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Rationale and design of the STEP for MS Trial: Comparative effectiveness of Supervised versus Telerehabilitation Exercise Programs for Multiple Sclerosis

Robert W. Motl[a,*], Deborah Backus[b], Whitney N. Neal[a], Gary Cutter[c], Louise Palmer[b], Robert McBurney[d], Hollie Schmidt[d], Francois Bethoux[e], Jeffrey Hebert[f], Alexander Ng[g], Kevin K. McCully[h], Prudence Plummer[i]

[a] Department of Physical Therapy, University of Alabama at Birmingham, United States of America
[b] Shepherd Center, United States of America
[c] Department of Biostatistics, University of Alabama at Birmingham, United States of America
[d] Accelerate Cure Project for Multiple Sclerosis, United States of America
[e] Mellen Center for MS, Neurological Institute, Cleveland Clinic, United States of America
[f] School of Medicine, University of Colorado Anschutz Medical Campus, United States of America
[g] Program in Exercise Science, Department of Physical Therapy, Marquette University, United States of America
[h] Department of Kinesiology, University of Georgia, United States of America
[i] Division of Physical Therapy, University of North Carolina at Chapel-Hill, United States of America

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ABSTRACT

Background: We propose a Phase III trial that compares the effectiveness of an exercise training program delivered in a facility-based setting with direct, in-person supervision or a home-based setting with remote supervision via telerehabilitation for improving walking performance in persons with multiple sclerosis(MS) who have walking dysfunction and mobility disability.

Methods/design: The study was developed with stakeholder engagement and is a multi-site trial that follows a 2-stage, randomized choice design. The trial compares the effectiveness of a 16-week evidence-based, individualized exercise program delivered in a supervised, facility-based setting versus a remotely coached/guided, home-based setting using telerehabilitation in physically inactive and cognitively intact people with MS who have walking dysfunction and mobility disability($N = 500$). The primary outcome is walking speed. The secondary outcomes are walking endurance, disability status, and patient-reported outcomes of physical activity, walking impairment, fatigue, and quality of life. The components of the exercise program itself are similar between the groups and follow the *Guidelines for Exercise in MS* protocol. This includes a program manual, exercise prescription, exercise equipment, social-cognitive theory materials including newsletters, logs, and calendars, and one-on-one behavioral coaching by exercise specialists with background in MS. The main difference between groups is the coaching approach and setting for delivering the exercise training program. The outcomes will be collected by treatment-blinded assessors at baseline(week 0), mid-intervention(week 8), post-intervention(week 16), and follow-up(week 52).

Discussion: The proposed study will provide evidence for the effectiveness of a novel, widely-scalable program for delivering exercise training in persons with MS who have walking dysfunction and mobility disability.

1. Introduction

Multiple sclerosis (MS) is a progressive, autoimmune-mediated disease with an estimated prevalence of nearly 900,000 adults in the United States and 2.5 million adults worldwide [1,2]. The expression of this disease typically begins with intermittent episodes of inflammation in the central nervous system (CNS) that result in the demyelination and transection of axons in the brain, optic nerves, and spinal cord; this transitions over time into a neurodegenerative disease associated with lack of neurotrophic support and neuronal loss [3,4]. The location and

* Corresponding author at: Department of Physical Therapy, University of Alabama at Birmingham, 336 SHPB, Birmingham, AL 35294, United States of America.
E-mail address: robmotl@uab.edu (R.W. Motl).

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degree of damage within the CNS results in heterogeneous outcomes, including neurological disability [5] and walking dysfunction [6,7] that compromise quality of life (QOL) [8].

The first-line approach for managing MS involves disease-modifying drugs that target specific components of the immune system, and this may be complemented by exercise training programs as part of symptom management and rehabilitation of function [9]. There is a large body of evidence from mostly small, phase II trials regarding the efficacy of exercise training programs for improving outcomes in adults with MS [9,10]. Nevertheless, adults with MS generally do not engage in sufficient amounts of physical activity for health benefits, particularly when compared with healthy adults from the general population [11]. Such observations have supported the development of prescriptive guidelines [12] and social-cognitive theory (SCT) based behavioral interventions [13] that support exercise training programs delivered in facility-based environments with direct supervision or home-based settings with indirect supervision through telerehabilitation for managing the consequences of MS [14,15]. The comparison of home-based telerehabilitation with facility-based programs for improving walking outcomes has been previously undertaken in other populations [16], but not in MS; this disease has unique features and manifestations that support a focal examination rather than reliance upon other bodies of evidence. Importantly, the choice or preference for the environment/setting might influence adherence with and outcomes of exercise training programs, but this has not been explicitly examined in persons with MS.

This paper describes the scientific research protocol for the Supervised versus Telerehabilitation Exercise Programs for Multiple Sclerosis (STEP for MS) Trial (see lay description provided in clinicaltrials.gov, NCT03468868); this trial is not overlapping with other, ongoing registered trials involving MS (e.g., NCT03490240 or NCT03468868). The STEP for MS Trial is a Phase III study that is delivered using a 2-stage, randomized choice design [17]. The research design allows for separating treatment effects from those resulting from choosing the preferred delivery mode of exercise training. This design allows for a comparison of the effectiveness of an exercise training program delivered using two approaches (i.e., supervised, facility-based setting or a remotely coached/guided, home-based setting using telerehabilitation) for improving walking performance in persons with MS who have been prescreened for walking dysfunction and mobility disability. The exercise training program is based on the prescriptive guidelines for physical activity in MS [12] and supported by behavioral coaches delivering strategies that align with SCT for optimizing adherence and compliance with the intervention [13,18]. The root of the intervention has undergone feasibility testing [14,15] and informed the design of the STEP for MS Trial.

The primary hypothesis is one of noninferiority whereby we hypothesize that home-based exercise training is worse in favor of the alternative that there will be no difference in the improvement of walking speed when the exercise training program is delivered in a facility. The secondary hypothesis is one of superiority whereby we expect that choice-based conditions will yield larger improvements in walking speed than non-choice-based conditions (i.e., random assignment into group), as choice may result in greater adherence with the exercise training programs.

2. Methods

2.1. Study design and overview

The STEP for MS Trial was developed with stakeholder engagement and represents a multi-site trial that follows a 2-stage, randomized choice design [17]. This design was selected through the review process with PCORI and involves randomization into choice or no choice conditions in stage 1, and then choice of condition (i.e., participant selects the setting for performing the exercise training program) or further randomization of condition (i.e., random assignment into condition) in stage 2. The trial will compare the effectiveness of a 16-week evidence-based exercise program delivered in a supervised, facility-based setting versus a remotely coached/guided, home-based setting using telerehabilitation for improving walking in 500 volunteers with MS who have walking dysfunction and mobility disability. The primary outcome is walking speed based on the Timed 25-Foot Walk (T25FW) [19,20]. The T25FW is considered the best characterized measure of walking performance in MS [19] with strong psychometrics and real world relevance [20], and the T25FW can be administered based on standard instructions [19,20] for fidelity across sites. The secondary outcomes are walking endurance based on the 6-Minute Walk (6MW) [21], disability status measured by the Expanded Disability Status Scale (EDSS) [22], as well as patient-reported outcomes of physical activity participation (Godin Leisure-Time Exercise Questionnaire [GLTEQ]) [23], walking impairment measured by the 12-item Multiple Sclerosis Walking Scale (MSWS-12) [24], fatigue (Modified Fatigue Impact Scale-21 [MFIS-21]) [25], and QOL measured by the Quality of Life in Neurological Disorders (Neuro-QOL) [26] survey and the Multiple Sclerosis Impact Scale-29 (MSIS-29) [27]. Other endpoints include SCT variables of self-efficacy, outcome expectations, goal setting, self-regulation, and barriers/facilitators for physical activity. All outcomes were selected with stakeholder involvement. The components of the exercise training program itself are similar between conditions and follow the *Guidelines for Exercise in MS* (GEMS) protocol [14,15]. This includes a program manual, exercise prescription, exercise equipment, SCT materials including newsletters, logs, and calendars, and one-on-one behavioral coaching by exercise specialists with background in MS. The outcomes will be collected by treatment-blinded assessors at baseline (week 0), mid-intervention (week 8), post-intervention (week 16), and follow-up (week 52); the follow-up is essential for identifying sustainability of the exercise program beyond the formal intervention, training period. All data will be entered and stored on a secure web-based portal. The STEP for MS Trial includes a Data Safety and Monitoring Board and the protocol has been reviewed and approved by appropriate Institutional Review Boards. All participants will provide written informed consent consistent with standards set forth by the Office of Human Research Protection and outlined in the Common Rule.

2.2. Stakeholder engagement

The STEP for MS Trial is funded by the Patient-Centered Outcomes Research Institute (PCORI; MS-1610-36999). One hallmark feature of PCORI funding is a mandate requiring meaningful involvement of patients, caregivers, clinicians, and others as stakeholders in the health research process, from research topic development through the dissemination of study results [28]. Stakeholders for the STEP for MS Trial include people with MS, caregivers, clinicians (physicians and rehabilitation providers with experience in MS), community exercise specialists, and other healthcare stakeholders (e.g., representatives from MS advocacy groups, including the National MS Society (NMSS) and the PCORI-funded people-powered research network iConquerMS, a policy maker, and an insurance representative). These stakeholders have sustained involvement in the study, providing input and guidance as participants in earlier exercise trials, as co-investigators, as members on the study advisory board, and through participation in focus groups. The exercise intervention for this trial was developed and tested for feasibility with stakeholder input during previous feasibility and pilot trials of the intervention [14,15]. We included a person with MS as a co-investigator, member of the study steering committee, and chair of the advisory board. This person with MS and the other members of the STEP for MS advisory board provided input for the delivery and evaluation methods of the intervention, and revisions of the participant training manual and other study materials. The advisory board was involved in final determination of screening tools, selection of primary and secondary outcome measures, development and testing of the

study-specific web portal, and decisions regarding the frequency and length of assessment visits. The advisory board has further assisted in resolving issues regarding participant burden and portal interactions as well as identifying strategies for participant recruitment. The study advisory board met monthly during the planning phase and will meet every 2 months during the intervention phase for discussion of all trial activities. During the final, post-intervention phase, the advisory board will be engaged in data interpretation and determination of the appropriate messages and products for dissemination among the MS community.

2.3. Multi-site study settings

Seven study sites were selected for conducting this trial based on four criteria: (1) presence of investigators with both MS and exercise experience; (2) demonstrated accessibility to people with MS; (3) representation of geographic, racial and ethnic diversity, and (4) variability in site characteristics, based on the types of settings in which people with MS can safely exercise. Of the seven sites, two sites are located in purely clinical settings (Shepherd Center, the lead center, Atlanta, Georgia; and the Mellen Center at the Cleveland Clinic, Cleveland, Ohio), three in purely academic settings (Marquette University, Milwaukee, Wisconsin; the University of North Carolina, Chapel Hill, North Carolina; and the University of Georgia, Athens, Georgia), and two in hybrid environments described by a combined clinical and research emphasis (University of Alabama at Birmingham, the Intervention Center, Birmingham, Alabama; and the University of Colorado Anschutz Medical Campus, Aurora, Colorado).

The multi-site nature of the STEP for MS Trial requires a plan for maintaining data integrity and the implementation of intervention fidelity across sites. Accordingly, all research staff at collaborating sites received training on all study procedures and will receive annual follow-ups that ensure processes and procedures are being followed with fidelity. All research coordinators and evaluators are trained for administration of outcome measures and participate in periodic phone conferences targeting fidelity of the outcome measures. Study procedures are further detailed in a Study Operations Manual provided per site and maintained in a central location where research staff can access updates in a timely manner. The behavioral coaches receive training on both the GEMS program for exercise training and SCT principles of behavior change for physical activity. Coaches further meet weekly via teleconference with the project co-PI and intervention site project coordinator, as well as behavioral coaches from the other collaborating sites. This permits discussion of experiences and problems encountered with delivering the program elements for harmonization across sites.

2.4. Participant recruitment and screening

The target sample is 500 participants with MS who meet study eligibility criteria and voluntarily agree on participation (i.e., motivated volunteers). The participants will be enrolled in 8 waves across the seven centers between 2018 and 2022. Participants will be recruited through existing research and clinical databases per study site, direct contact with patients on site (by providers and other clinical or research staff), and word-of-mouth using a flyer. Recruitment will further be undertaken through social media (i.e. Facebook, Twitter), members of the study advisory board, and other patient advocates. The same recruitment strategies will be utilized per site and supplemented as needed through local NMSS chapters, iConquerMS, and other partners. Those who receive a study advertisement and who are interested in participating will contact the research coordinator at the nearest site either by email or telephone, and the research coordinator will describe the study and its procedures, answer any questions, and conduct a screening for inclusion criteria.

Screening will occur in three phases (Fig. 1). The 1st screening takes place over the phone and assesses basic eligibility criteria including self-reported diagnosis of MS, age, ability to travel to the site, relapse status, falls history, cognitive status and other comorbidities. Participants who meet the basic criteria will be read a consent script requesting permission to perform and record the responses to the surveys in the 2nd screen; this too will occur over the phone. The 2nd screening evaluates walking ability (MSWS-12) [24], disability status (Patient-Determined Disease Steps [PDDS]) [29], and physical activity participation (GLTEQ) [23]. These first two screens provide a cost-effective way of identifying individuals who meet the basic inclusion criteria before embarking on “on-site” screening and data collection; this is cost-effective for both the research institutions and candidate participants. Participants who meet all inclusion criteria within the two-part phone screen will complete the Exercise Preparticipation Health Screening [30] to determine if medical clearance from a medical provider is necessary before beginning an exercise program. If medical clearance is required, this must be obtained from the participant's medical provider prior to the 3rd screening. Medical clearance will be obtained using a standardized form that explains the nature of the exercise training program and identifies any reported contraindications. The 3rd screening for eligibility will be conducted on-site, wherein the participant will provide written informed consent and undergo additional clinician-administered assessments of walking (T25FW and 6MW) [19–21], disability status (EDSS) [22], and cognition (Mini-Mental State Examination [MMSE] [31]). Upon successful completion of the 3rd screen, participants will be enrolled in the study and randomized into the first level assignment (randomization or choice) and then further randomized or self-selected into an intervention condition. Those who are not eligible will be provided with the *Canadian Physical Activity Guidelines* [12].

2.5. Participant eligibility

The inclusion and exclusion criteria for this study are detailed in Table 1 by stage of screening. These criteria were selected in order to identify healthy people with MS who are ambulatory, but experience walking dysfunction, and who are not already meeting the guidelines for physical activity [12]. These criteria were further selected based on appropriateness of the sample for the MS guidelines for physical activity, and safe provision of the intervention within the facility-based or home-based settings.

2.6. Sample size calculations

This randomized choice design is aimed at demonstrating noninferiority of the remotely coached/guided, home-based exercise program delivered using telerehabilitation (GEMS-Telerehab or GEMS-T) compared with the supervised, facility-based exercise program (GEMS-Supervised or GEMS-S) using the T25FW as the primary outcome [19,20]. The noninferiority will combine both the Choice and No Choice (i.e., random assignment into group) and within subgroup comparisons. If we succeed in rejecting inferiority, we will test between the Choice and No Choice conditions within treatment arms (i.e., GEMS-S or GEMS-T).

We assume the difference between GEMS-S and GEMS-T is equivalent in both Choice and No Choice conditions with the expected difference set at 0 s. With the overall combined test of the two groups pooled, assumptions of the noninferiority margin of 2 s and expected difference of 0, we have 90% power to demonstrate noninferiority with 108 per group. The rationale for the 2 s margin is based on previous research demonstrating that a 20% difference in the T25FW is a meaningful difference (i.e., minimal clinically important difference) and that 2 s would be a conservative estimate [32,33].

Our approach is to also have power at the subgroup, Choice and No Choice levels. Thus, we will randomize 500 participants (125 each for GEMS-S and GEMS-T) to the Choice condition (250 participants) and No Choice condition (250 participants) providing adequate power at

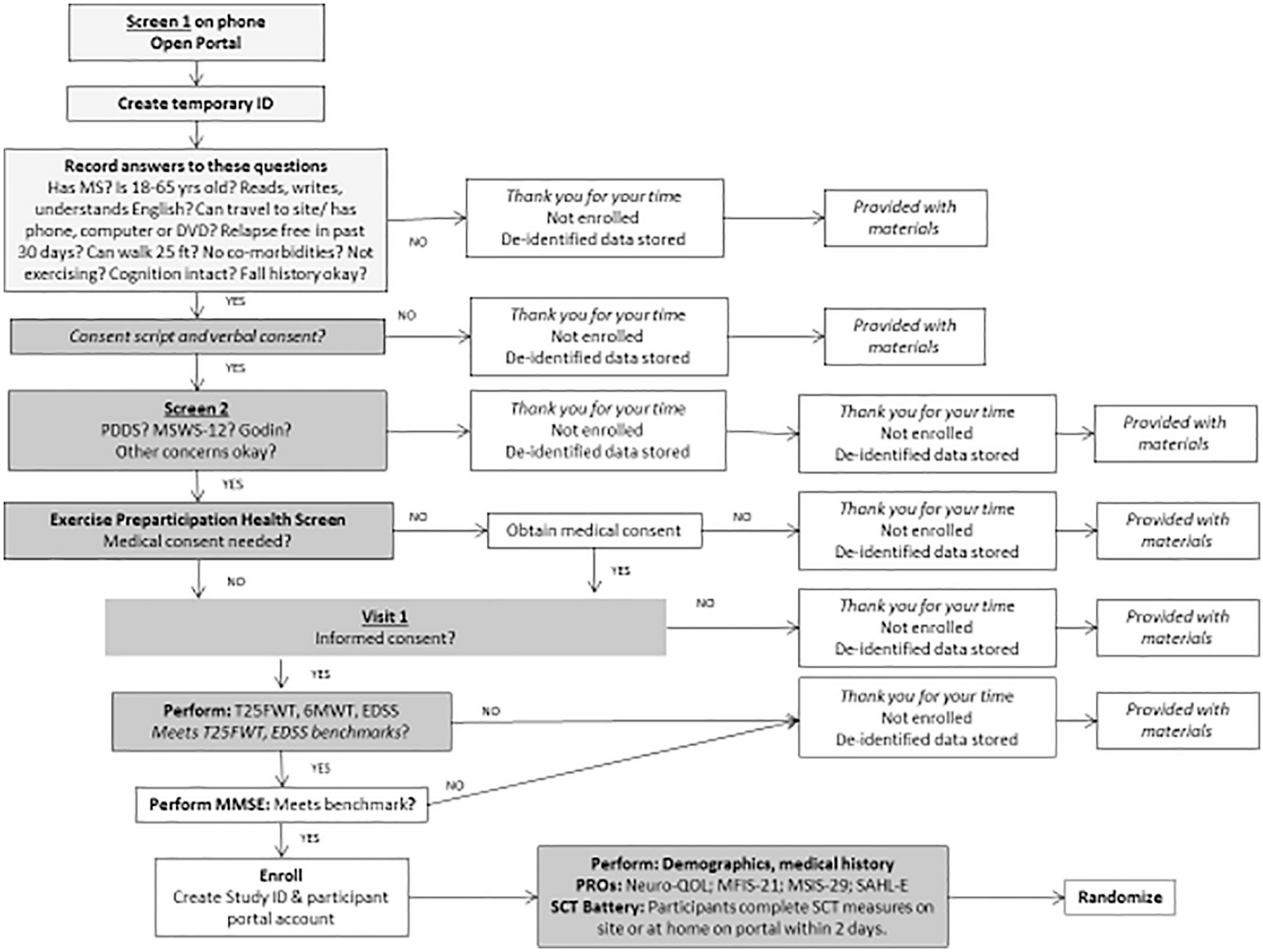

Fig. 1. Overview of screening procedures.

Table 1
Inclusion and exclusion criteria by screen.

Inclusion criteria	Exclusion criteria
Screen 1	
Self-reported diagnosis of MS	Documented MS relapse in the past 30 days
Accessible, technological platform for GEMS-T (i.e. computer or DVD player and TV, and telephone)	Occurrence of falls in the past three months that the study investigator determines makes participation unsafe
Able and willing to travel to a site for testing and/or training	Unable to walk 25 ft
	Not proficient in English
Age between 18 and 65 years	Other neurological (e.g., stroke) or musculoskeletal conditions or other comorbidities
	Any other concerns that the investigators deem would jeopardize the safety of the potential participant
Screen 2	
Score between 25 and 75 on the MSWS-12	Score of 25 or higher based on Health Contribution score from the GLTEQ
Score between 3 and 6 (inclusive) on the PDDS	
Medically stable as determined by the Exercise Preparticipation Health Screening or approval from physician to participate in exercise studies	
Screen 3, Visit 1	
EDSS score of 4.0 through 6.5	Cognitive difficulties as determined by a Mini Mental Status Exam score < 19
T25FW time between 6 s and 3 min	Any other concern that the investigators deem would jeopardize the safety of the potential participant

Note. MS = multiple sclerosis; GEMS-T = Guidelines for Exercise in Multiple Sclerosis-Telerehabilitation; MSWS-12 = Multiple Sclerosis Walking Scale-12; PDDS = Patient-Determined Disease Steps; GLTEQ = Godin Leisure-Time Exercise Questionnaire; EDSS = Expanded Disability Status Sale; T25FW = Timed 25-Foot Walk.

the Choice and No Choice levels to demonstrate noninferiority. We assume a 50/50 split in the Choice condition will result, but use 125 versus 108 required to insulate against deviations from this even split in the Choice condition. Even if all participants choose one treatment or another, the comparisons and information is still important. If GEMS-T is selected by most individuals, comparison of the treatment effects between the choice and randomized GEMS-T is important information and an important comparison and equivalently if a majority chooses GEMS-S. Thus, our concern for the 50/50 split is minimized since the choice itself is of importance and interest.

Within each treatment arm (GEMS-S vs GEMS-T) across Choice and No Choice, assuming we achieve noninferiority within both groups, we will test superiority of the Choice group compared to the No Choice group. Since this is conditional on the initial achievement of non-inferiority, this subgroup hypothesis test will be performed at the 0.05 level. Considering that we will be conducting two superiority tests, one for each Choice group, we use a two-sided type I error adjusted for the two comparisons of 0.025. If the mean difference between Choice and No Choice is 2 s (implying that Choice yields improved results), a sample size of 121 in each group will have 80% power to detect a difference in means of 2 s, assuming that the common standard deviation is 5 using a two-group *t*-test with a 0.025 two-sided significance level.

2.7. Randomization

Randomization is pre-programmed into the study web-based portal. We will randomize 250 participants into the Choice condition (i.e., preference for setting for performance of the exercise training program) and 250 participants into the No Choice condition (i.e., random assignment into an exercise training program). Those randomized into the Choice condition will select an exercise training program to undertake – GEMS-S or GEMS-T. Those randomized into the No Choice condition will be randomly assigned (1:1) into condition such that 125 participants will be randomized into GEMS-S and 125 participants into GEMS-T. Fig. 2 provides an overview of the randomization process.

2.8. Outcomes

Data for all outcome measures will be entered into the HIPAA-compliant study web-based portal. The performance/clinical outcomes will be administered by research staff per site, whereas the patient-reported outcomes (PROs) are completed on the portal by the participants. Research staff collecting clinical outcomes (evaluators) will be blinded regarding the intervention assignment per participant, and all PROs will be entered by the participant into the study web-based portal; data will be anonymous and linked only by the study ID number assigned during enrollment. Importantly, the outcomes were selected based on extensive discussion with the stakeholders, and the stakeholders and investigators agreed in consensus on the primary and secondary outcomes for this trial; these outcomes were all listed in our funded proposal.

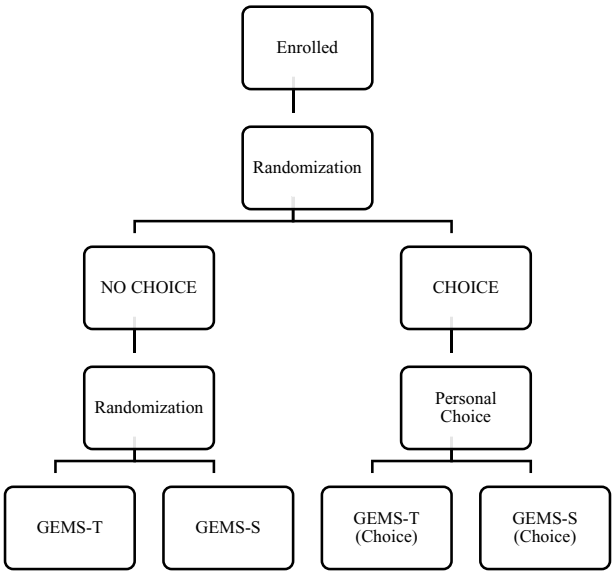

Fig. 2. Randomization scheme for the STEP for MS study.
Note. GEMS-S = Guidelines for Exercise in Multiple Sclerosis-Supervised; GEMS-T = Guidelines for Exercise in Multiple Sclerosis-Telerehabilitation.

2.8.1. Primary outcome

The Timed 25-Foot Walk (T25FW) is the primary outcome and provides an objective, performance-based measure of walking speed [19,20]. The T25FW expressed as 25/time in seconds yielding feet per second was selected as the primary outcome as it is considered the best characterized measure of walking performance in MS [19] with real world relevance [20] and can be administered based on standard instructions [19,20] for fidelity across sites. There further is strong and consistent evidence for the test-retest reliability and construct validity of scores from the T25FW in persons with MS. [19,20] The participant will walk across a marked, 25-foot path as quickly and as safely as possible on two consecutive trials, and the evaluator will record the time per trial in seconds. The average of the two trials will serve as the T25FW outcome for analysis.

2.8.2. Secondary/other outcomes

2.8.2.1. Six-minute walk (6MW). The 6-Minute Walk (6MW) represents an objective, performance-based measure of walking endurance with strong test-retest reliability and construct validity in MS [21]. The 6MW has been well characterized in MS [6], and will be administered based on standard instructions for MS[21]. The participant will walk as far and as fast as possible based on standardized instructions for MS [21]. The participant will be allowed to take rests as necessary, and the evaluator will record total distance walked over the 6-minute period in feet.

2.8.2.2. Expanded Disability Status Scale (EDSS). The Expanded Disability Status Scale (EDSS) is a common clinical endpoint for measuring disability status and its progression in MS [22]. The EDSS will be administered by a Neurostatus-certified examiner using the Neurostatus scoring grid, and consists of seven (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral) neurological functional systems. The scores from the functional systems plus ambulatory status are combined into a composite EDSS score that ranges between 0 (normal neurological examination) through 10 (death caused from MS); scores between 4 and 6.5 are considered as reflective of moderate disability status [5,22] and are required for inclusion in this study.

2.8.2.3. Questionnaires or PROs. The PROs will be completed by participants via the HIPAA-compliant study web-based portal, either at the study site or at the participant's home. Participants will be trained in use of the portal, and the research coordinator will assist only with technical and accessibility difficulties, as necessary. During working hours, a member of the Data Management team will be available for technical difficulties with the web-based portal. All of the PROs have evidence supporting the psychometric properties in MS.

Physical activity will be measured using the GLTEQ [23]. The GLTEQ includes 3 items for measuring physical activity participation during the previous 7-day period. Participant perceptions of walking impairment will be measured by the 12-item Multiple Sclerosis Walking Scale (MSWS-12) [24,34]. The MSWS-12 measures the impact of MS on walking ability and daily activities over the past 2 weeks. Fatigue will be measured by the Modified Fatigue Impact Scale (MFIS) [25], a 21-

item measure of the physical, cognitive, and psychosocial impact of fatigue on daily life over the past four weeks. QOL will be measured by the Quality of Life in Neurological Disorders (Neuro-QOL) [26] survey and the Multiple Sclerosis Impact Scale-29 (MSIS-29) [27]. The Neuro-QOL evaluates the physical, mental, and social effects experienced by adults and children with neurological disorders. The MSIS-29 is a 29-item, disease-specific measure of mental and physical domains of QOL over the past 4 weeks developed for people with MS.

We will measure the SCT variables of outcome expectations (Multidimensional Outcome Expectancies for Exercise Scale [MOEES]) [35], self-regulation (Physical Activity Self-Regulation scale [PASR-12]) [36], goal-setting (Exercise Goal-Setting scale [EGS]) [37], exercise self-efficacy (Exercise Self-Efficacy scale [ESE]) [38], barriers self-efficacy (Barriers for Self-Efficacy [BSE]) [39], and facilitators (Social Provisions Scale [SPS]) [40].

2.9. Exercise intervention – GEMS

The STEP for MS Trial delivers the Guidelines for Exercise in MS (GEMS) program [14,15] in one of two settings, namely supervised, facility-based exercise training (GEMS-S) or remotely coached/guided, home-based setting using telerehabilitation (GEMS-T). GEMS-S will be delivered directly through the seven recruiting sites and GEMS-T will be delivered via the Intervention Center, located at the Exercise Neuroscience Research Laboratory at the University of Alabama at Birmingham (UAB), and undertaken within a participant's home/community. Both intervention conditions consist of an exercise prescription, one-on-one coaching, newsletters, action-planning via calendars, and logs for self-monitoring. The schematic of the program and its elements is provided in Fig. 3.

2.9.1. Exercise prescription

The GEMS exercise prescription is based on the physical activity guidelines for adults with MS who are aged 18–64 years and who have mild-to-moderate disability (i.e., defined as EDSS 0-7) [12]. The guidelines outline the processes and conditions whereby a person with MS can safely, appropriately, and effectively engage in physical activity to promote fitness and health benefits. The guidelines specify 30+ minutes of moderate-intensity aerobic exercise twice per week and resistance training for major muscle groups twice per week [12]; the aerobic and resistance training sessions can occur on the same day of the week, but an individual should have one day of rest between sessions.

The aerobic exercise training will focus on walking as the modality. This decision was based on walking being the most common mode of exercise for people with mild to moderate MS [41] that can be administered in supervised and non-supervised environments. Walking as an aerobic exercise modality further is consistent with our primary and secondary outcomes of mobility disability, namely the T25FW, 6MW, and MSWS-12. The progression of the aerobic exercise training duration will follow three different trajectories for individualization. All participants will start with the same duration of aerobic exercise for the first, 2-week period, consisting of 10 min of walking per day undertaken twice per week. This first, 2-week period is deemed an accommodation period, and further serves as a benchmark for selecting a trajectory for the remaining 14 weeks of the program. There will be three trajectories of progression over the remaining 14 weeks (Orange, Blue, and White) whereby the minimal dose of aerobic exercise will be achieved by 6, 8, or 10 weeks respectively (see Table 2). The intensity will be based on a step rate of 100 steps per minute; this stepping rate corresponds with moderate-intensity exercise in persons with MS [42] and can be modified based on the degree of mobility disability. Participants who require an assistive or orthotic device for walking will be encouraged to utilize these during the walking exercise. In addition, participants will be instructed to walk as fast as is safely possible, even if they cannot achieve the intensity prescribed. GEMS-S participants will complete the aerobic portion of the intervention at the facility by walking on an indoor/outdoor track or treadmill, whereas GEMS-T participants will complete the aerobic training in the home and/or community (e.g., park, shopping mall, gym).

The strength training will consist of 1–2 sets, 10–15 repetitions of 5–10 exercises targeting lower body, upper body, and core muscle groups performed 2 days a week. The lower body exercises are the chair raise, calf raise, knee flexion, knee extension, and the lunge; the upper body resistance exercises are the shoulder row, shoulder raise, elbow flexion, and elbow extension; and the core exercise is the abdominal curl. There are further modifications of the exercises for ensuring safety (e.g., completing the shoulder row while seated, instructing the participant to hold on to a sturdy chair, piece of equipment, or wall for balance during the calf raise). As with the aerobic exercise training, the

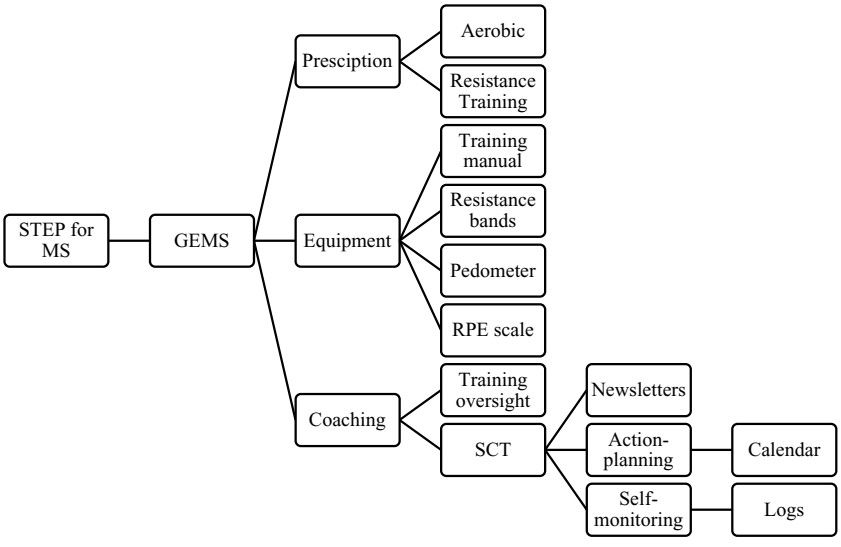

Fig. 3. Outline of the STEP for MS program.
Note. GEMS = Guidelines for Exercise in Multiple Sclerosis; RPE = rate of perceived exertion; SCT = social cognitive theory.

Table 2
Progression of the 3 levels of progression of the STEP for MS program.

Week	Orange		Blue		White	
	Aerobic Training	Resistance Training	Aerobic Training	Resistance Training	Aerobic Training	Resistance Training
Phase I						
1	10 min, ~1000 steps			1S, 10R, 5E		
2	10 min, ~1000 steps			1S, 12R, 5E		
Phase II						
3	15 min, ~1500 steps	1S, 15R, 5E	15 min, ~1500 steps	1S, 12R, 5E	10 min, ~1000 steps	1S, 12R, 5E
4	20 min, ~2000 steps	2S, 10R, 5E	15 min, ~1500 steps	1S, 15R, 5E	15 min, ~1500 steps	1S, 12R, 5E
5	25 min, ~2500 steps	2S, 12R, 5E	20 min, ~2000 steps	1S, 15R, 5E	15 min, ~1500 steps	1S, 15R, 5E
6	30 min, ~3000 steps	2S, 15R, 5E	20 min, ~2000 steps	2S, 10R, 5E	20 min, ~2000 steps	2S, 10R, 5E
7	30 min, ~3000 steps	2S, 15R, 6E	25 min, ~2500 steps	2S, 12R, 5E	20 min, ~2000 steps	2S, 10R, 5E
8	30 min, ~3000 steps	2S, 15R, 6E	30 min, ~3000 steps	2S, 15R, 5E	25 min, ~2500 steps	2S, 12R, 5E
9	30 min, ~3000 steps	2S, 15R, 7E	30 min, ~3000 steps	2S, 15R, 6E	25 min, ~2500 steps	2S, 12R, 5E
10	30 min, ~3000 steps	2S, 15R, 7E	30 min, ~3000 steps	2S, 15R, 6E	30 min, ~3000 steps	2S, 15R, 5E
11	30 min, ~3000 steps	2S, 15R, 8E	30 min, ~3000 steps	2S, 15R, 7E	30 min, ~3000 steps	2S, 15R, 6E
12	30 min, ~3000 steps	2S, 15R, 8E	30 min, ~3000 steps	2S, 15R, 8E	30 min, ~3000 steps	2S, 15R, 6E
13	30 min, ~3000 steps	2S, 15R, 9E	30 min, ~3000 steps	2S, 15R, 8E	30 min, ~3000 steps	2S, 15R, 7E
14	30 min, ~3000 steps	2S, 15R, 9E	30 min, ~3000 steps	2S, 15R, 9E	30 min, ~3000 steps	2S, 15R, 8E
15	30 min, ~3000 steps	2S, 15R, 10E	30 min, ~3000 steps	2S, 15R, 10E	30 min, ~3000 steps	2S, 15R, 9E
16	30 min, ~3000 steps	2S, 15R, 10E	30 min, ~3000 steps	2S, 15R, 10E	30 min, ~3000 steps	2S, 15R, 10E

Note. S = number of sets; R = number of repetitions; E = number of exercises.

progression of the resistance exercise training (sets, repetitions, and exercises) will follow three different trajectories for individualization. All participants will start with the same number of sets and repetitions of 5 exercises for the first, 2-week period, and this will consist of one set of 10 repetitions of the chair raise, shoulder row, elbow flexion, abdominal curl, and calf raise per exercise session. This first, 2-week period (Phase I) is deemed an accommodation period, and further serves as a benchmark for selecting a trajectory for the remaining 14 weeks of the program (Phase II). There will be three trajectories of progression for the sets, repetitions, and exercises over the remaining 14 weeks (Orange, Blue, and White) whereby the minimal dose of resistance exercise will be achieved by 6, 8, or 10 weeks respectively (see Table 2). The intensity will be controlled with a standardized resistance band for the first 2 weeks, and the participant can exercise with a self-selected resistance band based on the amount of resistance that permits 10–15 repetitions with appropriate technique for the remaining 14 weeks of the program. Importantly, all participants will be encouraged to undertake the resistance program with the bands, but GEMS-S participants will have access to free weights and/or appropriate exercise machines at the facility to complete the exercises, if requested.

2.9.2. Equipment

All participants will be provided with a NL-800 pedometer (NEW-LIFESTYLES, INC., Lee's Summit, MO) worn on the waist band for monitoring and tracking walking intensity based on steps per minute; the NL-800 was selected as it is an accelerometer-grade pedometer that is accurate for measuring steps taken, particularly during slow walking. Participants will monitor the exercise intensity using a step rate of 100 steps per minute, as measured by the pedometer. Initially, participants will undertake a 20-step test for confirming proper location of the pedometer for accuracy. The participants will then wear the pedometer in the proper location for monitoring and tracking the aerobic exercise intensity. During the first 4 sessions over the first 2 weeks, participants will check the pedometers after every 5 min of walking and ensure that it reads ~500 steps after the first 5 min and ~1000 steps after 10 min. If the reading is > 50 steps off in either direction per 5-minute increment, participants should speed up or slow down, if possible. After this initial accommodation period, participants increase the step increment by 500 steps for every 5 min of additional aerobic exercise training per session.

All participants, regardless of GEMS-S or GEMS-T, receive elastic resistance bands (Black Mountain Products, McHenry, IL) for completing the resistance training exercises. The resistance bands were chosen because they are versatile, portable, inexpensive, and require little space for storage. Additionally, performing resistance training exercises using resistance bands may provide similar benefits when compared with traditional resistance training equipment such as free weights and resistance machines, and this is consistent with the physical activity guidelines for MS. The packet of elastic bands includes 5 levels of resistance (ranging from 2lbs through 30lbs) in addition to a door anchor, ankle strap, and carrying case. Participants are to start the resistance training exercises with the lightest resistance band (2-4lbs). After selecting an exercise program following the first 2 weeks of training, participants may then exercise with a self-selected amount of resistance but must do so with resistance that permits 10–15 repetitions with appropriate technique. Participants will be instructed to complete the repetitions consecutively and take a rest of 1–2 min between sets.

All participants will receive a training manual containing demonstrations of the entire program, including all of the resistance training exercises, but GEMS-T participants will further receive a DVD and can view videos on the study web-based portal. The videos include modifications based on different levels of physical capability, and this is intended for maximizing safety. GEMS-S participants will have access to a coach within the facility who can provide guidance on modifications, whereas this can be done remotely via videoconference with GEMS-T participants.

2.9.3. One-on-one coaching

The STEP for MS Trial involves one-on-one semi-structured sessions with MS exercise specialists (i.e., behavioral coaches). These one-on-one sessions focus on exercise training guidance and oversight, discussion of the behavioral strategies of action planning and self-monitoring, and presentation and discussion of newsletters; these latter parts are based on SCT and designed for optimizing exercise compliance [14,15].

One of the primary objectives of the coaching sessions is to provide guidance and oversight on exercise training. The behavioral coaches receive standardized training from experts on exercise prescription and behavior change for physical activity before working with research participants. The sessions with the behavioral coach are designed, in part, for the provision of feedback and information on appropriate exercise technique and strategies, as well as progression through the exercise program. There are three levels of difficulty of the exercise

Table 3
Summary and comparison of GEMS-S and GEMS-T intervention conditions.

Feature	GEMS-S	GEMS-T
Prescription		Based on the Guidelines for Exercise in MS Individually-tailored Based on level of comfort/trainability
Frequency		2 times/week
Exercise Session Duration		Approximately 1 h
Exercise Intensity		Moderate 100 steps/min (pedometer) Rate of Perceived Exertion (RPE)
Intervention Length		16 weeks
Meetings with Coach		
Weeks 1–4		1 time/week
Weeks 5–8		Bi-weekly (weeks 6, 8)
Weeks 9–16		Monthly (weeks 12, 16)
Setting	Facility	Home
Supervision		
Who	Trained personnel	Trained personnel
Mode	Direct, in-person coaching	Remote, telecoaching
Exercise Modes		
Aerobic	Walking	Walking
Resistance	Bands, body weight, free weights, machines	Bands, body weight
Provided Materials	Program Manual	Program Manual
	Newsletters	Newsletters
	Logbook	Logbook
	Calendars	Calendars
		Internet-based exercise videos
Provided Equipment	Treadmill, track	
	Pedometer	Pedometer
	Bands, machines, free weights	Bands
Training Oversite	In-person	Zoom/exercise videos
Behavioral Intervention	In-person	Zoom
Intervention Safety	Fall risk assessment	Fall risk assessment
	NMSS resources	NMSS resources
	Fall prevention instructions	Fall prevention instructions
	In-person falls oversite	Zoom/portal falls oversite

Note. GEMS-S = Guidelines for Exercise in Multiple Sclerosis-Supervised; GEMS-T = Guidelines for Exercise in Multiple Sclerosis-Telerehabilitation.

intervention that the participants may choose to discuss with the behavioral coach. This mutual decision will be based on experiences during the first two weeks of the program of both the participant and coach. The levels of difficulty vary in terms of progression toward meeting the exercise guidelines; this is critical for accommodating the various levels of ability in persons with MS. The one-on-one coaching sessions further focus on action planning and self-monitoring as well as delivery and discussion of SCT constructs based on content-relevant newsletters.

2.9.4. Action planning and self-monitoring

Action planning and self-monitoring are essential for the long-term success of the STEP for MS Trial in maximizing behavior change and compliance with the interventions. Action-planning will be accomplished by providing participants with calendars as a schedule or plan for conducting the aerobic and resistance training sessions. The calendars can further be used by participants to arrange exercise sessions around other life events such as doctor visits or vacations, or even as a memory device for planning future events. Self-monitoring is accomplished through the provision of exercise adherence logs for tracking completion of the exercise sessions over the 16-week intervention (see example log in Appendix). The logs will permit the recording of missed sessions and the reason, the completion status of resistance training exercises, as well as document step information from the pedometer after each exercise session.

2.9.5. Newsletters

Participants will receive newsletters on a pre-determined schedule throughout the program (i.e. weeks 1, 3, 5, 7, 11, and 15) that involve six, SCT-based topics, namely outcome expectations, self-monitoring, goal-setting, self-efficacy, barriers, and facilitators. These newsletters provide instructional material per topic, websites for more information, personal testimonials of success with exercise behavior change, and tips for application in the behavior change process.

2.9.6. Intervention comparison and similarity

Table 3 provides a summary and comparison of the GEMS-S and GEMS-T conditions. The prescription of exercise training and scheduled meetings with a behavioral coach are identical between conditions. There is variation in the setting, supervision, exercise modes, materials, equipment, oversite, and behavioral intervention. For example, GEMS-S participants are provided with resistance bands and the same exercises as GEMS-T participants, but we recognize that some participants who come into supervised settings seek and desire weights/machines. To that end, we considered this as an important option for the supervised setting, and therefore justified the use of weights/machines as an option for GEMS-S participants. We are recording this usage for the GEMS-S and GEMS-T participants in the log books, as we note that some GEMS-T participants have reported the presence of weights/machines in the home environment that may be preferred over the bands. This collectively indicates our standardized, yet pragmatic approach for the intervention programs.

Table 4
Outcomes and administration timeline.

Outcome	Baseline	Midway (Week 8)	Post (Week 16)	Follow-up (12 months)
T25FW	×		×	×
6MW	×		×	×
EDSS	×		×	×
GLTEQ	×	×	×	×
MSWS-12	×	×	×	×
MFIS	×	×	×	×
Neuro-QOL	×	×	×	×
MSIS-29	×	×	×	×
SCT Variables (MOEES, PASR-12, EGS, ESE, BSE and SPS)	×	×	×	×

Note. T25FW = Timed 25-Foot Walk; 6MW = 6-Minute Walk; EDSS = Expanded Disability Status Scale; GLTEQ = Godin Leisure-Time Exercise Questionnaire; MSWS-12 = Multiple Sclerosis Walking Scale-12; MFIS = Modified Fatigue Impact Scale; Neuro-QOL = Quality of Life in Neurological Disorders survey; MSIS-29 = Multiple Sclerosis Impact Scale-20; SCT = Social Cognitive Theory; MOEES = Multidimensional Outcome Expectancies for Exercise Scale; PASR-12 = Physical Activity Self-Regulation-12 scale; EGS = Exercise Goal-Setting scale; ESE = Exercise Self-Efficacy scale; BSE = Barriers for Self-Efficacy scale; SPS = Social Provisions Scale.

2.9.6.1. GEMS-S. Participants within the GEMS-S condition (Choice or No Choice) will immediately be assigned an on-site MS behavioral coach and scheduled for the first one-on-one session. The behavioral coaches will be site-specific research staff and will undergo standardized training by the UAB Intervention Center for ensuring fidelity with the intervention delivery. GEMS-S participants will receive a packet containing the intervention materials (resistance bands, pedometer, logbooks, calendar, and training manual) from the behavioral coach during the first one-on-one session; this session will serve as an orientation to the exercise intervention. Immediately following the first one-on-one session, the behavioral coaches will oversee the first exercise training session to demonstrate the exercises, and then provide light-touch supervision and monitoring throughout the 16-week intervention. The behavioral coaches will directly provide participants with the SCT-based newsletters in person instead of mailing them. The one-on-one sessions will be conducted in person following the second exercise session of the week. The GEMS-S coach will collect the exercise adherence log on a weekly basis and enter the data into the study web-based portal. Participants will be instructed to notify the behavioral coach of an adverse event or other problem; this information will further be collected during the one-on-one sessions with behavioral coaches.

2.9.6.2. GEMS-T. Participants randomized to GEMS-T will be contacted by the Intervention Center research coordinator within one week for a brief overview of the GEMS-T protocol, notification of the assigned behavioral coach, and scheduling the first one-on-one session. The research coordinator for the Intervention Center will then mail a packet containing the intervention materials (resistance bands, pedometer, logbooks, calendar, and training manual) via certified postal mail. The site research coordinator will further provide the behavioral coach with participant-specific information regarding fall risk, EDSS level, and any other information that will inform the coach's oversight and interaction with the GEMS-T participant. As with GEMS-S participants, the first one-on-one session will serve as an orientation to the exercise intervention. The behavioral coach will confirm receipt of the intervention materials, gather more information about motivations and experiences with exercise, and provide an overview of the exercise program. Participants will be asked to contact the research coordinator via phone or e-mail in the occurrence of an adverse event or any other problem; this information will further be collected during the chat sessions with behavioral coaches.

The one-on-one chat sessions will be conducted via a HIPAA-compliant teleconferencing system (e.g. Zoom). If a participant in the GEMS-T arm does not have access to the Internet, the video-chats will be replaced with the phone calls. In contrast to the data entry process for GEMS-S, GEMS-T participants will enter data from the exercise adherence log directly into the study portal; this can be supported through entry by the behavioral coach in the event of problems with accessing the Internet. Importantly, the telerehabilitation behavioral coaches too will attend regular teleconferences with the UAB Intervention Center for ongoing dialogue on fidelity in delivering the interventions.

2.10. Intervention safety protocols

Participant safety considerations are particularly imperative for this trial, as approximately half of the participants (n = 250) will be performing the exercise intervention at home without direct supervision. Several measures will be undertaken for maximizing participant safety. All participants will complete a fall risk assessment during the screening process. This information, along with the participant's EDSS level, will be provided to the participant's behavioral coach within both GEMS-S and GEMS-T. The participants will be provided with an NMSS educational packet “Minimizing your risk for falls: A guide for people with MS”, and a study-specific instruction sheet on fall prevention. Instructions for participants who are considered a fall risk include (a) use of an assistive or orthotic device during the walking intervention if these are typically used for the participant's safety or independence during walking; (b), walking at a speed that is safe; and (c) walking in a controlled environment (e.g., indoors) when necessary. Participants will be instructed to inform the research coordinator or coach should any safety concerns arise. GEMS-S participants will receive exercise program oversight from the behavioral coach within the facility. GEMS-T participants will be instructed to document any concerns or adverse events in both the paper exercise adherence log and when entering this information in the portal. The UAB Intervention Center research coordinator will further review the weekly exercise adherence log information that is entered into the portal. The DSMB will provide further study oversight and be notified of any falls or other serious adverse events in a timely manner. Adverse events will be documented using the HIPAA-compliant study web-based portal, including monitoring and managing potential adverse events and notifying the site investigators, and the PI at the lead center. Ongoing reporting of adverse events to the DSMB and relevant IRBs and PCORI will follow the policies and procedures of the Shepherd Center and participating IRBs.

2.11. Procedures

Participant recruitment, contact, and screening will be undertaken by the research coordinator per site. Interested participants will contact the research coordinator who will describe the study (i.e., comparing the outcomes of an exercise program delivered via telerehabilitation and in a facility) and what participation entails, and conduct the first

two screenings for inclusion criteria over the phone using the study web-based portal. Participants who pass the first two screens will be scheduled for the final, in-person screening for eligibility within a site clinic. The research coordinator will describe the study and its procedures and ask participants to sign the informed consent before completing the final clinician-administered screening assessments and questionnaires. Participants who meet the final inclusion criteria will be enrolled in the study and then complete the final set of patient-reported outcomes on the study portal. Once all measures are completed, participants will be randomized into the Choice or No Choice conditions, as described previously.

All clinician-reported outcomes and PROs will be assessed at baseline, post-intervention (16 weeks), and follow-up (52 weeks) (Table 4). PROs will further be collected at 8 weeks post-start of the intervention via the study portal (mid-point). Site research coordinators will schedule both GEMS-S and GEMS-T participants for all evaluation visits at the respective sites. All participants will be remunerated $25 for each assessment that requires them to travel to the study site.

In order to reduce the likelihood of missed assessment visits, five strategies will be utilized: (a) a stipend will be provided to participants to assist with travel for assessment sessions; (b) participants will be provided with written and electronic schedules of all assessment visits immediately after being randomized into an intervention condition; (c) the study portal will send electronic notices to participants and research coordinators about upcoming assessment appointments and PROs that are available to be completed, as well as additional reminders regarding incomplete PROs one week and three days prior to the deadline and the day the PROs are due, if necessary; (d) the behavioral coach will remind the participant about the completion of pending PROs; and (e) the site research coordinator will place a reminder phone call to the participant one day before an assessment visit, and will further contact the participant if the 8-week PROs are not completed by the due date. If a participant misses the assessment visit for the 16-week or 52-week assessments, the visit will be rescheduled as soon as possible.

2.12. Data management and analysis

2.12.1. Study portal

We developed a web-based study portal as a partition of the iConquerMS portal. The principal investigators, data management center, and engineers at Life Data Systems, Inc., worked collaboratively to determine the elements and features of the portal necessary for all data collection. The portal was developed in compliance with Section 508 of the 1998 amended Rehabilitation Act. All data collected through the study web-based portal are stored in a commercial-grade, cloud-based, HIPAA-compliant, secure data center.

2.12.2. Data entry and management

The data will be entered directly into the web-based study portal where it will then be maintained in a secure, HIPAA-compliant database. The portal provides real-time data analysis and feedback, with the capability to alert users, both research personnel and participant, immediately if required data are not entered or if there is a logical inconsistency with the data entered. This system-automated error checking provides the first of multiple levels of data quality and completeness assurance. In addition to the automated data verification feature, dedicated staff will monitor completeness and fidelity of data on an ongoing basis and provide feedback to each site regarding missing data.

2.12.3. Data analysis

The primary hypothesis is one of non-inferiority in changes in T25FW performance between GEMS-T and GEMS-S conditions. This will be tested using a linear model with site as the stratification factor and applying an intent-to-treat approach. The primary analysis will adjust for the covariates of age, gender and baseline EDSS. Additional covariates may be examined in sensitivity analyses based on any differences seen on examination of baseline variables between groups. Secondary endpoints include change in 6MW and EDSS. Across all endpoints, we are assessing changes from baseline values. We will examine the frequency of worsening as a safety comparison. We will examine the primary endpoint of noninferiority using least squares means of the feet per second and additionally of a 20% improvement in the T25FW (yes or no) using logistic regression with the same strata and covariates. Further, to characterize the changes over time, we will use linear mixed models to assess the slopes of change for GEMS-S versus GEMS-T conditions using all the timed walk data and other assessments. We will examine the relationship between the dose of exercise measured by compliance (i.e., exercise adherence logs) and the change in the primary and secondary outcomes using mediation analyses following the approach by MacKinnon built on Judd and Kenny [43–46]. These are exploratory outcomes to see if the compliance measures predict (mediate) the benefits on the outcomes. This information is understanding the choice comparisons and is also important for translation and information dissemination to people with MS.

Assuming noninferiority is demonstrated, we will use the same analysis model to evaluate and compare the effectiveness between participants randomized based on preferred delivery mode (GEMS-T [Choice] or GEMS-S [Choice]) with those who are not randomized based on preferred delivery mode, and will examine an interaction term for choice and treatment. We will examine time to dropout and/or time until dropout or poor compliance (which will be defined prior to final analyses). We are interested in examining the intensity or compliance of the intervention to the choice as well as the impact on the primary outcome as noted above.

We will utilize mediation analyses to further understand if the changes induced by exercise are mediated via the changes in SCT variables using the approaches noted above. The MSWS-12, MFIS-21 and Neuro-QOL will all be analyzed using regression models similar to the timed-walk models above and will utilize the same contrasts for examining choice as well as treatment effects.

Subgroups will be defined and analyses undertaken only after the main outcomes/hypotheses are tested. The subgroups will be identified by the study team in a collective dialogue for informing such analyses. As exploratory analyses, we will caution the reader that *p*-values, if used, are nominal and subject to inflated type I errors due to the post-hoc nature of these subgroup analyses.

2.13. Publication plan

Beyond this protocol paper, we have a priori plans for three additional papers and will publish other papers that are exploratory in nature, only after completion of the three, focal papers. The three papers will focus on (a) the process of developing the study portal; (b) primary outcomes from the trial; and (c) SCT-related outcomes from the trial. There further is a dissemination plan for regulating all other papers from this trial, and one of the defining principles is that additional papers can only be pursued after publication of the main outcomes of the trial.

2.14. Trial status

The trial was successfully registered on ClinicalTrials.gov on March 19, 2018, and all three institutional review boards approved the study protocol on September 1, 2018. Participant recruitment for the pilot phase began on July 1, 2018. The pilot phase involved subjects from two of the sites for identifying and resolving problems before starting the first wave of the trial. Recruitment for the first wave of participants (Wave 1) began on September 1, 2018. The final outcome assessments for all waves of participants are planned for January 1, 2022.

3. Discussion

The STEP for MS Trial represents the first comparative effectiveness research study focusing on exercise training for improving walking performance in persons with MS who are prescreened for walking dysfunction and mobility disability. People with MS and other stakeholders are included throughout the research process, consistent with patient-centered research, and this informed the study and its design, including the choice of setting, methods, and outcomes. Accordingly, the study addresses an important evidence gap identified, not only in existing MS literature [9,10], but further reported by people with MS. People with MS report needing ways to remain physically active and engage in exercise, but encounter barriers, including (1) inaccessible gyms/equipment, (2) inability to find exercise specialists who are educated about MS and exercise, (3) lack of knowledge about how to safely exercise with MS, (4) lack of understanding about the types of exercise that would be beneficial, and (5) costs that undermine the ability and desire to exercise [47,48]. This trial specifically addresses whether the same evidence-based, individualized exercise training program that is supported by principles of behavior theory and coaching, but delivered in two different settings and modes of interactions with coaches, will yield similar improvements in walking performance in persons with MS who have walking dysfunction and mobility disability. The two different settings for delivery and modes of interactions with behavioral coaches were chosen based on existing research suggesting the need for different options for exercise training that overcome barriers [49–51] and meet individual preferences [52,53], and further address stakeholder feedback. Such research is important for informing the MS field if the treatment environment and mode of interaction with behavioral coaches matter for exercise benefits (e.g., improving walking performance). Additionally, results from this trial will provide evidence for persons with MS, clinicians and policy makers when making informed treatment and policy decisions that will ultimately improve the lives of persons with MS who present with walking dysfunction and mobility disability.

The 2-stage, randomized choice design [17] used in this trial permits the first direct examination of the importance of choice or preference in exercise training outcomes for persons with MS. There is a significant gap in the understanding of whether or how an individual's preference for an environment, independent of the intervention itself, influences the adoption and benefits of exercise training [48,49]. This is important, as an individual's preference (or choice) of setting where the intervention is delivered might influence motivation to participate in exercise, and this likely will influence primary and secondary outcomes [50–53]. If we have equivalent results between delivery methods and choice conditions for improving walking performance, this would suggest that people with MS can self-select an exercise training environment based on personal interests and needs (e.g., need for social interaction, financial concerns, and transportation or accessibility issues). If we have non-equivalent results, particularly in favor of the supervised environment, this would suggest that people with MS should opt for an exercise training program within a supervised environment, regardless of personal interests and needs, in order to maximize outcomes. This would support the approach and need for the establishment of accessible and affordable supervised exercise programs with knowledgeable exercise staff for persons with MS.

The intervention for the STEP for MS Trial itself consists of comprehensive, integrative components. The innovative components include an evidence-based, individualized prescription for aerobic and resistance training modalities; real-world exercise equipment that is accessible and affordable; inclusion of behavior change techniques that align with SCT for promoting adoption and sustained participation; and adoption of behavioral coaching for optimizing compliance, uptake, and penetration of the intervention materials. This is highly novel as other programs often provide only an exercise prescription [10], despite the large body of evidence that demonstrates the poor uptake of exercise among people with MS [11] based on environmental, personal, and behavioral barriers [47]. To that end, the current intervention has the potential for long-term uptake and involvement of exercise training in MS, and this might be essential for optimizing and sustaining behavior change and associated outcomes.

One of the major limitations of previous exercise training research in MS has been the inclusion of samples that are not prescreened for the presence of a focal problem [9]. For example, studies of exercise training and fatigue have generally not prescreened samples for the presence of fatigue [54], and the same is true of exercise training and walking/mobility outcomes [55]. This is a problem for the conclusion and uptake of exercise training as a “therapeutic modality” for treating walking dysfunction and mobility disability in MS [55]. The present study will use a three-stage screening process to ensure that our sample presents with walking dysfunction and mobility disability. The inclusion of the outcome of interest (T25FW) in the screening process, for example, will permit a focal comparison of the two modes for delivering the same intervention on walking endpoints. If our trial is successful, it will fill a meaningful gap in our understanding of the potential for both modes of exercise training as viable options for people with MS who present with walking dysfunction and significant mobility disability.

Another strength of the current study is the multi-site trial design. Indeed, one limitation of previous exercise research has been the lack of multi-site clinical trials conducted in people with MS [56] despite evidence of the benefits [57]. The examination of an intervention within a single site has several strengths including lower costs, simplified logistics, and less onerous data collection, but has limitations involving external validity and small samples sizes that can undermine statistical power for detecting small effect sizes. To that end, this study will enroll 500 participants with MS across 7 sites throughout the United States, making it the largest known multi-site trial that examines the effects of exercise training on walking performance in people with MS. Notably, the centers represent differing geographical areas, participant demographics, and clinical settings, and this enables comparison of the intervention modalities across a range of settings. Such an endeavor will provide important insight regarding the development and implementation of systematic, multi-site exercise training interventions for people with MS. The outcomes selected for this study further are practical endpoints that can easily be collected across sites (i.e. T25FW or EDSS that will be administered by a Neurostatus-certified examiner who is not required to be a neurologist).

Overall, the STEP for MS Trial represents major progress in the design to examine the effectiveness of evidence-based, individualized exercise training programs for improving walking performance in people with MS who have walking dysfunction and mobility disability. The comparison of the relative effectiveness of delivery of the same intervention in a facility or in the home using telerehabilitation will fill a meaningful gap in our understanding of the potential viability of GEMS-T as an exercise training option among people with MS who prefer to exercise outside of a facility. This study seeks to further understand whether or how an individual's preference for exercise in a facility or at home, and SCT variables, play a role in whether an individual will exercise, or influence the outcomes achieved with exercise training. We postulate that participating in the preferred mode of exercise will further increase adherence and physical activity levels and secondarily improve walking and mobility, resulting in improvements in productive and meaningful participation and quality of life for people with MS who have difficulties with walking and mobility.

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Disclaimer

All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2019.04.013.

References

[1] K. Sharma, F. Bittner, J. Kamholz, Epidemiology of multiple sclerosis in the United States (P1.140), Neurology 90 (2018) (15 Supplement), http://n.neurology.org/content/90/15_Supplement/P1.140.abstract.

[2] P. Browne, D. Chandraratna, C. Angood, et al., Atlas of Multiple Sclerosis 2013: a growing global problem with widespread inequity, Neurology. 83 (11) (2014) 1022–1024, https://doi.org/10.1212/WNL.0000000000000768.

[3] B. Hemmer, S. Nessler, D. Zhou, B. Kieseier, H.-P. Hartung, Immunopathogenesis and immunotherapy of multiple sclerosis, Nat. Clin. Pract. Neurol. 2 (4) (2006) 201–211, https://doi.org/10.1038/ncpneuro0154.

[4] B.D. Trapp, K.-A. Nave, Multiple sclerosis: An immune or neurodegenerative disorder? Annu. Rev. Neurosci. 31 (1) (2008) 247–269, https://doi.org/10.1146/annurev.neuro.30.051606.094313.

[5] C. Confavreux, S. Vukusic, Natural history of multiple sclerosis: a unifying concept, Brain. 129 (3) (2006) 606–616, https://doi.org/10.1093/brain/awl007.

[6] R.W. Motl, Ambulation and multiple sclerosis, Phys. Med. Rehabil. Clin. N. Am. 24 (2) (2013) 325–336, https://doi.org/10.1016/j.pmr.2012.11.004.

[7] R.W. Motl, Y.C. Learmonth, Neurological disability and its association with walking impairment in multiple sclerosis: brief review, Neurodegener. Dis. Manag. 4 (6) (2014) 491–500, https://doi.org/10.2217/nmt.14.32.

[8] J. Benito-León, J. Manuel Morales, J. Rivera-Navarro, A.J. Mitchell, A review about the impact of multiple sclerosis on health-related quality of life, Disabil. Rehabil. 25 (23) (2003) 1291–1303, https://doi.org/10.1080/09638280310001608591.

[9] R.W. Motl, B.M. Sandroff, G. Kwakkel, et al., Exercise in patients with multiple sclerosis, Lancet Neurol. 16 (10) (2017) 848–856, https://doi.org/10.1016/S1474-4422(17)30281-8.

[10] B. Lai, H.-J. Young, C.S. Bickel, R.W. Motl, J.H. Rimmer, Current trends in exercise intervention research, technology, and behavioral change strategies for people with disabilities: a scoping review, Am J Phys Med Rehabil. 96 (10) (2017) 748–761, https://doi.org/10.1097/PHM.0000000000000743.

[11] D. Kinnett-Hopkins, B. Adamson, K. Rougeau, R.W. Motl, People with MS are less physically active than health controls but as active as those with other chronic disease: an updated meta-analysis, Mult. Scler. Related Disord. 13 (2017) 38–43, https://doi.org/10.1016/j.msard.2017.01.016.

[12] A.E. Latimer-Cheung, K.A. Martin Ginis, A.L. Hicks, et al., Development of evidence-informed physical activity guidelines for adults with multiple sclerosis, Arch. Phys. Med. Rehabil. 94 (9) (2013), https://doi.org/10.1016/J.APMR.2013.05.015 1829-1836.e7.

[13] R.W. Motl, D. Pekmezi, B.C. Wingo, Promotion of physical activity and exercise in multiple sclerosis: importance of behavioral science and theory, Mult. Scler. J. Exp. Transl. Clin. 4 (3) (2018), https://doi.org/10.1177/2055217318786745 205521731878674.

[14] B.C. Adamson, Y.C. Learmonth, D. Kinnett-Hopkins, M. Bohri, R.W. Motl, Feasibility study design and methods for project GEMS: guidelines for exercise in multiple sclerosis, Contemp. Clin. Trials. 47 (2016) 32–39, https://doi.org/10.1016/j.cct.2015.12.002.

[15] Y.C. Learmonth, B.C. Adamson, D. Kinnett-Hopkins, M. Bohri, R.W. Motl, Results of a feasibility randomised controlled study of the guidelines for exercise in multiple sclerosis project, Contemp. Clin. Trials. 54 (2017) 84–97, https://doi.org/10.1016/J.CCT.2016.11.012.

[16] I. Fredrick, L. Vanhees, P. Dendale, K. Goetschalckx, A review of telerehabilitation for cardiac patients, J. Telemed. Telecare 21 (1) (2015) 45–53, https://doi.org/10.1177/1357633X14562732.

[17] S. Walter, R. Turner, P. Macaskill, K. McCaffery, L. Irwig, Beyond the treatment effect: evaluating the effects of patient preferences in randomised trials, Stat. Methods Med. Res. 26 (1) (2017) 489–507, https://doi.org/10.1177/0962280214550516.

[18] B. Casey, S. Coote, C. Shirazipour, et al., Modifiable psychosocial constructs associated with physical activity participation in people with mulitple sclerosis: a systematic review and meta-analysis, Arch. Phys. Med. Rehabil. 98 (7) (2017) 1453–1475, https://doi.org/10.1016/j.apmr.2017.01.027.

[19] B.C. Kieseier, C. Pozzilli, Assessing walking disability in multiple sclerosis, Mult. Scler. J. 18 (7) (2012) 914–924, https://doi.org/10.1177/1352458512444498.

[20] R.W. Motl, J. Cohen, R. Benedict, Phillips, et al., Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis, Mult. Scler. J. 23 (5) (2017) 704–710, https://doi.org/10.1177/https.

[21] M.D. Goldman, R.A. Marrie, J.A. Cohen, Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls, Mult. Scler. J. 14 (3) (2008) 383–390, https://doi.org/10.1177/1352458507082607.

[22] J.F. Kurtzke, Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS), Neurology. 33 (11) (1983) 1444–1452, https://doi.org/10.1212/WNL.33.11.1444.

[23] E.M. Sikes, E.V. Richardson, K.J. Cederberg, J.E. Sasaki, B.M. Sandroff, R.W. Motl, Use of the Godin leisure-time exercise questionnaire in multiple sclerosis research: a comprehensive narrative review, Disabil. Rehabil. (2018) 1–25, https://doi.org/10.1080/09638288.2018.1424956.

[24] J.C. Hobart, A. Riazi, D.L. Lamping, R. Fitzpatrick, A.J. Thompson, Measuring the impact of MS on walking ability: the 12-item MS walking scale (MSWS-12), Neurology. 60 (1) (2003) 31–36, https://doi.org/10.1212/WNL.60.1.31.

[25] P. Flachenecker, T. Kümpfel, B. Kallmann, et al., Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters, Mult. Scler. J. 8 (6) (2002) 523–526, https://doi.org/10.1191/1352458502ms839oa.

[26] D. Cella, J.-S. Lai, C.J. Nowinski, et al., Neuro-QOL: brief measures of health-related quality of life for clinical research in neurology, Neurology 78 (23) (2012) 1860–1867, https://doi.org/10.1212/WNL.0b013e318258f744.

[27] J. Hobart, D. Lamping, R. Fitzpatrick, A. Riazi, A. Thompson, The multiple sclerosis impact scale (MSIS-29). A new patient-based outcome measure, Brain 124 (Pt 5) (2001) 962–973.

[28] J.R. Kirwan, M. de Wit, L. Frank, et al., Emerging guidelines for patient engagement in research, Value Health 20 (3) (2017) 481–486, https://doi.org/10.1016/j.jval.2016.10.003.

[29] Y.C. Learmonth, R.W. Motl, B.M. Sandroff, J.H. Pula, D. Cadavid, Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis, BMC Neurol. 13 (2013) 37, , https://doi.org/10.1186/1471-2377-13-37.

[30] D. Riebe, B.A. Franklin, P.D. Thompson, et al., Updating ACSM's recommendations for exercise Preparticipation health screening, Med. Sci. Sports Exerc. 47 (8) (2015) 2473–2479, https://doi.org/10.1249/MSS.0000000000000664.

[31] W.W. Beatty, D.E. Goodkin, Screening for cognitive impairment in multiple sclerosis. An evaluation of the mini-mental state examination, Arch. Neurol. 47 (3) (1990) 297–301 http://www.ncbi.nlm.nih.gov/pubmed/2310313 , Accessed date: 12 December 2018.

[32] M.D. Goldman, R.W. Motl, J. Scagnelli, J.H. Pula, J.J. Sosnoff, D. Cadavid, Clinically meaningful performance benchmarks in MS: timed 25-foot walk and the real world, Neurology. 81 (21) (2013) 1856–1863, https://doi.org/10.1212/01.wnl.0000436065.97642.d2.

[33] C.I. Coleman, D.M. Sobieraj, L.N. Marinucci, Minimally important clinical difference of the timed 25-foot walk test: results from a randomized controlled trial in patients with multiple sclerosis, Curr. Med. Res. Opin. 28 (1) (2012) 49–56, https://doi.org/10.1185/03007995.2011.639752.

[34] C. McGuigan, M. Hutchinson, Confirming the validity and responsiveness of the multiple sclerosis walking Scale-12 (MSWS-12), Neurology 62 (11) (2004) 2103 LP–2105 http://n.neurology.org/content/62/11/2103.abstract.

[35] E. McAuley, R.W. Motl, S.M. White, T.R. Wójcicki, Validation of the multidimensional outcome expectations for exercise scale in ambulatory, symptom-free persons with mutliple sclerosis, Arch. Phys. Med. Rehabil. 91 (1) (2010) 100–105, https://doi.org/10.1016/j.apmr.2009.09.011.

[36] K.L. Cederberg, J.M. Balto, R.W. Motl, Self-regulatory strategies as correlates of physical activity behavior in persons with multiple sclerosis, Arch. Phys. Med. Rehabil. 99 (5) (2018) 920–926, https://doi.org/10.1016/j.apmr.2017.12.037.

[37] L.S. Rovniak, E.S. Anderson, R.A. Winett, R.S. Stephens, Social cognitive determinants of physical activity in young adults: a prospective structural equation analysis, Ann. Behav. Med. 24 (2) (2002) 149–156, https://doi.org/10.1207/S15324796ABM2402_12.

[38] E. McAuley, Self-efficacy and the maintenance of exercise participation in older adults, J. Behav. Med. 16 (1) (1993) 103–113, https://doi.org/10.1007/BF00844757.

[39] E. McAuley, The role of efficacy cognitions in the prediction of exercise behavior in middle-aged adults, J. Behav. Med. 15 (1) (1992) 65–88 http://www.ncbi.nlm.nih.gov/pubmed/1583674 , Accessed date: 12 December 2018.

[40] C. Cutrona, D. Russell, The provisions of social relationships and adaptation to stress, in: W.H. Jones, D. Perlman (Eds.), Advances in Personal Relationships, vol 1, JAI Press, Stamford, CT, 1987, pp. 37–67.

[41] M. Weikert, D. Dlugonski, S. Balantrapu, R.W. Motl, Most common types of physical activity self-selected by people with multiple sclerosis, Int. J. MS Care. 13 (1) (2011) 16–20, https://doi.org/10.7224/1537-2073-13.1.16.

[42] S. Agiovlasitis, B.M. Sandroff, R.W. Motl, Step-rate cut-points for physical activity intensity in patients with multiple sclerosis: the effect of disability status, J. Neurol. Sci. 361 (2016) 95–100, https://doi.org/10.1016/j.jns.2015.12.027.

[43] D.P. MacKinnon, Analysis of mediating variables in prevention and intervention research, NIDA Res. Monogr. 139 (1994) 127–153, https://doi.org/10.1037/e495892006-09.

[44] M.E. Sobel, Asymptotic confidence intervals for indirect effects in structural equation models, Sociol. Methodol. 13 (1982) 290, https://doi.org/10.2307/270723.

[45] K.J. Preacher, A.F. Hayes, SPSS and SAS procedures for estimating indirect effects in simple mediation models, Behav. Res. Methods Instrum. Comput. 36 (4) (2004) 717–731, https://doi.org/10.3758/BF03206553.

[46] D.P. MacKinnon, C.M. Lockwood, J.M. Hoffman, S.G. West, V. Sheets, A comparison of methods to test mediation and other intervening variable effects, Psychol. Methods 7 (1) (2002) 83–104.

[47] Y.C. Learmonth, R.W. Motl, Physical activity and exercise training in multiple sclerosis: a review and content analysis of qualitative research identifying perceived determinants and consequences, Disabil. Rehabil. 38 (13) (2016) 1227–1242, https://doi.org/10.3109/09638288.2015.1077397.

[48] S. Kasser, Exercising with multiple sclerosis: insights into meaning and motivation,

Adapt. Phys. Act. Q. 26 (3) (2009) 274–289.
[49] M. Asano, P. Duquette, R. Andersen, Y. Lapierre, N.E. Mayo, Exercise barriers and preferences among women and men with multiple sclerosis, Disabil. Rehabil. 35 (5) (2013) 353–361, https://doi.org/10.3109/09638288.2012.742574.
[50] N.M. Kayes, K.M. McPherson, P. Schluter, D. Taylor, M. Leete, G.S. Kolt, Exploring the facilitators and barriers to engagement in physical activity for people with multiple sclerosis, Disabil. Rehabil. 33 (12) (2011) 1043–1053, https://doi.org/10.3109/09638288.2010.520801.
[51] L.A. Hale, C. Smith, H. Mulligan, G.J. Treharne, "Tell me what you want, what you really really want….": asking people with multiple sclerosis about enhancing their participation in physical activity, Disabil. Rehabil. 34 (22) (2012) 1887–1893, https://doi.org/10.3109/09638288.2012.670037.
[52] N.M. Clark, N.K. Janz, J.A. Dodge, et al., The effect of patient choice of intervention on health outcomes, Contemp. Clin. Trials. 29 (5) (2008) 679–686, https://doi.org/10.1016/j.cct.2008.04.002.
[53] K.J. McCaffery, R. Turner, P. Macaskill, S.D. Walter, S.F. Chan, L. Irwig, Determining the impact of informed choice, Med. Decis. Mak. 31 (2) (2011) 229–236, https://doi.org/10.1177/0272989X10379919.
[54] L.A. Pilutti, T.A. Greenlee, R.W. Motl, M.S. Nickrent, S.J. Petruzzello, Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis, Psychosom. Med. 75 (6) (2013) 575–580, https://doi.org/10.1097/PSY.0b013e31829b4525.
[55] J.F. Baird, B.M. Sandroff, R.W. Motl, Therapies for mobility disability in persons with multiple sclerosis, Expert. Rev. Neurother. 18 (6) (2018) 493–502, https://doi.org/10.1080/14737175.2018.1478289.
[56] B.M. Sandroff, R.E. Bollaert, L.A. Pilutti, et al., Multimodal exercise training in multiple sclerosis: a randomized controlled trial in persons with substantial mobility disability, Contemp. Clin. Trials. 61 (2017) 39–47, https://doi.org/10.1016/j.cct.2017.07.016.
[57] L. Flynn, The benefits and challenges of multisite studies, AACN Adv. Crit. Care. 20 (4) (2009) 388–391, https://doi.org/10.1097/NCI.0b013e3181ac228a.