Protocol Title: Comparative Effectiveness of an Exercise Intervention Delivered via Telerehabilitation and Conventional Mode of Delivery

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Abbreviations

GEMS-T:	Guidelines for Exercise in MS - Telerehabilitation
GEMS-S:	Guidelines for Exercise in MS - Supervised
UAB:	University of Alabama at Birmingham
iCMS:	iConquer MS
EDSS:	Expanded Disability Scale Score
PDDS:	Patient Determined Disability Steps
EPHS:	Exercise Preparticipation Health Screening
T25FWT:	Timed 25-Foot Walk Test
6MWT:	Six Minute Walk Test
MSWS-12:	12-item, Multiple Sclerosis Walking Scale
GLTEQ:	Godin Leisure-Time Exercise Questionnaire
MSIS-29:	29-item, Multiple Sclerosis Impact Scale
MFIS-21	Modified Fatigue Impact scale-21
Neuro-QOL	Neuro Quality of Life
SAHL-E	Short Assessment of Health Literacy - English
HR:	Heart Rate
SCT:	Social Cognitive Theory
HIPAA:	The Health Insurance Portability and Accountability Act
MAR:	Missing at Random
HTE:	Heterogeneity of Treatment Effect
DMT:	Disease Modifying Therapy
RRMS:	Relapsing-remitting Multiple Sclerosis
PMS:	Progressive Multiple Sclerosis
CI:	Confidence Interval
DSMB:	Data Safety Monitoring Board
MGH:	Massachusetts General Hospital
UGA:	University of Georgia
UNC:	University of North Carolina

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Abstract

This protocol outlines the methodology and procedures for implementing and evaluating *Comparative Effectiveness of an Exercise Intervention Delivered via Telerehabilitation and Conventional Mode of Delivery*. Funded by PCORI, this four-year, multi-site study aims to assess the comparative impact of a 16-week telerehabilitation exercise program and a facility-based exercise program on MS outcomes. The research study design is a two-stage randomized choice design aimed at non-inferiority.

Four hundred participants who have ambulatory difficulties will be recruited across eight sites. First level randomization will assign participants to one of two groups – choice or no choice. The participants in choice will be able to choose in which program they wish to participate (telerehabilitation or facility-based). Individuals in the no choice group, will be randomized to either the telerehabilitation or facility-based program. The research protocol and associated tools will be reviewed and approved by the Shepherd Center Research Review Committee before any research takes place. The study will comply with best practices in human subjects' research including following HIPAA guidelines and using strict informed consent procedures. Clinical reported outcome measures and patient reported outcome measures will be administered at baseline, immediately post-intervention (at 16-weeks), and at 12 months post-intervention. Patient reported outcomes will also be administered at 2-months after the start of the intervention and at 6 months post exercise.

Dr. Deborah Backus is the principal investigator (PI) and Prof. Robert Motl is the co-Principal Investigator supported by collaborating Co-Investigators at six other research sites and the iConquerMS outcomes data collaborative. Shepherd Center is the primary and coordinating site for all study activities under Dr. Backus, who is supported by Louise Palmer, Project Manager. University of Alabama at Birmingham (UAB) under the leadership of Prof. Motl will oversee delivery of the training programs, and under the direction of Dr. Gary Cutter will provide research design, statistical analysis and randomization expertise.

This study will yield important data regarding the comparative impact of exercise programs on MS outcomes and provide information to people with MS, health providers, payers, exercise partners, and policy makers about how people with MS who have ambulatory difficulties can safely and effectively exercise.

BACKGROUND AND SIGNIFICANCE

Multiple Sclerosis (MS) is a chronic, often progressive disease of the central nervous system affecting over 400,000 people in the United States and over 2.5 million people worldwide. One of the most common problems reported by people with MS is impaired mobility.[1] Most people living with MS will eventually require assistance with mobility due to disease progression.[2,3,4] Decreased mobility leads to less physical activity.[5,6,7] Physical inactivity in turn leads to and perpetuates deconditioning, which in turn will lead to further mobility impairment.[8,9] At some critical point, mobility will be limited to such an extent that there is irreversible disability resulting in secondary health conditions that will be difficult, if not impossible, to treat.[10,11,12] This progression of disability can result in apathy and depression,[11] further contributing to decreased social, recreational, and vocational participation and ultimately a poor quality of life.[13-18] The decrease in participation and work productivity together with an increase in secondary health conditions and medical needs have a significant economic impact in both the United States[19] and Europe.[20]

Although evidence suggests that exercise can improve mobility and perhaps decrease the rate and extent of disability (i.e. impaired function) in people with MS, most studies related to exercise have failed to screen for people with walking problems using objective assessment.[21-38] Evidence does show, however, that traditional, facility-based exercise training, particularly in a setting where other people with MS are exercising or under the supervision of exercise personnel, may help people with MS consistently participate in exercise or to exercise at a higher, more intense level. Despite this evidence, lack of access to these programs may make it difficult to engage in a GEMS-S program.[39-43] Telerehabilitation (telerehab) has great potential to overcome challenges associated with facility-based programs. Telerehab can include videoconferencing, remote monitoring of signs and activity, and dissemination of specialized and individualized information via electronic mechanisms. Both facility-based and telerehab exercise training have yielded positive results in people with MS,[21-38] but have not been compared head-to-head. The current study will fill this gap in the evidence base and compare the outcomes of delivering the same exercise interventions in a facility (facility-based exercise training or GEMS-S) or in the home/community using a telerehab approach (telerehab delivered exercise training or GEMS-T). The interventions are designed to be identical in content, with the only difference being the mode of training delivery.

This study will yield important data to inform people with MS who have objective walking impairment, as well as healthcare providers, exercise trainers, payers, and policy makers, about exercise options for people with MS. Our **main hypothesis** is that there will be no difference in outcomes when the evidence-based individualized exercise program is delivered in a facility (GEMS-S) or via telerehab (GEMS-T) (i.e., walking and other outcomes will improve similarly between conditions). Our null hypothesis is that GEMS-T is inferior to GEMS-S. A secondary hypothesis is that patients who perform their preferred **choice** of program (GEMS-T(Choice) or GEMS-S(Choice)) will have better outcomes in self-efficacy, adherence, and adoption of exercise than no choice conditions.

SPECIFIC AIMS

Our specific aims (SAs) are as follows:

SA1: Compare the extent of change pre-test to post-test in walking and mobility outcomes, social and vocational participation, and quality of life between the identical evidence-based individualized exercise program delivered via GEMS-S or GEMS-T in adults with MS who have slowed walking (greater than 6 seconds on the T25FWT);

SA2: Evaluate and compare the effectiveness between participants randomized to their preferred delivery mode (GEMS-T(Choice) or GEMS-S(Choice)) and those who are not randomized to their preferred delivery mode (GEMS-T or GEMS-S);

SA3: Evaluate changes in self-efficacy, and adoption of exercise between these groups (GEMS-T, GEMS-S, GEMS-T(Choice), GEMS-S(Choice)).

RESEARCH METHODS

Design

This is a multi-site, 2-staged randomized, choice design study aimed at noninferiority, to compare the effectiveness of delivering an individualized exercise program in a facility (facility-based exercise training or GEMS-S) versus via telerehabilitation (telerehab-based exercise training or GEMS-T) in people with MS. Noninferiority assumes both interventions (GEMS-S and GEMS-T) produce no statistically different outcomes.

Shepherd Center is the Clinical Coordinating site, led by Dr. Deborah Backus, and UAB is the Training Site, led by Dr. Rob Motl. UAB will also house the Statistical Center, led by Dr. Gary Cutter. The Data Management Center led by Dr. Robert McBurney will be maintained by iConquerMS of the Accelerated Cure Project.

This protocol will first outline site specific procedures and tools, and then will provide details regarding the coordination of the multiple study sites by the investigators at the Shepherd Center.

Participants

We will enroll 400 participants across the following eight centers: The Shepherd Center, Atlanta, GA; the University of Georgia, Athens; the Cleveland Clinic Mellen Center for MS Treatment and Research, Ohio; the University of North Carolina, Chapel Hill; Massachusetts General Hospital, Boston (MGH); the University of Colorado; the University of Alabama, Birmingham (UAB) in collaboration with The Tanner Center and Foundation for Neurological Diseases (Tanner Center); and Marquette University, Wisconsin. The criteria for eligibility will be identical at all sites. Participants will qualify for the study if they meet the following criteria:

<u>Inclusion criteria</u>:

1. Physician-confirmed diagnosis of MS
2. Expanded Disability Status Scale (EDSS) score of 4.0 through 6.5
3. Age between 18 and 65 years
4. Able to travel to a GEMS-S site for testing and training
5. Accessible, technological platform for GEMS-T (i.e. computer or DVD player and TV,

and telephone)
6. A score of between 25 and 75 on the MSWS-12
7. Timed 25-foot walk test (T25FWT) time of between 6 seconds and 3 minutes
8. Medically stable or approval from physician to participate in exercise studies
9. A score of between 3 and 6 (inclusive) on the Patient Determined Disability Steps

Exclusion criteria:
1. Documented MS relapse in the past 30 days
2. Have had falls in the past three months that the study investigator determines makes participation unsafe
3. Unable to walk 25 feet
4. Already exercises at recommended levels as determined by a score of 25 or higher on the Godin Leisure-Time Exercise questionnaire
5. Has other neurological (e.g., stroke) or musculoskeletal conditions or other co-morbidities
6. Has cognitive difficulties as determined by a Mini Mental Status Exam score <19
7. Is not proficient in English
8. Is physically unable to complete the second T25FWT trial
9. Any other concern that the investigators deem would jeopardize the safety of the potential participant.

We will randomize 200 participants to the Choice group and 200 to the No Choice group. Those in the Choice group will choose which exercise program to undertake – GEMS-T or GEMS-S. In the No Choice group, we will randomize 100 participants to GEMS-S and 100 to GEMS-T (see Figure 1). Four sites (Shepherd Center with help from UGA, Marquette University, Cleveland Clinic, and University of Colorado) will each recruit 80 participants. UNC and MGH will together recruit a total of 40 participants. UAB will recruit at least 40 participants with help from the Tanner Center, a Birmingham-based multidisciplinary center providing neurology, nursing, infusion, clinical research, neurodiagnostic testing, occupational therapy, physical therapy, speech/language pathology, licensed professional counseling, group wellness classes, and individual personal training in one central location.

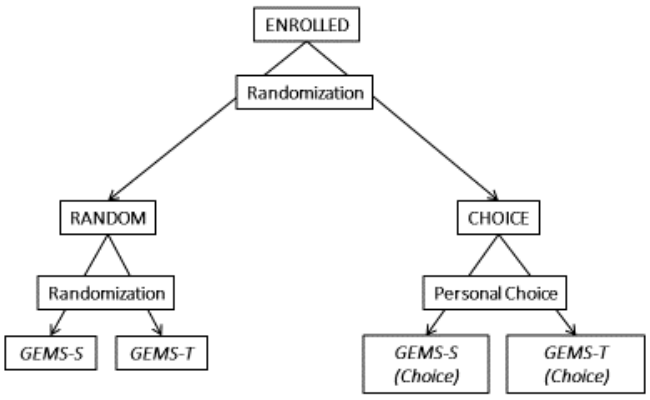


Figure 1: Randomization Scheme for Each Participant

Recruitment methods
The same recruitment strategies will be utilized at all sites. Participants will be recruited via existing research databases and clinical databases at each site, or by direct contact on site (by providers and other clinical or research staff), or by word-of-mouth using a flyer describing the research study and participation requirements. We will supplement this recruitment strategy as needed by advertising through local National MS Society chapters, iConquerMS, and other partners. We will also develop recruitment advertisements to be shared via social media, such as Facebook and Twitter (see sample post in the Appendix).

UAB will collaborate with the Tanner Center for recruitment purposes only. The Tanner Center has a history of assisting UAB with participant recruitment efforts, including for PCORI trials. A research coordinator at the Tanner Center will conduct a chart review of their patients to identify potentially eligible STEP for MS participants. The research coordinator will only review charts for those patients who have consented to be contacted about research studies, which is noted on their intake forms. The Tanner Center will also use the recruitment strategies outlined above.

After identifying potential participants, the Tanner Center research coordinator will contact the patient to describe the study and ask basic prescreening questions, such as: do you currently exercise? Can you travel to UAB at Lakeshore to exercise twice a week (in case they are randomized or desire the facility training, GEMS-S)? These prescreening questions will be logged in a securely stored spreadsheet and only used for the purposes of determining potential eligibility for the STEP trial. If a potentially eligible participant expresses interest in being screened, the Tanner Center research coordinator will send the potential participant a URL link to an online consent form hosted on REDCap. The consent form will ask the potential participant to authorize the Tanner Center to release their contact information and basic medical information, such as a diagnosis of MS and EDSS score, if available, to UAB. Upon receipt of consent, the Tanner Center research coordinator will send this PHI via REDCap to the research coordinator at UAB. REDCap is a HIPAA-compliant, secure document transfer tool. The research coordinator at UAB will then conduct follow up and screening with the potential participant.

Study Procedures
Screening and Enrollment

The procedures outlined here will be utilized at each site. We anticipate screening approximately 800 individuals to reach our sample size goal of 400. Each site's research coordinator will be responsible for all recruitment and enrollment of participants.

An overview of procedures for each participant is provided in Figure 2. Screening will occur in three phases to determine eligibility.

Screen 1 assesses basic criteria such as age, ability to travel to the site, relapse status, other comorbidities (see Table 1 for full set of criteria). Screen 1 will also ask some questions regarding falls in the last three months and any other concerns to determine safety to participate in the exercise program. Given that the exercise program can be modified for people at risk of falling, a history of falls in the past three months will be collected but will not automatically exclude a participant. The research coordinator will gather as much information as possible about

any falls and determine with the site investigator if the potential participant is eligible to participate.

If the individual meets the basic criteria, the research coordinator will read a consent script (see telephone consent script in the appendix) requesting permission to perform and record the responses to three additional surveys (**Screen 2**). The telephone consent script will describe the purpose of the assessments and how the data will be used and securely stored. The research coordinator will document whether verbal consent is provided, or not. If an individual declines to provide verbal telephone consent, the screening ends. If the individual provides verbal telephone consent, the research coordinator will proceed to Screen 2.

Screen 2 implements the MS Walking Scale-12 (MSWS-12), the Patient Determined Disability Steps (PDDS), and the Godin Leisure-Time assessments.

If the individual passes Screens 1 and 2 and still wishes to be considered for enrollment in the study, the research coordinator will complete the Exercise Preparticipation Health Screening questionnaire (EPHS) to determine if the participant requires medical consent to participate. Once the individual obtains medical clearance, they will notify the research coordinator who will schedule them for Visit 1 for final screening assessments and enrollment. The research coordinator will send any potential participant who meets these initial criteria the informed consent form for their review prior to Visit 1. All screening will be conducted by the research coordinator or designee. Screening measures and instruments are outlined in Tables 1 and 2. Screens 1 and 2 will be conducted either by phone or in person by the research coordinator or designee.

Screens 1 and 2 are necessary to ensure that we are asking only the individuals who meet the basic inclusion criteria to come to the center for further testing. For instance, if they are already performing adequate levels of exercise per week, they would be unlikely to experience substantial gains through our program and would thus be inappropriate for this study. Likewise, if an individual is unable to ambulate at all, they will be unable to perform the evidence-based exercise program for this study. Therefore, this three-stage screening approach will decrease the screening burden on individuals by screening out those who are obviously unqualified for the study. This approach will also ensure efficient use of resources, such as the award funds and personnel time to perform the assessments.

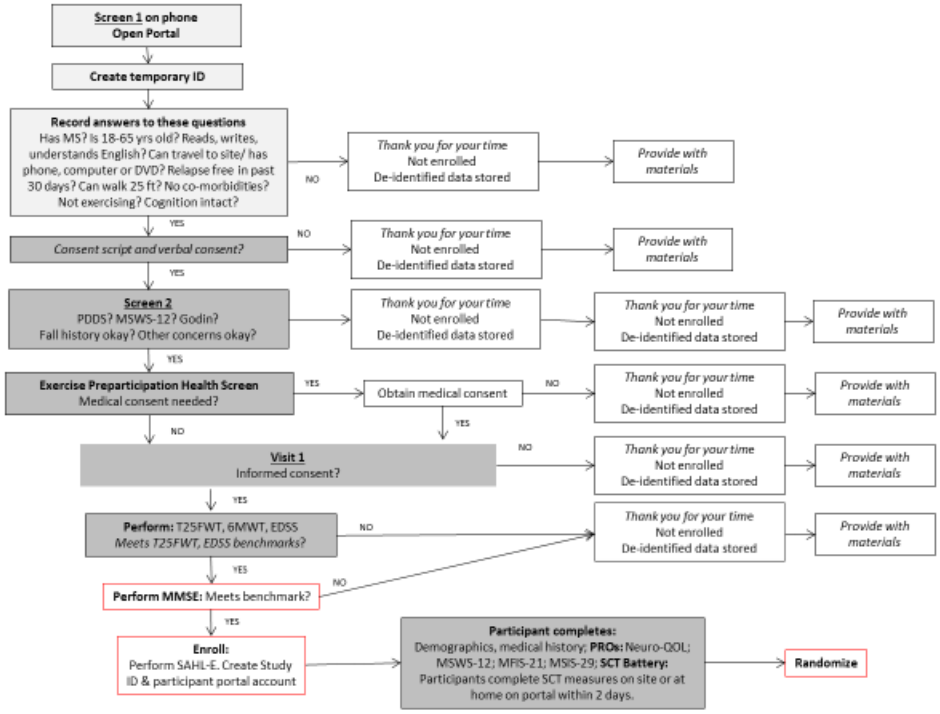


Figure 2: Study procedures for each participant

Visit 1 will be conducted at the study site. At the beginning of this visit, the research coordinator will review the informed consent process with the individual, providing additional detail and answering questions as necessary. If the individual agrees to continue with the process and provides informed consent (see Appendix for informed consent form), the individual will complete additional clinician administered screening assessments and questionnaires. Specifically, a blinded, NeuroStatus certified evaluator will perform the Expanded Disability Status Scale (EDSS) assessment. A trained blinded evaluator will conduct the Timed 25 Foot Walk Test (T25FWT) and the Six-Minute Walk Test (6MWT) per the respective data collection protocols. If the participant is physically unable to perform the second T25FWT trial, they will not complete the 6MWT, but will complete the EDSS. If the participant has an EDSS score between 4.0 and 6.5 and can complete the T25FWT in 6 to 180 seconds, they will undergo a Mini-Mental Status Exam (MMSE) to determine if they have the cognitive abilities to safely participate in the intervention for this study. If they score at least a 19 or greater, they will be considered eligible for the study. If not, they will not be enrolled in the study.

Enrollment

After a participant is determined eligible to participate, the research coordinator will input the results from the 6MWT and implement a final instrument - Short Assessment on Health Literacy (SAHL-E). The research coordinator will subsequently enroll the participant in the study by creating a participant account in the Portal. The participant will then complete a demographics and medical history survey and additional baseline patient reported outcome (PRO) measures, including the Modified Fatigue Impact scale-21 (MFIS-21), the MSWS-12, the Neuro Quality of Life (Neuro-QOL) scale, and a social cognitive theory (SCT) battery of measures (see Tables 1 and 2). Individuals will have the option of completing measures remotely at home, if necessary.

Table 1: Study measures									
Tool	**Description**	**Screen 1**	**Screen 2**	**Visit 1**	**Enrollment**	**8 weeks**	**16 weeks**	**6 months**	**12 months**
Basic eligibility criteria – screen 1 instrument	Self-report question to assess basic eligibility: Age 18-65; confirmed MS diagnosis; relapse in past 30 days; ability to travel to facility; technical requirements for telerehab; other neurological/ musculoskeletal conditions & co-morbidities; English proficiency; exercise habits; self-reported ability to walk 25ft; basic cognitive screen questions; how did you hear about the study?	X							
Fall assessment – included in screen 1 instrument	Self-report questions to assess whether a history of falls in the last 3 months prevents safe participation: Have you experienced more than one fall in the last three months? Have you experienced an injurious fall in the past three months that required medical attention?	X							
Patient Determined Disability Steps	Participant chooses one of 9 categories that describes their MS disability level.		X				X		X
MS Walking Scale-12	A 12-item self-report survey; measures the impact of MS on walking ability and daily activities over the past 2 weeks.		X		X	X	X	X	X
Godin Leisure-Time Exercise Questionnaire	4 questions; 7-day recall of leisure-time physical activity to determine if individual is already exercising at adequate levels.		X			X	X	X	X
Exercise Preparticipation Health Screening	Questionnaire about physical health to determine if medical consent to participate is required.		X						
Expanded Disability Status Scale	A 30-minute multiple item disease-specific instrument that characterizes disability level and determines disability progression in people with MS.			X			X		X
Timed 25 Foot Walk Test	Measure of walking speed; participant will perform twice. Only one trial must be in the eligibility range for inclusion (6 to 180 seconds). The time of both trials will be averaged for the outcome measure. Participants will be ineligible if physically unable to complete trial 2. If the assistive device/orthosis changes from pre- to post training, participants will be tested with the previous device.			X			X		X
6-Minute Walk Test	Measures the distance an individual can walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual can self-pace and rest as needed as they traverse back and forth along a marked walkway. If the assistive device/orthosis changes from pre- to post training, participants can choose device type, or no device at all.			X			X		X
Mini-Mental Status Exam	11-item test of cognitive impairment.			X					
Demographic survey/medication	Age; gender; type and history of MS; race/ethnicity; insurance status; living arrangements.				X	X	X	X	X
Short Assessment of Health Literacy-English (SAHL-E)	SAHL-E contains 18 items to assess an English-speaking adult's ability to read and understand common medical terms and estimate an adult's health literacy level.				X				
Neuro-QOL	A validated outcome measure of quality of life sponsored by the National Institute of Health recommended by the American Academy of Neurology.				X	X	X	X	X
Modified Fatigue Impact Scale-21	A 21-item self-report of the severity of fatigue and its effect on the participant's activities and lifestyle over the past 4 weeks.				X	X	X	X	X
Multiple Sclerosis Impact Scale-29	A 29-item self-report of participant's views on the impact of MS on day-to-day life during the past two weeks.				X	X	X	X	X
Social Cognitive Battery	See Table 2.				X	X	X	X	X
Participant Feedback Survey	27-item survey obtaining participants' feedback with the exercise program to assist with program modification and post-study dissemination.						X		

Adherence log is maintained weekly by participant to evaluate fidelity of the intervention across groups, as well as measure adherence with the protocol.

Reason for group choice: If randomized to the choice group, the research coordinator will complete the Choice form, which asks questions to determine if the COVID pandemic influenced their decision-making process. If not administered at randomization, the Choice form will be completed at 16 weeks.

Table 2. Social Cognitive Theory Battery

Tool	Description
Exercise Self Efficacy Scale[78]	10-item Likert scale measuring an individual's self-efficacy to undertake exercise related tasks and overcome barriers related to exercising.
Exercise Goal Setting Scale[79]	10-item Likert scale assessing the extent an individual sets exercise goals.
Multidimensional Outcome Expectancies for Exercise Scale[80]	19-item Likert scale measuring an individual's beliefs or expectations about the benefits of regular exercise or physical activity.
Exercise Barriers	8 questions to measure an individual's beliefs about the barriers related to exercising.
Social Provisions Scale[82]	6-item scale measuring the degree to which respondent's social relationships provide various dimensions of social support in relation to physical activity.
Physical Activity Self-Regulatory Scale[84]	12-item scale measuring an individual's self-regulation in relation to exercise.
Barriers for Self-Efficacy	13-item scale measuring individual's self-efficacy to participate in exercise when encountering barriers.

Once all baseline outcome measures are obtained, participants will be randomized and notified soon after by the site research coordinator of their group assignment. Randomization completes enrollment.

COVID-19 Screening and Enrollment Procedures

While trial sites are closed due to the COVID-19 pandemic, no screen 1s, screen 2s, Visit 1s, or associated enrollment activities will take place. Participants currently in the screening and enrollment process, will pause where they are. The recruitment coordinator from the enrolling site will contact those participants and let them know the study is on pause due to the pandemic and that they will be contacted again when enrollment resumes.

- If enrollment resumes past the 60-day screening eligibility window (60 days from screen 2 to visit 1; 60 days from visit 1 to starting exercise), the participant will be rescreened as determined appropriate by the site investigators.

Prescreening activities, such as chart review and preliminary phone calls with interested participants will continue. Interested people will be informed the study is on hold and they will be contacted when enrollment resumes.

Transfer of participant to coach

Once a participant is randomized to their intervention group (GEMS-T or GEMS-S), the research coordinator will provide the respective coach the contact information for the participant. They will also provide the following information:

- If the site PI or RC deems the participant is a fall risk
- The participant's EDSS score
- Whether the participant uses an assistive device

To convey this information to the GEMS-T for the GEMS-T participants, the research coordinators will send an encrypted email to a secure, HIPAA-compliant email address at UAB with this information. This information is to inform the coach of functional status of the participant so that they can modify exercises to prevent falls.

Follow-Up Assessment Procedures
Timing of subsequent outcome assessments are summarized in Table 1. CROs and PROs will be administered again immediately post-intervention (at 16-weeks), and at 12 months post-intervention. PROs will also be assessed at 8-weeks after the start of the intervention and at 6 months post-intervention. Participants will complete their PROs at Visit 1, and 16-weeks, and 12 months post-intervention in a private onsite room with the support of the research staff as needed, with the option of completing the SCT battery at home via the study portal. The research staff will not influence the survey responses but provide technical support to enhance completeness and quality of data. Participants will complete the 8-week and 6-month PROs via the secure online study portal (described below).

COVID-19 Follow-up Assessment Procedures
All enrolled participants will continue with their assessments on schedule. However, the type of assessments administered will differ from Table 1 while there are restrictions on accessing trial site facilities due to the pandemic. Specifically, no clinically reported outcomes (T25FWT, EDSS, 6MWT) will be administered. Research coordinators will verbally consent participants in waves 1 through 9 who are due for assessments via telephone prior to administering the PDDS at 16 weeks and 12 months. Once COVID-19 restrictions are lifted, participants will be reconsented at their next on-site assessment visit to take the PDDS. Participants from wave 10 onwards will sign the amended ICF that includes the PDDS as a follow up assessment measure at enrollment.

Data Collection Procedures
All study data will be collected and maintained in a database accessible through a secure, HIPAA compliant study portal, developed by iConquerMS. To maintain confidentiality, all data collected and input to the portal will be linked to individuals via an individual identifying number, as described below under "Study portal security" (p18-19) and in the informed consent form. The research coordinator will help each individual create a portal account at Visit 1.

We will use several measures to ensure that all post-intervention assessments (summarized in Table 1) are completed on time: 1) the research coordinator will contact participants 2 weeks prior to when outcomes are required via the participant's preferred mode of communication (eg., email, text to smartphone or phone call; 2) the research coordinator will also place a reminder communication as above 24-48 hours before the post-test appointment; 3) the portal will also send electronic reminders to research coordinators and participants when assessments need to be completed and when PROs are not fully completed; and 4) the coaches will also remind participants during their scheduled coaching sessions about upcoming data collection dates.

The PRO and CRO data collected at each site will be entered into the study portal. The study portal provides real-time data checking alerting both research personnel and the participant immediately if data are not entered, or if there is a logical inconsistency with the data entered. In addition to the automated data verification, dedicated staff at iConquerMS will monitor completeness and fidelity of data on an ongoing basis and provide feedback to each site weekly regarding missing data. Simultaneously, the Project Manager at the Clinical Coordinating Center (Shepherd Center) will be provided with a report regarding data completeness and fidelity. Thus, there are daily indicators of completeness and quality of data, as well as daily oversight and weekly opportunities to rectify problems with data collection, entry and flow. The Project Manager, along with the PI (Backus) will work with the research coordinator at each site not only to obtain missing data when possible, but also to devise an individualized plan at any site that is routinely missing data.

6-Month Assessments: The 6-month assessments were implemented after waves 1 through 4 were consented and enrolled. The procedures for contacting and consenting these participants is as follows:

- Waves 1 and 2 will receive an email from the Portal at 6 months post intervention explaining the addition of the 6-month assessments and requesting participants click on a link to an online consent form and complete the assessments (see email and online consent form in Appendix)
- Waves 3 and 4 will be re-consented at their 16-week visit with a new paper informed consent form (ICF) that includes a description of the 6-month assessment
- Waves 6 onwards will sign a new ICF that includes a description of the 6-month assessment at their baseline visit
- Depending on the consenting date for wave 5, they will either be consented with the new ICF at baseline, or will follow the procedure for wave 3 and 4.
- At 6 months, waves 3 onwards will receive an email from the Portal alerting them that it is time for them to log on and complete the 6-month surveys.

All participants with outstanding assessments will receive weekly email reminders to log on and complete the 6-month assessments, and a reminder two days before the deadline. Research Coordinators will receive similar emails alerting them to contact participants to remind them to complete the assessments.

Management of Withdrawals or Dropped Participants

Lost to Contact

If a participant is lost to contact for 2 weeks, the research coordinator will try to contact them via all modes of communication, including personal phone, emergency contact, text, email, and postal service.

If the participant is lost for an additional 2 weeks (a total of 4 weeks), then they will be considered lost and dropped from the study.

If a participant is randomized to a treatment group but makes no contact in the first week, they will be dropped from the study.

If a participant withdraws or is dropped from the study, the research coordinator documents the date and reason in the Portal. This information will be summarized annually for the site-specific IRBs as well as for the Shepherd (Primary site) IRB, the Advisory Board, and the Data Safety Monitoring Board (DSMB), and will be reported in the Final Project report. We will not automatically replace withdrawals, but will develop a strategy based on the attrition rate after the first few waves have completed the study.

Other Withdrawals

To assist with the study intent to treat analyses, the study will attempt to collect data from withdrawals. Research Coordinators will offer participants who withdraw three options:

1) Early Termination Visit: Participants will return to the facility to complete a full set of CRO and PRO assessments (including the feedback survey) and subsequently their withdrawal will be processed. Participants receive the $25 travel stipend for the visit.
2) Continue with assessments only: Participants will cease the exercise program but continue with assessments on schedule and per protocol.
3) Complete an immediate withdrawal: Participants withdraw immediately and fully from both the exercise program and assessments.

Should a participant choose 1) or 2), they will sign a new consent form with information about participating in these withdrawal assessments (ICF Withdrawal – Early Termination Visit or ICF Withdrawal – Assessments Only).

INTERVENTION

There are two modes of delivering the evidence-based, individualized exercise program: Facility-based exercise training (GEMS-S) and Telerehab-based exercise training (GEMS-T). GEMS-S will be delivered at each of the eight recruiting sites (n=200) and GEMS-T will be delivered via UAB within a participant's home/community (n=200). Both GEMS-S and GEMS-T consist of an identical, individualized exercise program based on evidence-based exercise guidelines. Participants will undertake both aerobic and resistance training of moderate intensity twice per week for 16 weeks (4 months), based on these conditions:

a. The prescription is individualized, based on each participant's ability. All participants are provided a low-level prescription to try for one week. They are asked to monitor how they feel, and at the end of the first week, they are contacted by a coach (GEMS-S participants in person at the facility; GEMS-T participants via video-chat). The goal is for the participant to gradually progress toward meeting the exercise guidelines.
b. The elements of the intervention were chosen to facilitate self-management of exercise, as well as to maintain the integrity of the intervention across delivery modes (GEMS-S and GEMS-T). All participants will receive a hip-worn pedometer to monitor steps. This information is to monitor fidelity of the exercise implementation only, and the participant will also record this information on their adherence log for each session. For aerobic training, the walking speed in the natural environment (GEMS-T) are adjusted to get the desired 100 steps/minute and target heart rate (HR) based on HR reserve and target zones

defined by the American College of Sports Medicine.[44] The target stepping rate and HR correspond to moderate-intensity exercise in persons with MS.

c. Resistance training consists of 1-2 sets, 10-15 repetitions of 10 exercises targeting lower body, upper body, and core muscle groups performed 2 days per week. Participants start with the amount of resistance at which they can perform 10-15 repetitions. GEMS-T participants will receive bands to use at home, and GEMS-S participants will be given bands to use and keep by each site.
d. There are three separate levels of difficulty of the exercise intervention (orange, blue, white) that the participant chooses in discussion with their behavioral coach. This mutual decision is based on participants' experience following the first two weeks of the program and coaches' perception of how they did. The levels of difficulty vary in terms of progression toward meeting the exercise guidelines. This feature is critical for accommodating the various levels of ability we anticipate for our participants. Much like those who do not have a disability, each participant may start at a different level; the goal is for each participant to exercise at moderate intensity by week 10 of the intervention.
e. Participants in both groups receive a detailed manual outlining safety information, description of equipment/materials, and all exercises. GEMS-S participants will have access to a coach in the facility who can provide guidance regarding exercise training. GEMS-T participants will receive a DVD and a printed exercise manual with actual demonstrations of all the resistance exercises, including modifications for differing levels of physical capability to maximize safety. Two people with MS and one member of the research team serve as the models for the exercises.
f. Procedures to prevent falls include providing all participants with a fall risk prevention information packet during enrollment and or during the first coaching session. Coaches will also implement the following coaching instructions:
    a. If the participant is at risk for falls, they will perform the resistance exercises in sitting;
    b. If the participant uses an assistive device, they will be instructed to use one while doing the walking exercises;
    c. If the participant needs someone with them to be steady, or if there is a wall where they can walk, they should use these resources to be safe;
    d. The participant will be instructed to only walk as fast as they can do so safely, and to focus on increasing their number of steps first.
g. Each participant will maintain an exercise logbook that will provide training specific data that will be used to evaluate fidelity of the intervention across groups, as well as to measure adherence with the protocol. Participants will record missed sessions and the reason for the miss, and if the session was made up during the corresponding week. Participants will also log steps information from their pedometers on the exercise logbook after each exercise session. For GEMS-S, the site coach will collect the exercise logbook on a weekly basis and enter the data into the Portal. For GEMS-T, participants will input their adherence data directly into the Portal each week.
h. The exercise coach will check the exercise logbook for each participant and will document in the study portal:
    i. Missed sessions
    ii. Any reports of adverse events

GEMS-T coaches will review participant logs prior to their scheduled one-on-one sessions. If there is missing data, the coach will obtain the information during the coaching session, including any information about adverse events (AEs). The GEMS-T Project Coordinator will review the exercise logs each Friday on non-coaching weeks for submission status and notification of AEs. For participants who have missing data, the GEMS-T Project Coordinator will attempt to contact them to remind them to complete the missing log entries and check to see if they are having any issues accessing the portal.

If a GEMS-S participant misses an exercise session, the facility coach will attempt to contact the participant to find out why and if the participant has had an AE. For follow up calls regarding missed exercise logs or sessions, the GEMS-T and GEMS-S Coaches will log the call date, result (reached/message left), and any important details in their log. If the coach cannot reach the participant, they should leave a voicemail reminding the participant to complete the log. If the participant has not updated their weekly log by the following Friday, the coach will attempt to contact them again.

i. At the end of the 16 weeks of exercise, GEMS-S coaches will make a copy of the exercise logbook and upload it to a site-specific, secure Microsoft OneDrive folder housed by UAB. Research coordinators will request that GEMS-T participants bring in their exercise logbooks to their 16-week visit, whereupon they will make a copy of the logbook and upload to OneDrive. GEMS-T participants who forget to bring their logbook to the visit, will be given a stamped, addressed envelope to mail it to the site. The logbook will subsequently be returned by mail to the participant. See Data Safety and Adequacy section below for details on Microsoft HIPAA compliance.
j. In order to respond to adverse events in a timely manner, the Project Coordinator at UAB will check exercise logs weekly and follow the adverse event reporting procedures outlined below.
k. The project manager will follow up with the coaches for all the above items and take any necessary appropriate action.

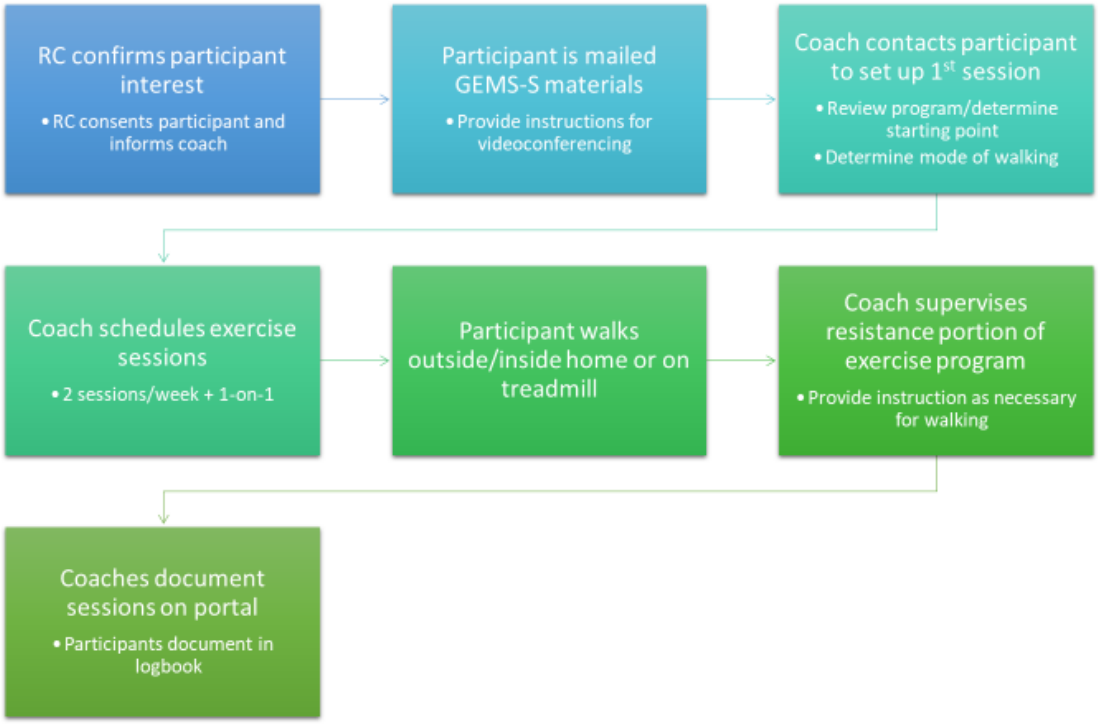
COVID-19 Intervention Procedures

While site training facilities are closed, we will implement the following procedures for GEMS-S participants in weeks 1 to 16 of exercise:

- Wave 7: Wave 7 participants were in weeks 15 or 16 of the intervention at the time of the March 2020 COVID shutdown. Participants ceased on-site exercise and received their exercise materials and final instructions by mail.
    - Both coaches and research coordinators called participants to let them know that while the training in the facility had to stop, they remained active participants in the trial. This meant that research staff would contact them to complete follow up assessments at 16 weeks, 6 months, and 12 months as per the protocol and schedule.
- Wave 8: Wave 8 participants were in weeks 5 or 6 at the time trial facilities were closed and were informed their exercise on-site and their one-on-one coaching sessions would cease. Subsequently, the Steering Committee decided to offer these participants the opportunity to continue their GEMS program with supervision at home "GEMS-S

remote." GEMS-S remote exercise continued per the procedures described below and in the figure.

- GEMS-S remote intervention procedures: In the case of site restrictions for on-site research activities, Research Coordinators will call the GEMS-S participants to describe the option to continue exercising at home (GEMS-S remote) with supervision by the facility coach provided via IRB-approved video conferencing or telephone.
    - Interested participants will provide verbal consent, which will be logged in the study portal.
    - Research staff will mail each participant their exercise kits and the coach will schedule twice weekly exercise sessions and the one-on-one coaching session if appropriate (dependent on the week of the exercise program).
    - The exercises will be performed per the GEMS-S protocol starting at a week agreed upon by the coach and participant. Only the resistance exercises (not walking) will take place by videoconferencing/phone call. The exercise sessions will not be recorded.
    - The schedule will continue as originally defined with the exercise ending at 16 weeks.
    - Participants can opt to not participate in the GEMS-S remote option. Those who decline consent will be asked to continue in the trial by completing assessments on schedule. Those who decline will be withdrawn from the trial.



GEMS-S remote Exercise Procedures

- GEMS-T participants will continue with their virtual coaching and exercise sessions on schedule. GEMS-T coaches will add advice to their coaching sessions relating to how to exercise while maintain safe COVID-19 social distancing measures. They will also log any interruptions in training related to COVID-19.
- Any participants enrolled in wave 9 will not begin exercising until site COVID-19 restrictions are lifted. Research coordinators will call wave 9 participants and let them know that they will contact them again when the study resumes exercising. Depending on when this is, participants may require further screening.

Behavioral Training

The physical exercise program is supplemented with a behavioral training intervention developed by Motl et al., based on Social Cognitive Theory (SCT) in people with MS.[56] The behavioral component entails regular meetings with MS exercise specialists (i.e., behavioral coaches), informational newsletters, detailed training manuals, and log books for self-monitoring. Personal interactions with coaches are conducted in person for GEMS-S participants and via one-on-one, semi-structured, online video-chat sessions for GEMS-T participants using web cameras and a HIPAA compliant teleconference system based on participant resources and preferences. If participants do not have access to the internet, the video-chats are replaced with phone calls. The in-person and online video-chat sessions will coincide with delivery of newsletters and supplement the content of the newsletters. The newsletters provide instructional material, websites for more information, testimonials of individuals who have experienced benefits of exercise, and tips for participants to try at home. GEMS-S participants will receive newsletters in person and GEMS-T participants will receive them electronically.

The sessions with the coach are designed to provide participants with feedback and information on how to progress through the exercise program as well as social accountability. Coaches will be research staff at each site for GEMS-S and at UAB for GEMS-T. Participants will be assigned to one coach based on availability. Before beginning the study, coaches will receive training from Dr. Motl in behavior change for physical activity, and this will be comprised of information regarding SCT and its application for motivating ongoing behavior change through supportive accountability and discussions of newsletter content. We will maximize consistency among coaches by using standardized scripts for guiding each video-chat. The scripts will contain (a) questions to obtain feedback from participants on progress in the program, (b) confirmation of receipt and reading of the relevant newsletter (c) discussion points linked with the relevant newsletter, and (d) opportunities for participants to ask any questions. Coaches will meet weekly and discuss interactions with participants to facilitate cohesion on how coaches respond to participants' needs, questions and experiences.

Coach auditing

Coaching sessions will be audited to ensure that coaches are delivering the intervention as intended. Once per week, on coaching weeks (when coaches discuss newsletters), a coach will randomly choose a coaching session to audio record. A different participant will be audited each time a coaching session occurs. Coaches may record sessions on whichever recording device they choose, as long as it is in compliance with site IRB regulations.

Prior to audio recording, the coach will obtain the participant's permission by asking the participant to sign the HIPAA authorization and release agreement to be audio-recorded.

UAB will review the audio and conduct the audit using a coaching audit checklist. Subsequently, UAB will then provide feedback to the coaches via email.

See Data Safety and Adequacy section below for details on how the audio will be securely shared with UAB and audio recording security measures.

ADVERSE EVENT MANAGEMENT

We define adverse events as follows:

- Adverse Event - Any untoward medical event occurring in a patient or subject enrolled in a clinical trial, regardless of whether the event has a causal relationship with the treatment under investigation.
- Serious Adverse Event - Any adverse experience that results in any of the following outcomes: death, a life-threatening event, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse event when: a) they may jeopardize the patient or subject, b) may require medical or surgical intervention to prevent one of the outcomes listed in this definition, or c) a reasonable possibility exists that the event may have been caused by the test article.

Ongoing reporting of adverse events (AEs) and serious adverse events (SAEs) to the IRB and PCORI will follow the policies and procedures of the Shepherd Center, as outlined in policy AC.RES.01.06 "Unanticipated Problem, Death, and Adverse Event Reporting" and participating IRBs. Specifically:

- The Study PI is responsible for accurate and timely reporting of adverse events in the source documentation. The PI is responsible for reporting SAEs and unanticipated problems (UPs) to the IRB within 10 days of their occurrence.
- Site Co-Investigators are responsible for reporting SAEs and UPs to the study PI at Shepherd within 72 hours using the portal AE form. For SAEs and UPs only, the reporting site personnel should also send an email to the study PI, site PI, coach, research coordinator, and the study Project Manager to ensure all receive timely notification.
- Either coaches or research coordinators can file the AE/SAE form on the portal and must communicate with each other to ensure the report is filed within the required timeline (see Table 3). If coaches start an AE form, they should simultaneously email the site research coordinator with a description of the event and the research coordinator will complete follow up and submit the form.
- All study investigators are responsible for recording all new clinical experiences, exacerbations, and/or deterioration of any existing clinical condition occurring after a study subject has signed informed consent. Research staff will also provide follow-up information on all adverse events until resolution or an appropriate endpoint is reached.
- Adverse Events will be documented and reported as follows:
    - Participant experiences an event, logs a description of the event in their participant diary/log and immediately contacts his/her coach or site research

coordinator, who follows the site-specific reporting steps (see Table 3 and Figure 3).
- The UAB Project Coordinator checks the exercise logs weekly for GEMS-T participants and identifies an AE, and follows the reporting steps in Table 3 and Figure 3. Or,
- Participant experiences an event while with his/her coach, and the coach logs the event and follows the site-specific next steps (Table 3 and Figure 3).

Table 3. Unanticipated Problem, Death, and Adverse Event Reporting (AC.RES.01.06)

Internal Event	**Reporting Timeline**
Internal Death of any subject	Report promptly within 72 hours of site's knowledge of event using the portal AE form and send email to study PI, site PI, Project Manager (PM), and site research coordinator (RC). PM reports to Shepherd RRC within 10 calendar days using Shepherd Research Review Committee (RRC) "UP, Death & SAE Report Form."
Internal Unanticipated Problem (UP)	Report promptly within 72 hours of site's knowledge of event using the portal AE form and send email to study PI, site PI, PM and RC. PM reports to Shepherd RRC within 10 calendar days using Shepherd RRC "UP, Death & SAE Report Form" on the study Portal.
Internal Serious Adverse Event (SAE) (non-UP)	Report promptly within 72 hours of site's knowledge of event using the portal and send email to study PI, site PI, PM and RC. PM reports to Shepherd RRC within 10 calendar days using Shepherd RRC "UP, Death & SAE Report Form."
Internal Adverse Event (AE) that is Not Serious	Do not report to RRC. Record event using the AE reporting form on the study Portal within 10 days of initial report. Note: An Adverse Event that is not serious by definition may be reported promptly, if in the opinion of the investigator, the event occurred with greater frequency, duration, or at a higher level of severity than expected.
Internal Unanticipated Adverse Device effect (UADE)	Report promptly within 10 calendar days of site's knowledge of event using Shepherd RRC "UP, Death & SAE Report Form" on the study Portal.
Internal Investigational New Drug Safety Reports, i.e. investigator initiated	If the report meets the criteria for UP, report promptly within 10 calendar days of site's knowledge of event using Shepherd RRC "UP, Death & SAE Report Form" on the study Portal

If a physician instructs a participant to pause exercising, the site research coordinator must obtain medical clearance from the participant's physician before resuming exercise. If the participant's physician does not instruct a participant to stop exercising, the site PI determines whether or not medical clearance after an AE is required.

Site research coordinators will inform the participant's coaches when medical consent has been obtained and the participant is approved to resume exercising.

Figure 3 below provides additional detail regarding how AEs are reported and addressed.

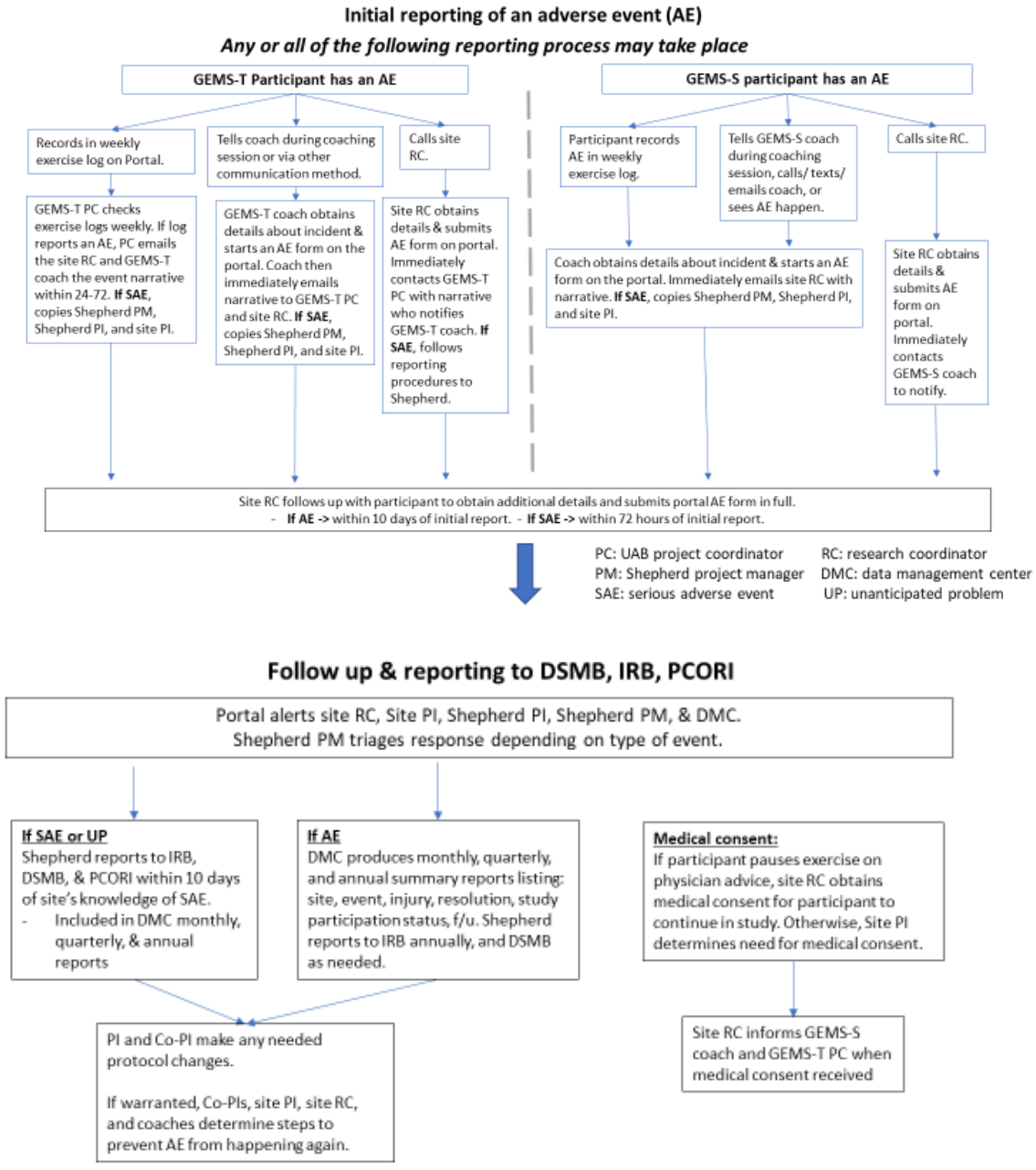


Figure 3: AE Reporting and Follow up Procedures

DATA ANALYSIS

Data analysis plan

The primary hypothesis is a non-inferiority test of the changes in T25FWT between GEMS-T and GEMS-S. This will be tested using a linear model with site as the stratification factor and an intention to treat approach. The primary analysis will adjust for covariates age, gender and baseline EDSS or PDDS. Further addition of covariates may be examined in sensitivity analyses based on any differences seen on examination of baseline variables between groups. Secondary endpoints include change in 6MWT and EDSS/PDDS. In all endpoints, we are assessing

improvement over baseline values. We will examine the frequency of worsening as a safety comparison. We will also examine the primary endpoint of a 20% improvement in the T25FWT (yes or no) using logistic regression. 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 groups. We will also examine the relationship between the dose of exercise measured by compliance and the change in the primary and secondary outcomes. These are exploratory outcomes to see if the compliance measures predict the benefits on the outcomes. This information is important for translation and information dissemination to people with MS.

To evaluate and compare the effectiveness between participants randomized to their preferred delivery mode (GEMS-T [Choice] or GEMS-S [Choice]) with those who are not randomized to their preferred delivery mode, we will use the same analysis model but examine an interaction term for choice and treatment. We will assess if the effect of Choice is the same for both treatments. Logistic regression will be used to assess the interaction between choice and adherence and attendance or dropouts. We also will examine time to dropout and/or time until dropout or poor compliance (which will be defined prior to final analyses). We also are interested in examining the intensity or compliance of the intervention to the choice as well as impact on the primary endpoint as noted above.

We will also utilize mediation analyses to understand if the changes induced by exercise are mediated via the changes in self-efficacy. Here we will use the approach by MacKinnon built on Judd and Kenny.[45-51] 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.

DATA MANAGEMENT

The Data Management Center (DMC) will be housed at the Accelerated Cure Project/iConquerMS led by project co-investigator, Robert McBurney, PhD. The DMC will collaborate and communicate with the Steering Committee and Advisory Board as outlined in Table 4.

Table 4. Responsibilities/Tasks of Data Management Center (iConquerMS/McBurney)
Review the proposed trial protocol and contribute to finalizing that document
Develop electronic and paper case report forms for data collection
Develop Standard Operating Procedures and a study *Manual of Procedures*
Develop and maintain an electronic data management system that will include a web-based data entry system and project website for the study
Create, distribute and oversee data entry processes for all sites
Train and certify users from each site in the data entry
Receive, collect, process, store provide quality control and assist in data analysis of data collected from the participating clinical sites and central reading centers
Prepare and distribute periodic technical and statistical reports to the Steering Committee, participating sites, committees (including the DSMB) and the PCORI office, as appropriate

Data safety and adequacy
Each participant will be assigned a study ID number when they create an account after passing eligibility criteria. This will be the only identifier in all databases and systems used in this study. Each site investigator will have access to their own master file linking participants with their randomized assignment, but this file will be stored on the Portal and kept separately from participants' assessments.

Research data will be entered online through the secure portal system and source documents, such as the CRO forms, will be kept in a secure fashion. All hard copy documents, such as consent forms, will be kept in a locked cabinet, and all soft copy documents, such as screening and adherence logs, will be password protected.

To ensure the EDSS is performed uniformly across all sites, research coordinators will upload scanned, completed EDSS source documents to Shepherd Center's Microsoft 365 cloud. In order to ensure HIPAA compliance, Shepherd Center has a Business Associates Agreement (BAA) with Microsoft as well as appropriate security controls in place to ensure the confidentiality, integrity, and availability of the source documents.. Each research site will have their own site-specific folder to upload their EDSS forms to. EDSS forms should not contain any personally identifiable information, only the participant ID number and evaluator name.

For coaching audits, the coach will upload the file to their site-specific folder housed by UAB's Microsoft 365 cloud. UAB also have a BAA with Microsoft. Files will be labeled: [site name]_[wave #]_ session #_ date_participant ID. After uploading the file, the coach will delete the audio file from the recording device. Audio recordings will be stored on a password-protected computer on a server central to UAB. All audio data will be erased upon the completion of each wave of recruitment.

Copies of exercise log books we be uploaded to a site-specific Microsoft 365 cloud folder housed by UAB, saved with the participant's study ID.

Staff from iConquerMS will monitor and track errors, completeness with routine reports and feedback to the sites. Data will be shared with the Statistical Center at UAB, who will provide analyses using SAS, SPSS, R and other programs, as necessary.

Study portal security
The Portal components are created in the web content management system Drupal (https://drupal.org/). The Portal has design aspects that are sensitive to those with vision issues due to symptoms of the disease (e.g. color, size of type, etc.,) as well as compliance with Section 508 of the 1998 amended Rehabilitation Act. The portal has been designed to be usable on tablets and higher resolution smart phones to make it possible for all users – those with access to PCs or without – to participate. The portal's Survey Engine leverages the CURE framework, an enterprise data collection tool (eDCT) originally developed for the NIH-NCI (https://github.com/NCIP/edct-formbuilder).

Data collected through the Portal is stored in a commercial-grade, cloud-based, HIPAA compliant, secure data center. Data is backed up daily. Offsite backups may be held by a third party to guard against data loss.

Appropriate security measures have been put in place to minimize risks such as loss of confidentiality, identity theft, electronic fraud/security breaches, electronic monitoring, stalking or bullying, hacking, and phishing. Access to the data center is physically limited to authorized personnel. Password-protected access to the server will be granted to study staff and vendors with access permissions set based on their roles in the study. Data is encrypted at rest with keys available only to appropriate users. All data transmission (uploading and downloading) occurs over secure, encrypted channels.

Individual accounts requiring unique usernames and passwords will be created for participants. Identifiers will be stored separately from other data types to protect the privacy of individual participants. Data will be de-identified when viewed by anyone but the participants themselves and authorized study staff. ACP will legally require anyone accessing participant-contributed data to agree not to attempt to learn the identity of any participant, or present or publish data in which an individual can be identified.

STUDY SITE COORDINATION

This is a multi-site trial, with Shepherd Center as the prime site and eight other collaborating sites: the University of Alabama, Birmingham; the Tanner Center, Birmingham; the University of Georgia, Athens; the Cleveland Clinic Mellen Center for MS Treatment and Research, Ohio; the University of North Carolina, Chapel Hill; Massachusetts General Hospital, Boston; the University of Colorado; and Marquette University, Wisconsin.

Figure 4 presents the organizational structure for the study. Dr. Backus and Dr. Motl will provide oversight of all study activities.

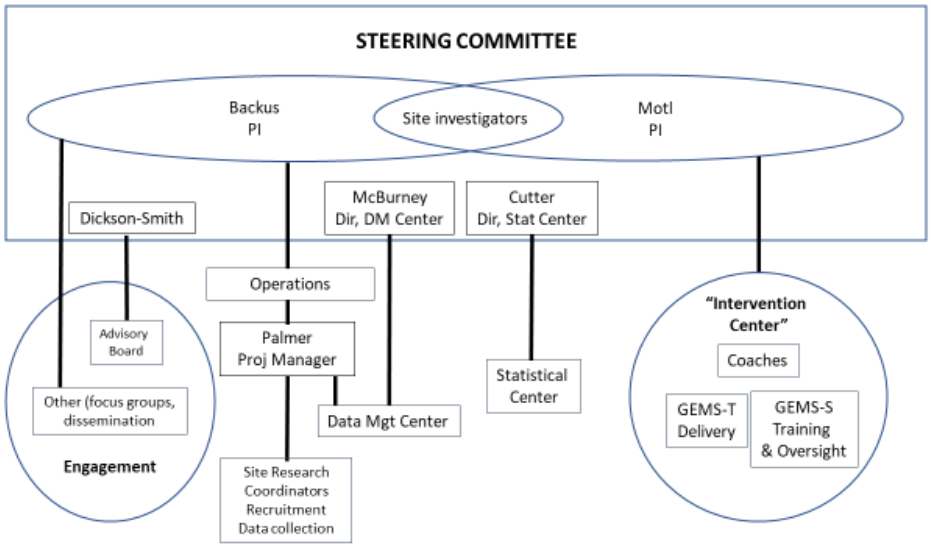


Figure 4: Organizational Structure

Training
A Study Binder will be created that will specifically define all data collection and recording processes, and provided to each site. Training materials will be accessible electronically by all sites.

Shepherd Center investigators will train all collaborating sites in all study procedures as defined in this protocol, and provide each site with the Study Binder that will provide detail of all study procedures and processes. All research staff collecting outcomes will be trained in these procedures prior to the commencement of the study. This will include training in all recruitment and enrollment procedures for which they will use IRB-approved recruitment tools that we develop. We will provide each site with the appropriate forms for data collection, and training regarding recording procedures, as well as use of the study portal and database.

There will be an annual follow up at each site to ensure that processes and procedures are being followed with fidelity. If there is a change in the study personnel, the new personnel will be fully trained in the same processes and procedures. Data collection training will also be repeated annually. Data will be entered in the HIPAA-compliant, secure portal and maintained by iConquerMS with oversight by Ms. Palmer and Dr. Backus. Sites will be responsible for maintaining all aspects of the database entered from the clinic, and staff support from iConquerMS will be available to trouble shoot technical questions. Access to this data will be restricted to study personnel only. Individual site coordinators will each have a unique username and password to enter the participant information.

The Project Manager will monitor enrollment numbers monthly to ensure that all sites are reaching milestones for recruitment. If one site is not reaching milestones, the co-PIs will reevaluate the recruitment strategy and determine if another site(s) can recruit/enroll more participants to cover the shortfall.

APPENDICES

Consent Script for Verbal Consent

Informed Consent Form

Informed Consent Form for Withdrawal - Early Termination Visit

Informed Consent Form for Withdrawal – Assessments Only

Recruitment Flyer

Social Media Recruitment Post

Staff CVs

CITI Certificates

Project Milestones

Fall prevention packet

Medical consent form – follow up after Adverse Events

Consent to audio record coaching sessions

Email to wave 1 and 2 participant

Email to wave 3 onwards participants

Online consent for wave 1 and 2 participants

NMSS Mood and Cognition Handout

Tanner Center online consent

Letter to wave 7 GEMS-S participants

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