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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.

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SCHOLARONE™
Manuscripts

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3 1 **A randomized controlled pilot and feasibility study of multimodal agility-based exercise**
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5 2 **training versus strength and endurance training to improve Multiple Sclerosis-related**
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7 3 **fatigue and fatigability during inpatient rehabilitation [ReFEx] – study protocol.**
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12 5 **Akronym: ReFEx (Rehabilitation, Fatigue, and Exercise)**
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3 25 **Trial status:** The first participant has been enrolled on 18 November 2021. At the time of
4
5 26 submission, 9/24 participants have been recruited, 3/24 participants have finished the
6
7 27 intervention period and completed the primary measurement time point one week after the end
8
9 28 of the intervention period.
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15 30 **ABSTRACT**

16
17 31 **Introduction:** Subjective fatigue and objectively assessed fatigability are common symptoms
18
19 32 in persons with Multiple Sclerosis (pwMS). Recent work has suggested a positive effect of
20
21 33 balance and motor control training (BMCT) in reducing fatigue. It is unclear whether this effect
22
23 34 can also be attained during inpatient rehabilitation. This study will evaluate the feasibility of a
24
25 35 randomized controlled trial comparing BMCT with added agility components (i.e., multimodal
26
27 36 agility-based exercise training [MAT]) with strength and endurance training (SET) for the
28
29 37 improvement of MS-related fatigue and fatigability in a German neurologic rehabilitation
30
31 38 center. With the conductance of the ReFEx (Rehabilitation, Fatigue, and Exercise) project we
32
33 39 plan to (I) translate existing evidence on BMCT in pwMS to the setting of inpatient
34
35 40 rehabilitation, (II) introduce the framework of MAT, and (III) apply a clear focus on the
36
37 41 treatment of fatigue as one of the most challenging symptoms in MS.
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42 42 **Methods and analysis:** A total of 24 pwMS (Expanded Disability Status Scale ≤ 5.0 , Fatigue
43
44 43 Scale for Motor and Cognitive Functions ≥ 53) will be randomly assigned to either SET or land-
45
46 44 based and water-based MAT for 4 to 6 weeks during inpatient rehabilitation. Assessments of
47
48 45 subjective fatigue, motor and cognitive fatigability, cognitive and cardiorespiratory
49
50 46 performance, and balance confidence will be performed at admission and discharge. Subjective
51
52 47 fatigue will also be assessed 1, 4, and 12 weeks after discharge. Feasibility outcomes will
53
54 48 include patients' acceptance of study procedures and interventions, recruitment rate, retention
55
56 49 rate, time needed to complete baseline assessments, intervention adherence, and fidelity. A
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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) register². 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}.

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3 75 Data from the MS register also show that only 35% of fatigued pwMS receive any kind of
4
5 76 treatment and among them only 15% receive pharmacological treatment to specifically handle
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7 77 fatigue symptoms². No clear pathomechanisms for fatigue have been defined yet leading to the
8
9 78 consequence of still limited pharmacotherapy options for the treatment of fatigue⁶.
10
11
12 79 According to the established taxonomy by Kluger and colleagues⁷ two concepts must be
13
14 80 separated when considering fatigue: (I) the subjective experience of fatigue and (II) objective
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16 81 performance fatigability during motor or cognitive tasks. Whether improvements in fatigability
17
18 82 also transfer to subjective fatigue is still unclear. Interestingly, the association between the two
19
20 83 constructs seems to be relatively weak^{8 9}.
21
22
23 84 Next to distinguishing between ‘fatigue’ and ‘fatigability’, a further dichotomy exists with
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25 85 ‘primary fatigue’ resulting from pathophysiological processes of the disease itself (e.g., central
26
27 86 nervous system, immunologic or endocrine changes) and ‘secondary fatigue’ resulting from
28
29 87 mechanisms not directly related to the disease (e.g., sleep, depression, medication)¹⁰.
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32 88 To reduce subjective fatigue, exercise interventions have been studied as a non-
33
34 89 pharmacological treatment option. However, several methodological issues exist. As fatigue is
35
36 90 frequently assessed as a secondary outcome variable, subjects are often not pre-screened for
37
38 91 fatigue symptoms at baseline and the intervention is not primarily designed to reduce fatigue¹¹
39
40 92 ¹². Consequently, to date, there are few studies investigating the specific pathophysiological
41
42 93 pathways of primary or secondary fatigue that are altered by exercise¹⁰.
43
44
45 94 In a recent meta-analysis Moss-Morris and colleagues¹¹ performed a detailed review of
46
47 95 exercise intervention studies, that specifically aimed at fatigue reduction. Here, the authors
48
49 96 reported variance in the effects of different types of exercise. For example, endurance exercise
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51 97 has been frequently investigated, as it can be easily standardized, but was reported to have only
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53 98 small effects on fatigue outcomes measured with self-report questionnaires¹³. If combined with
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55 99 other modalities such as resistance exercise, effects might be greater (e.g., strength and
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3 100 endurance training [SET]). Lastly, exercise types primarily consisting of stimuli targeting
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5 101 motor control (e.g., balance and motor control training [BMCT]) were described as
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8 102 promising¹⁴⁻¹⁶.

9
10 103 In the special setting of inpatient rehabilitation, the number of exercise studies for subjective
11
12 104 fatigue reduction is very limited. In their review, Moss-Morris and colleagues¹¹ identified only
13
14 105 one study conducted in an inpatient rehabilitation setting. However, this trial was restricted
15
16 106 from the meta-analysis because of methodological limitations, indicating the need for future
17
18 107 systematic research on fatigue-specific therapy. This is also evident in the first German practice
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20 108 guideline for exercise therapy in pwMS, which highlights mobility rehabilitation but does not
21
22 109 consider symptoms of fatigue or fatigability¹⁷.

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25
26 110 Therefore, the ReFEx (Rehabilitation, Fatigue, and Exercise) project aims to transfer BMCT,
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28 111 which is promising for subjective fatigue reduction, to inpatient rehabilitation and compare it
29
30 112 with SET, which is considered the control group or 'usual care'. We also adapted the BMCT
31
32 113 to be based on the agility framework described by Donath and colleagues¹⁸. Thus, the treatment
33
34 114 manual will also include functional leg strength and agility-based exercises (i.e., multimodal
35
36 115 agility-based exercise training [MAT]). This is the first study applying the agility framework
37
38 116 to pwMS. In doing so, we not only expect to target subjective fatigue, but also other frequent
39
40 117 MS-specific symptoms including performance fatigability as well as disturbed gait and
41
42 118 balance. Applying the agility framework to BMCT could further provide an opportunity for
43
44 119 combined motor and cognitive rehabilitation¹⁹, that is fun, enjoyable, and social¹⁸.

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49 120 Referring to the pathophysiological framework by Langeskov-Christensen and colleagues¹⁰ we
50
51 121 hypothesize that the SET will improve secondary fatigue via improved aerobic capacity and
52
53 122 motor function, while the MAT intervention will improve secondary fatigue via improved
54
55 123 motor function and reduced cognitive effort in daily life (as hypothesized by Moss-Morris and
56
57 124 colleagues¹¹ and others^{14-16 20}). Based on the existing evidence, we expect greater benefits on
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3 125 secondary fatigue parameters from MAT than for SET. Regarding performance fatigability, we
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5 126 hypothesize, that MAT will be superior to SET in improving motor and cognitive fatigability.
6
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8 127 In a first step, the pilot and feasibility study (PAFS) described in this protocol will be used to
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10 128 determine whether the adapted MAT and SET are feasible in the inpatient rehabilitation setting
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12 129 with a special emphasis on patients' acceptance. This will include both, a quantitative, and
13
14 130 qualitative evaluation.
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17 131

19 132 **METHODS AND ANALYSIS**

21 133 **Study design**

23
24 134 The PAFS will be conducted at the Neurological Rehabilitation Center (NRC) 'Godeshoehe'
25
26 135 (Bonn; certified MS Rehabilitation Center). It will have a two-armed, parallel-group,
27
28 136 randomized-controlled design with twelve weeks follow-up, following a mixed-methods
29
30 137 approach. Measurement time points are provided in the Standard Protocol Items:
31
32 138 Recommendations for Interventional Trials (SPIRIT) figure (Table 1).
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34

35 139

37 140 **Patient and public involvement**

39
40 141 In our therapeutic work of several years in a specialized rehabilitation clinic for MS, the
41
42 142 majority of pwMS report that fatigue is difficult to cope with and limits quality of life. These
43
44 143 patient reports were the impetus for the conception of this study, especially as there are few
45
46 144 evaluated therapy approaches. In the conception of this PAFS, it was important for us to
47
48 145 appreciate the patient perspective and to include the affected persons as 'experts of their
49
50 146 disease'. In particular, this takes the form of qualitative interviews, which we base on a
51
52 147 constructivist paradigm that allows for the co-creation of knowledge by the participants and
53
54 148 the researcher.
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150 **Table 1** SPIRIT figure depicting the schedule of enrollment, interventions and assessments for
 151 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							
<i>MAT</i>			↔				
<i>SET</i>			↔				
ASSESSMENTS:							
<i>Fatigue (WEIMuS)</i>	X			X	X	X	X
<i>Fatigue (FSMC)</i>	X			X	X	X	X
<i>Cognitive fatigability (TAP-Alert)</i>			X	X			
<i>Motor fatigability (6MWT)</i>	X			X			
<i>Cognitive performance (CVLT, SDMT)</i>			X	X			
<i>Cardiorespiratory fitness (GXT)</i>			X	X			
<i>Motor function (T25FW, SSST, FGA)</i>	X			X			
<i>Balance confidence (ABC)</i>	X			X			
<i>Depression (CES-D)</i>			X	X			
<i>Feasibility outcomes</i>	↔						
<i>Interview 1 (Feasibility)</i>				X			
<i>Interview 2 (Fatigue responder)</i>					X		

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3 152
4 153 $-T_0$ = admission; 0 = after written informed consent; T_0 = post-randomization; T_1 = prior to
5
6 154 discharge; T_2 = 1 - 2 weeks after discharge; T_3 = 4 weeks after discharge; T_4 = 12 weeks after
7
8 155 discharge; *MAT* = Multimodal Agility-based exercise Training; *SET* = Strength and Endurance
9
10 156 Training; *WEIMuS* = Würzburg Fatigue Inventory for Multiple Sclerosis; *FSMC* = Fatigue
11
12 157 Scale for Motor and Cognitive Functions; *TAP-Alert* = Test Battery of Attention Performance
13
14 158 – Alertness; *6MWT* = 6-Minute Walk Test; *CVLT* = California Verbal Learning Test; *SDMT* =
15
16 159 Symbol Digit Modalities Test; *GXT* = Graded Exercise Test; *T25FW* = Timed 25-foot Walk
17
18 160 Test; *SSST* = Six Spot Step Test; *FGA* = Functional Gait Assessment; *ABC* = Activities-
19
20 161 Specific Balance Confidence Scale; *CES-D* Center for Epidemiological Studies Depression
21
22 162 Scale (German version)
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163

164 **Screening and recruitment**

31
32 165 Individuals admitted to the NRC will be screened for pwMS. All pwMS will then be scheduled
33
34 166 for neuropsychological examination the day after admission, according to usual practice. Here,
35
36 167 patients will be asked to complete the Fatigue Scale for Motor and Cognitive Functions
37
38 168 (*FSMC*). If a patient is classified as, at least, ‘moderately fatigued’ and the patient fulfils all
39
40 169 other eligibility criteria (Table 2), he or she will be informed about the study by his or her
41
42 170 neuropsychologist (JN, JS, EH), verbally, and in written form.
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45

171

172 **Randomization**

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49 173 If patients provide the written informed consent to one of the study staff members within a
50
51 174 maximum of three days, they will be randomly allocated (1:1) to the intervention or control
52
53 175 group according to the minimization procedure²¹ and stratified by Expanded Disability Status
54
55 176 Scale (*EDSS*, ≤ 3 or ≥ 3.5), Würzburg Fatigue Inventory for Multiple Sclerosis (*WEIMuS*, < 38
56
57 177 or ≥ 38), age (< 45 or ≥ 45), and MS disease course (relapsing-remitting or secondary-

1
2
3 178 progressive). Randomization will be provided by an independent researcher from the German
4
5 179 Sport University Cologne using RITA ('Randomization-In-Treatment-Arms', Evident,
6
7
8 180 Germany).

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10 181

12 182 **Sample size and duration**

14 183 Data from the PAFS is planned to be pooled with data from the full trial in case no major
15
16
17 184 changes of study protocol will be necessary (see progression requirements). Acceptability of
18
19 185 pooling will be evaluated according to components listed in the 'Acceptance checklist for
20
21 186 clinical effectiveness pilot trials'²². As the primary aim of this trial is to evaluate the feasibility,
22
23
24 187 no sample size calculation based on statistical assumptions will be performed. However, we
25
26 188 consider a minimum of twelve recruited patients per study arm to be a reasonable sample size
27
28 189 for this setting²³.

30 190 The NRC treats about 100 – 120 pwMS per year. According to previous data collections for
31
32
33 191 the German MS register no more than 25% of patients will have to be excluded, based on EDSS
34
35 192 and FSMC screening (see eligibility criteria). We further predict no more than 10% of eligible
36
37
38 193 patients to be unwilling to participate, based on previously conducted studies. Comparable
39
40 194 studies have had low drop-out rates (5%²⁴) but did not choose a primary endpoint after patients
41
42 195 returned home. Consequently, we plan with up to 20% drop-out between T₀ and T₂. This will
43
44 196 result in a feasibility period of about six to eight months. Drop-out and retention-rates will be
45
46
47 197 used to inform the sample size calculation for the full randomized controlled trial (RCT).

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49 198

51 199 **Participants**

52 200 PwMS will be eligible to participate in this trial according to the inclusion and exclusion criteria
53
54
55 201 stated in Table 2.

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203 **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	

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

207 Interventions

208 The intervention period includes the time from admission to discharge, which usually
 209 comprises four to six weeks for this group of patients. Multidisciplinary inpatient rehabilitation
 210 can consist of various diagnostic and therapeutic components such as exercise training,
 211 occupational and physical therapy, health education, neuropsychological assessment, or
 212 assessment of working capacity. Thus, interactions between treatments as well as flexibility in
 213 the treatment schedule are common²⁵. For this reason, we designed the schedules of the two
 214 study groups to ensure the following:

- 215 (I) Distinct differences in the amount of therapy targeting cognitive and sensory integration.
- 216 (II) Standardization of treatment as strictly as possible within this specific clinical setting.
- 217 (III) Equivalent amount of total therapy time.

218 See Table 3 for an overview of intervention components. Reporting of the interventions will
 219 follow the modified Consensus on Exercise Reporting Template (CERT) for Therapeutic
 220 Exercise Interventions²⁶.

221

222 **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

223

224 Standard treatment for both groups

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

230

231 Strength and Endurance Training (SET)

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

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3 238 Endurance training will be performed according to the standard protocol in this clinic, with
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5 239 22min per session (3min of gradual increase, 17min steady and 2min cool-down) on a cycle
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8 240 ergometer (ergoselect 5, ergoline GmbH, Bitz, Germany) with continuous monitoring of power
9
10 241 output and heart rate (ers.2 software, ergoline GmbH, Bitz, Germany). Endurance training will
11
12 242 be performed in groups of max. eight patients. In the first session, participants will start their
13
14 243 training at an intensity that was rated “light” to “somewhat hard” by themselves during the
15
16 244 baseline graded exercise test (GXT) (equivalent to 11-13 on the 6-20 Rated Perceived Exertion
17
18 245 [RPE] – scale). In the following sessions, therapists will regulate the power output so that
19
20 246 participants stay between 11 and 13 on the RPE-scale. If a pwMS is unable to complete the
21
22 247 total duration, the session duration can be initially reduced and then progressed in the following
23
24 248 sessions. The range of 11 to 13 was chosen based on recent evidence-based recommendations
25
26 249 for pwMS with similar EDSS²⁷.

30 250 Resistance training will be adapted from Callesen and colleagues¹⁴ to fit the inpatient setting.
31
32 251 Each session will start with a 5min warm-up on an elliptical trainer, treadmill, or recumbent
33
34 252 stepper, followed by three to four exercises targeting hip, knee, and ankle flexion and
35
36 253 extension, as well as hip abduction. Exercises will be progressed as follows:

- 40 254 • Session 1-5: 3x10 repetitions with the 15 repetitions maximum (RPM)
- 42 255 • Session 6-T₁ (session 10-16): 3x12 repetitions with 12RPM

44 256 In detail, for every new exercise, therapists will initially determine the respective weight the
45
46 257 participant is able to move no more than the intended RPM. Therapists will be given the
47
48 258 necessary room for individualization but will be instructed to follow pre-specified exercises
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50 259 (see Supplemental File [Strength Protocol]).

53 260

56 261 Multimodal agility-based exercise training (MAT)

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3 262 For the treatment manual see Supplemental File [MAT-Manual]. All sessions will be guided
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5 263 by max. three different exercise therapists (including FW) from the NRC, experienced with
6
7 264 providing balance exercises on land and in the water in group settings. However, as MAT also
8
9 265 comprises other/new elements, exercise therapists will be specifically trained by FW and
10
11 266 instructed to follow the treatment manual.

12
13
14 267 Both parts (i.e., water and land) will be installed within existing group therapies. Each group
15
16 268 will consist of max. eight participants. Empty spots will be filled with other patients from the
17
18 269 NRC. The intervention program will consist of three main components: (1) standing balance
19
20 270 exercises, (2) dynamic balance exercises including functional leg strength, (3) agility-like
21
22 271 exercises including change of direction and change of velocity²⁸. Each main component will
23
24 272 be represented in several modules. Each module is constructed as a basic set-up, that can be
25
26 273 progressed in terms of difficulty. Additionally, modifications on a cognitive (e.g., memory,
27
28 274 attention, inhibition) and sensory (i.e., visual, somatosensory, vestibular) level are described.
29
30 275 As stated by Callesen and colleagues¹⁴ there is no consensus yet on how to define intensity or
31
32 276 progression in balance and motor control exercises. Thus, for this intervention, therapists will
33
34 277 be instructed to aim for a level of difficulty and complexity that keeps exercises manageable
35
36 278 and safe for participants, but also provokes motor or cognitive errors. This is in line with
37
38 279 recommendations for neurorehabilitation from basic science²⁹.

39
40 280 For load management in the land-based therapy, there will be three sessions with higher
41
42 281 physical strain (i.e., agility-like components and functional leg strength) interspersed with two
43
44 282 sessions with lower physical strain (i.e., standing balance and exercises with a cognitive focus).
45
46 283 Due to water immersion, physical strain in the water-based therapy should be lower in general.
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48 284 Participants will be instructed to take individual breaks whenever they need to. They will also
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50 285 be advised to monitor their fatigue during their stay and skip a session when they need more
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52 286 time to regenerate.
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45 288 **Blinding**6
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8 289 The neuropsychological staff conducting the cognitive tests will be blinded to the study groups.
910 290 However, for organizational reasons and specifics of the study setting, blinding of participants,
1112 291 therapists conducting the interventions as well as personnel conducting the motor and
1314 292 cardiorespiratory fitness (CRF) tests and analyzing the questionnaires will not be possible.
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18
19 294 **Outcomes**20
21 295 As depicted in Table 1, assessments will be carried out at admission (i.e., pre-intervention, T₀)
2223 296 and discharge (i.e., post-intervention, T₁), as well as after participants have returned home (i.e.,
2425 297 follow-up, T₂-T₄).
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30 299 Feasibility (quantitative)31
32 300 To generate the quantitative feasibility outcomes, we adopted the categories described by
3334 301 Thabane and colleagues³⁰ and promoted for exercise studies in MS by Learmonth and Motl³¹
3536 302 (see Table 4).
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303 **Table 4** Description of quantitative feasibility outcomes (adapted from³²).

Classification	Outcome	Operationalization	Importance for future RCT
Process	1. Recruitment rate	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Number of patients completing the intervention period, relative to patients dropping out before T₁ Number of patients returning the WEIMuS at T₂, relative to patients not responding 	<p>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.</p> <p>Gives information on the feasibility of the primary endpoint and outcome being assessed post-discharge and via an online platform.</p>
	3. Refusal rate	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Number of positive versus negative cases for each criterium 	Determines criteria that might produce too many non-eligible patients
	5. Adherence	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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.

		<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 T₀ and T₁, (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	<ul style="list-style-type: none"> • Number of missing items for FSMC and WEIMuS for all measurement timepoints • Number 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"> • Number 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 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 T₁ 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	<ul style="list-style-type: none"> • Estimation of treatment effect (Cohen’s <i>d</i>) on all primary and secondary outcomes 	Establishes data for possible impact of interventions

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3 304 *RCT* = randomized-controlled trial; T_0 = post-randomization; T_1 = prior to discharge; T_2 = 1 - 2 weeks after discharge; *WEIMuS* = Würzburg
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5 305 Fatigue Inventory for Multiple Sclerosis; *MAT* = Multimodal Agility-based exercise Training; *SET* = Strength and Endurance Training; *RPE* =
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7 306 Rated Perceived Exertion; *GXT* = Graded Exercise Test; *T25FW* = Timed 25-foot Walk Test; *SSST* = Six Spot Step Test; *FGA* = Functional Gait
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10 307 Assessment; *FSMC* = Fatigue Scale for Motor and Cognitive Functions
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3 308 Feasibility (qualitative)
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5 309 The qualitative evaluation aims to (a) capture patients' views on acceptance, benefits, and
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7 310 satisfaction with study participation, (b) assess their experiences with the intervention methods,
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9 311 and (c) identify necessary adaptations. For this purpose, we designed a semi-structured interview.
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11 312 Six participants from each study arm will be interviewed face-to-face at T₁. The selection of
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13 313 participants will reflect the greatest possible diversity in terms of gender, age, and EDSS³⁶. The
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15 314 interview will include a total of 14 questions and will last approximately 20min. Key categories
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17 315 of the interview are the concept of fatigue, experiences and demands of the interventions,
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19 316 personal relevance, and goal achievement. All interviews will be recorded digitally and
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21 317 transcribed verbatim by an independent transcription service.
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26 318 Both interviewers (JN, FW) have several years of clinical experience with pwMS. A first draft
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28 319 of this interview was piloted with three pwMS prior to the start of the feasibility study to ensure
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30 320 that the questions allow valid insights into participants' experiences.
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33 321 The interview will be supplemented by a customized questionnaire asking for prior knowledge
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35 322 of fatigue, prior experiences with MAT and SET, and comprehensibility of the study
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37 323 instructions and questionnaires. The questionnaire also asks about fun and relevance of training
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39 324 for daily life (see Table 4), and the motivation to continue a comparable training at home.
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44 326 Primary outcome for the full RCT
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47 327 Fatigue questionnaires presuppose internal averaging of the amount of fatigue experienced
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49 328 during a certain timeframe¹. This has been a problem for studies evaluating short-term
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51 329 interventions, as in some questionnaires patients are asked to evaluate their fatigue in
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53 330 timeframes of up to four weeks. As we are interested in the change in fatigue experienced in
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55 331 daily life from before the inpatient stay to afterwards, we (I) chose the WEIMuS³⁷ as the
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57 332 primary outcome measure to assess the fatigue experienced during the past week and (II)
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3 333 established the primary endpoint to be one to two weeks after participants have returned home
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5 334 (T₂). The WEIMuS has 17 items (scored 0 - 4) with higher total scores indicating higher fatigue
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7 335 (range 0 – 68, cut-off for classification as fatigued: 32).

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10 336 For fatigue screening (that is necessary for study eligibility) we will apply the FSMC. It is a 20
11
12 337 item Likert-type scale (1 – 5) with a total score (0 – 100) and two subscales relating to motor
13
14 338 and cognitive fatigue³⁸. The FSMC provides cut-off scores to classify cases of no (total score
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16 339 < 43), mild (≥ 43), moderate (≥ 53) and severe (≥ 63) fatigue, which makes it especially suitable
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18 340 as a tool for classification of fatigue severity^{1 38}.

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20 341 Paper versions of both questionnaires will be handed out to participants. When at home,
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22 342 participants will be followed up via e-mail to fill out questionnaires on an online platform
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24 343 (Qualtrics) at timepoints T₂-T₄. Participants will be able to respond to the e-mail request within
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26 344 seven days.

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33 346 Secondary outcomes for the full RCT

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35 347 MS-fatigue is a multifactorial construct that requires assessment of other interrelated
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37 348 constructs⁷. This will include measures of cognitive (Test Battery of Attention Performance –
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39 349 Alertness³⁹) and motor fatigability (6-Minute Walk Test [6MWT], Distance Walked Index⁴⁰),
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41 350 cognitive performance (California Verbal Learning Test, Symbol Digit Modalities Test^{24 41})
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43 351 and cardiorespiratory fitness (GXT on a cycle ergometer, protocol: start 25W, progression
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45 352 10W/min.). Dynamic balance and motor function (Timed 25-Foot Walk Test [T25FW], Six
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47 353 Spot Step Test [SSST], Functional Gait Assessment [FGA]) will also be assessed as well as
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49 354 self-reported balance confidence (Activities-specific Balance Confidence scale). Depression
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51 355 (Center for Epidemiological Studies Depression Scale [German version]) will be assessed as a
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56 356 confounder variable.
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3 357 The subsequent full trial will also include qualitative data to explore the subjective experiences
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5 358 in participants showing a WEIMuS change of 6 or more points from T₀ to T₂ (positive or
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7 359 negative). These “responders” will be contacted for a short telephone interview. Previous data
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10 360 has shown large differences in fatigue questionnaire change scores¹³. However, the scores do
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12 361 not provide any detail on individual circumstances, including, for example, social or work-
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14 362 related influences, that might be independent of intervention effects. Therefore, we decided to
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17 363 specifically ask participants:

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19 364 ‘The analysis of your questionnaires shows a relevant positive/negative change of
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21 365 your fatigue symptoms, when comparing your scores from pre-rehab to the online
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23 366 questionnaire. What do you personally think is the reason for this?’.

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26 367 No minimal clinically relevant change scores have been established yet⁴². Thus, the relevant
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28 368 change score was chosen as a pragmatic value of 0.5 SD from the validation study⁴³. A similar
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30 369 procedure has been described by Sander and colleagues¹.

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34 35 371 **Data analysis**

36 37 372 Quantitative data analysis

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40 373 Descriptive statistics will be used to summarize feasibility outcomes. The results are given as
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42 374 mean and standard deviation for parametric distribution, median and interquartile range for
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44 375 non-parametric distribution, or frequencies (%), as appropriate. Baseline data for
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46 376 sociodemographic, primary, and secondary outcomes will be compared between SET and
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48 377 MAT groups using independent-samples *t*-tests for continuous data, and chi-squared tests for
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50 378 categorical data. Paired *t*-tests will be used to assess within-group change over time.
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52 379 Independent-samples *t*-tests will be used on change scores (post- vs. pre-rehabilitation) to
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54 380 assess between-group effects. In case of non-normal distributions, non-parametric tests will be
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56 381 used. As described by Sim⁴⁴, estimation of treatment effects (Cohen’s *d*) will be conducted and
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3 382 reported with 95% confidence intervals but will not be used as a progression requirement. All
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5 383 analyses will be performed using IBM SPSS Statistics in the most up to date version.
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10 385 **Qualitative data analysis**

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12 386 Coding of the interviews will be performed according to qualitative content analysis, using a
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14 387 combined model of deductive (a priori) and inductive coding (on the text material) to identify
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16 388 themes and sub-themes⁴⁵. Deductive coding will be based on preliminary considerations and
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18 389 hypotheses in the study planning and on reviews of relevant literature. Coding will be carried
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20 390 out by at least two individuals (JN, FW) to ensure intercoder reliability⁴⁶. The analysis will be
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22 391 supported by MAXQDA® software in the most up to date version⁴⁷. JN and FW will compile
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24 392 the themes emerging from the interview data and discuss these with the wider research team.
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31 394 **Progression requirements to full RCT**

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33 395 Falling short of the following feasibility values will necessitate changes to the protocol of the
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35 396 full RCT:

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- 39 • Adherence: Average of at least 18 therapy sessions during the stay (equals 6x30min
40 sessions per week for 3 weeks [28 days admission to discharge minus 5 days for pre-
41 and post-testing])
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 - 43 • Recruitment rate: 4 participants/month, <25% non-eligible pwMS, <10% eligible but
44 unwilling to participate
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 - 46 • Drop-out before T₁: <10%
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 - 48 • Retention at T₂: >80%
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 - 50 • Time requirements for baseline assessments: >80% able to complete all assessments
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 - 52 within the first three days of therapy
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3 406 • If the interview statements indicate that the interventions are perceived as irrelevant,
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5 407 not comprehensible, or even unpleasant
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10 409 **Data management**
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12 410 The principal investigator (FW) will be responsible for data management. Demographic and
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14 411 clinical characteristics will be taken from the electronic health record. All other data will be
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16 412 collected on forms during the inpatient stay and via an online tool for follow-up. Data will be
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18 413 entered into a secure internal network database by study personnel in the NRC. Entered data
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20 414 will be checked for plausibility and compared to the collection forms if necessary. Data will be
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22 415 collected and stored in accordance with the General Data Protection Regulation.
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28 417 **ETHICS AND DISSEMINATION**
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30 418 Written informed consent will be obtained from each participant. Ethical approval was
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32 419 obtained from the Ethics Committee at the Medical Faculty, University of Bonn (reference
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34 420 number: 543/20).
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37 421 The results of this feasibility study will be disseminated regardless of the magnitude or
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39 422 direction of effect in peer-reviewed journals, conferences and the website and magazines of the
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41 423 German Sport University Cologne.
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47 425 **DISCUSSION**
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49 426 This PAFS will give relevant insights for conducting a future RCT in this special setting of
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51 427 inpatient rehabilitation for pwMS. Content-wise, it will (I) translate existing evidence on
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53 428 BMCT in pwMS to this setting, (II) add to this BMCT by introducing the framework of MAT,
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55 429 and (III) apply a clear focus on fatigue as the primary outcome. Specifically, we see the
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57 430 potential of a relatively large training volume (e.g., about eight therapy sessions per week)
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3 431 compared to studies in outpatient settings, and a high amount of supervised exercise, which
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5 432 should provide good adherence and fidelity. Having a therapist as a supervisor is especially
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8 433 important for a rather complex type of exercise as is MAT. For example, there are no simple
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10 434 ‘numbers’ like sets or repetitions one can follow. Quicker movements relating to agility, like
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12 435 changes of direction, acceleration, and deceleration, frequently lie outside the ‘comfort zone’
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14 436 of pwMS, which necessitates guidance of a therapist. Lastly, in the group format, a therapist is
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17 437 mandatory to provide modifications for pwMS with higher disability or very low disability.
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19 438 We also anticipate certain issues in conducting this study. For example, scheduling of
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21 439 appointments for testing will be challenging, as there will be several testing blocks (i.e., motor
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23 440 function, GXT, cognitive tests, interview), conducted in different departments of the NRC,
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25 441 which must be fitted into certain timeslots around admission and discharge. These
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28 442 appointments will compete against other study unrelated appointments (e.g., ward rounds,
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30 443 urology assessments, etc.). Regarding the eligibility and randomization criteria, it will be
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33 444 challenging to have all the correct data within the first two days as there can be delays in the
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35 445 admission process.
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37 446 Lastly, analysis of blood-based biomarkers is planned to be part of the ReFEx study project.
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39 447 However, as these outcomes are connected to comparably high costs for materials and analysis,
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41 448 addition of blood sampling is postponed to the start of a full RCT. Nevertheless, information
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43 449 gathered during the feasibility study will be used to allow for smooth integration of blood draws
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45 450 and storage during assessments at admission and discharge. As the blood draws can be regarded
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47 451 as the most unpleasant part of the assessments for patients, feasibility of the interventions and
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49 452 patient acceptance should be established first.
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56 454 **Author contributions**

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3 455 FW, JN, ME, PZ designed the overall study. FW & JN designed the feasibility study and wrote
4
5 456 the protocol. FW, JN, JS, EH implemented the screening and assessment procedures. All
6
7 457 authors revised the manuscript. All authors read and approved the final manuscript.
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10 458

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19 462

20 463 **Competing interests**

21
22
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24
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26
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30
31 468 Germany. AFK is author of the cognitive training program NEUROvitalis but receives no
32
33 469 corresponding honoraria. HK: none. PZ: none.
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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		

1	"Movement memory"			DB
2	<i>Participants move through the gym while performing gait variations coded with various commands given by therapist.</i>			
3	Progression: Movement	Progression: Number of pairs		
4	Tasks for one side of body	4 to 8		
5	Tasks for both sides of body (e.g. left knee up & right hand to left shoulder)			
6	Similarity of movements			
7	Sensory modification	Visual: -		
8		Somatosensory: -		
9		Vestibular: -		
10	Cognitive add-on (main focus)	Memory: Recall pairs (movement+number / movement+color word / movement+number or color word)		
11		Inhibition: command = stop		
12	"Remote control"			DB
13	<i>Pairs of two: a participant is steered through the room with closed eyes via tactile cues of the partner.</i>			
14	Progression: number of cues	Progression: movement		
15	3 to 6	Tandem walk, high knees		
16	Sensory modification	Visual: closed eyes		
17		Somatosensory: -		
18		Vestibular: turning in place		
19	Cognitive add-on	Spatial orientation: report location in space to partner (closed eyes)		
20	Walking with tasks			AG
21	<i>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.</i>			
22	Progression: DOM, speed	Progression: movement	Progression: tools	
23	Forwards, backwards, sideways	Tasks for one side of body	Kind of objects (small sacks, balls, ...)	
24	walking, jogging	Tasks for both sides of body (e.g. left knee, right hand)		
25	Sensory modification	Visual: -		
26		Somatosensory: -		
27		Vestibular: Head turns (horizontal)		
28	Cognitive add-on	-		
29	Agility ladder			AG
30	<i>Participants perform exercises in an agility ladder on the floor. Number and type of foot contacts in each field are varied.</i>			
31	Progression: DOM, speed	Progression: complexity	Progression: tools	
32	Forwards, backwards, sideways	Easier sequences (2 / 3 touches)	Kind of objects (small sacks, balls, ...)	
33		Harder sequences (1,2,3,2,1 / 2 forwards 1 back / 2 in 1 out)		
34	Sensory modification	Visual: -		
35		Somatosensory: -		
36		Vestibular: Head turns		
37	Cognitive add-on	Divided attention: Participants have to call numbers shown by therapist		
38		Divided attention: Participants have to catch objects thrown by therapist		
39	Cone tipping			AG
40	<i>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.</i>			
41	Progression: speed, duration	Progression: number of cones		
42	Walking, jogging	4 to 8		
43	1 round = 30s			
44	Sensory modification	Visual: -		
45		Somatosensory: -		
46		Vestibular: -		
47	Cognitive add-on	Spatial orientation & memory: directions are given by numbers, colors or alphabet		
48	Slalom			AG
49	<i>Participants move through a slalom parcour.</i>			
50	Progression: speed, duration	Progression: number of obstacles	Progression: competition	
51	Walking, jogging	4 to 8	Hit a target with an object at the end of slalom	
52	1 round = 60-90s			
53	Sensory modification	Visual: -		
54		Somatosensory: -		
55		Vestibular: -		
56	Cognitive add-on	-		
57	Soccer			AG
58	<i>Participants move and pass a ball.</i>			
59	Progression: speed, duration	Progression: number of players	Progression: change of direction	
60	Walking, jogging	1 to 4	Front - back	
61	1 round = 60-90s	Front - back and sideways		
62		Random		
63	Sensory modification	Visual: -		
64		Somatosensory: -		
65		Vestibular: -		
66	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]

For peer review only

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



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 ___

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	___3-5___
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	___5___
7				
8	Objectives	7	Specific objectives or hypotheses	___5___
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	___5;8___
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	___6___
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	___9-10___
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	___10-13___
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___11-13___
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	___15-16___
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___10-11___
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	___14-20___
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	___6-8___
39			participants. A schematic diagram is highly recommended (see Figure)	
40				
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1	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___
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8___
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	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___
11				
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16	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___
17				
18				
19				
20				
21	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___8___
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___13___
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___n/a___
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	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___
34				
35				
36				
37				
38				
39		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___
40				
41				
42				

1	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_____
2				
3				
4				
5	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_____
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____n/a_____
9				
10		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_____
11				
12				
13				
14	Methods: Monitoring			
15				
16	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_____
17				
18				
19				
20				
21				
22		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_____
23				
24				
25	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_____
26				
27				
28	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_____
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____22_____
35				
36				
37	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_____
38				
39				
40				
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42				
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46				

1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____8_____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____n/a_____
5				
6				
7	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_____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____24_____
11				
12				
13	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_____
14				
15				
16	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_____
17				
18				
19				
20	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_____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____23-24_____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a_____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____n/a_____
32				
33				
34	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_____
35				
36				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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

SCHOLARONE™
Manuscripts

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3 1 **A randomized controlled pilot and feasibility study of multimodal agility-based exercise**
4
5 2 **training (MAT) versus strength and endurance training (SET) to improve Multiple**
6
7 3 **Sclerosis-related fatigue and fatigability during inpatient rehabilitation [ReFEx] – study**
8
9 4 **protocol.**
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14

15 6 **Akronym: ReFEx (Rehabilitation, Fatigue, and Exercise)**
16
17 7

18
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58 25 **Word count: 4336**

1
2
3 26 **Trial status:** The first participant has been enrolled on 18 November 2021. At the time of
4
5 27 submission, 9/24 participants have been recruited, 3/24 participants have finished the
6
7 28 intervention period and completed the primary measurement time point one week after the end
8
9 29 of the intervention period.
10
11
12
13

30

31 **ABSTRACT**

32 **Introduction:** Subjective fatigue and objectively assessed fatigability are common symptoms
33
34 in persons with Multiple Sclerosis (pwMS). Recent work has suggested a positive effect of
35
36 balance and motor control training (BMCT) in reducing fatigue. It is unclear whether this effect
37
38 can also be attained during inpatient rehabilitation. Multimodal agility-based exercise training
39
40 (MAT) has been developed as a framework that incorporates BMCT with added agility
41
42 components but has not been applied to pwMS. Therefore, this study will evaluate the
43
44 feasibility of a randomized controlled trial comparing MAT against strength and endurance
45
46 training (SET) for the improvement of MS-related fatigue and fatigability in a German
47
48 neurologic rehabilitation center.

49 **Methods and analysis:** A total of 24 pwMS (Expanded Disability Status Scale ≤ 5.0 , Fatigue
50
51 Scale for Motor and Cognitive Functions ≥ 53) will be randomly assigned to either SET or land
52
53 and water-based MAT for 4 to 6 weeks during inpatient rehabilitation. Assessments of
54
55 subjective fatigue, motor and cognitive fatigability, cognitive and cardiorespiratory
56
57 performance, and balance confidence will be performed at admission and discharge. Subjective
58
59 fatigue will also be assessed at 1, 4, and 12 weeks after discharge. Feasibility outcomes will
60
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.

1
2
3 51 **Ethics and dissemination:** Ethical approval has been obtained from the Ethics Committee of
4
5 52 the University of Bonn (reference number: 543/20). Dissemination of findings is planned via
6
7 53 peer-reviewed journals, conferences, and media releases.
8
9

10 54
11
12 55 **Trial registration:** German Clinical Trials Register: DRKS00023943, date of registration: 23
13
14 56 September 2021
15
16

17 57
18
19 58 **Keywords**

20 59 multiple sclerosis, sports medicine, rehabilitation medicine
21
22
23
24 60

25
26 61 **Strengths and limitations**

- 27
28 62 • Comprehensive assessment of subjective fatigue, as well as objective cognitive and
29
30 63 motor fatigability
31
32 64 • First application of agility-based exercise training to pwMS
33
34 65 • Mixed-methods approach to acquire patient perspective and acceptance
35
36 66 • Clinical inpatient setting will challenge standardization of study procedures
37
38
39
40 67

41
42 68 **INTRODUCTION**

43
44 69 Fatigue, described as ‘a subjective sensation of lack of energy and exhaustion’ (p. E79)[1], was
45
46 70 reported as the most common symptom (58%) among 35,000 patients from the German
47
48 71 multiple sclerosis (MS) register[2]. It is also reported as one of the most disabling symptoms[3]
49
50 72 with high socioeconomic relevance as 25% of persons with MS (pwMS) have impaired
51
52 73 working capacity because of ‘invisible symptoms’ such as fatigue and impaired cognition[4,
53
54 74 5].
55
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1
2
3 75 Data from the MS register also show that only 35% of fatigued pwMS receive any kind of
4
5 76 treatment and among them only 15% receive pharmacological treatment to specifically handle
6
7 77 fatigue symptoms[2]. No clear pathomechanisms for fatigue have been defined yet leading to
8
9 78 the consequence of still limited pharmacotherapy options for the treatment of fatigue[6].
10
11
12 79 According to the established taxonomy by Kluger and colleagues[7] two concepts must be
13
14 80 separated when considering fatigue: (I) the subjective experience of fatigue and (II) objective
15
16 81 performance fatigability during motor or cognitive tasks. Whether improvements in fatigability
17
18 82 also transfer to subjective fatigue is still unclear. Interestingly, the association between the two
19
20 83 constructs seems to be relatively weak[8, 9].
21
22
23 84 Next to distinguishing between ‘fatigue’ and ‘fatigability’, a further dichotomy exists with
24
25 85 ‘primary fatigue’ resulting from pathophysiological processes of the disease itself (e.g., central
26
27 86 nervous system, immunologic or endocrine changes) and ‘secondary fatigue’ resulting from
28
29 87 mechanisms not directly related to the disease (e.g., sleep, depression, medication)[10].
30
31
32 88 To reduce subjective fatigue, exercise interventions have been studied as a non-
33
34 89 pharmacological treatment option. However, several methodological issues exist. As fatigue is
35
36 90 frequently assessed as a secondary outcome variable, subjects are often not pre-screened for
37
38 91 fatigue symptoms at baseline and the intervention is not primarily designed to reduce
39
40 92 fatigue[11, 12]. Consequently, to date, there are few studies investigating the specific
41
42 93 pathophysiological pathways of primary or secondary fatigue that are altered by exercise[10].
43
44
45 94 In a recent meta-analysis Moss-Morris and colleagues[11] performed a detailed review of
46
47 95 exercise intervention studies, that specifically aimed at fatigue reduction. Here, the authors
48
49 96 reported variance in the effects of different types of exercise. For example, endurance exercise
50
51 97 has been frequently investigated, as it can be easily standardized, but was reported to have only
52
53 98 small effects on fatigue outcomes measured with self-report questionnaires[13]. If combined
54
55 99 with other modalities such as resistance exercise, effects might be greater (e.g., strength and
56
57
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1
2
3 100 endurance training [SET]). Lastly, types of exercise consisting primarily of stimuli targeting
4
5 101 motor control (e.g., balance and motor control training [BMCT]) were described as promising,
6
7
8 102 due to their relatively large effect sizes and specification of a mechanistic pathway.

9
10 103 In the special setting of inpatient rehabilitation, the number of exercise studies for subjective
11
12 104 fatigue reduction is very limited. In their review, Moss-Morris and colleagues[11] identified
13
14 105 only one study conducted in an inpatient rehabilitation setting. However, this trial was
15
16 106 restricted from the meta-analysis because of methodological limitations, indicating the need
17
18 107 for future systematic research on fatigue-specific therapy. This is also evident in the first
19
20 108 German practice guideline for exercise therapy in pwMS, which highlights mobility
21
22 109 rehabilitation but does not consider symptoms of fatigue or fatigability[14].

23
24
25 110 Therefore, the ReFEx (Rehabilitation, Fatigue, and Exercise) project aims to transfer the
26
27 111 promising results of interventions focused on balance and motor control to inpatient
28
29 112 rehabilitation and compare it with SET, which is considered the control group or 'usual care'.
30
31 113 Importantly, we will adapt the existing approaches on BMCT to be based on the agility
32
33 114 framework described by Donath and colleagues[15]. Therefore, besides exercises focused on
34
35 115 balance and sensory integration, the treatment manual will also include functional leg strength
36
37 116 and agility-based exercises. This approach can be characterized as 'multimodal agility-based
38
39 117 exercise training' (MAT)[16] and the ReFEx project will be the first to apply it to pwMS. In
40
41 118 doing so, we not only expect to target subjective fatigue, but also other frequent MS-specific
42
43 119 symptoms including performance fatigability as well as disturbed gait and balance. Applying
44
45 120 the agility framework could further provide an opportunity for combined motor and cognitive
46
47 121 rehabilitation[17], that is fun, enjoyable, and social[15].

48
49 122 Referring to the pathophysiological framework by Langeskov-Christensen and colleagues[10]
50
51 123 we hypothesize that the SET will improve secondary fatigue via improved aerobic capacity
52
53 124 and motor function, while the MAT intervention will improve secondary fatigue via improved
54
55
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60

1
2
3 125 motor function and reduced cognitive effort in daily life (as hypothesized by Moss-Morris and
4
5 126 colleagues[11] and others[18-21]). Based on the existing evidence, we expect greater benefits
6
7 127 on secondary fatigue parameters from MAT than for SET. Regarding performance fatigability,
8
9 128 we hypothesize, that MAT will be superior to SET in improving motor and cognitive
10
11 129 fatigability.
12
13

14
15 130 In a first step, the pilot and feasibility study (PAFS) described in this protocol will be used to
16
17 131 determine whether the adapted MAT and SET are feasible in the inpatient rehabilitation setting
18
19 132 with a special emphasis on patients' acceptance. This will include both, a quantitative, and
20
21 133 qualitative evaluation.
22
23

24 134

25 26 135 **METHODS AND ANALYSIS**

27 28 136 **Study design**

29
30 137 The PAFS will be conducted at the Neurological Rehabilitation Center (NRC) 'Godeshoehe'
31
32 138 (Bonn; certified MS Rehabilitation Center). It will have a two-armed, parallel-group,
33
34 139 randomized-controlled design with twelve weeks follow-up, following a mixed-methods
35
36 140 approach. Measurement time points are provided in the Standard Protocol Items:
37
38 141 Recommendations for Interventional Trials (SPIRIT) figure (Table 1).
39
40
41

42 142

43 44 143 **Patient and public involvement**

45
46 144 In our therapeutic work of several years in a specialized rehabilitation clinic for MS, the
47
48 145 majority of pwMS report that fatigue is difficult to cope with and limits quality of life. These
49
50 146 patient reports were the impetus for the conception of this study, especially as there are few
51
52 147 evaluated therapy approaches. In the conception of this PAFS, it was important for us to
53
54 148 appreciate the patient perspective and to include the affected persons as 'experts of their
55
56 149 disease'. In particular, this takes the form of qualitative interviews, which we base on a
57
58
59
60

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

152

153 **Table 1** SPIRIT figure depicting the schedule of enrollment, interventions and assessments for
 154 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							
<i>MAT</i>			↔				
<i>SET</i>			↔				
ASSESSMENTS:							
<i>Fatigue (WEIMuS)</i>	X			X	X	X	X
<i>Fatigue (FSMC)</i>	X			X	X	X	X
<i>Cognitive fatigability (TAP-Alert)</i>			X	X			
<i>Motor fatigability (6MWT)</i>	X			X			
<i>Cognitive performance (CVLT, SDMT)</i>			X	X			
<i>Cardiorespiratory fitness (GXT)</i>			X	X			
<i>Motor function (T25FW, SSST, FGA)</i>	X			X			
<i>Balance confidence (ABC)</i>	X			X			
<i>Depression (CES-D)</i>			X	X			

<i>Feasibility outcomes</i>									
<i>Interview 1 (Feasibility)</i>				X					
<i>Interview 2 (Fatigue responder)</i>					X				

155
 156 $-T_0$ = admission; 0 = after written informed consent; T_0 = post-randomization; T_1 = prior to
 157 discharge; T_2 = 1 - 2 weeks after discharge; T_3 = 4 weeks after discharge; T_4 = 12 weeks after
 158 discharge; *MAT* = Multimodal Agility-based exercise Training; *SET* = Strength and Endurance
 159 Training; *WEIMuS* = Würzburg Fatigue Inventory for Multiple Sclerosis; *FSMC* = Fatigue
 160 Scale for Motor and Cognitive Functions; *TAP-Alert* = Test Battery of Attention Performance
 161 – Alertness; *6MWT* = 6-Minute Walk Test; *CVLT* = California Verbal Learning Test; *SDMT* =
 162 Symbol Digit Modalities Test; *GXT* = Graded Exercise Test; *T25FW* = Timed 25-foot Walk
 163 Test; *SSST* = Six Spot Step Test; *FGA* = Functional Gait Assessment; *ABC* = Activities-
 164 Specific Balance Confidence Scale; *CES-D* Center for Epidemiological Studies Depression
 165 Scale (German version)

166

167 **Screening and recruitment**

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

174

175 **Randomization**

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

1
2
3 178 group according to the minimization procedure[23] and stratified by Expanded Disability
4
5 179 Status Scale (EDSS, ≤ 3 or ≥ 3.5), Würzburg Fatigue Inventory for Multiple Sclerosis
6
7 180 (WEIMuS, < 38 or ≥ 38), age (< 45 or ≥ 45), and MS disease course (relapsing-remitting or
8
9 181 secondary-progressive). Randomization will be provided by an independent researcher from
10
11 182 the German Sport University Cologne using RITA ('Randomization-In-Treatment-Arms',
12
13 183 Evident, Germany).
14
15
16

17 184

185 **Sample size and duration**

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

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

201

202 **Participants**

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

205

206 **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	

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

209

210 Interventions

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

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

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

220 (III) Approximately equivalent amount of total therapy time.

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

225 **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

227 Standard treatment for both groups

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

234 Strength and Endurance Training (SET)

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

1
2
3 239 instructed by FW and will follow a training protocol (see Supplemental File [Strength
4
5 240 Protocol]).

6
7
8 241 Endurance training will be performed according to the standard protocol in this clinic, with
9
10 242 22min per session (3min of gradual increase, 17min steady and 2min cool-down) on a cycle
11
12 243 ergometer (ergoselect 5, ergoline GmbH, Bitz, Germany) with continuous monitoring of power
13
14 244 output and heart rate (ers.2 software, ergoline GmbH, Bitz, Germany). Endurance training will
15
16
17 245 be performed in groups of max. eight patients. In the first session, participants will start their
18
19 246 training at an intensity that was rated “light” to “somewhat hard” by themselves during the
20
21 247 baseline graded exercise test (GXT) (equivalent to 11-13 on the 6-20 Rated Perceived Exertion
22
23 248 [RPE] – scale). In the following sessions, therapists will regulate the power output so that
24
25 249 participants stay between 11 and 13 on the RPE-scale. If a pwMS is unable to complete the
26
27 250 total duration, the session duration can be initially reduced and then progressed in the following
28
29 251 sessions. The range of 11 to 13 was chosen based on recent evidence-based recommendations
30
31 252 for pwMS with similar EDSS[29].

32
33
34
35 253 Resistance training will be adapted from Callesen and colleagues[18] to fit the inpatient setting.
36
37 254 Each session will start with a 5min warm-up on an elliptical trainer, treadmill, or recumbent
38
39 255 stepper, followed by three to four exercises targeting hip, knee, and ankle flexion and
40
41 256 extension, as well as hip abduction. Exercises will be progressed as follows:

- 42
43
44
45 257 • Session 1-5: 3x10 repetitions with the 15 repetitions maximum (RM)
46
47 258 • Session 6-T₁ (session 10-16): 3x12 repetitions with 12RM

48
49 259 In detail, for every new exercise, therapists will initially determine the respective weight the
50
51 260 participant is able to move no more than the intended RM. Therapists will be given the
52
53 261 necessary room for individualization but will be instructed to follow pre-specified exercises
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55 262 (see Supplemental File [Strength Protocol]).

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3 264 Multimodal agility-based exercise training (MAT)
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5 265 For the treatment manual see Supplemental File [MAT-Manual]. All sessions will be guided
6
7 266 by max. three different exercise therapists (including FW) from the NRC, experienced with
8
9 267 providing balance exercises on land and in the water in group settings. However, as MAT also
10
11 268 comprises other/new elements, exercise therapists will be specifically trained by FW and
12
13 269 instructed to follow the treatment manual.
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16
17 270 Both parts (i.e., water and land) will be installed within existing group therapies. Each group
18
19 271 will consist of max. eight participants. Empty spots will be filled with other patients from the
20
21 272 NRC. The intervention program will consist of three main components: (1) standing balance
22
23 273 exercises, (2) dynamic balance exercises including functional leg strength, (3) agility-like
24
25 274 exercises including change of direction and change of velocity[16]. Each main component will
26
27 275 be represented in several modules. Each module is constructed as a basic set-up, that can be
28
29 276 progressed in terms of difficulty. Additionally, modifications on a cognitive (e.g., memory,
30
31 277 attention, inhibition) and sensory (i.e., visual, somatosensory, vestibular) level are described.
32
33 278 As stated by Callesen and colleagues[18] there is no consensus yet on how to define intensity
34
35 279 or progression in balance and motor control exercises. Thus, for this intervention, therapists
36
37 280 will be instructed to aim for a level of difficulty and complexity that keeps exercises
38
39 281 manageable and safe for participants, but also provokes motor or cognitive errors. This is in
40
41 282 line with recommendations for neurorehabilitation from basic science[30].
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46 283 For load management in the land-based therapy, there will be three sessions with higher
47
48 284 physical strain (i.e., agility-like components and functional leg strength) interspersed with two
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50 285 sessions with lower physical strain (i.e., standing balance and exercises with a cognitive focus).
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52 286 Due to water immersion, physical strain in the water-based therapy should be lower in general.
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3 287 Participants will be instructed to take individual breaks whenever they need to. They will also
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5 288 be advised to monitor their fatigue during their stay and skip a session when they need more
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7 289 time to recuperate.
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11 291 **Blinding**

12 292 The neuropsychological staff conducting the cognitive tests will be blinded to the study groups.
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14 293 However, for organizational reasons and specifics of the study setting, blinding of participants,
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16 294 therapists conducting the interventions as well as personnel conducting the motor and
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18 295 cardiorespiratory fitness (CRF) tests and analyzing the questionnaires will not be possible.
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25 297 **Outcomes**

26 298 As depicted in Table 1, assessments will be carried out at admission (i.e., pre-intervention, T₀)
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28 299 and discharge (i.e., post-intervention, T₁), as well as after participants have returned home (i.e.,
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30 300 follow-up, T₂-T₄).
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34 302 Baseline sample characteristics

35 303 Demographic data on age and sex will be taken from electronic records. Height will be
36
37 304 ascertained from participants. Bodyweight at T₀ will be assessed with normal clothing, but
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39 305 without shoes, prior to GXT using a digital scale. The corresponding Body Mass Index will
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41 306 then be calculated (kg/m²).
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45 307 Clinical data will include the following. MS disease course, and time since diagnosis (years)
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47 308 will be taken from available medical records in the screening process. In case of an unspecified
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49 309 MS disease course, the participant and the treating physician will be contacted for any further
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51 310 information. EDSS, disease-modifying drugs, fatigue-specific drugs (Amantadine, Modafinil),
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53 311 and drugs decreasing heart rate will be assessed by the treating physician on the day of arrival
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3 312 and made available for the study staff in the electronic health record. Use of assistive devices
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5 313 for walking will be ascertained in conjunction with motor function testing.
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10 315 Feasibility (quantitative)

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12 316 To generate the quantitative feasibility outcomes, we adopted the categories described by
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14 317 Thabane and colleagues[31] and promoted for exercise studies in MS by Learmonth and
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16 318 Motl[32] (see Table 4).
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319 **Table 4** Description of quantitative feasibility outcomes (adapted from[33]).

Classification	Outcome	Operationalization	Importance for future RCT
Process	1. Eligibility rate	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Number/rate of patients completing the intervention period Number/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 organization of the study. Gives information on the feasibility of the primary outcome being assessed post-discharge and via an online platform.
	5. Adherence	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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.

		<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Number 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 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* =

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3 322 Rated Perceived Exertion; *GXT* = Graded Exercise Test; *T25FW* = Timed 25-foot Walk Test; *SSST* = Six Spot Step Test; *FGA* = Functional Gait
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5 323 Assessment; *FSMC* = Fatigue Scale for Motor and Cognitive Functions
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For peer review only

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3 324 Feasibility (qualitative)
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5 325 The qualitative evaluation aims to (a) capture patients' views on acceptance, benefits, and
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7 326 satisfaction with study participation, (b) assess their experiences with the intervention methods,
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10 327 and (c) identify necessary adaptations. For this purpose, we designed a semi-structured interview.
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12 328 Six participants from each study arm will be interviewed face-to-face at T₁. The selection of
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14 329 participants will reflect the greatest possible diversity in terms of gender, age, and EDSS[37].
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17 330 The interview will include a total of 14 questions and will last approximately 20min. Key
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19 331 categories of the interview are the concept of fatigue, experiences and demands of the
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21 332 interventions, personal relevance, and goal achievement. All interviews will be recorded
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23 333 digitally and transcribed verbatim by an independent transcription service.
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26 334 Both interviewers (JN, FW) have several years of clinical experience with pwMS. A first draft
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28 335 of this interview was piloted with three pwMS prior to the start of the feasibility study to ensure
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30 336 that the questions allow valid insights into participants' experiences.
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33 337 The interview will be supplemented by a customized questionnaire asking for prior knowledge
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35 338 of fatigue, prior experiences with MAT and SET, and comprehensibility of the study
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37 339 instructions and questionnaires. The questionnaire also asks about fun and relevance of training
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39 340 for daily life (see Table 4), and the motivation to continue a comparable training at home.
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44 342 Primary outcome for the full RCT
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46 343 Fatigue questionnaires presuppose internal averaging of the amount of fatigue experienced
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48 344 during a certain timeframe[1]. This has been a problem for studies evaluating short-term
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50 345 interventions, as in some questionnaires patients are asked to evaluate their fatigue in
51
52 346 timeframes of up to four weeks. As we are interested in the change in fatigue experienced in
53
54 347 daily life from before the inpatient stay to afterwards, we (I) chose the WEIMuS[38] as the
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56 348 primary outcome measure to assess the fatigue experienced during the past week and (II)
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3 349 established the primary endpoint to be one to two weeks after participants have returned home
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5 350 (T₂). The WEIMuS has 17 items (scored 0 - 4) with higher total scores indicating higher fatigue
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7 351 (range 0 – 68, cut-off for classification as fatigued: 32).

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10 352 For fatigue screening (that is necessary for study eligibility) we will apply the FSMC. It is a 20
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12 353 item Likert-type scale (1 – 5) with a total score (0 – 100) and two subscales relating to motor
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14 354 and cognitive fatigue[39]. The FSMC provides cut-off scores to classify cases of no (total score
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16 355 < 43), mild (≥ 43), moderate (≥ 53) and severe (≥ 63) fatigue, which makes it especially suitable
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18 356 as a tool for classification of fatigue severity[1, 39].

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21 357 Paper versions of both questionnaires will be handed out to participants. When at home,
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23 358 participants will be followed up via e-mail to fill out questionnaires on an online platform
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25 359 (Qualtrics) at timepoints T₂-T₄. Participants will be able to respond to the e-mail request within
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27 360 seven days.

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33 362 Secondary outcomes for the full RCT

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35 363 MS-fatigue is a multifactorial construct that requires assessment of other interrelated
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37 364 constructs[7]. This will include measures of cognitive (Test Battery of Attention Performance
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39 365 – Alertness[40]) and motor fatigability (6-Minute Walk Test [6MWT], Distance Walked
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41 366 Index[41]), cognitive performance (California Verbal Learning Test, Symbol Digit Modalities
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43 367 Test[26, 42]) and cardiorespiratory fitness (GXT on a cycle ergometer, protocol: start 25W,
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45 368 progression 10W/min.). Dynamic balance and motor function (Timed 25-Foot Walk Test
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47 369 [T25FW][43], Six Spot Step Test [SSST][44], Functional Gait Assessment [FGA][45]) will
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49 370 also be assessed as well as self-reported balance confidence (Activities-specific Balance
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51 371 Confidence scale[46]). Depression (Center for Epidemiological Studies Depression Scale
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53 372 [German version][47]) will be assessed as a confounder variable.
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3 373 The subsequent full trial will also include qualitative data to explore the subjective experiences
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5 374 in participants showing a WEIMuS change of 6 or more points from T₀ to T₂ (positive or
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8 375 negative). These ‘responders’ will be contacted for a short telephone interview. Previous data
9
10 376 has shown large differences in fatigue questionnaire change scores[13]. However, the scores
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12 377 do not provide any detail on individual circumstances, including, for example, social or work-
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14 378 related influences, that might be independent of intervention effects. Therefore, we decided to
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17 379 specifically ask participants:

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19 380 ‘The analysis of your questionnaires shows a relevant positive/negative change of
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21 381 your fatigue symptoms, when comparing your scores from pre-rehab to the online
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24 382 questionnaire. What do you personally think is the reason for this?’.

25
26 383 No minimal clinically relevant change scores have been established yet[48]. Thus, the relevant
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28 384 change score (≥ 6 or ≤ -6) was chosen as a pragmatic value of 0.5 SD from the validation
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30 385 study[49]. A similar procedure has been described by Sander and colleagues[1].
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35 387 **Data analysis**

37 388 Quantitative data analysis

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40 389 Descriptive statistics will be used to summarize quantitative feasibility outcomes (Table 4),
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42 390 and baseline sample characteristics. Retention, adherence, fidelity, adverse events, and
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44 391 acceptability measures will be calculated per group. The results will be given as mean and
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46
47 392 standard deviation for continuous data, median and interquartile range, or frequencies (number,
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49 393 %) for categorical data. The same will be applied to baseline and follow-up data for primary
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51 394 and secondary outcomes of the potential full trial. Change scores from baseline will be reported
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53 395 for these outcomes for each of the measurement timepoints. The frequency of participants in
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56 396 each group with a relevant change related to the WEIMuS total score (≥ 6 or ≤ -6 , as described
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58 397 above), will be calculated. However, hypothesis testing of within- or between-group treatment
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3 398 effects will not be performed due to the inherent problems of hypothesis testing based on
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5 399 (small) pilot study data[50, 51]. For the same reasons, no effect sizes will be presented, as they
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8 400 will have a high risk of under- or overestimating the ‘true effect’ of the interventions[52].
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10 401 All analyses will be performed using IBM SPSS Statistics in the most up to date version.
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12 402

14 403 Qualitative data analysis

16 404 Coding of the interviews will be performed according to qualitative content analysis, using a
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18 405 combined model of deductive (a priori) and inductive coding (on the text material) to identify
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20 406 themes and sub-themes[53]. Deductive coding will be based on preliminary considerations and
21
22 407 hypotheses in the study planning and on reviews of relevant literature[37, 54-57]. Coding will
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24 408 be carried out by at least two individuals (JN, FW) to ensure intercoder reliability[58]. The
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26 409 analysis will be supported by MAXQDA® software in the most up to date version[59]. JN and
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28 410 FW will compile the themes emerging from the interview data and discuss these with the wider
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30 411 research team.
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37 413 **Progression requirements to full RCT**

38 414 Falling short of the following feasibility values will necessitate changes to the protocol of the
39
40 415 full RCT:

- 41 416 • Adherence: Average of at least 18 therapy sessions during the stay per group (equals
42 417 6x30min sessions per week for 3 weeks [28 days admission to discharge minus 5 days
43 418 for pre- and post-testing])
 - 44 419 • Recruitment rate: 4 participants/month, <25% non-eligible pwMS, <10% eligible but
45 420 unwilling to participate
 - 46 421 • Retention at T₁: >90% per group
 - 47 422 • Retention at T₂: >80% per group
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3 423 • Time requirements for baseline assessments: >80% able to complete all assessments
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5 424 within the first three days of therapy
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8 425 • Interview statements indicating that the interventions are perceived as relevant,
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10 426 comprehensible, and pleasant
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15 428 **Data management**

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17 429 The principal investigator (FW) will be responsible for data management. Demographic and
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19 430 clinical characteristics will be taken from the electronic health record. All other data will be
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21 431 collected on forms during the inpatient stay and via an online tool for follow-up. Data will be
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23 432 entered into a secure internal network database by study personnel in the NRC. Entered data
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25 433 will be checked for plausibility and compared to the collection forms if necessary. Data will be
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27 434 collected and stored in accordance with the General Data Protection Regulation.
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33 436 **ETHICS AND DISSEMINATION**

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35 437 Written informed consent will be obtained from each participant. Ethical approval was
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37 438 obtained from the Ethics Committee at the Medical Faculty, University of Bonn (reference
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39 439 number: 543/20).
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42 440 The results of this feasibility study will be disseminated regardless of the magnitude or
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44 441 direction of effect in peer-reviewed journals, conferences and the website and magazines of the
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46 442 German Sport University Cologne.
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51 444 **DISCUSSION**

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53 445 This PAFS will give relevant insights for conducting a future RCT in this special setting of
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55 446 inpatient rehabilitation for pwMS. Content-wise, it will (I) translate existing evidence on
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57 447 BMCT in pwMS to this setting, (II) add to this BMCT by introducing the framework of MAT,
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3 448 and (III) apply a clear focus on fatigue as the primary outcome. Specifically, we see the
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5 449 potential of a relatively large training volume (e.g., about eight therapy sessions per week)
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7 450 compared to studies in outpatient settings, and a high amount of supervised exercise, which
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9 451 should provide good adherence and fidelity. Having a therapist as a supervisor is especially
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11 452 important for a rather complex type of exercise as is MAT. For example, there are no simple
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13 453 ‘numbers’ like sets or repetitions one can follow. Quicker movements relating to agility, like
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15 454 changes of direction, acceleration, and deceleration, frequently lie outside the ‘comfort zone’
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17 455 of pwMS, which necessitates guidance of a therapist. Lastly, in the group format, a therapist is
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19 456 mandatory to provide modifications for pwMS with higher disability or very low disability.
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21 457 We also anticipate certain issues in conducting this study. For example, scheduling of
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23 458 appointments for testing will be challenging, as there will be several testing blocks (i.e., motor
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25 459 function, GXT, cognitive tests, interview), conducted in different departments of the NRC,
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27 460 which must be fitted into certain timeslots around admission and discharge. These
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29 461 appointments will compete against other study unrelated appointments (e.g., ward rounds,
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31 462 urology assessments, etc.). Regarding the eligibility and randomization criteria, it will be
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33 463 challenging to have all the correct data within the first two days as there can be delays in the
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35 464 admission process. Intervention duration can be regarded as a general limitation of this project,
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37 465 as it is restricted to the usual inpatient stay for this group of patients in the German national
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39 466 health care system (i.e., four to six weeks). Land- and water-based MAT might have different
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41 467 mechanisms of action, especially when considering the effect of body temperature on
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43 468 demyelinated axons, and the cooling effect present in water[60]. Still, water-based MAT was
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45 469 developed to allow for a greater amount of standardized MAT therapy time. As inpatients must
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47 470 receive a certain amount of therapy time during their stay, not including water-based MAT
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49 471 would have resulted in a greater amount of uncontrolled therapy in the intervention group. In
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3 472 a main trial this would only permit conclusions to be drawn on the treatment effect of
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5 473 concomitant land- and water-based MAT.

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8 474 Lastly, analysis of blood-based biomarkers is planned to be part of the ReFEx study project.
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10 475 However, as these outcomes are connected to comparably high costs for materials and analysis,
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12 476 addition of blood sampling is postponed to the start of a full RCT. Nevertheless, information
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14 477 gathered during the feasibility study will be used to allow for smooth integration of blood draws
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17 478 and storage during assessments at admission and discharge. As the blood draws can be regarded
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19 479 as the most unpleasant part of the assessments for patients, feasibility of the interventions and
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21 480 patient acceptance should be established first.
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25 26 482 **Author contributions**

27
28 483 FW, JN, ME, PZ designed the overall study. FW & JN designed the feasibility study and wrote
29
30 484 the protocol. FW, JN, JS, EH implemented the screening and assessment procedures. JS, EH,
31
32 485 ME, AKF, HK, PZ revised the manuscript. All authors read and approved the final manuscript.
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35 486

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46 47 491 **Competing interests**

48
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50
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55 495 Fortbildungszentrum Rheine, Germany, and LOGOMANIA, Fendt & Sax GbR, Munich,
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3 496 Germany. AFK is author of the cognitive training program NEUROvitalis but receives no
4
5 497 corresponding honoraria. HK: none. PZ: none.
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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		

1	"Movement memory" DB		
2	<i>Participants move through the gym while performing gait variations coded with various commands given by therapist.</i>		
3	Progression: Movement	Progression: Number of pairs	
4	Tasks for one side of body	4 to 8	
5	Tasks for both sides of body (e.g. left knee up & right hand to left shoulder)		
6	Similarity of movements		
7	Sensory modification	Visual: - Somatosensory: - Vestibular: -	
8	Cognitive add-on (main focus)	Memory: Recall pairs (movement+number / movement+color word / movement+number or color word) Inhibition: command = stop	
9			
10			
11	"Remote control" DB		
12	<i>Pairs of two: a participant is steered through the room with closed eyes via tactile cues of the partner.</i>		
13	Progression: number of cues	Progression: movement	
14	3 to 6	Tandem walk, high knees	
15	Sensory modification	Visual: closed eyes Somatosensory: - Vestibular: turning in place	
16	Cognitive add-on	Spatial orientation: report location in space to partner (closed eyes)	
17			
18			
19	Walking with tasks AG		
20	<i>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.</i>		
21	Progression: DOM, speed	Progression: movement	Progression: tools
22	Forwards, backwards, sideways	Tasks for one side of body	Kind of objects (small sacks, balls, ...)
23	walking, jogging	Tasks for both sides of body (e.g. left knee, right hand)	
24	Sensory modification	Visual: - Somatosensory: - Vestibular: Head turns (horizontal)	
25	Cognitive add-on	-	
26			
27	Agility ladder AG		
28	<i>Participants perform exercises in an agility ladder on the floor. Number and type of foot contacts in each field are varied.</i>		
29	Progression: DOM, speed	Progression: complexity	Progression: tools
30	Forwards, backwards, sideways	Easier sequences (2 / 3 touches) Harder sequences (1,2,3,2,1 / 2 forwards 1 back / 2 in 1 out)	Kind of objects (small sacks, balls, ...)
31	Sensory modification	Visual: - Somatosensory: - Vestibular: Head turns	
32	Cognitive add-on	Divided attention: Participants have to call numbers shown by therapist Divided attention: Participants have to catch objects thrown by therapist	
33			
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35			
36	Cone tipping AG		
37	<i>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.</i>		
38	Progression: speed, duration	Progression: number of cones	
39	Walking, jogging 1 round = 30s	4 to 8	
40	Sensory modification	Visual: - Somatosensory: - Vestibular: -	
41	Cognitive add-on	Spatial orientation & memory: directions are given by numbers, colors or alphabet	
42			
43			
44	Slalom AG		
45	<i>Participants move through a slalom parcour.</i>		
46	Progression: speed, duration	Progression: number of obstacles	Progression: competition
47	Walking, jogging 1 round = 60-90s	4 to 8	Hit a target with an object at the end of slalom
48	Sensory modification	Visual: - Somatosensory: - Vestibular: -	
49	Cognitive add-on	-	
50			
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52			
53	Soccer AG		
54	<i>Participants move and pass a ball.</i>		
55	Progression: speed, duration	Progression: number of players	Progression: change of direction
56	Walking, jogging 1 round = 60-90s	1 to 4	Front - back Front - back and sideways Random
57	Sensory modification	Visual: - Somatosensory: - Vestibular: -	
58	Cognitive add-on	Attention: participants have to react to stop and change of direction signals by therapist	
59			
60			

"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.

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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]

For peer review only



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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 ___

1 **Introduction**

2

3 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___

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6 6b Explanation for choice of comparators ___4-5___

7

8 Objectives 7 Specific objectives or hypotheses ___5-6___

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10 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___

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14 **Methods: Participants, interventions, and outcomes**

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16 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___

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19 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___

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered ___10-13___

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24 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___

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26 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) ___16-17___

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28 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial ___10-11___

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30 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___

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34 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___

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1	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___
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___8___
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7	Methods: Assignment of interventions (for controlled trials)			
8	Allocation:			
9				
10	Sequence	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___
11	generation			
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16	Allocation	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___
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___8-9___
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___14___
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___n/a___
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31	Methods: Data collection, management, and analysis			
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33	Data collection	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___
34	methods			
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39		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___
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1	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____
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5	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____
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____n/a____
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10		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____
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14	Methods: Monitoring			
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16	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____
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22		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____
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25	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____
26				
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28	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____
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____23____
35				
36				
37	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____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____8_____
2				
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____n/a_____
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7	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_____
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10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____25-26_____
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13	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_____
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16	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_____
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20	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_____
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24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____25_____
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26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____n/a_____
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___Supplement___
32				
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34	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_____
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
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