

BMJ Open Randomised 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

Florian Wolf ^{1,2}, Jörn Nielsen,^{1,3} Jochen Saliger,¹ Eva Hennecken,¹ Mareike Eschweiler,^{1,4} Ann-Kristin Folkerts,³ Hans Karbe,¹ Philipp Zimmer⁵

To cite: Wolf F, Nielsen J, Saliger J, *et al.* Randomised 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. *BMJ Open* 2022;**12**:e062160. doi:10.1136/bmjopen-2022-062160

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-062160>).

FW and JN are joint first authors.

Received 23 February 2022

Accepted 14 August 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Florian Wolf;
f.wolf@godshoehe.de

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 randomised controlled trial comparing MAT against strength and endurance training (SET) for the improvement of MS-related fatigue and fatigability in a German neurological rehabilitation centre.

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 4–6 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 number DRKS00023943.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Comprehensive assessment of subjective fatigue, as well as objective cognitive and motor fatigability.
- ⇒ First application of agility-based exercise training to persons with multiple sclerosis.
- ⇒ Mixed-methods approach to acquire patient perspective and acceptance.
- ⇒ Clinical inpatient setting will challenge standardisation 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 symptoms³ 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 *et al.*⁷ two concepts must be separated when considering fatigue: (1) the subjective experience of fatigue and (2) 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 (eg, central nervous system, immunological or endocrine changes) and ‘secondary fatigue’ resulting from mechanisms not directly related to the disease (eg, 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 prescreened 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 *et al*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 standardised, 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 (eg, strength and endurance training (SET)). Lastly, types of exercise consisting primarily of stimuli targeting motor control (eg, 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 *et al*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 *et al*.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 characterised as ‘multi-modal 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 *et al*,¹⁰ we hypothesise 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 hypothesised by Moss-Morris *et al*¹¹ and Callesen *et al*^{18–21}). Based on the existing evidence, we expect greater benefits on secondary fatigue parameters from MAT than for SET. Regarding performance fatigability, we hypothesise, 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 Centre (NRC) ‘Godeshoehe’ (Bonn; certified MS Rehabilitation Centre). It will have a two-armed, parallel-group, randomised-controlled design with 12 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 specialised 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

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

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

Timepoint	Study period						
	Enrolment	Allocation	Post-allocation				
	-T ₀	0	T ₀	T ₁	T ₂	T ₃	T ₄
Enrolment:							
Eligibility screen	X						
Informed consent	X						
Stratified randomisation		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		

0, after written informed consent; ABC, Activities-Specific Balance Confidence Scale; CES-D, Centre for Epidemiological Studies Depression Scale (German version); CVLT, California Verbal Learning Test; FGA, Functional Gait Assessment; FSMC, Fatigue Scale for Motor and Cognitive Functions; GXT, Graded Exercise Test; MAT, Multimodal Agility-based exercise Training; 6MWT, 6 min Walk Test; SDMT, Symbol Digit Modalities Test; SET, Strength and Endurance Training; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SSST, Six Spot Step Test; -T₀, admission; T₀, postrandomisation; T₁, prior to discharge; T₂, 1–2 weeks after discharge; T₃, 4 weeks after discharge; T₄, 12 weeks after discharge; TAP-Alert, Test Battery of Attention Performance – Alertness; T25FW, Timed 25-foot Walk Test; WEIMuS, Würzburg Fatigue Inventory for Multiple Sclerosis.

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 and EH), verbally and in written form.

Randomisation

If patients provide the written informed consent to one of the study staff members within a maximum of 3 days, they will be randomly allocated (1:1) to the intervention or control group according to the minimisation procedure²³ 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). Randomisation will be provided by an independent researcher from the German Sport University Cologne using ‘Randomisation-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 the 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

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 neurological 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	
EDSS, Expanded Disability Status Scale; FSMC, Fatigue Scale for Motor and Cognitive Functions; MS, multiple sclerosis; RR, relapsing-remitting; SP, secondary-progressive.	

home. Consequently, we plan with 80% retention from T_0 to T_2 . This will result in a feasibility period of about six to 8 months. Retention rates will be used to inform the sample size calculation for the full randomised controlled trial (RCT).

Participants

PwMS will be eligible to participate in this trial according to the inclusion and exclusion criteria stated in [table 2](#).

Interventions

The intervention period includes the time from admission to discharge, which usually comprises 4–6 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:

- ▶ Distinct differences in the amount of therapy targeting cognitive and sensory integration.
- ▶ Standardisation of treatment as strictly as possible within this specific clinical setting.
- ▶ 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 for Therapeutic Exercise Interventions.²⁸

Standard treatment for both groups

Both groups will attend the ‘MS group’, a specific group for all pwMS, focusing on body awareness and relaxation

Table 3 Frequency, time and type of intervention components

MAT (intervention)	SET (control)
5x/wk, 30 min, ‘MS group’	
5x/wk, 30 min, land-based MAT	5x/wk, 22 min, endurance training
3x/wk, 30 min, water-based MAT	3x/wk, 30 min, strength training
MAT, multimodal agility-based exercise training; SET, strength and endurance training.	

techniques. It consists of maximum eight pwMS, lasts 30 min 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 maximise standardisation.

Strength and endurance training

The combined SET programme 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 online supplemental file (Strength Protocol)).

Endurance training will be performed according to the standard protocol in this clinic, with 22 min per session (3 min of gradual increase, 17 min steady and 2 min cool-down) on a cycle ergometer (ergoselect 5, ergoline, Bitz, Germany) with continuous monitoring of power output and heart rate (ers.2 software, ergoline, Bitz, Germany). Endurance training will be performed in groups of maximum 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 11–13 was chosen based on recent evidence-based recommendations for pwMS with similar EDSS.²⁹

Resistance training will be adapted from Callesen *et al*.¹⁸ to fit the inpatient setting. Each session will start with a 5 min warm-up on an elliptical trainer, treadmill or recumbent stepper, followed by 3–4 exercises targeting hip, knee, and ankle flexion and extension, as well as hip abduction. Exercises will be progressed as follows:

- ▶ Session 1–5: 3×10 repetitions with the 15 repetitions maximum (RM).
- ▶ Session 6– T_1 (T_1 will be around session 10–16): 3×12 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 individualisation but will be instructed to follow prespecified exercises (see online supplemental file (Strength Protocol)).

Multimodal agility-based exercise training

For the treatment manual see online supplemental file (MAT-Manual). All sessions will be guided by maximum 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 (ie, water and land) will be installed within existing group therapies. Each group will consist of maximum eight participants. Empty spots will be filled with other patients from the NRC. The intervention programme 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 setup, that can be progressed in terms of difficulty. Additionally, modifications on a cognitive (eg, memory, attention, inhibition) and sensory (ie, visual, somatosensory, vestibular) level are described. As stated by Callesen *et al*,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 (ie, agility-like components and functional leg strength) interspersed with two sessions with lower physical strain (ie, 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 organisational 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 analysing the questionnaires will not be possible.

Outcomes

As depicted in table 1, assessments will be carried out at admission (ie, preintervention, T₀) and discharge (ie, postintervention, T₁), as well as after participants have returned home (ie, follow-up, T₂-T₄).

Baseline sample characteristics

Demographic data on age and sex will be taken from electronic records. Height will be self-reported from participants. Bodyweight at T₀ 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/m²).

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 *et al*³¹ and promoted for exercise studies in MS by Learmonth and Motl³² (see table 4).

Feasibility (qualitative)

The qualitative evaluation aims to (1) capture patients' views on acceptance, benefits, and satisfaction with study participation, (2) assess their experiences with the intervention methods and (3) identify necessary adaptations. For this purpose, we designed a semistructured interview. Six participants from each study arm will be interviewed face-to-face at T₁. The selection of participants will reflect the greatest possible diversity in terms of gender, age and EDSS.³³ The interview will include a total of 14 questions and will last approximately 20 min. Key topics 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 and 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 customised 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

Table 4 Description of quantitative feasibility outcomes (adapted from Hubbard *et al*⁵⁷)

Classification	Outcome	Operationalisation	Importance for future RCT
Process	1. Eligibility rate	<ul style="list-style-type: none"> ▶ No/rate of patients being eligible ▶ No/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	<ul style="list-style-type: none"> ▶ No of patients successfully randomised per month 	Evaluates whether the no of participants randomised is high enough to allow for a time-efficient execution
	3. Refusal rate	<ul style="list-style-type: none"> ▶ No/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	<ul style="list-style-type: none"> ▶ No/rate of patients completing the intervention period ▶ No/rate of patients returning the WEIMuS at T₂ 	Provides information on the risk of subjects dropping out during the intervention period, which might necessitate adaptations to the interventions or the organisation of the study. Gives information on the feasibility of the primary outcome being assessed postdischarge and via an online platform.
	5. Adherence	<ul style="list-style-type: none"> ▶ No 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	<ul style="list-style-type: none"> ▶ SET: training protocols will be reviewed to ensure that communicated principles were followed: (1) no of exercises performed each session, (2) total training load prescribed relative to actual training load per exercise (eg, target: 3 (sets) × 10 (repetitions) × 20 (weight)=600, moved: 3×10×15 = 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. ▶ 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 (standing balance, dynamic balance and functional leg strength, agility like) to get an approximate distribution. 	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.
Resources	Time	<ul style="list-style-type: none"> ▶ No of days needed to complete baseline assessments ▶ Time requirements for (1) the first (T25FW, SSST, FGA, 6MWT) and second (GXT) physical testing blocks at T₀ and T₁, (2) 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	<ul style="list-style-type: none"> ▶ No of missing items for FSMC and WEIMuS for all measurement time points ▶ No of missing outcomes for T₀ and T₁ 	Provides information on actions to take to ensure questionnaires will be fully completed and all assessments taken.
Scientific	1. Adverse events	<ul style="list-style-type: none"> ▶ No and kind of adverse events related to study interventions 	Establishes the safety of all interventions.
	2. Acceptability	<ul style="list-style-type: none"> ▶ Perceived exertion: Session-RPE after each endurance, strength, and MAT session (Category Ratio (CR-10) RPE scale as developed by Foster <i>et al.</i>^{58 59} 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 T₁ by using customised questions with a four-point Likert-type scale ranging from 'not at all' to 'very much'.⁶⁰ 	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.

FGA, Functional Gait Assessment; FSMC, Fatigue Scale for Motor and Cognitive Functions; GXT, Graded Exercise Test; MAT, Multimodal Agility-based exercise Training; 6MWT, 6 min Walk Test; RCT, randomised controlled trial; RPE, Rated Perceived Exertion; SET, Strength and Endurance Training; SSST, Six Spot Step Test; T₀, postrandomisation; T₁, prior to discharge; T₂, 1–2 weeks after discharge; T25FW, Timed 25-foot Walk Test; WEIMuS, Würzburg Fatigue Inventory for Multiple Sclerosis.

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 time frame.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 4 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 WEIMuS³⁴ as the primary outcome measure to assess the fatigue experienced during the past week and (II) established the primary endpoint to be 1–2 weeks after participants have returned home (T₂). 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.³⁵ 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 35}

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 email request within 7 days.

Secondary outcomes for the full RCT

MS-fatigue is a multifactorial construct that requires assessment of other inter-related constructs.⁷ This will include measures of cognitive (Test Battery of Attention Performance -Alertness³⁶) and motor fatigability (6min Walk Test, Distance Walked Index³⁷), cognitive performance (California Verbal Learning Test, Symbol Digit Modalities Test^{26 38}) and CRF (GXT on a cycle ergometer, protocol: start 25W, progression 10W/min). Dynamic balance and motor function (Timed 25-Foot Walk Test,³⁹ Six Spot Step Test (SSST),⁴⁰ Functional Gait Assessment (FGA)⁴¹) will also be assessed as well as self-reported balance confidence (Activities-specific Balance Confidence scale⁴²). Depression (Centre for Epidemiological Studies Depression Scale (German version)⁴³) 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.⁴⁴ Thus, the relevant change score (≥ 6 or ≤ -6) was chosen as a pragmatic value of 0.5 SD from the validation study.⁴⁵ A similar procedure has been described by Sander *et al.*¹

Data analysis

Quantitative data analysis

Descriptive statistics will be used to summarise 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 SD for continuous data, median and IQR, 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-group or between-group treatment effects will not be performed due to the inherent problems of hypothesis testing based on (small) pilot study data.^{46 47} 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.⁴⁸

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 subthemes.⁴⁹ Deductive coding will be based on preliminary considerations and hypotheses in the study planning and on reviews of relevant literature.^{33 50–53} Coding will be carried out by at least two individuals (JN and FW) to ensure intercoder reliability.⁵⁴ The analysis will be supported by MAXQDA software in the most up-to-date version.⁵⁵ 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 6×30 min sessions per week for 3 weeks (28 days admission to discharge minus 5 days for pretesting 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 3 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 with 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 (1) translate existing evidence on BMCT in pwMS to this setting, (2) add to this BMCT by introducing the framework of MAT and (3) apply a clear focus on fatigue as the primary outcome. Specifically, we see the potential of a relatively large training volume (eg, about eight therapy sessions per week) compared with 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 (ie, 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 (eg, ward rounds, urology assessments). Regarding the eligibility and randomisation criteria, it will be challenging to have all the correct data within the first 2 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 healthcare system (ie, 4–6 weeks). Land-based 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.⁵⁶ Still, water-based MAT was developed to allow for a greater amount of standardised 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-based 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 affiliations

¹Neurological Rehabilitation Centre Godeshoehe, Bonn, Germany

²Department of Molecular and Cellular Sports Medicine, Institute of Cardiovascular Research and Sports Medicine, German Sport University Cologne, Cologne, Germany

³Department of Medical Psychology, Neuropsychology and Gender Studies, Center for Neuropsychological Diagnostics and Intervention (CeNDI), Faculty of Medicine and University Hospital Cologne, University Cologne, Cologne, Germany

⁴Department of Epidemiology, CAPHRI Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands

⁵Division of Performance and Health (Sports Medicine), Institute for Sport and Sport Science, TU Dortmund University, Dortmund, Germany

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

Funding This work is supported by the Internal Research Funds of the German Sport University Cologne, Cologne, Germany, grant agreement number L-11-10011-238-102000.

Competing interests FW: none. JN: none. JS: none. EH: none. ME: none. A-KF has received grants from the German Parkinson Society and the German Alzheimer's Society, as well as honoraria from ProLog Wissen, Cologne, Germany, pro audit Switzerland, Zürich, Switzerland, Seminar- und Fortbildungszentrum Rheine, Germany, and LOGOMANIA, Fendt & Sax GbR, Munich, Germany. A-KF is author of the cognitive training programme NEUROvitalis but receives no corresponding honoraria. HK: none. PZ: none.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Florian Wolf <http://orcid.org/0000-0003-0777-866X>

REFERENCES

- 1 Sander C, Voelter H-U, Schlake H-P, et al. Assessment of fatigue in multiple sclerosis. *Neurology International Open* 2017;1:E79–85.
- 2 Rommer PS, Eichstädt K, Ellenberger D, et al. Symptomatology and symptomatic treatment in multiple sclerosis: results from a nationwide MS registry. *Mult Scler* 2019;25:1641–52.
- 3 Barin L, Salmen A, Disanto G, et al. The disease burden of multiple sclerosis from the individual and population perspective: which symptoms matter most? *Mult Scler Relat Disord* 2018;25:112–21.
- 4 Kobelt G, Langdon D, Jönsson L. The effect of self-assessed fatigue and subjective cognitive impairment on work capacity: the case of multiple sclerosis. *Mult Scler* 2019;25:740–9.
- 5 Nielsen J, Schnell R, Markett S. Are “invisible MS symptoms” (fatigue, cognitive dysfunction, depression) significant in the professional performance assessment of multiple sclerosis patients two years after the inpatient primary evaluation? *Zeitschrift für Neuropsychologie* 2020;31:11–25.
- 6 Manjaly Z-M, Harrison NA, Critchley HD, et al. Pathophysiological and cognitive mechanisms of fatigue in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2019;90:642–51.
- 7 Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology* 2013;80:409–16.
- 8 Behrens M, Broscheid K-C, Schega L. Taxonomie und Determinanten motorischer Performance Fatigability bei Multipler Sklerose [Taxonomy and determinants of motor performance fatigability in multiple sclerosis]. *Neurologie und Rehabilitation* 2021;27:3–12.
- 9 Loy BD, Taylor RL, Fling BW, et al. Relationship between perceived fatigue and performance fatigability in people with multiple sclerosis: a systematic review and meta-analysis. *J Psychosom Res* 2017;100:1–7.
- 10 Langeskov-Christensen M, Bisson EJ, Finlayson ML, et al. Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: a scoping review. *J Neurol Sci* 2017;373:307–20.
- 11 Moss-Morris R, Harrison AM, Safari R, et al. Which behavioural and exercise interventions targeting fatigue show the most promise in multiple sclerosis? A systematic review with narrative synthesis and meta-analysis. *Behav Res Ther* 2021;137:103464.
- 12 Motl RW, Sandroff BM, Kwakkel G, et al. Exercise in patients with multiple sclerosis. *Lancet Neurol* 2017;16:848–56.
- 13 Wolf F, Rademacher A, Joisten N, et al. The aerobic capacity - fatigue relationship in persons with Multiple Sclerosis is not reproducible in a pooled analysis of two randomized controlled trials. *Mult Scler Relat Disord* 2022;58:103476.
- 14 Tholen R, Dettmers C, Henze T. Bewegungstherapie zur Verbesserung der Mobilität von Patienten mit Multipler Sklerose : Konsensusfassung für die S2e-Leitlinie der DGNR in Zusammenarbeit mit Physio Deutschland – Deutscher Verband für Physiotherapie (ZVK) e.V.. *Neurologie und Rehabilitation* 2019;25:3–40.
- 15 Donath L, van Dieën J, Faude O. Exercise-Based fall prevention in the elderly: what about Agility? *Sports Med* 2016;46:143–9.
- 16 Morat M, Morat T, Zijlstra W, et al. Effects of multimodal agility-like exercise training compared to inactive controls and alternative training on physical performance in older adults: a systematic review and meta-analysis. *Eur Rev Aging Phys Act* 2021;18:4.
- 17 Motl RW, Sandroff BM, DeLuca J. Exercise training and cognitive rehabilitation: a symbiotic approach for rehabilitating walking and cognitive functions in multiple sclerosis? *Neurorehabil Neural Repair* 2016;30:499–511.
- 18 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;26:1420–32.
- 19 Hebert JR, Corboy JR. The association between multiple sclerosis-related fatigue and balance as a function of central sensory integration. *Gait Posture* 2013;38:37–42.
- 20 Hebert JR, Corboy JR, Manago MM, et al. Effects of vestibular rehabilitation on multiple sclerosis-related fatigue and upright postural control: a randomized controlled trial. *Phys Ther* 2011;91:1166–83.
- 21 Hebert JR, Corboy JR, Vollmer T, et al. Efficacy of balance and eye-movement exercises for persons with multiple sclerosis (BEEMS). *Neurology* 2018;90:e797–807.
- 22 Wright MT. Was IST Partizipative Gesundheitsforschung? *Prävention und Gesundheitsförderung* 2013;8:122–31.
- 23 Scott NW, McPherson GC, Ramsay CR, et al. The method of minimization for allocation to clinical trials. A review. *Control Clin Trials* 2002;23:662–74.
- 24 Charlesworth G, Burnell K, Hoe J, et al. Acceptance checklist for clinical effectiveness pilot trials: a systematic approach. *BMC Med Res Methodol* 2013;13:78.
- 25 Ladlow P, Coppack RJ, Dharm-Datta S, et al. The effects of low-intensity blood flow restricted exercise compared with conventional resistance training on the clinical outcomes of active UK military personnel following a 3-week in-patient rehabilitation programme: protocol for a randomized controlled feasibility study. *Pilot Feasibility Stud* 2017;3:71.
- 26 Zimmer P, Bloch W, Schenk A, et al. High-Intensity interval exercise improves cognitive performance and reduces matrix metalloproteinases-2 serum levels in persons with multiple sclerosis: a randomized controlled trial. *Mult Scler* 2018;24:1635–44.
- 27 Voigt-Radloff S, Stemmer R, Korporal J. Forschung zu komplexen Interventionen in Der Pflege- und Hebammenwissenschaft und in den Wissenschaften Der Physiotherapie, Ergotherapie und Logopädie: ein forschungsmethodischer Leitfaden Zur Ermittlung, evaluation und implementation evidenzbasierter Innovationen. *Version* 2016;2.
- 28 Page P, Hoogenboom B, Voight M. Improving the reporting of therapeutic exercise interventions in rehabilitation research. *Int J Sports Phys Ther* 2017;12:297–304.
- 29 Kalb R, Brown TR, Coote S, et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Mult Scler* 2020;26:1459–69.
- 30 Nielsen JB, Willerslev-Olsen M, Christiansen L, et al. Science-Based neurorehabilitation: recommendations for neurorehabilitation from basic science. *J Mot Behav* 2015;47:7–17.
- 31 Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010;10:1.
- 32 Learmonth YC, Motl RW. Important considerations for feasibility studies in physical activity research involving persons with multiple sclerosis: a scoping systematic review and case study. *Pilot Feasibility Stud* 2018;4:1.
- 33 Hersche R, Weise A, Michel G, et al. Three-week inpatient energy management education (IEME) for persons with multiple sclerosis-related fatigue: feasibility of a randomized clinical trial. *Mult Scler Relat Disord* 2019;35:26–33.
- 34 Flachenecker P, Müller G, König H, et al. [“Fatigue” in multiple sclerosis. Development and validation of the “Würzburger Fatigue Inventory for MS”]. *Nervenarzt* 2006;77:165–6, 168–70, 172–4.
- 35 Penner IK, Raselli C, Stöcklin M, et al. The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult Scler* 2009;15:1509–17.
- 36 Dettmers C, Marchione S, Weimer-Jaekel A, et al. Cognitive fatigability, not fatigue predicts employment status in patients with MS three months after rehabilitation. *Mult Scler Relat Disord* 2021;56:103215.
- 37 Van Geel F, Veldkamp R, Severijns D, et al. Day-To-Day reliability, agreement and discriminative validity of measuring walking-related performance fatigability in persons with multiple sclerosis. *Mult Scler* 2020;26:1785–9.
- 38 Costa SL, Genova HM, DeLuca J, et al. Information processing speed in multiple sclerosis: past, present, and future. *Mult Scler* 2017;23:772–89.
- 39 Motl RW, Cohen JA, Benedict R, et al. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. *Mult Scler* 2017;23:704–10.
- 40 Nieuwenhuis MM, Van Tongeren H, Sørensen PS, et al. The six spot step test: a new measurement for walking ability in multiple sclerosis. *Mult Scler* 2006;12:495–500.
- 41 Thieme H, Ritschel C, Zange C. Functional gait assessment – Deutsche version. *Physioscience* 2009;5:5–11.
- 42 Schott N. [German adaptation of the “Activities-Specific Balance Confidence (ABC) scale” for the assessment of falls-related self-efficacy]. *J Gerontol Geriatr* 2008;41:475–85.

- 43 Hautzinger M, Bailer M. *Allgemeine Depressions Skala. Die Deutsche Version des CES-D*. Weinheim: Beltz, 1993.
- 44 Flachenecker P, Bures AK, Gawlik A, et al. Efficacy of an Internet-based program to promote physical activity and exercise after inpatient rehabilitation in persons with multiple sclerosis: a randomized, single-blind, controlled study. *Int J Environ Res Public Health* 2020;17. doi:10.3390/ijerph17124544. [Epub ahead of print: 24 06 2020].
- 45 Flachenecker P, König H, Meissner H. Fatigue in multiple sclerosis: Validation of the WEIMuS scale ("Würzburger Erschöpfungs-Inventar bei Multipler Sklerose"). *Neurologie und Rehabilitation* 2008;14:299–306.
- 46 Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res* 2011;45:626–9.
- 47 Sim J. Should treatment effects be estimated in pilot and feasibility studies? *Pilot Feasibility Stud* 2019;5.
- 48 Kistin C, Silverstein M. Pilot studies: a critical but potentially misused component of interventional research. *JAMA* 2015;314:1561–2.
- 49 Kuckartz U. *Qualitative Inhaltsanalyse. Methoden, Praxis, Computerunterstützung*. Weinheim: Beltz Verlagsgruppe, 2018.
- 50 Gunn H, Andrade J, Paul L, et al. Balance right in multiple sclerosis (BRIMS): a guided self-management programme to reduce falls and improve quality of life, balance and mobility in people with secondary progressive multiple sclerosis: a protocol for a feasibility randomised controlled trial. *Pilot Feasibility Stud* 2018;4:26.
- 51 Learmonth YC, Kinnett-Hopkins D, Motl RW. Capitalising on the opinions of persons with multiple sclerosis to inform the main trial - participant opinions from participation in a feasibility study, a qualitative extension study. *Disabil Rehabil* 2019;41:3071–8.
- 52 O'Cathain A, Hoddinott P, Lewin S, et al. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. *Pilot Feasibility Stud* 2015;1:32.
- 53 Smith M, Williams G, Barker R. Finding the right balance with participation in exercise and sport for individuals with multiple sclerosis: protocol for a pre and post intervention feasibility study. *BMJ Open* 2020;10:e035378.
- 54 Flick U. *Qualitative Sozialforschung: eine Einführung*. 6. Auflage. Reinbek bei Hamburg: Rowohlt Taschenbuch Verlag, 2014.
- 55 Rädiker S, Kuckartz U. *Analyse qualitativer Daten mit MAXQDA: Text, Audio und Video*. Wiesbaden: Springer VS, 2019.
- 56 Frohman AN, Okuda DT, Beh S, et al. Aquatic training in MS: neurotherapeutic impact upon quality of life. *Ann Clin Transl Neurol* 2015;2:864–72.
- 57 Hubbard EA, Motl RW, Elmer DJ. Feasibility and initial efficacy of a high-intensity interval training program using adaptive equipment in persons with multiple sclerosis who have walking disability: study protocol for a single-group, feasibility trial. *Trials* 2020;21:972.
- 58 Foster C, Florhaug JA, Franklin J, et al. A new approach to monitoring exercise training. *J Strength Cond Res* 2001;15:109–15.
- 59 Haddad M, Stylianides G, Djaoui L, et al. Session-RPE method for training load monitoring: validity, ecological usefulness, and influencing factors. *Front Neurosci* 2017;11:612.
- 60 Gooßes M, Saliger J, Folkerts A-K, et al. Feasibility of Music-Assisted Treadmill Training in Parkinson's Disease Patients With and Without Deep Brain Stimulation: Insights From an Ongoing Pilot Randomized Controlled Trial. *Front Neurol* 2020;11.

ReFEx Strength Protocol

Principles:	Intensity:	
<ul style="list-style-type: none">• Frequency: 3x/week• Focus on leg strength/no balance training• 5min warm-up, 3-4 exercises/session	<ul style="list-style-type: none">• Session 1-5: 3x10 repetitions at 15 RPM• Session 6 to T₁: 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):		
<ul style="list-style-type: none">• 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) <ul style="list-style-type: none">• Start: hip angle as small as possible	b) Flexion Standing knee raises (cable) <ul style="list-style-type: none">• With balance support (chair)	c) Abduction Standing abduction (cable) <ul style="list-style-type: none">• With balance support
2 knee		
a) Extension Leg press (supine)	b) Flexion Prone leg curls (cable) <ul style="list-style-type: none">• End: >90° flexion	
3 foot		
a) Plantar flexion Calf raises on leg press <ul style="list-style-type: none">• Large ankle ROM		

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

Manual for the land-based and water-based MAT (adapted from¹)

1. Land-based MAT

Standing balance			SB
<i>Participants perform various exercises while standing.</i>			
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
<i>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.</i>			
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
<i>Participants follow the lines on the gym floor.</i>			
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
<i>Participants perform various forms of steps.</i>			
Progression: DOM	Progression: Movement	Progression: Tools	
Forwards, backwards, sideways	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
<i>Over 5-10m each participant follows a line, but after each collective step an object is "transported" (e.g. thrown).</i>			
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
<i>Pairs of two: one participant has to react to the commands of the other. Commands are different combinations of a step and simultaneous catch.</i>			
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, sideways	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, sideways	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 parcours.			
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
<i>The length of the gym is split into 3 sections. Participants cover each section in different speeds, accelerating and decelerating</i>			
Progression: speed, duration	Progression: Stops at end of section	Progression: competition	
Walking, jogging	touch a cone	Hit a target with an object at the end	
1 round = 45-90s	circle a cone		
	stop - 2 steps back - accelerate forwards		
Sensory modification	Visual: - Somatosensory: - Vestibular: -		
Cognitive add-on	-		

2. Water-based MAT

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

Gait and jump variations			DB
<i>Participants perform gait and jump variations in a lane.</i>			
Progression: BOS, DOM	Progression: movement	Progression: hands	
Narrow gait	High knees	Inside water	
Tandem gait	Lunges	Outside water	
Forwards, backwards, sideways	Hot steps, skipping gait Single-leg, two-legged jumps, hold landing position 3s jumping jack		
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
<i>Participants move through the water while performing gait variations coded with various commands given by therapist.</i>			
Progression: movement	Progression: number of pairs		
Only legs/only arms	4 to 8		
Combination of arms + legs, one-side of body			
Combination of arms + legs, both sides of body			
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		

"Commander"			DB
<i>Pairs of two. One participant must respond to the commands of the partner. The commands consist of different combinations of a catch and step.</i>			
Progression: movement	Progression: starting position	Progression: number of commands	
Catch/step = same side of body	Floor	2 to 8	
Catch/step = diagonal	standing on kickboard 180° turns before catching		
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
<i>Participants complete a circuit as pairs, consisting of various functional leg strength exercises.</i>			
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
<i>Participants stand in a circle and throw a ball to each other in a certain order. Various attributes of other participants must be remembered in the process.</i>		
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
<i>Participants balance a ball on a kickboard and simultaneously perform different exercises.</i>		
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
<i>Participants move in the directions given by therapist.</i>		
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
<i>Pairs of two. One participant leads, the other follows while always keeping the same distance.</i>		
Progression: speed, duration	Progression: fakes	
Walking, jogging, competition (shake off)	Leader fakes change of direction Leader changes speeds	
45-60sec.		
Sensory modification	Visual: - Somatosensory: - Vestibular: -	
Cognitive add-on	-	

"Beachball"		AG
<i>Participants play with a beachball.</i>		
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]