms', Evident, Germany).

Sample size and duration

Data from the PAFS is planned to be pooled with data from the full trial in case no major changes of study protocol will be necessary (see progression requirements). Acceptability of pooling will be evaluated according to components listed in the 'Acceptance checklist for clinical effectiveness pilot trials'[22]. As the primary aim of this trial is to evaluate the feasibility, no sample size calculation based on statistical assumptions will be performed. However, we consider a minimum of twelve recruited patients per study arm to be a reasonable sample size for this setting[23].

The NRC treats about 100 – 120 pwMS per year. According to previous data collections for the German MS register no more than 25% of patients will have to be excluded, based on EDSS and FSMC screening (see eligibility criteria). We further predict no more than 10% of eligible patients to be unwilling to participate, based on previously conducted studies. Comparable studies have had low drop-out rates (5%[24]) but did not choose a primary endpoint after patients returned home. Consequently, we plan with up to 20% drop-out between T_0 and T_2. This will result in a feasibility period of about six to eight months. Drop-out and retention-rates will be used to inform the sample size calculation for the full randomized controlled trial (RCT).

Participants

PwMS will be eligible to participate in this trial according to the inclusion and exclusion criteria stated in Table 2.

Table 2 Eligibility criteria.

Inclusion	Exclusion
1. MS disease course RR or SP	**1. Unable to attend water therapy**
2. Age 18 - 67	**2. Comorbidities** That prevent attending study therapies, chronic neurologic conditions other than MS
3. EDSS ≤5.0	**3. German language skills** That interfere with understanding of testing and instructions
4. FSMC total score ≥53	**4. Current fatigue medication** Amantadin, Modafinil started <3 months
5. Written informed consent	

RR = Relapsing-remitting; *SP* = Secondary-progressive; *EDSS* = Expanded Disability Status Scale; *FSMC* = Fatigue Scale for Motor and Cognitive Functions.

Interventions

The intervention period includes the time from admission to discharge, which usually comprises four to six weeks for this group of patients. Multidisciplinary inpatient rehabilitation can consist of various diagnostic and therapeutic components such as exercise training, occupational and physical therapy, health education, neuropsychological assessment, or assessment of working capacity. Thus, interactions between treatments as well as flexibility in the treatment schedule are common[25]. For this reason, we designed the schedules of the two study groups to ensure the following:

(I) Distinct differences in the amount of therapy targeting cognitive and sensory integration.

(II) Standardization of treatment as strictly as possible within this specific clinical setting.

(III) Equivalent amount of total therapy time.

See Table 3 for an overview of intervention components. Reporting of the interventions will follow the modified Consensus on Exercise Reporting Template (CERT) for Therapeutic Exercise Interventions[26].

Table 3 Frequency, time, and type of intervention components.

MAT (intervention)	SET (control)
5x/w, 30min, 'MS-group'	
5x/w, 30min, land-based MAT	5x/w, 22min, endurance training
3x/w, 30min, water-based MAT	3x/w, 30min, strength training

Standard treatment for both groups

Both groups will attend the 'MS-group', a specific group for all pwMS, focusing on body awareness and relaxation techniques. It consists of max. eight pwMS, lasts 30min and is led by an exercise therapist. Both groups will also attend MS-specific lectures once a week. All other available therapies, which are not part of standard treatment, will be included only after individual consideration to maximize standardization.

Strength and Endurance Training (SET)

The combined strength and endurance training program will be considered the control condition. All endurance training sessions will be supervised by exercise therapists from the NRC. Strength training sessions will be supervised by exercise science students or therapists in one-on-one sessions. Students and therapists conducting the strength training will be instructed by FW and will follow a training protocol (see Supplemental File [Strength Protocol]).

Endurance training will be performed according to the standard protocol in this clinic, with 22min per session (3min of gradual increase, 17min steady and 2min cool-down) on a cycle ergometer (ergoselect 5, ergoline GmbH, Bitz, Germany) with continuous monitoring of power output and heart rate (ers.2 software, ergoline GmbH, Bitz, Germany). Endurance training will be performed in groups of max. eight patients. In the first session, participants will start their training at an intensity that was rated "light" to "somewhat hard" by themselves during the baseline graded exercise test (GXT) (equivalent to 11-13 on the 6-20 Rated Perceived Exertion [RPE] – scale). In the following sessions, therapists will regulate the power output so that participants stay between 11 and 13 on the RPE-scale. If a pwMS is unable to complete the total duration, the session duration can be initially reduced and then progressed in the following sessions. The range of 11 to 13 was chosen based on recent evidence-based recommendations for pwMS with similar EDSS[27].

Resistance training will be adapted from Callesen and colleagues[14] to fit the inpatient setting. Each session will start with a 5min warm-up on an elliptical trainer, treadmill, or recumbent stepper, followed by three to four exercises targeting hip, knee, and ankle flexion and extension, as well as hip abduction. Exercises will be progressed as follows:

- Session 1-5: 3x10 repetitions with the 15 repetitions maximum (RPM)
- Session 6-T_1 (session 10-16): 3x12 repetitions with 12RPM

In detail, for every new exercise, therapists will initially determine the respective weight the participant is able to move no more than the intended RPM. Therapists will be given the necessary room for individualization but will be instructed to follow pre-specified exercises (see Supplemental File [Strength Protocol]).

Multimodal agility-based exercise training (MAT)

For the treatment manual see Supplemental File [MAT-Manual]. All sessions will be guided by max. three different exercise therapists (including FW) from the NRC, experienced with providing balance exercises on land and in the water in group settings. However, as MAT also comprises other/new elements, exercise therapists will be specifically trained by FW and instructed to follow the treatment manual.

Both parts (i.e., water and land) will be installed within existing group therapies. Each group will consist of max. eight participants. Empty spots will be filled with other patients from the NRC. The intervention program will consist of three main components: (1) standing balance exercises, (2) dynamic balance exercises including functional leg strength, (3) agility-like exercises including change of direction and change of velocity[28]. Each main component will be represented in several modules. Each module is constructed as a basic set-up, that can be progressed in terms of difficulty. Additionally, modifications on a cognitive (e.g., memory, attention, inhibition) and sensory (i.e., visual, somatosensory, vestibular) level are described. As stated by Callesen and colleagues[14] there is no consensus yet on how to define intensity or progression in balance and motor control exercises. Thus, for this intervention, therapists will be instructed to aim for a level of difficulty and complexity that keeps exercises manageable and safe for participants, but also provokes motor or cognitive errors. This is in line with recommendations for neurorehabilitation from basic science[29].

For load management in the land-based therapy, there will be three sessions with higher physical strain (i.e., agility-like components and functional leg strength) interspersed with two sessions with lower physical strain (i.e., standing balance and exercises with a cognitive focus). Due to water immersion, physical strain in the water-based therapy should be lower in general. Participants will be instructed to take individual breaks whenever they need to. They will also be advised to monitor their fatigue during their stay and skip a session when they need more time to regenerate.

Blinding

The neuropsychological staff conducting the cognitive tests will be blinded to the study groups. However, for organizational reasons and specifics of the study setting, blinding of participants, therapists conducting the interventions as well as personnel conducting the motor and cardiorespiratory fitness (CRF) tests and analyzing the questionnaires will not be possible.

Outcomes

As depicted in Table 1, assessments will be carried out at admission (i.e., pre-intervention, T_0) and discharge (i.e., post-intervention, T_1), as well as after participants have returned home (i.e., follow-up, T_2-T_4).

Feasibility (quantitative)

To generate the quantitative feasibility outcomes, we adopted the categories described by Thabane and colleagues[30] and promoted for exercise studies in MS by Learmonth and Motl[31] (see Table 4).

Table 4 Description of quantitative feasibility outcomes (adapted from[32]).

Classification	Outcome	Operationalization	Importance for future RCT
Process	1. Recruitment rate	• Number of patients successfully randomized per month	Evaluates whether the number of patients participating is high enough to allow for a time-efficient conductance of a study with a larger sample size
	2. Retention rate	• Number of patients completing the intervention period, relative to patients dropping out before T_1 • Number of patients returning the WEIMuS at T_2, relative to patients not responding	Provides information on the risk of subjects dropping out during the intervention period, which might necessitate adaptations to the interventions or the organization of the study to reduce dropouts. Gives information on the feasibility of the primary endpoint and outcome being assessed post-discharge and via an online platform.
	3. Refusal rate	• Number of patients eligible and willing to participate, relative to patients eligible but unwilling to participate (with reasons)	Provides insights on possible barriers for participation, which might be counteracted by better study information and addressing these barriers.
	4. Eligibility criteria	• Number of positive versus negative cases for each criterium	Determines criteria that might produce too many non-eligible patients
	5. Adherence	• Number of therapy sessions conducted relative to sessions scheduled	Gives information on how many sessions would normally be feasible to conduct during the inpatient stay
	6. Fidelity	• SET: training protocols will be reviewed to ensure that communicated principles were followed: (I) number of exercises performed each session, (II) total training load prescribed relative to actual training load per exercise (e.g., target: 3 (sets) x 10 (repetitions) x 20 (weight) = 600, moved: 3 x 10 x 15 = 450, percentage: 75%). The ers.2 software will document all endurance training sessions, which will provide measures of training duration and intensity (average heart rate, average power, 6-20 RPE) relative to the prescribed values.	Gives detailed information on whether subjects were able to perform the SET as planned. In the MAT, therapist's usage of the manual will be observable. This will allow for guided adaptations of the intervention protocols, if necessary.

		• MAT: To quantify the degree of aerobic challenge, in the land-based sessions, patients will be wearing heart rate sensors (Verity Sense, Polar, Kempele, Finland). Average heart rate values for each session and patient will be tracked using software (Polar Team App). • MAT: Components of each session will be coded by the operating therapist according to the MAT manual (SB = standing balance, DB = dynamic balance and functional leg strength, AG = agility-like) to get an approximate distribution.	
Resources	Time	• Number of days needed to complete baseline assessments • Time requirements for (I) the first (T25FW, SSST, FGA, 6MWT) and second (GXT) physical testing blocks at T_0 and T_1, (II) preparation of MAT sessions	Evaluates whether baseline assessments can be scheduled in a timely manner before the start of the intervention period. Precise time requirements will allow for better scheduling of study-related appointments.
Management	Data	• Number of missing items for FSMC and WEIMuS for all measurement timepoints • Number of missing outcomes for T_0 and T_1	Provides information on actions to take to ensure questionnaires will be fully completed and all assessments taken.
Scientific	1. Adverse events	• Number and kind of adverse events related to study interventions	Establishes the safety of all interventions.
	2. Acceptability	• Perceived exertion: Session-RPE after each endurance, strength, and MAT session (Category Ratio (CR-10) RPE scale as developed by Foster and colleagues [33 34]). After each session patients will be asked: "How strenuous was the session as a whole?". Patients will be instructed to provide a global rating of the complete session and not to focus on specific aspects. • Fun during training and relevance of training for daily life: assessed at T_1 by using customized questions with a four-point Likert-type scale ranging from "not at all" to "very much" [35].	Perceived exertion in both groups will determine whether the interventions are perceived to be too strenuous or too easy. Fun and relevance are important measures of motivation. In case of low values, additional actions will be necessary to ensure sufficient motivation.
	3. Treatment effect	• Estimation of treatment effect (Cohen's *d*) on all primary and secondary outcomes	Establishes data for possible impact of interventions

RCT = randomized-controlled trial; T_0 = post-randomization; T_1 = prior to discharge; T_2 = 1 - 2 weeks after discharge; *WEIMuS* = Würzburg Fatigue Inventory for Multiple Sclerosis; *MAT* = Multimodal Agility-based exercise Training; *SET* = Strength and Endurance Training; *RPE* = Rated Perceived Exertion; *GXT* = Graded Exercise Test; *T25FW* = Timed 25-foot Walk Test; *SSST* = Six Spot Step Test; *FGA* = Functional Gait Assessment; *FSMC* = Fatigue Scale for Motor and Cognitive Functions

Feasibility (qualitative)

The qualitative evaluation aims to (a) capture patients' views on acceptance, benefits, and satisfaction with study participation, (b) assess their experiences with the intervention methods, and (c) identify necessary adaptions. For this purpose, we designed a semi-structured interview. Six participants from each study arm will be interviewed face-to-face at T_1. The selection of participants will reflect the greatest possible diversity in terms of gender, age, and EDSS[36]. The interview will include a total of 14 questions and will last approximately 20min. Key categories of the interview are the concept of fatigue, experiences and demands of the interventions, personal relevance, and goal achievement. All interviews will be recorded digitally and transcribed verbatim by an independent transcription service.

Both interviewers (JN, FW) have several years of clinical experience with pwMS. A first draft of this interview was piloted with three pwMS prior to the start of the feasibility study to ensure that the questions allow valid insights into participants' experiences.

The interview will be supplemented by a customized questionnaire asking for prior knowledge of fatigue, prior experiences with MAT and SET, and comprehensibility of the study instructions and questionnaires. The questionnaire also asks about fun and relevance of training for daily life (see Table 4), and the motivation to continue a comparable training at home.

Primary outcome for the full RCT

Fatigue questionnaires presuppose internal averaging of the amount of fatigue experienced during a certain timeframe[1]. This has been a problem for studies evaluating short-term interventions, as in some questionnaires patients are asked to evaluate their fatigue in timeframes of up to four weeks. As we are interested in the change in fatigue experienced in daily life from before the inpatient stay to afterwards, we (I) chose the WEIMuS[37] as the primary outcome measure to assess the fatigue experienced during the past week and (II)

established the primary endpoint to be one to two weeks after participants have returned home (T_2). The WEIMuS has 17 items (scored 0 - 4) with higher total scores indicating higher fatigue (range 0 – 68, cut-off for classification as fatigued: 32).

For fatigue screening (that is necessary for study eligibility) we will apply the FSMC. It is a 20 item Likert-type scale (1 – 5) with a total score (0 – 100) and two subscales relating to motor and cognitive fatigue[38]. The FSMC provides cut-off scores to classify cases of no (total score < 43), mild (≥43), moderate (≥53) and severe (≥63) fatigue, which makes it especially suitable as a tool for classification of fatigue severity[1 38].

Paper versions of both questionnaires will be handed out to participants. When at home, participants will be followed up via e-mail to fill out questionnaires on an online platform (Qualtrics) at timepoints T_2-T_4. Participants will be able to respond to the e-mail request within seven days.

Secondary outcomes for the full RCT

MS-fatigue is a multifactorial construct that requires assessment of other interrelated constructs[7]. This will include measures of cognitive (Test Battery of Attention Performance – Alertness[39]) and motor fatigability (6-Minute Walk Test [6MWT], Distance Walked Index[40]), cognitive performance (California Verbal Learning Test, Symbol Digit Modalities Test[24 41]) and cardiorespiratory fitness (GXT on a cycle ergometer, protocol: start 25W, progression 10W/min.). Dynamic balance and motor function (Timed 25-Foot Walk Test [T25FW], Six Spot Step Test [SSST], Functional Gait Assessment [FGA]) will also be assessed as well as self-reported balance confidence (Activities-specific Balance Confidence scale). Depression (Center for Epidemiological Studies Depression Scale [German version]) will be assessed as a confounder variable.

The subsequent full trial will also include qualitative data to explore the subjective experiences in participants showing a WEIMuS change of 6 or more points from T_0 to T_2 (positive or negative). These "responders" will be contacted for a short telephone interview. Previous data has shown large differences in fatigue questionnaire change scores[13]. However, the scores do not provide any detail on individual circumstances, including, for example, social or work-related influences, that might be independent of intervention effects. Therefore, we decided to specifically ask participants:

> 'The analysis of your questionnaires shows a relevant positive/negative change of your fatigue symptoms, when comparing your scores from pre-rehab to the online questionnaire. What do you personally think is the reason for this?'.

No minimal clinically relevant change scores have been established yet[42]. Thus, the relevant change score was chosen as a pragmatic value of 0.5 SD from the validation study[43]. A similar procedure has been described by Sander and colleagues[1].

Data analysis

Quantitative data analysis

Descriptive statistics will be used to summarize feasibility outcomes. The results are given as mean and standard deviation for parametric distribution, median and interquartile range for non-parametric distribution, or frequencies (%), as appropriate. Baseline data for sociodemographic, primary, and secondary outcomes will be compared between SET and MAT groups using independent-samples *t*-tests for continuous data, and chi-squared tests for categorical data. Paired *t*-tests will be used to assess within-group change over time. Independent-samples *t*-tests will be used on change scores (post- vs. pre-rehabilitation) to assess between-group effects. In case of non-normal distributions, non-parametric tests will be used. As described by Sim[44], estimation of treatment effects (Cohen's *d*) will be conducted and

reported with 95% confidence intervals but will not be used as a progression requirement. All analyses will be performed using IBM SPSS Statistics in the most up to date version.

Qualitative data analysis

Coding of the interviews will be performed according to qualitative content analysis, using a combined model of deductive (a priori) and inductive coding (on the text material) to identify themes and sub-themes[45]. Deductive coding will be based on preliminary considerations and hypotheses in the study planning and on reviews of relevant literature. Coding will be carried out by at least two individuals (JN, FW) to ensure intercoder reliability[46]. The analysis will be supported by MAXQDA® software in the most up to date version[47]. JN and FW will compile the themes emerging from the interview data and discuss these with the wider research team.

Progression requirements to full RCT

Falling short of the following feasibility values will necessitate changes to the protocol of the full RCT:

- Adherence: Average of at least 18 therapy sessions during the stay (equals 6x30min sessions per week for 3 weeks [28 days admission to discharge minus 5 days for pre- and post-testing])
- Recruitment rate: 4 participants/month, <25% non-eligible pwMS, <10% eligible but unwilling to participate
- Drop-out before T_1: <10%
- Retention at T_2: >80%
- Time requirements for baseline assessments: >80% able to complete all assessments within the first three days of therapy

- If the interview statements indicate that the interventions are perceived as irrelevant, not comprehensible, or even unpleasant

Data management

The principal investigator (FW) will be responsible for data management. Demographic and clinical characteristics will be taken from the electronic health record. All other data will be collected on forms during the inpatient stay and via an online tool for follow-up. Data will be entered into a secure internal network database by study personnel in the NRC. Entered data will be checked for plausibility and compared to the collection forms if necessary. Data will be collected and stored in accordance with the General Data Protection Regulation.

ETHICS AND DISSEMINATION

Written informed consent will be obtained from each participant. Ethical approval was obtained from the Ethics Committee at the Medical Faculty, University of Bonn (reference number: 543/20).

The results of this feasibility study will be disseminated regardless of the magnitude or direction of effect in peer-reviewed journals, conferences and the website and magazines of the German Sport University Cologne.

DISCUSSION

This PAFS will give relevant insights for conducting a future RCT in this special setting of inpatient rehabilitation for pwMS. Content-wise, it will (I) translate existing evidence on BMCT in pwMS to this setting, (II) add to this BMCT by introducing the framework of MAT, and (III) apply a clear focus on fatigue as the primary outcome. Specifically, we see the potential of a relatively large training volume (e.g., about eight therapy sessions per week)

compared to studies in outpatient settings, and a high amount of supervised exercise, which should provide good adherence and fidelity. Having a therapist as a supervisor is especially important for a rather complex type of exercise as is MAT. For example, there are no simple 'numbers' like sets or repetitions one can follow. Quicker movements relating to agility, like changes of direction, acceleration, and deceleration, frequently lie outside the 'comfort zone' of pwMS, which necessitates guidance of a therapist. Lastly, in the group format, a therapist is mandatory to provide modifications for pwMS with higher disability or very low disability.

We also anticipate certain issues in conducting this study. For example, scheduling of appointments for testing will be challenging, as there will be several testing blocks (i.e., motor function, GXT, cognitive tests, interview), conducted in different departments of the NRC, which must be fitted into certain timeslots around admission and discharge. These appointments will compete against other study unrelated appointments (e.g., ward rounds, urology assessments, etc.). Regarding the eligibility and randomization criteria, it will be challenging to have all the correct data within the first two days as there can be delays in the admission process.

Lastly, analysis of blood-based biomarkers is planned to be part of the ReFEx study project. However, as these outcomes are connected to comparably high costs for materials and analysis, addition of blood sampling is postponed to the start of a full RCT. Nevertheless, information gathered during the feasibility study will be used to allow for smooth integration of blood draws and storage during assessments at admission and discharge. As the blood draws can be regarded as the most unpleasant part of the assessments for patients, feasibility of the interventions and patient acceptance should be established first.

Author contributions

FW, JN, ME, PZ designed the overall study. FW & JN designed the feasibility study and wrote the protocol. FW, JN, JS, EH implemented the screening and assessment procedures. All authors revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

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Manual for the land-based and water-based MAT (adapted from[1])

1. Land-based MAT

Standing balance		**SB**
Participants perform various exercises while standing.		
Progression: BOS	Progression: Catching & Throwing	Progression: Tools
Narrow BOS	Alone	Number of objects for throwing
Semi-tandem stance	With partner	Kind of objects (small sacks, balls, …)
Tandem stance		
One leg stance (+movements of opposite leg)		
Half kneeling		
Sensory modification	Visual: closed eyes	
	Somatosensory: various unstable support surfaces	
	Vestibular: head turns (horizontal, vertical)	
Cognitive add-on	-	

"Chaosball"		**SB**
An object (e.g. ball) is passed in a group in a certain sequence, participants follow the sequence and recall certain attributes of the group members.		
Progression: Number of sequences/objects		
1 sequence (= 1 object)		
Switching: 2 sequences (= 2 objects)		
Simultaneously: 2 sequences (= 2 objects)		
Simultaneously: 3 sequences (= 3 objects)		
Sensory modification	Visual: -	
	Somatosensory: various unstable support surfaces	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: Recall orders	
	Divided attention: more than one object	

Balancing on lines		**DB**
Participants follow the lines on the gym floor.		
Progression: BOS, DOM	Progression: Movement	Progression: Speed of movement
Narrow gait	High knees	Slow swing phase (e.g., 3s)
Tandem gait	Lunges	
Forwards, backwards		
Sensory modification	Visual: Perform several steps with eyes closed	
	Somatosensory: -	
	Vestibular: Upper body & head turns	
Cognitive add-on	Double-task: Pairs of two, trailing partner gives commands for stops or turns for leading partner	
	Double-task: Pairs of two, trailing partner has to move synchronously with leading partner	

Stepping		**DB**
Participants perform various forms of steps.		
Progression: DOM	Progression: Movement	Progression: Tools
Forwards, backwards, sidewards	High knees	Stepping out of hoop
Combination of directions	Lunges	
	Floor "touches"	
Sensory modification	Visual: closed eyes	
	Somatosensory: Various unstable support surfaces	
	Vestibular: Head turns (horizontal, vertical, diagonal)	
Cognitive add-on	Memory: Each direction gets a number (e.g. front = 1)	

"Transport chain"		**DB**
Over 5-10m each participant follows a line, but after each collective step an object is "transported" (e.g. thrown).		
Progression: BOS, DOM	Progression: Movement	Progression: Tools
Narrow gait	High knees	Number of tools to be thrown
Tandem gait	Lunges	Kind of objects (small sacks, balls, …)
forwards, backwards		
Sensory modification	Visiual: -	
	Somatosensory: -	
	Vestibular: Upper body & head turns (horizontal)	
Cognitive add-on	-	

"Commander"		**DB**
Pairs of two: one participant has to react to the commands of the other. Commands are different combinations of a step and simultaneous catch.		
Progression: Movement	Progression: Starting position	Progression: Number of commands
Tasks for one side of body	On the floor	2 to 8
Tasks for both sides of body (e.g. step left, catch right)	On the floor but inside a hoop	
	On unstable support surface	
	180° turn before step and catch	
Sensory modification	Visual: closed eyes (starting position)	
	Somatosensory: Various unstable support surfaces (starting position)	
	Vestibular: 180° turns before catch	
Cognitive add-on (main focus)	Memory: Recall pairs (movement+number / movement+color word / movement+number or color word)	
	Inhibition: command = stay in place	
	Reaction: commander minimizes time to react	

"Movement memory"		**DB**
Participants move through the gym while performing gait variations coded with various commands given by therapist.		
Progression: Movement	Progression: Number of pairs	
Tasks for one side of body	4 to 8	
Tasks for both sides of body (e.g. left knee up & right hand to left shoulder)		
Similarity of movements		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: Recall pairs (movement+number / movement+color word / movement+number or color word)	
	Inhibition: command = stop	

"Remote control"		**DB**
Pairs of two: a participant is steered through the room with clsoed eyes via tactile cues of the partner.		
Progression: number of cues	Progression: movement	
3 to 6	Tandem walk, high knees	
Sensory modification	Visual: closed eyes	
	Somatosensory: -	
	Vestibular: turning in place	
Cognitive add-on	Spatial orientation: report location in space to partner (closed eyes)	

Walking with tasks			**AG**
Each participant performs various tasks (e.g. touch opposite knee while throwing an object left to right) while walking back and forth on a 20m lane.			
Progression: DOM, speed	Progression: movement	Progression: tools	
Forwards, backwards, sidewards	Tasks for one side of body	Kind of objects (small sacks, balls, ...)	
walking, jogging	Tasks for both sides of body (e.g. left knee, right hand)		
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: Head turns (horizontal)		
Cognitive add-on	-		

Agility ladder			**AG**
Participants perform exercises in an agility ladder on the floor. Number and type of foot contacts in each field are varied.			
Progression: DOM, speed	Progression: complexity	Progression: tools	
Forwards, backwards, sidewards	Easier sequences (2 / 3 touches)	Kind of objects (small sacks, balls, ...)	
	Harder sequences (1,2,3,2,1 / 2 forwards 1 back / 2 in 1 out)		
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: Head turns		
Cognitive add-on	Divided attention: Participants have to call numbers shown by therapist		
	Divided attention: Participants have to catch objects thrown by therapist		

Cone tipping		**AG**
Pairs of two: one participant starts surrounded by an assemble of cones. The partner outside of the cones says which cones have to be touched.		
Progression: speed, duration	Progression: number of cones	
Walking, jogging	4 to 8	
1 round = 30s		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	Spatial orientation & memory: directions are given by numbers, colors or alphabet	

Slalom			**AG**
Participants move through a slalom parcour.			
Progression: speed, duration	Progression: number of obstacles	Progression: competition	
Walking, jogging	4 to 8	Hit a target with an object at the end of slalom	
1 round = 60-90s			
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: -		
Cognitive add-on	-		

Soccer			**AG**
Participants move and pass a ball.			
Progression: speed, duration	Progression: number of players	Progression: change of direction	
Walking, jogging	1 to 4	Front - back	
1 round = 60-90s		Front - back and sideways	
		Random	
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: -		
Cognitive add-on	Attention: participants have to react to stop and change of direction signals by therapist		

"Suicide runs"		**AG**
The length of the gym is split into 3 sections. Participants cover each section in different speeds, accelerating and decelerating		
Progression: speed, duration	Progression: Stops at end of section	Progression: competition
Walking, jogging 1 round = 45-90s	touch a cone circle a cone stop - 2 steps back - accelerate forwards	Hit a target with an object at the end
Sensory modification	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on	-	

2. Water-based MAT

Standing balance		**SB**
Participants perform various exercises while standing in the pool.		
Progression: BOS	Progression: free leg	Progression: hands
Narrow BOS Semi-tandem stance Tandem stance One leg stance (+movements of free leg)	Floor "touches" Leg swings Number, amplitude, direction of swings	Inside water Outside water
Sensory modification	Visual: closed eyes Somatosensory: standing on kickboard Vestibular: head turns (horizontal, vertical)	
Cognitive add-on	-	

Gait and jump variations		**DB**
Participants perform gait and jump variations in a lane.		
Progression: BOS, DOM	Progression: movement	Progression: hands
Narrow gait Tandem gait Forwards, backwards, sidewards	High knees Lunges Hot steps, skipping gait Single-leg, two-legged jumps, hold landing position 3s jumping jack	Inside water Outside water
Sensory modification	Visual: closed eyes Somatosensory: walking with feet on 1-2 kickboard(s) Vestibular: head turns (horizontal, vertical, diagonal)	
Cognitive add-on	Memory: 4 variations of jumping jack	

"Movement memory"		**DB**
Participants move through the water while performing gait variations coded with various commands given by therapist.		
Progression: movement	Progression: number of pairs	
Only legs/only arms Combination of arms + legs, one-side of body Combination of arms + legs, both sides of body Similarity of movements	4 to 8	
Sensory modification	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on (main focus)	Memory: recall pairs (movement+number / movement+color word / movement+number or color word) Inhibition: command = stop	

"Commander"		**DB**
Pairs of two. One participant must respond to the commands of the partner. The commands consist of different combinations of a catch and step.		
Progression: movement	Progression: starting position	Progression: number of commands
Catch/step = same side of body Catch/step = diagonal	Floor standing on kickboard 180° turns before catching	2 to 8
Sensory modifications	Visual: starting position with closed eyes Somatosensory: kickboard (starting position) Vestibular: 180° turns (starting position)	
Cognitive add-on (main focus)	Memory: recall pairs (movement + number / movement + color / movement + number or color) Inhibition: command = stop Reaction: reduce response time	

"Circuit Training"		**DB**
Participants complete a circuit as pairs, consisting of various functional leg strength exercises.		
Progression: duration, speed		
45-60s per exercise, 2-3 rounds, 3-4 exercises per round Exercises include: running, swimming, jumping, step-ups		
Sensory modifications	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on	-	

"Chaosball"		**SB/AG**
Participants stand in a circle and throw a ball to each other in a certain order. Various attributes of other participants must be rememberd in the process.		
Progression: number of orders / objects		
1 order (= 1 object)		
Change: 2 orders (= 2 objects)		
Simultaneously: 2 orders (= 2 objects)		
Simultaneously: 3 orders (= 3 objects)		
Sensory modifications	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: recall orders	
	Divided attention: more than one object	
	Spatial orientation: comply with order, while participants no longer stand in a circle, but walk/run around in the pool	

"Waiter"		**AG**
Participants balance a ball on a kickboard and simultaneously perfom different exercises.		
Progression: DOM, speed	Progression: movement	
Walk, jog	Balance ball, throw & catch ball	
Forwards, backwards, turns	Change hands on kickboard	
	Throw & catch ball while changing hands	
Sensory modification	Visual: Move eyes away from ball	
	Somatosensory: -	
	Vestibular: throw & catch with 180°/360° turns	
Cognitive add-on (main focus)	Dual-task: walk/jog & balance ball & react to commands from therapist	
	Divided attention: balance ball while commands given by therapist include hand signs	
	Memory: commands from therapist are given via numbers or via a mix of numbers, hand signs, and/or clapping	
	Processing speed: react as fast as possible to commands given by therapist	

"Compass"		**AG**
Participants move in the directions given by therapist.		
Progression: speed, duration	Progression: number of directions	
Walking, jogging	4 to 8 (front, back, side, diagonal)	
1 round = 45-60s		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	Memory: recall pairs (direction+number / direction+color word)	
	Inhibition: therapist gives false cues	
	Processing speed: react as fast as possible to commands	

"Mirror"		**AG**
Pairs of two. One participant leads, the other follows while always keeping the same distance.		
Progression: speed, duration	Progression: fakes	
Walking, jogging, competition (shake off)	Leader fakes change of direction	
45-60sec.	Leader changes speeds	
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	-	

"Beachball"		**AG**
Participants play with a beachball.		
Progression: number of players		
2 to whole group		
Sensory modification	Visual: -	
	Somatosensory: standing on kickboard	
	Vestibular: -	
Cognitive add-on	-	

MAT = multimodal agility-based exercise training; BOS = Base of support; DOM = Direction of movement

Components

- SB = Standing balance
- DB = Dynamic balance & functional leg strength
- AG = Agility

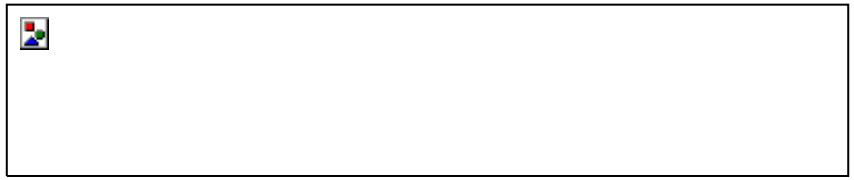
Each bracket represents a module. Each module targets one of the three components.

1. Callesen J, Cattaneo D, Brincks J, et al. How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study. *Mult Scler* 2020;26(11):1420-32. doi: 10.1177/1352458519865740 [published Online First: 20190724]

ReFEx Strength Protocol

Principles:	**Intensity:**	
• Frequency: 3x/week • Focus on leg strength/no balance training • 5min warm-up, 3-4 exercises/session	• Session 1-5: 3x10 repetitions at 15 RPM • Session 6 to T_1: 3x12 repetitions at 12 RPM • Break between sets: 1min	
Session-RPE:		
At the end of every training the participant is requested to provide a rating on perceived exertion (i.e., session-RPE) for the complete session		
Warm-up (5min):		
• Participants can choose between treadmill, cross trainer, stepper, and recumbent stepper		
Exercise pool: Always determine 15RPM before starting a new exercise!		
1 hip		
a) Extension Leg press (upper body upright) • Start: hip angle as small as possible	b) Flexion Standing knee raises (cable) • With balance support (chair)	c) Abduction Standing abduction (cable) • With balance support
2 knee		
a) Extension Leg press (supine)	b) Flexion Prone leg curls (cable) • End: >90° flexion	
3 foot		
a) Plantar flexion Calf raises on leg press • Large ankle ROM		

RPM = Repetition maximum; RPE = Rated perceived exertion; ROM = Range of motion



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1;24
	5b	Name and contact information for the trial sponsor	24
	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	24
	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)	n/a

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	3-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
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)	5;8
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
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)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	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)	11-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	15-16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
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	14-20
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)	6-8

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	8-9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	8
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	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
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	14-20
	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	15-17

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
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	20-21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	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)	n/a
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	n/a
	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	n/a
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	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	22
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)	21-22

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	22
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
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	n/a
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	22
	31b	Authorship eligibility guidelines and any intended use of professional writers	23-24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
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	n/a

*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.

BMJ Open

A randomized controlled pilot and feasibility study of multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve Multiple Sclerosis-related fatigue and fatigability during inpatient rehabilitation [ReFEx] – study protocol.

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology, Qualitative research, Sports and exercise medicine
Keywords:	Multiple sclerosis < NEUROLOGY, SPORTS MEDICINE, REHABILITATION MEDICINE

A randomized controlled pilot and feasibility study of multimodal agility-based exercise training (MAT) versus strength and endurance training (SET) to improve Multiple Sclerosis-related fatigue and fatigability during inpatient rehabilitation [ReFEx] – study protocol.

Akronym: ReFEx (Rehabilitation, Fatigue, and Exercise)

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Word count: 4336

Trial status: The first participant has been enrolled on 18 November 2021. At the time of submission, 9/24 participants have been recruited, 3/24 participants have finished the intervention period and completed the primary measurement time point one week after the end of the intervention period.

ABSTRACT

Introduction: Subjective fatigue and objectively assessed fatigability are common symptoms in persons with Multiple Sclerosis (pwMS). Recent work has suggested a positive effect of balance and motor control training (BMCT) in reducing fatigue. It is unclear whether this effect can also be attained during inpatient rehabilitation. Multimodal agility-based exercise training (MAT) has been developed as a framework that incorporates BMCT with added agility components but has not been applied to pwMS. Therefore, this study will evaluate the feasibility of a randomized controlled trial comparing MAT against strength and endurance training (SET) for the improvement of MS-related fatigue and fatigability in a German neurologic rehabilitation center.

Methods and analysis: A total of 24 pwMS (Expanded Disability Status Scale ≤5.0, Fatigue Scale for Motor and Cognitive Functions ≥53) will be randomly assigned to either SET or land and water-based MAT for 4 to 6 weeks during inpatient rehabilitation. Assessments of subjective fatigue, motor and cognitive fatigability, cognitive and cardiorespiratory performance, and balance confidence will be performed at admission and discharge. Subjective fatigue will also be assessed at 1, 4, and 12 weeks after discharge. Feasibility outcomes will include patients' acceptance of study procedures and interventions, recruitment rate, retention rate, time needed to complete baseline assessments, intervention adherence, and fidelity. All quantitative outcomes will be reported descriptively. A total of 12 pwMS (6 per group) will be interviewed to gain insights into participants' experiences during study participation.

Ethics and dissemination: Ethical approval has been obtained from the Ethics Committee of the University of Bonn (reference number: 543/20). Dissemination of findings is planned via peer-reviewed journals, conferences, and media releases.

Trial registration: German Clinical Trials Register: DRKS00023943, date of registration: 23 September 2021

Keywords

multiple sclerosis, sports medicine, rehabilitation medicine

Strengths and limitations

- Comprehensive assessment of subjective fatigue, as well as objective cognitive and motor fatigability
- First application of agility-based exercise training to pwMS
- Mixed-methods approach to acquire patient perspective and acceptance
- Clinical inpatient setting will challenge standardization of study procedures

INTRODUCTION

Fatigue, described as 'a subjective sensation of lack of energy and exhaustion' (p. E79)[1], was reported as the most common symptom (58%) among 35,000 patients from the German multiple sclerosis (MS) register[2]. It is also reported as one of the most disabling symptoms[3] with high socioeconomic relevance as 25% of persons with MS (pwMS) have impaired working capacity because of 'invisible symptoms' such as fatigue and impaired cognition[4, 5].

Data from the MS register also show that only 35% of fatigued pwMS receive any kind of treatment and among them only 15% receive pharmacological treatment to specifically handle fatigue symptoms[2]. No clear pathomechanisms for fatigue have been defined yet leading to the consequence of still limited pharmacotherapy options for the treatment of fatigue[6].

According to the established taxonomy by Kluger and colleagues[7] two concepts must be separated when considering fatigue: (I) the subjective experience of fatigue and (II) objective performance fatigability during motor or cognitive tasks. Whether improvements in fatigability also transfer to subjective fatigue is still unclear. Interestingly, the association between the two constructs seems to be relatively weak[8, 9].

Next to distinguishing between 'fatigue' and 'fatigability', a further dichotomy exists with 'primary fatigue' resulting from pathophysiological processes of the disease itself (e.g., central nervous system, immunologic or endocrine changes) and 'secondary fatigue' resulting from mechanisms not directly related to the disease (e.g., sleep, depression, medication)[10].

To reduce subjective fatigue, exercise interventions have been studied as a non-pharmacological treatment option. However, several methodological issues exist. As fatigue is frequently assessed as a secondary outcome variable, subjects are often not pre-screened for fatigue symptoms at baseline and the intervention is not primarily designed to reduce fatigue[11, 12]. Consequently, to date, there are few studies investigating the specific pathophysiological pathways of primary or secondary fatigue that are altered by exercise[10].

In a recent meta-analysis Moss-Morris and colleagues[11] performed a detailed review of exercise intervention studies, that specifically aimed at fatigue reduction. Here, the authors reported variance in the effects of different types of exercise. For example, endurance exercise has been frequently investigated, as it can be easily standardized, but was reported to have only small effects on fatigue outcomes measured with self-report questionnaires[13]. If combined with other modalities such as resistance exercise, effects might be greater (e.g., strength and

endurance training [SET]). Lastly, types of exercise consisting primarily of stimuli targeting motor control (e.g., balance and motor control training [BMCT]) were described as promising, due to their relatively large effect sizes and specification of a mechanistic pathway.

In the special setting of inpatient rehabilitation, the number of exercise studies for subjective fatigue reduction is very limited. In their review, Moss-Morris and colleagues[11] identified only one study conducted in an inpatient rehabilitation setting. However, this trial was restricted from the meta-analysis because of methodological limitations, indicating the need for future systematic research on fatigue-specific therapy. This is also evident in the first German practice guideline for exercise therapy in pwMS, which highlights mobility rehabilitation but does not consider symptoms of fatigue or fatigability[14].

Therefore, the ReFEx (Rehabilitation, Fatigue, and Exercise) project aims to transfer the promising results of interventions focused on balance and motor control to inpatient rehabilitation and compare it with SET, which is considered the control group or ‘usual care’. Importantly, we will adapt the existing approaches on BMCT to be based on the agility framework described by Donath and colleagues[15]. Therefore, besides exercises focused on balance and sensory integration, the treatment manual will also include functional leg strength and agility-based exercises. This approach can be characterized as ‘multimodal agility-based exercise training’ (MAT)[16] and the ReFEx project will be the first to apply it to pwMS. In doing so, we not only expect to target subjective fatigue, but also other frequent MS-specific symptoms including performance fatigability as well as disturbed gait and balance. Applying the agility framework could further provide an opportunity for combined motor and cognitive rehabilitation[17], that is fun, enjoyable, and social[15].

Referring to the pathophysiological framework by Langeskov-Christensen and colleagues[10] we hypothesize that the SET will improve secondary fatigue via improved aerobic capacity and motor function, while the MAT intervention will improve secondary fatigue via improved

motor function and reduced cognitive effort in daily life (as hypothesized by Moss-Morris and colleagues[11] and others[18-21]). Based on the existing evidence, we expect greater benefits on secondary fatigue parameters from MAT than for SET. Regarding performance fatigability, we hypothesize, that MAT will be superior to SET in improving motor and cognitive fatigability.

In a first step, the pilot and feasibility study (PAFS) described in this protocol will be used to determine whether the adapted MAT and SET are feasible in the inpatient rehabilitation setting with a special emphasis on patients' acceptance. This will include both, a quantitative, and qualitative evaluation.

METHODS AND ANALYSIS

Study design

The PAFS will be conducted at the Neurological Rehabilitation Center (NRC) 'Godeshoehe' (Bonn; certified MS Rehabilitation Center). It will have a two-armed, parallel-group, randomized-controlled design with twelve weeks follow-up, following a mixed-methods approach. Measurement time points are provided in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure (Table 1).

Patient and public involvement

In our therapeutic work of several years in a specialized rehabilitation clinic for MS, the majority of pwMS report that fatigue is difficult to cope with and limits quality of life. These patient reports were the impetus for the conception of this study, especially as there are few evaluated therapy approaches. In the conception of this PAFS, it was important for us to appreciate the patient perspective and to include the affected persons as 'experts of their disease'. In particular, this takes the form of qualitative interviews, which we base on a

constructivist paradigm that allows for the co-creation of knowledge by the participants and the researcher[22].

Table 1 SPIRIT figure depicting the schedule of enrollment, interventions and assessments for the pilot and feasibility study.

	STUDY PERIOD						
	Enrolment	**Allocation**	**Post-Allocation**				
TIMEPOINT	**$-T_0$**	**0**	**T_0**	**T_1**	**T_2**	**T_3**	**T_4**
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Stratified randomization		X					
INTERVENTIONS							
MAT			⟷	⟷			
SET			⟷	⟷			
ASSESSMENTS:							
Fatigue (WEIMuS)	X			X	X	X	X
Fatigue (FSMC)	X			X	X	X	X
Cognitive fatigability (TAP-Alert)			X	X			
Motor fatigability (6MWT)	X			X			
Cognitive performance (CVLT, SDMT)			X	X			
Cardiorespiratory fitness (GXT)			X	X			
Motor function (T25FW, SSST, FGA)	X			X			
Balance confidence (ABC)	X			X			
Depression (CES-D)			X	X			

Feasibility outcomes	◆	———	———	———	———	◆	
Interview 1 (Feasibility)				X			
Interview 2 (Fatigue responder)					X		

-T_0 = admission; *0* = after written informed consent; T_0 = post-randomization; T_1 = prior to discharge; T_2 = 1 - 2 weeks after discharge; T_3 = 4 weeks after discharge; T_4 = 12 weeks after discharge; *MAT* = Multimodal Agility-based exercise Training; *SET* = Strength and Endurance Training; *WEIMuS* = Würzburg Fatigue Inventory for Multiple Sclerosis; *FSMC* = Fatigue Scale for Motor and Cognitive Functions; *TAP-Alert* = Test Battery of Attention Performance – Alertness; *6MWT* = 6-Minute Walk Test; *CVLT* = California Verbal Learning Test; *SDMT* = Symbol Digit Modalities Test; *GXT* = Graded Exercise Test; *T25FW* = Timed 25-foot Walk Test; *SSST* = Six Spot Step Test; *FGA* = Functional Gait Assessment; *ABC* = Activities-Specific Balance Confidence Scale; *CES-D* Center for Epidemiological Studies Depression Scale (German version)

Screening and recruitment

Individuals admitted to the NRC will be screened for pwMS. All pwMS will then be scheduled for neuropsychological examination the day after admission, according to usual practice. Here, patients will be asked to complete the Fatigue Scale for Motor and Cognitive Functions (FSMC). If a patient is classified as, at least, 'moderately fatigued' and the patient fulfills all other eligibility criteria (Table 2), he or she will be informed about the study by his or her neuropsychologist (JN, JS, EH), verbally, and in written form.

Randomization

If patients provide the written informed consent to one of the study staff members within a maximum of three days, they will be randomly allocated (1:1) to the intervention or control

group according to the minimization procedure[23] and stratified by Expanded Disability Status Scale (EDSS, ≤3 or ≥3.5), Würzburg Fatigue Inventory for Multiple Sclerosis (WEIMuS, <38 or ≥38), age (<45 or ≥45), and MS disease course (relapsing-remitting or secondary-progressive). Randomization will be provided by an independent researcher from the German Sport University Cologne using RITA ('Randomization-In-Treatment-Arms', Evident, Germany).

Sample size and duration

Data from the PAFS is planned to be pooled with data from the full trial in case no major changes of study protocol will be necessary (see progression requirements). Acceptability of pooling will be evaluated according to components listed in the 'Acceptance checklist for clinical effectiveness pilot trials'[24]. As the primary aim of this trial is to evaluate the feasibility, no sample size calculation based on statistical assumptions will be performed. However, we consider a minimum of twelve recruited patients per study arm to be a reasonable sample size for this setting[25].

The NRC treats about 100 – 120 pwMS per year. According to previous data collections for the German MS register no more than 25% of patients will have to be excluded, based on EDSS and FSMC screening (see eligibility criteria). We further predict no more than 10% of eligible patients to be unwilling to participate, based on previously conducted studies. Comparable studies have had high retention rates (95%[26]) but did not choose a primary endpoint after patients returned home. Consequently, we plan with 80% retention from T_0 to T_2. This will result in a feasibility period of about six to eight months. Retention rates will be used to inform the sample size calculation for the full randomized controlled trial (RCT).

Participants

PwMS will be eligible to participate in this trial according to the inclusion and exclusion criteria stated in Table 2.413

Table 2 Eligibility criteria.

Inclusion	Exclusion
1. MS disease course RR or SP	**1. Unable to attend water therapy**
2. Age 18 - 67	**2. Comorbidities** That prevent attending study therapies, chronic neurologic conditions other than MS
3. EDSS ≤5.0	**3. German language skills** That interfere with understanding of testing and instructions
4. FSMC total score ≥53	**4. Current fatigue medication** Amantadine, Modafinil started <3 months
5. Written informed consent	

RR = Relapsing-remitting; *SP* = Secondary-progressive; *EDSS* = Expanded Disability Status Scale; *FSMC* = Fatigue Scale for Motor and Cognitive Functions.

Interventions

The intervention period includes the time from admission to discharge, which usually comprises four to six weeks for this group of patients. Multidisciplinary inpatient rehabilitation can consist of various diagnostic and therapeutic components such as exercise training, occupational and physical therapy, health education, neuropsychological assessment, or assessment of working capacity. Thus, interactions between treatments as well as flexibility in the treatment schedule are common[27]. For this reason, we designed the schedules of the two study groups to ensure the following:

(I) Distinct differences in the amount of therapy targeting cognitive and sensory integration.

(II) Standardization of treatment as strictly as possible within this specific clinical setting.

(III) Approximately equivalent amount of total therapy time.

See Table 3 for an overview of intervention components. Reporting of the interventions will follow the modified Consensus on Exercise Reporting Template (CERT) for Therapeutic Exercise Interventions[28].

Table 3 Frequency, time, and type of intervention components.

MAT (intervention)	**SET (control)**
5x/w, 30min, 'MS-group'	
5x/w, 30min, land-based MAT	5x/w, 22min, endurance training
3x/w, 30min, water-based MAT	3x/w, 30min, strength training

Standard treatment for both groups

Both groups will attend the 'MS-group', a specific group for all pwMS, focusing on body awareness and relaxation techniques. It consists of max. eight pwMS, lasts 30min and is led by an exercise therapist. Both groups will also attend MS-specific lectures once a week. All other available therapies, which are not part of standard treatment, will be included only after individual consideration to maximize standardization.

Strength and Endurance Training (SET)

The combined strength and endurance training program will be considered the control condition. All endurance training sessions will be supervised by exercise therapists from the NRC. Strength training sessions will be supervised by exercise science students or therapists in one-on-one sessions. Students and therapists conducting the strength training will be

instructed by FW and will follow a training protocol (see Supplemental File [Strength Protocol]).

Endurance training will be performed according to the standard protocol in this clinic, with 22min per session (3min of gradual increase, 17min steady and 2min cool-down) on a cycle ergometer (ergoselect 5, ergoline GmbH, Bitz, Germany) with continuous monitoring of power output and heart rate (ers.2 software, ergoline GmbH, Bitz, Germany). Endurance training will be performed in groups of max. eight patients. In the first session, participants will start their training at an intensity that was rated "light" to "somewhat hard" by themselves during the baseline graded exercise test (GXT) (equivalent to 11-13 on the 6-20 Rated Perceived Exertion [RPE] – scale). In the following sessions, therapists will regulate the power output so that participants stay between 11 and 13 on the RPE-scale. If a pwMS is unable to complete the total duration, the session duration can be initially reduced and then progressed in the following sessions. The range of 11 to 13 was chosen based on recent evidence-based recommendations for pwMS with similar EDSS[29].

Resistance training will be adapted from Callesen and colleagues[18] to fit the inpatient setting. Each session will start with a 5min warm-up on an elliptical trainer, treadmill, or recumbent stepper, followed by three to four exercises targeting hip, knee, and ankle flexion and extension, as well as hip abduction. Exercises will be progressed as follows:

- Session 1-5: 3x10 repetitions with the 15 repetitions maximum (RM)
- Session 6-T_1 (session 10-16): 3x12 repetitions with 12RM

In detail, for every new exercise, therapists will initially determine the respective weight the participant is able to move no more than the intended RM. Therapists will be given the necessary room for individualization but will be instructed to follow pre-specified exercises (see Supplemental File [Strength Protocol]).

Multimodal agility-based exercise training (MAT)

For the treatment manual see Supplemental File [MAT-Manual]. All sessions will be guided by max. three different exercise therapists (including FW) from the NRC, experienced with providing balance exercises on land and in the water in group settings. However, as MAT also comprises other/new elements, exercise therapists will be specifically trained by FW and instructed to follow the treatment manual.

Both parts (i.e., water and land) will be installed within existing group therapies. Each group will consist of max. eight participants. Empty spots will be filled with other patients from the NRC. The intervention program will consist of three main components: (1) standing balance exercises, (2) dynamic balance exercises including functional leg strength, (3) agility-like exercises including change of direction and change of velocity[16]. Each main component will be represented in several modules. Each module is constructed as a basic set-up, that can be progressed in terms of difficulty. Additionally, modifications on a cognitive (e.g., memory, attention, inhibition) and sensory (i.e., visual, somatosensory, vestibular) level are described. As stated by Callesen and colleagues[18] there is no consensus yet on how to define intensity or progression in balance and motor control exercises. Thus, for this intervention, therapists will be instructed to aim for a level of difficulty and complexity that keeps exercises manageable and safe for participants, but also provokes motor or cognitive errors. This is in line with recommendations for neurorehabilitation from basic science[30].

For load management in the land-based therapy, there will be three sessions with higher physical strain (i.e., agility-like components and functional leg strength) interspersed with two sessions with lower physical strain (i.e., standing balance and exercises with a cognitive focus). Due to water immersion, physical strain in the water-based therapy should be lower in general.

Participants will be instructed to take individual breaks whenever they need to. They will also be advised to monitor their fatigue during their stay and skip a session when they need more time to recuperate.

Blinding

The neuropsychological staff conducting the cognitive tests will be blinded to the study groups. However, for organizational reasons and specifics of the study setting, blinding of participants, therapists conducting the interventions as well as personnel conducting the motor and cardiorespiratory fitness (CRF) tests and analyzing the questionnaires will not be possible.

Outcomes

As depicted in Table 1, assessments will be carried out at admission (i.e., pre-intervention, T_0) and discharge (i.e., post-intervention, T_1), as well as after participants have returned home (i.e., follow-up, T_2-T_4).

Baseline sample characteristics

Demographic data on age and sex will be taken from electronic records. Height will be ascertained from participants. Bodyweight at T_0 will be assessed with normal clothing, but without shoes, prior to GXT using a digital scale. The corresponding Body Mass Index will then be calculated (kg/m^2).

Clinical data will include the following. MS disease course, and time since diagnosis (years) will be taken from available medical records in the screening process. In case of an unspecified MS disease course, the participant and the treating physician will be contacted for any further information. EDSS, disease-modifying drugs, fatigue-specific drugs (Amantadine, Modafinil), and drugs decreasing heart rate will be assessed by the treating physician on the day of arrival

and made available for the study staff in the electronic health record. Use of assistive devices for walking will be ascertained in conjunction with motor function testing.

Feasibility (quantitative)

To generate the quantitative feasibility outcomes, we adopted the categories described by Thabane and colleagues[31] and promoted for exercise studies in MS by Learmonth and Motl[32] (see Table 4).

Table 4 Description of quantitative feasibility outcomes (adapted from[33]).

Classification	Outcome	Operationalization	Importance for future RCT
Process	1. Eligibility rate	• Number/rate of patients being eligible • Number/rate of negative cases for each eligibility criterium	Determines criteria that might produce too many non-eligible patients for the trial to be conducted in a reasonable timeframe
	2. Recruitment rate	• Number of patients successfully randomized per month	Evaluates whether the number of participants randomized is high enough to allow for a time-efficient execution
	3. Refusal rate	• Number/rate of patients eligible but unwilling to participate (with reasons)	Provides insights on possible barriers for participation, which might be counteracted by better study information and addressing these barriers.
	4. Retention rate	• Number/rate of patients completing the intervention period • Number/rate of patients returning the WEIMuS at T_2	Provides information on the risk of subjects dropping out during the intervention period, which might necessitate adaptations to the interventions or the organization of the study. Gives information on the feasibility of the primary outcome being assessed post-discharge and via an online platform.
	5. Adherence	• Number of therapy sessions conducted relative to sessions scheduled	Gives information on how many sessions would normally be feasible to conduct during the inpatient stay
	6. Fidelity	• SET: training protocols will be reviewed to ensure that communicated principles were followed: (I) number of exercises performed each session, (II) total training load prescribed relative to actual training load per exercise (e.g., target: 3 (sets) x 10 (repetitions) x 20 (weight) = 600, moved: 3 x 10 x 15 = 450, percentage: 75%). The ers.2 software will document all endurance training sessions, which will provide measures of training duration and intensity (average heart rate, average power, 6-20 RPE) relative to the prescribed values.	Gives detailed information on whether subjects were able to perform the SET as planned. In the MAT, therapist's usage of the manual will be observable. This will allow for guided adaptations of the intervention protocols, if necessary.

		• MAT: To quantify the degree of aerobic challenge, in the land-based sessions, patients will be wearing heart rate sensors (Verity Sense, Polar, Kempele, Finland). Average and maximum heart rate values for each session and patient will be tracked using software (Polar Team App). • MAT: Components of each session will be coded by the operating therapist according to the MAT manual (SB = standing balance, DB = dynamic balance and functional leg strength, AG = agility-like) to get an approximate distribution.	
Resources	Time	• Number of days needed to complete baseline assessments • Time requirements for (I) the first (T25FW, SSST, FGA, 6MWT) and second (GXT) physical testing blocks at T_0 and T_1, (II) preparation of MAT sessions	Evaluates whether baseline assessments can be scheduled in a timely manner before the start of the intervention period. Precise time requirements will allow for better scheduling of study-related appointments.
Management	Data	• Number of missing items for FSMC and WEIMuS for all measurement timepoints • Number of missing outcomes for T_0 and T_1	Provides information on actions to take to ensure questionnaires will be fully completed and all assessments taken.
Scientific	1. Adverse events	• Number and kind of adverse events related to study interventions	Establishes the safety of all interventions.
	2. Acceptability	• Perceived exertion: Session-RPE after each endurance, strength, and MAT session (Category Ratio (CR-10) RPE scale as developed by Foster and colleagues [34, 35]). After each session patients will be asked: "How strenuous was the session as a whole?". Patients will be instructed to provide a global rating of the complete session and not to focus on specific aspects. • Fun during training and relevance of training for daily life: assessed at T_1 by using customized questions with a four-point Likert-type scale ranging from "not at all" to "very much" [36].	Perceived exertion in both groups will determine whether the interventions are perceived to be too strenuous or too easy. Fun and relevance are important measures of motivation. In case of low values, additional actions will be necessary to ensure sufficient motivation.

320 *RCT* = randomized-controlled trial; T_0 = post-randomization; T_1 = prior to discharge; T_2 = 1 - 2 weeks after discharge; *WEIMuS* = Würzburg

321 Fatigue Inventory for Multiple Sclerosis; *MAT* = Multimodal Agility-based exercise Training; *SET* = Strength and Endurance Training; *RPE* =

Rated Perceived Exertion; *GXT* = Graded Exercise Test; *T25FW* = Timed 25-foot Walk Test; *SSST* = Six Spot Step Test; *FGA* = Functional Gait Assessment; *FSMC* = Fatigue Scale for Motor and Cognitive Functions

Feasibility (qualitative)

The qualitative evaluation aims to (a) capture patients' views on acceptance, benefits, and satisfaction with study participation, (b) assess their experiences with the intervention methods, and (c) identify necessary adaptions. For this purpose, we designed a semi-structured interview. Six participants from each study arm will be interviewed face-to-face at T_1. The selection of participants will reflect the greatest possible diversity in terms of gender, age, and EDSS[37]. The interview will include a total of 14 questions and will last approximately 20min. Key categories of the interview are the concept of fatigue, experiences and demands of the interventions, personal relevance, and goal achievement. All interviews will be recorded digitally and transcribed verbatim by an independent transcription service.

Both interviewers (JN, FW) have several years of clinical experience with pwMS. A first draft of this interview was piloted with three pwMS prior to the start of the feasibility study to ensure that the questions allow valid insights into participants' experiences.

The interview will be supplemented by a customized questionnaire asking for prior knowledge of fatigue, prior experiences with MAT and SET, and comprehensibility of the study instructions and questionnaires. The questionnaire also asks about fun and relevance of training for daily life (see Table 4), and the motivation to continue a comparable training at home.

Primary outcome for the full RCT

Fatigue questionnaires presuppose internal averaging of the amount of fatigue experienced during a certain timeframe[1]. This has been a problem for studies evaluating short-term interventions, as in some questionnaires patients are asked to evaluate their fatigue in timeframes of up to four weeks. As we are interested in the change in fatigue experienced in daily life from before the inpatient stay to afterwards, we (I) chose the WEIMuS[38] as the primary outcome measure to assess the fatigue experienced during the past week and (II)

established the primary endpoint to be one to two weeks after participants have returned home (T_2). The WEIMuS has 17 items (scored 0 - 4) with higher total scores indicating higher fatigue (range 0 – 68, cut-off for classification as fatigued: 32).

For fatigue screening (that is necessary for study eligibility) we will apply the FSMC. It is a 20 item Likert-type scale (1 – 5) with a total score (0 – 100) and two subscales relating to motor and cognitive fatigue[39]. The FSMC provides cut-off scores to classify cases of no (total score < 43), mild (≥43), moderate (≥53) and severe (≥63) fatigue, which makes it especially suitable as a tool for classification of fatigue severity[1, 39].

Paper versions of both questionnaires will be handed out to participants. When at home, participants will be followed up via e-mail to fill out questionnaires on an online platform (Qualtrics) at timepoints T_2-T_4. Participants will be able to respond to the e-mail request within seven days.

Secondary outcomes for the full RCT

MS-fatigue is a multifactorial construct that requires assessment of other interrelated constructs[7]. This will include measures of cognitive (Test Battery of Attention Performance – Alertness[40]) and motor fatigability (6-Minute Walk Test [6MWT], Distance Walked Index[41]), cognitive performance (California Verbal Learning Test, Symbol Digit Modalities Test[26, 42]) and cardiorespiratory fitness (GXT on a cycle ergometer, protocol: start 25W, progression 10W/min.). Dynamic balance and motor function (Timed 25-Foot Walk Test [T25FW][43], Six Spot Step Test [SSST][44], Functional Gait Assessment [FGA][45]) will also be assessed as well as self-reported balance confidence (Activities-specific Balance Confidence scale[46]). Depression (Center for Epidemiological Studies Depression Scale [German version][47]) will be assessed as a confounder variable.

The subsequent full trial will also include qualitative data to explore the subjective experiences in participants showing a WEIMuS change of 6 or more points from T_0 to T_2 (positive or negative). These 'responders' will be contacted for a short telephone interview. Previous data has shown large differences in fatigue questionnaire change scores[13]. However, the scores do not provide any detail on individual circumstances, including, for example, social or work-related influences, that might be independent of intervention effects. Therefore, we decided to specifically ask participants:

> 'The analysis of your questionnaires shows a relevant positive/negative change of your fatigue symptoms, when comparing your scores from pre-rehab to the online questionnaire. What do you personally think is the reason for this?'.

No minimal clinically relevant change scores have been established yet[48]. Thus, the relevant change score (≥6 or ≤-6) was chosen as a pragmatic value of 0.5 SD from the validation study[49]. A similar procedure has been described by Sander and colleagues[1].

Data analysis

Quantitative data analysis

Descriptive statistics will be used to summarize quantitative feasibility outcomes (Table 4), and baseline sample characteristics. Retention, adherence, fidelity, adverse events, and acceptability measures will be calculated per group. The results will be given as mean and standard deviation for continuous data, median and interquartile range, or frequencies (number, %) for categorical data. The same will be applied to baseline and follow-up data for primary and secondary outcomes of the potential full trial. Change scores from baseline will be reported for these outcomes for each of the measurement timepoints. The frequency of participants in each group with a relevant change related to the WEIMuS total score (≥6 or ≤-6, as described above), will be calculated. However, hypothesis testing of within- or between-group treatment

effects will not be performed due to the inherent problems of hypothesis testing based on (small) pilot study data[50, 51]. For the same reasons, no effect sizes will be presented, as they will have a high risk of under- or overestimating the 'true effect' of the interventions[52].

All analyses will be performed using IBM SPSS Statistics in the most up to date version.

Qualitative data analysis

Coding of the interviews will be performed according to qualitative content analysis, using a combined model of deductive (a priori) and inductive coding (on the text material) to identify themes and sub-themes[53]. Deductive coding will be based on preliminary considerations and hypotheses in the study planning and on reviews of relevant literature[37, 54-57]. Coding will be carried out by at least two individuals (JN, FW) to ensure intercoder reliability[58]. The analysis will be supported by MAXQDA® software in the most up to date version[59]. JN and FW will compile the themes emerging from the interview data and discuss these with the wider research team.

Progression requirements to full RCT

Falling short of the following feasibility values will necessitate changes to the protocol of the full RCT:

- Adherence: Average of at least 18 therapy sessions during the stay per group (equals 6x30min sessions per week for 3 weeks [28 days admission to discharge minus 5 days for pre- and post-testing])
- Recruitment rate: 4 participants/month, <25% non-eligible pwMS, <10% eligible but unwilling to participate
- Retention at T_1: >90% per group
- Retention at T_2: >80% per group

- Time requirements for baseline assessments: >80% able to complete all assessments within the first three days of therapy
- Interview statements indicating that the interventions are perceived as relevant, comprehensible, and pleasant

Data management

The principal investigator (FW) will be responsible for data management. Demographic and clinical characteristics will be taken from the electronic health record. All other data will be collected on forms during the inpatient stay and via an online tool for follow-up. Data will be entered into a secure internal network database by study personnel in the NRC. Entered data will be checked for plausibility and compared to the collection forms if necessary. Data will be collected and stored in accordance with the General Data Protection Regulation.

ETHICS AND DISSEMINATION

Written informed consent will be obtained from each participant. Ethical approval was obtained from the Ethics Committee at the Medical Faculty, University of Bonn (reference number: 543/20).

The results of this feasibility study will be disseminated regardless of the magnitude or direction of effect in peer-reviewed journals, conferences and the website and magazines of the German Sport University Cologne.

DISCUSSION

This PAFS will give relevant insights for conducting a future RCT in this special setting of inpatient rehabilitation for pwMS. Content-wise, it will (I) translate existing evidence on BMCT in pwMS to this setting, (II) add to this BMCT by introducing the framework of MAT,

and (III) apply a clear focus on fatigue as the primary outcome. Specifically, we see the potential of a relatively large training volume (e.g., about eight therapy sessions per week) compared to studies in outpatient settings, and a high amount of supervised exercise, which should provide good adherence and fidelity. Having a therapist as a supervisor is especially important for a rather complex type of exercise as is MAT. For example, there are no simple 'numbers' like sets or repetitions one can follow. Quicker movements relating to agility, like changes of direction, acceleration, and deceleration, frequently lie outside the 'comfort zone' of pwMS, which necessitates guidance of a therapist. Lastly, in the group format, a therapist is mandatory to provide modifications for pwMS with higher disability or very low disability.

We also anticipate certain issues in conducting this study. For example, scheduling of appointments for testing will be challenging, as there will be several testing blocks (i.e., motor function, GXT, cognitive tests, interview), conducted in different departments of the NRC, which must be fitted into certain timeslots around admission and discharge. These appointments will compete against other study unrelated appointments (e.g., ward rounds, urology assessments, etc.). Regarding the eligibility and randomization criteria, it will be challenging to have all the correct data within the first two days as there can be delays in the admission process. Intervention duration can be regarded as a general limitation of this project, as it is restricted to the usual inpatient stay for this group of patients in the German national health care system (i.e., four to six weeks). Land- and water-based MAT might have different mechanisms of action, especially when considering the effect of body temperature on demyelinated axons, and the cooling effect present in water[60]. Still, water-based MAT was developed to allow for a greater amount of standardized MAT therapy time. As inpatients must receive a certain amount of therapy time during their stay, not including water-based MAT would have resulted in a greater amount of uncontrolled therapy in the intervention group. In

a main trial this would only permit conclusions to be drawn on the treatment effect of concomitant land- and water-based MAT.

Lastly, analysis of blood-based biomarkers is planned to be part of the ReFEx study project. However, as these outcomes are connected to comparably high costs for materials and analysis, addition of blood sampling is postponed to the start of a full RCT. Nevertheless, information gathered during the feasibility study will be used to allow for smooth integration of blood draws and storage during assessments at admission and discharge. As the blood draws can be regarded as the most unpleasant part of the assessments for patients, feasibility of the interventions and patient acceptance should be established first.

Author contributions

FW, JN, ME, PZ designed the overall study. FW & JN designed the feasibility study and wrote the protocol. FW, JN, JS, EH implemented the screening and assessment procedures. JS, EH, ME, AKF, HK, PZ revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

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Germany. AFK is author of the cognitive training program NEUROvitalis but receives no corresponding honoraria. HK: none. PZ: none.

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ReFEx Strength Protocol

Principles:	**Intensity:**	
• Frequency: 3x/week • Focus on leg strength/no balance training • 5min warm-up, 3-4 exercises/session	• Session 1-5: 3x10 repetitions at 15 RPM • Session 6 to T_1: 3x12 repetitions at 12 RPM • Break between sets: 1min	
Session-RPE:		
At the end of every training the participant is requested to provide a rating on perceived exertion (i.e., session-RPE) for the complete session		
Warm-up (5min):		
• Participants can choose between treadmill, cross trainer, stepper, and recumbent stepper		
Exercise pool: Always determine 15RPM before starting a new exercise!		
1 hip		
a) Extension Leg press (upper body upright) • Start: hip angle as small as possible	b) Flexion Standing knee raises (cable) • With balance support (chair)	c) Abduction Standing abduction (cable) • With balance support
2 knee		
a) Extension Leg press (supine)	b) Flexion Prone leg curls (cable) • End: >90° flexion	
3 foot		
a) Plantar flexion Calf raises on leg press • Large ankle ROM		

RPM = Repetition maximum; RPE = Rated perceived exertion; ROM = Range of motion

Manual for the land-based and water-based MAT (adapted from[1])

1. Land-based MAT

Standing balance		**SB**
Participants perform various exercises while standing.		
Progression: BOS	Progression: Catching & Throwing	Progression: Tools
Narrow BOS	Alone	Number of objects for throwing
Semi-tandem stance	With partner	Kind of objects (small sacks, balls, …)
Tandem stance		
One leg stance (+movements of opposite leg)		
Half kneeling		
Sensory modification	Visual: closed eyes	
	Somatosensory: various unstable support surfaces	
	Vestibular: head turns (horizontal, vertical)	
Cognitive add-on	-	

"Chaosball"		**SB**
An object (e.g. ball) is passed in a group in a certain sequence, participants follow the sequence and recall certain attributes of the group members.		
Progression: Number of sequences/objects		
1 sequence (= 1 object)		
Switching: 2 sequences (= 2 objects)		
Simultaneously: 2 sequences (= 2 objects)		
Simultaneously: 3 sequences (= 3 objects)		
Sensory modification	Visual: -	
	Somatosensory: various unstable support surfaces	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: Recall orders	
	Divided attention: more than one object	

Balancing on lines		**DB**
Participants follow the lines on the gym floor.		
Progression: BOS, DOM	Progression: Movement	Progression: Speed of movement
Narrow gait	High knees	Slow swing phase (e.g., 3s)
Tandem gait	Lunges	
Forwards, backwards		
Sensory modification	Visual: Perform several steps with eyes closed	
	Somatosensory: -	
	Vestibular: Upper body & head turns	
Cognitive add-on	Double-task: Pairs of two, trailing partner gives commands for stops or turns for leading partner	
	Double-task: Pairs of two, trailing partner has to move synchronously with leading partner	

Stepping		**DB**
Participants perform various forms of steps.		
Progression: DOM	Progression: Movement	Progression: Tools
Forwards, backwards, sidewards	High knees	Stepping out of hoop
Combination of directions	Lunges	
	Floor "touches"	
Sensory modification	Visual: closed eyes	
	Somatosensory: Various unstable support surfaces	
	Vestibular: Head turns (horizontal, vertical, diagonal)	
Cognitive add-on	Memory: Each direction gets a number (e.g. front = 1)	

"Transport chain"		**DB**
Over 5-10m each participant follows a line, but after each collective step an object is "transported" (e.g. thrown).		
Progression: BOS, DOM	Progression: Movement	Progression: Tools
Narrow gait	High knees	Number of tools to be thrown
Tandem gait	Lunges	Kind of objects (small sacks, balls, …)
forwards, backwards		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: Upper body & head turns (horizontal)	
Cognitive add-on	-	

"Commander"		**DB**
Pairs of two: one participant has to react to the commands of the other. Commands are different combinations of a step and simultaneous catch.		
Progression: Movement	Progression: Starting position	Progression: Number of commands
Tasks for one side of body	On the floor	2 to 8
Tasks for both sides of body (e.g. step left, catch right)	On the floor but inside a hoop	
	On unstable support surface	
	180° turn before step and catch	
Sensory modification	Visual: closed eyes (starting position)	
	Somatosensory: Various unstable support surfaces (starting position)	
	Vestibular: 180° turns before catch	
Cognitive add-on (main focus)	Memory: Recall pairs (movement+number / movement+color word / movement+number or color word)	
	Inhibition: command = stay in place	
	Reaction: commander minimizes time to react	

"Movement memory"		**DB**
Participants move through the gym while performing gait variations coded with various commands given by therapist.		
Progression: Movement	Progression: Number of pairs	
Tasks for one side of body	4 to 8	
Tasks for both sides of body (e.g. left knee up & right hand to left shoulder)		
Similarity of movements		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: Recall pairs (movement+number / movement+color word / movement+number or color word)	
	Inhibition: command = stop	

"Remote control"		**DB**
Pairs of two: a participant is steered through the room with closed eyes via tactile cues of the partner.		
Progression: number of cues	Progression: movement	
3 to 6	Tandem walk, high knees	
Sensory modification	Visual: closed eyes	
	Somatosensory: -	
	Vestibular: turning in place	
Cognitive add-on	Spatial orientation: report location in space to partner (closed eyes)	

Walking with tasks			**AG**
Each participant performs various tasks (e.g. touch opposite knee while throwing an object left to right) while walking back and forth on a 20m lane.			
Progression: DOM, speed	Progression: movement	Progression: tools	
Forwards, backwards, sidewards	Tasks for one side of body	Kind of objects (small sacks, balls, …)	
walking, jogging	Tasks for both sides of body (e.g. left knee, right hand)		
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: Head turns (horizontal)		
Cognitive add-on	-		

Agility ladder			**AG**
Participants perform exercises in an agility ladder on the floor. Number and type of foot contacts in each field are varied.			
Progression: DOM, speed	Progression: complexity	Progression: tools	
Forwards, backwards, sidewards	Easier sequences (2 / 3 touches)	Kind of objects (small sacks, balls, …)	
	Harder sequences (1,2,3,2,1 / 2 forwards 1 back / 2 in 1 out)		
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: Head turns		
Cognitive add-on	Divided attention: Participants have to call numbers shown by therapist		
	Divided attention: Participants have to catch objects thrown by therapist		

Cone tipping		**AG**
Pairs of two: one participant starts surrounded by an assemble of cones. The partner outside of the cones says which cones have to be touched.		
Progression: speed, duration	Progression: number of cones	
Walking, jogging	4 to 8	
1 round = 30s		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	Spatial orientation & memory: directions are given by numbers, colors or alphabet	

Slalom			**AG**
Participants move through a slalom parcour.			
Progression: speed, duration	Progression: number of obstacles	Progression: competition	
Walking, jogging	4 to 8	Hit a target with an object at the end of slalom	
1 round = 60-90s			
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: -		
Cognitive add-on	-		

Soccer			**AG**
Participants move and pass a ball.			
Progression: speed, duration	Progression: number of players	Progression: change of direction	
Walking, jogging	1 to 4	Front - back	
1 round = 60-90s		Front - back and sideways	
		Random	
Sensory modification	Visual: -		
	Somatosensory: -		
	Vestibular: -		
Cognitive add-on	Attention: participants have to react to stop and change of direction signals by therapist		

"Suicide runs"		**AG**
The length of the gym is split into 3 sections. Participants cover each section in different speeds, accelerating and decelerating		
Progression: speed, duration	Progression: Stops at end of section	Progression: competition
Walking, jogging 1 round = 45-90s	touch a cone circle a cone stop - 2 steps back - accelerate forwards	Hit a target with an object at the end
Sensory modification	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on	-	

2. Water-based MAT

Standing balance		**SB**
Participants perform various exercises while standing in the pool.		
Progression: BOS	Progression: free leg	Progression: hands
Narrow BOS Semi-tandem stance Tandem stance One leg stance (+movements of free leg)	Floor "touches" Leg swings Number, amplitude, direction of swings	Inside water Outside water
Sensory modification	Visual: closed eyes Somatosensory: standing on kickboard Vestibular: head turns (horizontal, vertical)	
Cognitive add-on	-	

Gait and jump variations		**DB**
Participants perform gait and jump variations in a lane.		
Progression: BOS, DOM	Progression: movement	Progression: hands
Narrow gait Tandem gait Forwards, backwards, sidewards	High knees Lunges Hot steps, skipping gait Single-leg, two-legged jumps, hold landing position 3s jumping jack	Inside water Outside water
Sensory modification	Visual: closed eyes Somatosensory: walking with feet on 1-2 kickboard(s) Vestibular: head turns (horizontal, vertical, diagonal)	
Cognitive add-on	Memory: 4 variations of jumping jack	

"Movement memory"		**DB**
Participants move through the water while performing gait variations coded with various commands given by therapist.		
Progression: movement	Progression: number of pairs	
Only legs/only arms Combination of arms + legs, one-side of body Combination of arms + legs, both sides of body Similarity of movements	4 to 8	
Sensory modification	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on (main focus)	Memory: recall pairs (movement+number / movement+color word / movement+number or color word) Inhibition: command = stop	

"Commander"		**DB**
Pairs of two. One participant must respond to the commands of the partner. The commands consist of different combinations of a catch and step.		
Progression: movement	Progression: starting position	Progression: number of commands
Catch/step = same side of body Catch/step = diagonal	Floor standing on kickboard 180° turns before catching	2 to 8
Sensory modifications	Visual: starting position with closed eyes Somatosensory: kickboard (starting position) Vestibular: 180° turns (starting position)	
Cognitive add-on (main focus)	Memory: recall pairs (movement + number / movement + color / movement + number or color) Inhibition: command = stop Reaction: reduce response time	

"Circuit Training"		**DB**
Participants complete a circuit as pairs, consisting of various functional leg strength exercises.		
Progression: duration, speed		
45-60s per exercise, 2-3 rounds, 3-4 exercises per round Exercises include: running, swimming, jumping, step-ups		
Sensory modifications	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on	-	

"Chaosball"		**SB/AG**
Participants stand in a circle and throw a ball to each other in a certain order. Various attributes of other participants must be rememberd in the process.		
Progression: number of orders / objects		
1 order (= 1 object)		
Change: 2 orders (= 2 objects)		
Simultaneously: 2 orders (= 2 objects)		
Simultaneously: 3 orders (= 3 objects)		
Sensory modifications	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on (main focus)	Memory: recall orders	
	Divided attention: more than one object	
	Spatial orientation: comply with order, while participants no longer stand in a circle, but walk/run around in the pool	

"Waiter"		**AG**
Participants balance a ball on a kickboard and simultaneously perfom different exercises.		
Progression: DOM, speed	Progression: movement	
Walk, jog	Balance ball, throw & catch ball	
Forwards, backwards, turns	Change hands on kickboard	
	Throw & catch ball while changing hands	
Sensory modification	Visual: Move eyes away from ball	
	Somatosensory: -	
	Vestibular: throw & catch with 180°/360° turns	
Cognitive add-on (main focus)	Dual-task: walk/jog & balance ball & react to commands from therapist	
	Divided attention: balance ball while commands given by therapist include hand signs	
	Memory: commands from therapist are given via numbers or via a mix of numbers, hand signs, and/or clapping	
	Processing speed: react as fast as possible to commands given by therapist	

"Compass"		**AG**
Participants move in the directions given by therapist.		
Progression: speed, duration	Progression: number of directions	
Walking, jogging	4 to 8 (front, back, side, diagonal)	
1 round = 45-60s		
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	Memory: recall pairs (direction+number / direction+color word)	
	Inhibition: therapist gives false cues	
	Processing speed: react as fast as possible to commands	

"Mirror"		**AG**
Pairs of two. One participant leads, the other follows while always keeping the same distance.		
Progression: speed, duration	Progression: fakes	
Walking, jogging, competition (shake off)	Leader fakes change of direction	
45-60sec.	Leader changes speeds	
Sensory modification	Visual: -	
	Somatosensory: -	
	Vestibular: -	
Cognitive add-on	-	

"Beachball"		**AG**
Participants play with a beachball.		
Progression: number of players		
2 to whole group		
Sensory modification	Visual: -	
	Somatosensory: standing on kickboard	
	Vestibular: -	
Cognitive add-on	-	

MAT = multimodal agility-based exercise training; BOS = Base of support; DOM = Direction of movement

Components

- SB = Standing balance
- DB = Dynamic balance & functional leg strength
- AG = Agility

Each bracket represents a module. Each module targets one of the three components.

1. Callesen J, Cattaneo D, Brincks J, et al. How do resistance training and balance and motor control training affect gait performance and fatigue impact in people with multiple sclerosis? A randomized controlled multi-center study. *Mult Scler* 2020;26(11):1420-32. doi: 10.1177/1352458519865740 [published Online First: 20190724]

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	25
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1;25
	5b	Name and contact information for the trial sponsor	25
	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	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)	n/a

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	3-6
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5-6
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)	6;8-9
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
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)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	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)	11-13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16-17
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-11
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	14-21
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)	7-9

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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
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	8-9
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	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
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	14-21
	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	15-17

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	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	21-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	n/a
	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)	n/a
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	n/a
	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	n/a
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	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23
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)	22-23

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
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	23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	25-26
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	23
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	n/a
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	23
	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	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement
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	n/a

*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.