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The Feasibility and Efficacy of a Remotely Delivered Exercise Training Intervention for the Hispanic/Latino Community With Multiple Sclerosis

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1.0 Study Summary

Multiple sclerosis (MS) is an immune-mediated, neurodegenerative disease of the central nervous system that results in a diverse pattern of symptoms that compromise quality of life and independence. MS has a prevalence of 1 million adults in the United States, and recent evidence indicates health disparities as a function of race and ethnicity, particularly among the Hispanic/Latino community. Such disparities include limited access to healthcare and medical services, further lack of representation and inclusion in medical research, and highlights the role of social determinants of health (SDOH) in this population. We posit that exercise training represents a disease-modifying and symptom-managing intervention for enhancing health outcomes and quality of life within this underserved MS population. There is compelling evidence from randomized controlled trials (RCTs) that exercise training influences cellular function through societal outcomes in MS. Yet, this research is mainly focused on Caucasian samples with no representation of Hispanic/Latino participants in existing research on exercise training in MS. We have begun addressing this limitation by examining physical activity and associated health outcomes in cross-sectional research involving Hispanics/Latinos with MS. Such research has primed our interest in developing and testing exercise training studies for this population. To that end, we have developed a theory-based, remotely-delivered and supported exercise training intervention for MS over the past decade, and this approach with appropriate modification of content could provide a convenient, accessible, and scalable approach for promoting exercise training in Hispanics/Latinos with MS. We propose a feasibility and efficacy study of a theory-based, remotely-delivered and supported exercise training intervention for increasing physical activity and improving health outcomes among Hispanics/Latinos with MS. This study addresses the challenge of limited access regarding exercise programs by delivering and assessing the potential of a culturally-tailored, remotely-delivered program based on prescriptive guidelines for exercise training in MS. If successful, the proposed study will provide “proof of principle” evidence regarding the feasibility and efficacy of a 4-month exercise training intervention compared with an active control condition for improving health and disease outcomes in adult Hispanics/Latinos with MS who often have limited access to healthcare and rehabilitation support services. The proposed study will leverage existing networks and healthcare organizations serving a high proportion of Hispanics/Latinos with MS for refining and testing a highly effective exercise training intervention focusing on aerobic and resistance training for improving outcomes in MS. The primary outcome of this study is the feasibility of the remotely-delivered exercise program, with secondary outcomes including remotely-delivered 30-second sit-to-stand, objective measures of learning and memory, and self-reports of fatigue, depression, anxiety, and quality of life. The secondary outcomes will inform

decisions on end-points and power future trials. The proposed research, if successful, will inform future RCTs on the efficacy of a remotely-delivered and supported, theory-based exercise training intervention for addressing the unmet needs of Hispanics/Latinos with MS who disproportionately experience poor health and disease outcomes associated with SDOH.

2.0 Objectives

2.1 Aims

Aim #1: Assess the feasibility of a 4-month remotely-delivered exercise training intervention in Hispanics/Latinos with MS (total N = 50) based on (1) process measures (e.g., recruitment, enrollment, adherence and retention of participants, as well as participant feedback on the burden of the program), (2) resource measures (e.g., time, space, monetary cost, and equipment requirements per stage of the research), (3) management measures (e.g., the capacity and expertise of researchers, and identify strengths and weaknesses), and (4) scientific measures (e.g., safety of the program, and its efficacy and outcomes).

Aim #2: Evaluate the efficacy of the exercise intervention in improving physical function, symptom management, and quality of life compared with an active control condition.

Aim #3: Explore the impact of SDOH factors on the feasibility and potential efficacy of the exercise intervention for improving outcomes in Hispanics/Latinos with MS.

2.2 Hypotheses

Hypothesis 1: The remotely-delivered exercise training intervention will be feasible for Hispanics/Latinos with MS, as evidenced by (a) high rates of recruitment, enrollment, adherence, and retention of participants, (b) reasonable time, space, monetary cost, and equipment requirements, (c) adequate capacity and expertise of researchers with identified strengths and weaknesses, and (d) safe and effective delivery of the intervention leading to improvements in MS symptoms and outcomes.

Hypothesis 2: Participants in the intervention condition will demonstrate (a) significant improvements in the 30-second sit-to-stand, neuropsychological measures of cognition, and fatigue, depression, anxiety, and quality of life compared with the active control.

Hypothesis 3: SDOH factors, including income, education, access to healthcare, and social support, will have a significant influence on the feasibility of implementing the exercise intervention and its efficacy in improving physical and mental health outcomes for Hispanics/Latinos with MS.

3.0 Background

3.1 Multiple sclerosis (MS) is a life-altering, immune-mediated and neurogenerative disease of the central nervous system (Bjartmar & Trapp, 2001) with a prevalence of nearly 1 million adults in the United States (US) (Wallin et al., 2019; Walton et al., 2020). The Hispanic and Latino population represents 18.9% of the total US population (i.e., second largest racial ethnic group after non-Hispanic whites (Health, 2023)), yet Hispanics/Latinos with MS have not been a focus of research on approaches for disease and symptom management. This is noteworthy as Hispanics/Latinos with MS present with a younger age of disease onset (Amezcuca et al., 2018; Langille et al., 2016; Ontaneda et al., 2023) resulting in rapid disability accumulation, more aggressive disease progression, and greater long-term disability (Ventura et al., 2017). This is likely attributed to social determinants of health (SDOH) such as economic stability, education, and healthcare (U.S Department of Health and Human Services, 2023), the non-medical factors such as race, employment, and social support (WHO, 2018), that influence health behaviors, comorbidities, and disease-modifying therapies in MS-related outcomes (Dobson et al., 2022). This extends into the field of rehabilitation lifestyle medicine, and we propose a study that will address these public health problems through a feasibility, pilot study of exercise training in Hispanics/Latinos with MS.

The inclusion of Hispanic and Latino populations in MS research has been a subject of recent focus, particularly in rehabilitation and exercise training. One review paper identified that fewer than 10% of the 4,280 persons with MS enrolled in randomized controlled trials (RCTs) of rehabilitation were Hispanics/Latinos (Fakolade et al., 2023). We have reported an even worse omission in exercise training interventions for MS, where fewer than 1% of the 2,034 enrolled persons with MS were Hispanics/Latinos (Lai et al., 2021). Exercise training is a promising second-line therapy associated with disease-modifying effects and improved physical and mental health outcomes for persons with MS (Motl & Pilutti, 2012; Motl et al., 2017); however, the lack of racial and ethnic diversity in the samples limits the applicability and generalizability of findings. Currently, there are no exercise training interventions targeting Hispanics/Latinos with MS.

3.2 We have begun cross-sectional research on physical activity in this population and further note that Hispanics/Latinos with MS exhibit alarmingly lower rates of physical activity than the general population and experience a higher prevalence of mobility disability compared with other persons with MS (Silveira et al., 2022). Our analyses further identified several MS outcomes (e.g., mobility, fatigue, cognition, and depression) that may be associated with the lower physical activity rates (Silveira et al., 2022).

3.3 One strategy to mitigate sedentary behavior and its associated negative health consequences is through the promotion of physical activity in the form of structured exercise. However, the lack of access to adequate resources, facilities, and/or rehabilitation programs poses significant challenges for persons with MS to engage in structured exercise. Remote exercise interventions offer an accessible solution for underrepresented persons with MS, particularly those facing limited access to traditional exercise programs and living in remote or underserved areas with physical limitations and transportation issues. A growing body of research suggests that compared with other racial/ethnic groups, MS affects Hispanic/Latino individuals differently with more severe symptoms and higher rates of MS-related complications. This effect is further compounded by social and economic factors disproportionately affecting Hispanic/Latino individuals. A carefully designed trial with a remotely-delivered exercise program can effectively address health disparities and improve physical and mental health outcomes in this marginalized community. It is essential that researchers and healthcare providers understand the unique needs and experiences of different communities with MS to provide high-quality care that is both culturally and linguistically appropriate. The proposed study evaluates the feasibility and initial efficacy of a remotely-delivered and supported exercise program that focuses on aerobic and resistance exercise for improving physical function, cognitive function, fatigue, depression, and quality of life in Hispanics/Latinos with MS. We propose a single-blind, RCT that examines the feasibility and efficacy of a well-developed and refined exercise intervention that is culturally-tailored for Hispanics/Latinos with MS. This study is a crucial first step for understanding the possibility of exercise training for optimizing disease management and treatment of outcomes among Hispanics/Latino populations with MS. This investigation is significant in light of the current research landscape that emphasizes the need for systematic focus on race and ethnicity in MS trial designs (Fakolade et al., 2023; Motl et al., 2022), assessment of the impact of SDOH on MS (Dobson et al., 2022), and prescription of exercise as an effective treatment for MS symptoms (Dalgas et al., 2019). The results will aid in understanding the needs and unique opportunities for exercise training and promotion in this underserved yet prevalent population with MS. This is particularly salient for researchers and clinicians, as a culturally-tailored exercise intervention can be delivered remotely through on-going clinical care provided by MS healthcare providers.

4.0 Study Endpoints

4.1 The primary endpoint is the feasibility of the remotely-delivered exercise training intervention. The pilot will follow the proposed metrics from Guidelines for Exercise in Multiple Sclerosis (GEMS) (Adamson et al., 2016). Table 1 summarizes each metric based on major categories of feasibility that align with our methods for collecting and assessing

relevant data, and the importance of each feasibility metric to the development of future trials (Adamson et al., 2016).

Table 1

Feasibility metrics; proposed methodology and importance to future research in MS.

Metric	GEMS will monitor and assess	How this will be monitored and assessed	Importance to future Phase II and III studies
Process: assesses participant recruitment and retention.	a. Recruitment and refusal rates b. Retention, attrition and adherence rates	a. We will use USPS, phone and electronic mail recruitment and record all contact with potential participants and refusal reasons (through an online refusal feedback form, email and over the phone). b. We will record all participants' flow through the recruitment, enrollment and intervention sections of the study. We will record adherence with the intervention via log books and video chats, and time spent in physical activity as measured during follow-up assessment.	a. To provide information on optimal recruitment method expected recruitment, and refusal reasons. b. To provide target areas for optimizing participant retention and intervention adherence.
Resources: assesses communication and monetary requirements of the study.	c. Communication with participants. d. Communication needs of participants and staff. e. Monetary costs of research	c. We will utilize a password protected database to monitor contact with all potential and enrolled participants. d. We will establish and record all problems and communication alterations. e. We will establish and record all monetary costs for the study; for both the intervention and waitlist control participants.	c. To establish communication frequency, quality and highlight communication problems. d. To establish communication needs and anticipated communication problems. e. To establish monetary cost to conduct the research and establish areas for cost saving.
Management: assesses data management and safety reporting during the study.	f. IRB approval procedures. g. Staff preparation and report time for participant communication. h. Time and accuracy in data collection/entry. i. Reporting and handling of adverse events (AE), serious adverse events (SAE) and clinical emergencies.	f. We will document communications between University IRB and staff, and time from submission of IRB application to approval. g. We will document all preparation, call time, attempted call time and report-taking time for each participant during the intervention. h. We will check for data completeness, and record time to collect, enter and check data. i. We will record our use and handling of standard university protocol for reporting of all AEs, SAEs and clinical emergencies.	f. To detail staff time requirements. g. To detail staff time requirements and highlight considerations for alterations. h. To detail what safety procedures should be implemented
Scientific: assesses the safety, burden and treatment effect of the study.	j. AEs, SAEs and clinical emergencies. k. Participants' experience, burden, and compliance during the intervention. l. Treatment effect.	j. We will follow standard university protocol to record all AEs, SAEs and clinical emergencies, and ask participants to report and record all medical concerns via log-books and video chats. k. We will record participant feedback on the intervention during the video chats, a feedback interview and a feedback survey. We will use participant self-reporting of exercise time and exertion during each exercise session, reported via log-books and video chats. l. We will determine effect size and clinical meaningfulness of any change in physical activity, sedentary behavior, symptoms, and HRQOL outcomes.	i. To determine the safety and feasibility of the intervention and highlight considerations for alterations. j. To determine acceptability and highlight considerations for alterations. Determining compliance will further allow correct conclusions to be drawn from the results. k. To determine data for power calculations and anticipated clinical impact.

4.2 The secondary endpoints are the 30 second sit-to-stand test as a measure of physical function (Ozkeskin et al., 2022; Zheng et al., 2023), the Symbol Digit Modalities Test (SDMT) (Smith 1982, Rao, Leo et al. 1991) as measures of cognitive function, the Fatigue Severity Scale (FSS) as a measure of fatigue (Krupp, LaRocca, Muir-Nash & Steinberg, 1989), the Hospital Anxiety and Depression Scale (HADS) as a measure of anxiety and depression (Zigmond et al., 1983), the short-form 12-item health survey (SF-12) as a measure of health-related quality of life (Ware et al., 1992), the Patient Determined Disease Steps Scale (PDDS) as a measure of disability in MS (Hohol, Orav et al. 1995, Hohol, Orav et al. 1999), the 12-item MS Walking Scale (MSWS-12 as a measure of walking limitations with MS (Hobart et al., 2003), and the Godin Leisure-Time Exercise Questionnaire (GLTEQ) as a measure of exercise behavior (Godin & Shephard, 1985). The tertiary endpoints are individual and structural SDOH factors, assessed by the PhenX Toolkit (Cox et al., 2021). All outcomes will be assessed at baseline and immediately after the 4-month intervention by a treatment-blinded assessor.

5.0 Study Intervention/Investigational Agent

Study Design: The proposed study will utilize a parallel group, randomized controlled trial (RCT) design. Eligible individuals who meet the eligibility criteria will be contacted to confirm enrollment, and then scheduled for remote assessments undertaken by treatment-blinded data assessors, including cognitive and physical function (i.e., secondary outcomes), as well as symptoms and quality of life (i.e., secondary outcomes), and SDOH (i.e., tertiary outcomes). Following the baseline measures, participants will be randomly (1:1) assigned to either the remotely-delivered exercise intervention condition or remotely-delivered and supported flexibility control condition using computerized random numbers with allocation concealment.

The standardized exercise training and flexibility programs will be delivered over a 4-month period and supported through Zoom-based chats guided by social cognitive theory (SCT) via behavioral coaches who are uninvolved in screening, recruitment, random assignment, and outcome assessment. Once allocated, the research coordinator will then mail a packet containing the intervention materials (resistance bands, pedometer, logbooks, calendar, and training manual) via certified postal mail. Participants will be contacted by a member of the research team for a brief overview of the training protocol, notification of the assigned behavioral coach, and scheduling the first one-on-one session. The behavioral coach will be provided with participant-specific information regarding fall risk, disability level (assessed by Patient-Determined Disease Steps (PDDS) questionnaire), and any other information that will inform the coach's oversight and interaction with the participant. 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 behavioral coach via phone or e-mail in the occurrence of an adverse event or any other problem; this information will further be queried and collected during the chat sessions. All participants will undergo the same assessments as done for baseline, immediately after the 4-month intervention.

Intervention Exercise Condition: The delivered intervention will be a modified version of the GEMS program (Adamson et al., 2016) in English and will encompass aerobic and resistance training sessions for adults with MS who are 18+ years of age with mild-to-moderate disability (Table 2). Aerobic exercise will focus on moderate intensity walking as the exercise modality, with progression chosen from three different trajectories for individualization established from the GEMS protocol (Adamson et al., 2016; Motl et al., 2023). Participants will start with 10 minutes of walking per day for the first two weeks,

followed by an additional 14 weeks with different progression trajectories based on the minimal dose achieved within 6, 8, or 10 weeks. The intensity will be centered on a step rate of 100 steps per minute and can be completed at home or in the community. Resistance training will be completed using elastic resistance bands in the participant's home. The training manual will contain detailed instructions and video demonstrations of each exercise, additional challenges and modifications to ensure safety and progression, and three different trajectories for individualization.

Table 2

Summary of the 4-month home-based intervention and control exercise prescriptions, materials, and behavior change interactions.

Item	Intervention: Aerobic and Resistance	Control: Flexibility
Exercise Prescription	Based on the exercise training guidelines for adults with mild-to-moderate disability due to MS. Aerobic-training: 10-30 minutes of moderate-intensity walking. Resistance training: 1-2 sets, 10-15 repetitions of 1-10 exercises targeting lower and upper body, and core muscle groups.	Based on flexibility guidelines for adults with MS. Stretching and range of motion exercises (ROM): 5-30 minutes of total stretching time, 1-2 exercises from 5-8 categories of stretches and ROM exercises and completed in 1-2 sets, 15-60 seconds.
Program variation	Orange - Aerobic and resistance training time and intensity increased over 16 weeks, and aerobic exercise guideline achieved and maintained on week 6. Blue - As above, aerobic exercise guideline achieved and maintained on week 8. Green - As above exercise, aerobic guideline achieved and maintained on week 10.	Orange - Total stretch time, number of exercises per category, and number of categories increased over 16 weeks, and achieved and maintained on week 6. Blue - As above, flexibility guidelines achieved and maintained on week 8. Green - As above, flexibility guidelines achieved and maintained on week 10.
Materials	Aerobic equipment: Yamax CW-300 digi walker™ pedometer. Resistance equipment: Elastic resistance bands varying in 5 increments of resistance.	Yoga mat.
Program manual	An introduction to the staff, safety information, guidelines for exercise in MS, description of equipment, and a detailed description of the resistance and aerobic exercises to be performed and how to progress over 4-months. Comparison tables of orange, blue, and green programs.	An introduction to staff, safety, flexibility guidelines for MS, detailed description of all stretching and ROM exercises, and how to progress over 4-months. Comparison tables of orange, blue, and green programs
Log-book	Annotated booklet for noting exercise participation, feelings, and rating of perceived exertion (RPE) after each session. Aerobic: Recorded as duration walked (mins) and number of steps, feelings on a 5-point scale (stars), and RPE on 1-10 scale. Resistance: Recorded as number of sets and repetitions, resistance band utilized, for the prescribed exercise per session, feelings on a 5-point scale (stars), and RPE on 1-10 scale.	Annotated booklet for noting exercise participation and feelings. Stretching and ROM exercise: Recorded as exercise category performed, number of sets and repetitions (sec), and duration of flexibility session (mins).
Calendars	Four undated calendars to facilitate exercise planning.	
Tele-chats	To provide participants with feedback and information on progression through the program as well as to provide social accountability.	
Newsletter	To provide material on specific behavioral change content, information from other resources, testimonials of individuals who have experienced benefits of exercise, and tips for participants to try at home.	

- Aerobic Exercise:** The aerobic exercise training will focus on 30+ minutes of moderate-intensity walking as the exercise modality performed three days per week. This decision was based on walking being the most common mode of exercise for people with mild MS that can be administered and monitored in non-supervised environments. The progression of the aerobic exercise training duration will follow three different trajectories for individualization (Table 3). All participants will start with the same duration of aerobic exercise for the first, 2-week period, consisting of 10 minutes of walking per day undertaken three days 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 Green) whereby the minimal dose of aerobic exercise will be achieved on 6, 8 or 10 weeks, respectively. The intensity of the aerobic exercise will be based on a step rate of 100 steps per minute; this stepping rate corresponds with moderate-intensity exercise in persons with MS as well as other diseases and conditions. Participants will be instructed to walk as fast as is safely possible, even if they cannot achieve the intensity prescribed, and the participants can complete the aerobic portion of the intervention in the home and/or community (e.g., park, shopping mall, high school track).

Table 3

Progression of the 3 levels or trajectories of progression for the TEAAMS program.

Week	Orange		Blue		Green	
	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

Week	Orange		Blue		Green	
	Aerobic Training	Resistance Training	Aerobic Training	Resistance Training	Aerobic Training	Resistance Training
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.

- Resistance Exercise: The resistance training will consist of 1–2 sets, 10–15 repetitions of 5–10 exercises targeting lower body, upper body, and core muscle groups performed three days per week. The lower body exercises are the chair squat, calf raise, glute bridge, leg extension, hamstring curl, hip abduction, glute kickback, and the forward lunge; the upper body resistance exercises are the back row, bicep curl, shoulder front raise, overhead press, chest press, lateral raise, reverse fly, and triceps extension; and the core exercise is the abdominal crunch, standing ab twist, and modified plank. 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 progression of the resistance exercise training (sets, repetitions, and exercises) will follow three different trajectories for individualization (Table 3). 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 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 for the exercises, sets, and repetitions over the remaining 14 weeks (Orange, Blue, and Green) whereby the minimal dose of resistance exercise will be achieved on 6, 8, or 10 weeks respectively. The exercise 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 undertake the resistance program with the resistance bands in the home.

Control Flexibility Condition: The control condition will adhere to the recommended flexibility guidelines for individuals with MS and will be delivered through telerehabilitation via the ENRL. Participants assigned to the control condition will not receive exercise instruction or equipment for aerobic and resistance training. Instead, they will be provided with a yoga mat to facilitate stretching and range of motion (ROM) exercises to be completed at home or in their community (Table 2). Participants in the control condition will engage in 1-7 flexibility exercises spanning 8 categories, targeting body areas specific to MS such as the head and neck, shoulder, elbow and forearm, hand and wrist, trunk and hip, ankle and foot, positioning for spasticity, and balance and coordination. During the initial 2 weeks, participants will perform 5-10 minutes of total stretching from 1-2 exercises within 5 categories. Over the subsequent 14 weeks, participants will progress through different trajectories based on specific time points (6, 8, and 10 weeks) to achieve a gradual increase in flexibility. Similar to the intervention group, participants in the control condition will receive the same frequency of telerehabilitation sessions, covering the same topics for discussion. However, the discussions will focus on stretching and range of motion exercises, rather than walking and resistance training. These sessions will provide participants with tips and strategies to improve flexibility and enhance their overall ROM.

Behavioral, One-on-one Coaching: The exercise program involves one-on-one semi-structured sessions with MS exercise specialists (i.e., behavioral coaches) (Table 4). 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. 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 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. The one-on-one

chat sessions will be conducted via a HIPAA-compliant teleconferencing system (e.g., Zoom). If a participant does not have access to the Internet, the video-chats will be replaced with phone calls. Importantly, the telerehabilitation behavioral coaches (including the PI) will attend regular meetings with the faculty supervisor, Prof. Motl, for ongoing dialogue on fidelity in delivering the interventions.

Fidelity Monitoring: Action planning and self-monitoring are essential for the long-term success in an exercise program as it maximizes behavior change and compliance with the intervention. 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 the completion of the exercise sessions over the 16-week intervention. 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.

To ensure the fidelity of the study, the behavioral coach will document each coaching session and the delivery of newsletters to verify that they are delivered as intended. The PI will also conduct random spot-checks of the coaching sessions to ensure the proper delivery of the intervention. The PI and research team will meet regularly to review the study progress and identify any necessary adjustments to maintain intervention fidelity.

Compliance with study: Compliance will be ascertained through several methods. Firstly, participants will be provided with detailed instructions and guidelines on how to perform the exercises or activities as prescribed in the intervention protocol. These instructions will be provided verbally during the Zoom sessions and also supplemented with written materials, including exercise manuals and logbooks. To track adherence to the intervention, participants will be asked to record their exercise sessions in the logbooks, noting the duration, frequency, and intensity of each session. They will also be encouraged to provide any additional comments or feedback regarding their experience with the intervention or control exercises. To ensure ongoing compliance and address any challenges or barriers, participants will have regular check-ins with the behavioral coach. These check-ins may occur via phone calls, video conferences, or email communication. The research team will use these opportunities to provide support, answer questions, and address any concerns or difficulties participants may be facing in adhering to the intervention.

6.0 Study Timelines

The total time commitment for participants to complete this study is approximately 5 months. This includes recruitment, screening, and baseline measures (~1-2 weeks), structured exercise and accompanied by behavioral coaching (4 months), and post-intervention measures (~1-2 weeks). Enrollment duration to include all study subjects is anticipated to take approximately 2-3 months. The estimated date for investigators to complete this study, including recruitment, screening, data collection, analysis and dissemination is projected to be December 1, 2024.

7.0 Inclusion and Exclusion Criteria

Screening for eligibility will be undertaken by a member of the research team. The first level inclusion criteria will be completed via an initial phone screening interview to determine eligibility, and will require: (1) age between 18-65 years, (2) diagnosis of MS, (3) relapse-free for at least 30 days, (4) able to walk with or without an assistive device, (5) insufficient physical activity (i.e., not meeting current physical activity guidelines of 150 minutes of moderate to vigorous physical activity per week), (6) willingness to complete all required testing procedures, outcome questionnaires, and randomization, (7) identify as Hispanic/Latino, (8) able to speak, read, and understand English, (9) currently reside in Chicago, (10) access to the internet and email, and (11) safe for exercise based on the Physical Activity Readiness Questionnaire (PAR-Q).

We will exclude all individuals with moderate or high risk for contraindications of possible injury or death when undertaking strenuous or maximal exercise using the PAR-Q. This self-reported screening tool will determine safety and possible risk for starting exercise. During the initial phone screening interview, participants will verbally respond to the 7-items on the PAR-Q, and those individuals who report no more than one YES or affirmative on the seven PAR-Q items will be considered at low risk and included for participation. All other individuals will be considered at moderate or high risk for starting a PA program and excluded from participation, and further advised to seek medical guidance before becoming more physically active.

We will determine if the individual is unable to consent and/or has any serious medical contraindications that might impact consent capacity during the initial phone screening. Individuals who are under the age of 18 years, pregnant, imprisoned, unable to consent independently, does not speak, read, or understand English, wheelchair-bound, not living in Chicago, not safe for exercise based on the PAR-Q, and without access to Internet and e-mail will be excluded from this study.

9.0 Number of Subjects

A total of 80 participants with MS are expected to be recruited for a total number of 50 participants.

We expect enroll 50 participants (25 participants for the intervention group; 25 participants for the control group). To achieve this, we expect to screen 80 persons with MS.

11.0 Procedures Involved

The proposed study is an interventional, randomized controlled trial designed to measure the potential effect of a remotely-delivered exercise intervention on physical and mental health Hispanics/Latinos with MS.

Non-research procedures will include the following:

Flyers will be distributed across all channels of recruitment expressed in 10.2. Flyers will contain information regarding the study, benefits, compensation, eligibility, duration of study, and the phone number and email address of the ENRL to contact if interested.

Potential participants will see the advertisement and be asked to contact the ENRL lab. A member of the research team will then use the “FERLA-MS Screening Script” to return a call or receive call. Briefly, the lab member will describe the study (examining the effects of a remotely-delivered exercise training program for Hispanics/Latinos with MS residing in Chicago), ask if they are interested in doing the study, and if they would like to proceed with the screening script steps. The phone screening will about eligibility criteria which includes the following (a) age at least 18 years and older, (b) identify as Hispanic and/or Latino, (c) diagnosis of MS, (d) relapse-free within the past 30 days, (e) insufficient physical activity (i.e., not meeting current physical activity guidelines) defined as 150 minutes of exercise or more per week, (f) willing and able to complete the exercise program and all online surveys, (g) able to speak, read, and understand English, (h) able to access internet and/or Wifi, (i) not pregnant and/or nursing, (j) verbally responds to the 7-item Physical Activity Readiness Questionnaire (PAR-Q) with no more than one “YES” or affirmative on the seven items to be considered low risk and able to do exercise.

If the participant qualifies and would like to do the study, the member of the research team will proceed with the “FERLA-MS Consent Discussion Script.” Briefly, the script will walk the subject through the consent process, collect information (email, name, address), discuss the study components (the 4 month exercise program, online surveys to complete in the beginning and end of the program), what the studying is trying to do (determine the effects of a remotely-delivered exercise program on the physical and mental health outcomes of Hispanics/Latinos with MS), the exercise and flexibility training groups (exercise group will engage in walking and resistance training, while the flexibility group will focus on stretches and range of motion exercises), the time commitment for all

components (4-month exercise study, exercise 3 times per week, and meet with the behavioral coach to encourage them and discuss social-cognitive theory variables of change), the potential risks of the study (slips, trips, or falls, and loss of privacy), and finish with the signing of the informed consent signing via Adobe Sign, sending the online surveys through Qualtrics and RedCap, and scheduling them with the behavioral coach. The Qualtrics surveys include the following:

- **Demographics and Clinical Characteristics.** Participants will complete a demographic and clinical characteristics questionnaire for information regarding age, sex/gender, religion, address, country of birth, marital status, socioeconomic information (i.e., level of education, occupation, education, annual household income), and MS clinical characteristics (disease stage, MS phenotype, age at MS diagnosis, duration of MS, family history of MS, MS symptoms, and any drug prescriptions and disease modifying therapies).
- **Comorbidities Questionnaire for MS.** The occurrence of comorbidities will be assessed through a questionnaire that includes conditions frequently reported in the general and MS populations (Horton, Rudick et al. 2010). The questionnaire inquires about 37 total comorbidities (e.g., high cholesterol, cancer, diabetes, depression), with the exception of stroke. For each comorbidity, participants will be asked to indicate the presence or absence of the condition, the year of diagnosis, and whether they are currently being treated for the condition.
- **Health History Questionnaire.** A health history questionnaire (HHQ) is used to capture characteristics of the sample for cardiovascular disease, recent health disturbances (e.g., recent illness, recent hospitalization, etc.), daily habits (e.g., cups coffee a day, caffeinated soft drinks a day or cigarettes a day), and family history. The HHQ includes 45 total items: cardiovascular disease (9), recent health disturbances (10), other habits (20) and family history (6).
- **Fatigue Severity Scale.** The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash & Steinberg, 1989) will measure subjective fatigue and the impact of fatigue on the individual. The FSS includes 9 questions examining the severity of fatigue and the impact on the individual in the past week. Answers range from 1 to 7, with 1 indicating “strongly disagree” and 7 indicating “strongly agree.” The overall score is the average of the individual scores and can range between 1 and 7. A FSS score above 4 is indicative of severe MS-related fatigue (Andreasen, Stemager & Dalgas, 2011) and a score of 1.9 reflects the minimal detachable change (at 95% CI) (Learmonth, Dlugonski, Pilutti, Sandroff, Klaren and Motl, 2013).
- **Hospital Anxiety and Depression Scale.** The Hospital Anxiety and Depression scale (HADS; Zigmond & Snaith, 1983) will assess symptoms of depression and anxiety.

The HADS includes 14 items which can be subscored for depression (7 items) and anxiety (7 items) as separate measures. Both the anxiety and depression items have been validated in persons with MS (Honarmand & Feinstein, 2009). Statements in the scale are self-reported by participants as experienced “Most of the time”, “A lot of the time”, “From time to time, occasionally”, or “Not at all”. Scores for anxiety and depression subscales range from 0–21 and are categorized as ‘normal’ (0–7), ‘mild’ (8–10), ‘moderate’ (11–14), and ‘severe’ (15–21). Overall, scores range from 0 to 42 with higher scores indicating higher anxious and depressive symptoms.

- **Short-Form 12-Item Health Survey.** The short-form 12-item health survey (SF-12) is an abbreviated, 2–3-minute questionnaire of the short-form 36-item health survey that gives an overall measure of health status. The 12-item survey assesses eight concepts separated into a physical component summary (PCS) and a mental component summary (MCS) (Ware et al., 1996). These component scores are qualitatively measured and adjusted based on relative average (general average population is 50 with a standard deviation of 10). Scores above 50 are considered above average and scores below 50 are considered below average (Ware et al., 1996).
- **12-Item MS Walking Scale.** Walking limitations will be assessed with the 12-Item MS Walking Scale (MSWS-12; Hobart et al., 2003). The MSWS-12 posits 12 questions starting with “in the past two weeks, how much as your MS...” limited various aspects of walking (e.g., “Limited your ability to walk”, “Slowed down your walking?”, “Made you concentrate on your walking?”). Items are measured on a Likert scale from 1 (Not at all) to 5 (Extremely). Sum scores range from 12 to 60, and are then transformed into a scale from 0 to 100 in line with published guidelines (Hobart et al., 2003) with higher scores indicating higher rates of walking limitations as a consequence of MS. Data is then transformed into 0 to 100 scale by subtracting the minimum possible score from the sum (12), dividing this number by the range (48), and multiplying this result by 100. The MSWS-12 is valid and reliable for use in persons with MS (Hobart et al., 2003).
- **Patient Determined Disease Steps Scale.** The Patient Determined Disease Steps (PDDS) is a self-reported outcome of disability in MS (Hohol, Orav et al. 1995, Hohol, Orav et al. 1999). PDDS scores range between 0 (normal) and 8 (bedridden), and the scores have demonstrated evidence for validity and strong correlations with the Expanded Disability Status Scale, pyramidal and cerebellar functional scores, and walking ability in persons with MS (Learmonth, Motl et al. 2013).
- **Godin Leisure-Time Exercise Questionnaire.** The Godin Leisure-Time Exercise Questionnaire (GLTEQ) will assess subjective measure of physical activity in a 2-part questionnaire, with focus on the first part (Godin & Shephard, 1997; Godin, 2011).

The first part will prompt participants to record the number of bouts greater than 15 minutes in duration of mild, moderate, and strenuous physical activity engaged in over the course of a typical week. The second part will not be utilized as it inquires about sweat which is complicated in MS due to known disease-related alterations in sweating ability (Haensch & Jorg, 2006). A total leisure activity score will be determined by multiplying the recorded number of 15 min bouts of mild, moderate, and strenuous physical activity by weights of 3, 5, and 9 respectively, and then summing those values into an overall score that ranges between 0 and 119. Higher scores indicate higher levels of physical activity engagement.

- Individual and structural SDOH will be assessed with the PhenX Toolkit, a consensus measurement for phenotypes and exposures in human research (Cox et al., 2021). The PhenX Social Determinants of Health Core questions will be utilized from the RedCap library, and administered through RedCap. The instrument will assess individual and structural determinants of health through the following aspects: access to health services, prescription affordability, discrimination in health care, English proficiency, health literacy, job insecurity, neighborhood environment, racial/ethnic discrimination, religious behaviors, spirituality, wealth, educational attainment, water access and sanitation, and food insecurity.

Research Procedures include the following:

Once the participants have finished the consent form signing and the pre-intervention surveys, they will complete the following baseline measures:

- Symbol Digit Modalities Test. The Symbol Digits Modalities Test (SDMT) will assess visual information processing speed and will be administered to participants remotely via video conferencing through Zoom (Smith 1982, Rao, Leo et al. 1991). An examiner will present participants with a page displaying nine symbol-digit pairings in a key at the top of the page. A series of unpaired symbols will be presented under the key, and participants will be required to verbally identify the digit that paired with each symbol as quickly as possible according to the pairings key. The outcome is the total number of correct responses in 90 seconds.
- California Verbal Learning Test-II. The California Verbal Learning Test-Second Edition (CVLT-II) will assess verbal learning and memory and will be administered remotely via Zoom (Delis, Kramer et al. 2000). A list of 16 words will be read aloud by the examiner and participants will be asked to immediately recall as many of the words as possible, in any order. Five trials will be given, and the same list of words will be read aloud by the examiner at the beginning of each trial. The number of correct responses from each trail (T1 to T5) is summed for a total score out of 80.

- **30-Second Sit-to-Stand Test.** The 30-second sit-to-stand is a marker for impairment and muscular strength and endurance in persons with MS and will be administered through Zoom (Ozkeskin et al., 2022; Zheng et al., 2023). Participants will be asked to begin the test seated in the middle of a chair with their back straight, feet shoulder width apart, arms crossed at the wrists, and held against the chest. They will then be asked to complete as many stands as possible within 30 seconds while fully sitting between each stand. An examiner will silently count the number of correct stands and the score will be total number of stands within 30 seconds.

Once they have completed the baseline measures, participants will be randomly assigned into either of the intervention (exercise training) or control (flexibility training) conditions using random numbers sequence with concealed allocation (i.e., opaque sealed envelopes) generated by a member of the research team uninvolved in delivering the intervention.

A member of the research team will communicate the actual condition of the assignment to the participant by mailing a packet containing intervention materials (resistance bands, pedometer, logbook, calendar, and training manual focused on the NMSS Guidelines for exercise) or control materials (yoga mat, logbook, calendar, and training manual focused on the Stretching for People with MS: An illustrated Manual from the National MS Society) via certified postal mail.

Participants randomized in the intervention and control groups.

Participants will complete the 4-month intervention for their respective exercise group, and this will be delivered in three waves of 16 to 18 participants each (16, 16, and 18).

One-on-One Coaching: The study will involve one-on-one structured coaching sessions with an MS exercise specialist (i.e., behavioral coach) who will provide guidance and oversight on exercise training and feedback on appropriate exercise techniques and strategies. The coaching sessions will focus action planning and self-monitoring, and other SCT supplemental content including goal setting, planning, and self-efficacy, barriers, and facilitators, and will be delivered through either telephone or Zoom interfaces.

Upon completion of the 4-month exercise program, participants in both groups will complete the same set of online surveys they completed at the beginning of the program to capture any changes that may occur.

Participants will be compensated for their time by receiving two, \$50-dollar electronic gift cards, for a potential total of \$100 dollars, emailed to their preferred and confirmed email address upon of the assessments and online surveys before and after the intervention.

We will collect feedback after participants complete the study using a online survey for identifying opportunities for intervention improvement and refinement moving forward.

We will proceed with data analysis using intention-to-treat principles. We outline the analysis below:

- Analysis for Endpoint 1: Process, resource, management, and scientific feasibility will be examined via percentage, frequency analysis, and descriptive statistics.
- Analysis for Endpoint 2: The differences in physical function and ability, cognitive function, fatigue, depression, quality of life over time, and exercise behavior per condition will be examined using 2-way linear mixed model. Cohen's d will be used to calculate the effect sizes. Missing data will be addressed using multiple imputation with a sensitivity analysis.
- Analysis for Endpoint 3: The association between individual and structural SDOH factors and feasibility metrics will be analyzed using regression models, and subgroup analyses examining the effects of individual and structural SDOH factors on the intervention outcomes.

The main devices used in this study include coaching online through Zoom or telephone, and assessments and questionnaires administered through Zoom, Qualtrics, and UIC RedCap. There will be no drugs or additional devices used in this study. The source of records used to collect data include typed information on the Qualtrics and UIC RedCap participant link, typed information on eligibility status from phone screening, written results from the cognitive assessments (SDMT and CVLTII) and the 30-second sit to stand test administer through Zoom, electronic responses from surveys and questionnaires collected through Qualtrics and RedCap, and written information regarding notes during coaching sessions by the behavioral coach.

Participant demographic and clinical characteristics, physical function, cognitive function, symptoms and quality of life, exercise behavior and SDOH factors will be collected. To obtain demographic and clinical characteristics, participants will complete a Health History Questionnaire asking about age, sex/gender, address, country of birth, marital status, level of education, employment status, occupation, income, religion. Participants will also complete the Comorbidities Questionnaire for MS, MSWS-12, PDDS, and questions about disease stage/MS phenotype, age at MS diagnosis, duration of MS, family history of MS, MS symptoms, any drug prescription, and any disease-modifying therapies currently taking. To obtain physical function, participants will complete the 30 second sit-to-stand. To obtain quality of life data, participants will complete the FSS, HADS, and SF-12 surveys. To obtain exercise behavior, participants will complete the GLTEQ.

There will be no plans for long-term follow-up sessions to obtain longitudinal data once all research-related procedures are completed.

Humanitarian Use Device (HUD) will not be used and/or provided for this study.

14.0 Withdrawal of Subjects

If a subject fails to comply with the study procedures, putting themselves or the research personnel at risk, they may be removed from the study without their consent.

Once the cognitive assessments, 30 second sit-to-stand test, and at-home questionnaires and surveys are completed after the 4-month exercise program, the subject's participation in the study will be concluded. From that point on, the subject will not receive any further assessments or be contacted in relation to the study.

When subjects withdraw from the study, the time and reason of withdrawal will be recorded and reported to the UIC IRB. The subject's data will be stored and included in data analyses as applicable.

15.0 Risks to Subjects

The study intervention involves exercise training, which could potentially result in muscle soreness, fatigue, or injury. However, the exercise program will be tailored to accommodate abilities and limitations, and all participants will receive support from the trained behavioral coach to modify the exercise as necessary to minimize risk of injury.

Intervention: There are risks of injury for individuals engaging in an exercise program after a prolonged period of inactivity. Specific risks include strains, sprains, and muscle soreness associated with walking as part of ambulatory activities of daily living, but serious physical injury such as sudden death or heart attack is considered unlikely given the screening for contra-indications. We will attempt to reduce risks of injury and harm by promoting gradual increases in exercise across time. We will fully inform participants of the risks associated with initiating an exercise program in the informed consent.

Control: There are some potential risks to consider with flexibility training (stretching and ROM exercise). These may include mild muscle soreness, strains, or sprains related to flexibility. However, serious physical injuries or adverse events are unlikely given the nature of the control group's activities and the screening process conducted prior to participation. We will emphasize the importance of proper technique and caution during the flexibility exercises to minimize the risk of injury. Participants will be fully informed about the potential risks associated with engaging in flexibility training exercises during the informed consent process.

There are also potential social risks, such as participants feeling uncomfortable or embarrassed about their physical abilities or psychological risk with anxiety and/or depression due to the remote delivery of the program. These risks will be minimized by providing a supportive environment for participants, discussing SCT-related content about identifying and building support systems, and offering regular check-ins and support from the trained behavioral coach.

Participants may also experience some discomfort or inconvenience associated with the assessments, such as fatigue or frustration during cognitive testing, but these risks are expected to be minimal and will be carefully monitored.

There is a potential risk to privacy, as participants will be sharing personal information about their health and exercise habits. However, all data will be coded, stored in a password-protected data sheet in a password-protected computer that is only accessible to the research team behind locked doors in the ENRL at UIC. Written notes for coded participants taken by the behavioral coach during coaching sessions will be kept in a binder in a locked drawer in the ENRL. All measures will be taken to protect the privacy and confidentiality of participants, and no legal risks are anticipated.

To maintain confidentiality, all the data collected on the subjects will be numerically coded. This will be the only identifier in all databases and systems used in this study. There will be a password-protected master file linking participants with randomized assignment, but this file will be kept separately from participant assessments data. All data will be kept for 5 years after publication. 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 coaching binders and data center is physically limited to authorized personnel. Password-protected access to the server and keys for the locked drawers containing notes from coaching sessions with coded participants will be granted to UIC study staff with access permissions set based on their roles in the study. Data are encrypted with physical and electronic key access available only to appropriate study team members. All electronic data transmission (uploading and downloading) occurs over secure, encrypted channels, and all notes taken from the behavioral coach during the exercise program will occur in the ENRL.

To screen participants for suitability and safety, we will utilize the PAR-Q to identify any potential contraindications or health concerns. This screening process allows us to identify individuals who may require additional medical clearance or modifications to their exercise program. During the study, participants will receive one-on-one video coaching sessions with trained behavioral coaches. These sessions will emphasize the importance of gradual

changes in exercise behavior and provide guidance on proper technique and progression. The coaches will regularly check in with participants to offer support, monitor progress, and address any concerns or questions. It is important to note that these coaching sessions will focus on participant well-being and adherence to the exercise program, and the discussions will only refer to coded data to ensure confidentiality and privacy.

We have identified several minor risks to participants in the proposed study, as well as safeguards to minimize those risks. We will monitor any expected adverse events (AEs) throughout the course of the study and report to the UIC IRB as necessary. In the event of a serious AE (SAE; i.e., any fatal or life-threatening event, hospitalization or event leading to disability), we will report this to the UIC IRB within 48 hours of the AE. These reports will specify the severity and attribution of any SAE (i.e., assessment of the relationship between SAE and research protocols).

16.0 Potential Benefits to Subjects

There are multiple potential benefits that individual subjects may experience from taking part in this research.

1) Physical and Cognitive Improvements: Engaging in the exercise intervention program may lead to improvements in physical function, such as increased strength, endurance, and balance. It may also have positive effects on cognitive function, including enhanced information processing and memory. While the specific magnitude and duration of these benefits may vary among participants, previous studies have indicated that exercise can have a positive impact on both physical and cognitive abilities in persons with MS.

2) Enhanced Quality of Life: Regular exercise has been associated with improved overall quality of life. By participating in the exercise intervention, subjects may experience an increased sense of well-being, improved mood, and better management of MS-related symptoms, leading to a higher overall quality of life. The duration of these benefits may be long-term if participants continue to engage in regular exercise beyond the study period.

3) Social Support and Community Engagement: Participants will have the opportunity to interact with trained behavioral coaches and potentially connect with other individuals living with MS through support networks. This social support and sense of community can provide emotional encouragement, shared experiences, and a supportive environment, which may have a positive impact on participants' psychological well-being.

There is a direct benefit for individual subjects participating in this research study.

17.0 Data Management and Confidentiality

Descriptive statistics will be generated for all outcome measures (i.e., mean $\pm$ standard deviation for continuous variables; frequencies and percentages for categorical variables). The data analyses will follow intent-to-treat principles and will impute missing data using multiple imputation and last observation carried forward. Data will be checked for outliers and normality violations by using frequency distributions and plots, estimation of z-scores, estimation of skewness and kurtosis, and tests for normality (e.g., Shapiro-Wilk test). If necessary, we will transform the data points or distributions to minimize problems with violations of model assumptions.

We will perform univariate analyses to examine the statistical differences in physical function and ability, cognitive function, quality of life, and exercise behavior across both groups by using t-tests, analysis of variance (ANOVA), and the Kruskal-Wallis test (where the dependent variable was not normally distributed). Further, we will perform Pearson correlation analysis and/or multiple linear regression to examine the potential associations among SDOH and primary and secondary endpoints.

There are no published data for determining power a priori, but the expected sample size overall and per group should be sufficient for precise estimates, and we will provide confidence intervals and effects sizes (Cohen's d) with all analyses.

17.2 To ensure the security of the data, several steps will be taken throughout the study. These include providing training to personnel to ensure they are aware of the proper handling procedures for the data, authorizing access to the data only to those who require it, password protecting access to the data, encrypting the data both at rest and during transmission, implementing physical controls to restrict access to the data, and separating identifiers from the data to maintain confidentiality. The following measures will be in place during the storage, use, and transmission of the data to ensure its integrity and confidentiality:

Once participants have met the eligibility requirements and provided a verified signature through Adobe sign on the informed consent form, they will be assigned an identification number (ID).

For subjects who agree to have their contact information retained for future research opportunities, we will maintain a separate and secure, password-protected excel sheet specifically for this purpose saved on the ENRL, UIC-supported server. This information will be stored separately from any identifiable research data and will be accessed and used solely for the purpose of contacting individuals who may be eligible for future research studies or related opportunities. Access will be limited to authorized research personnel in the current study only.

Signed consent forms will be password-protected and electronically stored in a password-protected folder on the ENRL, a secure, UIC-supported server.

The data sheet linking ID to personal information and results from the screening will be password-protected and electronically stored in a separate folder on the ENRL server. We will NOT maintain the link between ID and the subject's name after completion of the study procedures, and there is no intention of linking data collected in the current project with data collected in another project. If the subject agrees to be contacted for future research studies, personal identifiers (contact information: name, address, phone number, and e-mail address) will be stored indefinitely. To protect confidentiality, all data collection, analysis, and presentation will use coded non-identifiable data. If any data is used for presentation or publication, it will only be presented in an aggregated form.

The data sheet linking participant ID with their randomized assignment will be maintained in a separate, password-protected folder on the ENRL server.

Qualtrics and RedCap responses will be exported to data management files (e.g., excel, SPSS), and electronically stored in a separate password-protected folder on the ENRL server.

Access to the ENRL server will be restricted to authorized personnel, and physical access to the server will be limited. The research team will be granted password-protected access to the ENRL server, with their access permissions determined by their respective roles in the study.

The data will be encrypted while at rest, and all data transmission, including uploading and downloading, will take place via UIC-secure, encrypted channels.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The proposed study does not fall under the category of a multi-site, NIH-defined Phase III clinical trial, there is no formal data monitoring committee included in the study. The proposed study is not a multi-site, NIH-defined Phase III clinical trial, and therefore we did not include a formal data monitoring committee in the current study. The PI will be primarily responsible for assuring that monitoring and safety are maintained and documented, as required. The PI will ensure that the data will be collected using a coded identification number for the maintenance of data confidentiality. However, we recognize the importance of monitoring data accuracy as well as the occurrence of any unexpected adverse events. We have therefore put into place a system to monitor these issues considering that the current study is a clinical trial. This system is in addition to the UIC IRB, which reviews and approves all study protocols, performs annual audits in which actual study materials are examined in detail, and monitor all adverse events. The PI will

monitor: (1) the rate of subject accrual; (2) adherence to inclusion/exclusion criteria; and (3) subject compliance based on the fidelity monitoring plan. In addition, the PI will monitor ongoing data collection, check actual participant files for scoring and recording accuracy, and monitor data entry for accuracy. These monitoring procedures will be performed on a scheduled monthly basis. The PI will further perform random data checks throughout the duration of the study. All adverse events and participant drop-outs will be reported to the PI immediately. The PI will then examine the case in detail, assess the information and the reason for the drop out and/or the circumstances behind the adverse event and report the findings to the UIC IRB immediately, if so required. Every 12-month period, the PI will report to the UIC IRB on the status of participant recruitment, drop-out rate, and preliminary data quality/control.

19.0 Provisions to Protect the Privacy Interests of Subjects

All conversations regarding the study, as well as the study procedures, will be conducted in a private setting (i.e., private assessment room, private exercise testing room in the ENRL). Others will not overhear conversations with potential participants, and there will be no video and/or audio recordings. Individuals will not be publicly identified or embarrassed.

We will ensure participants feel at ease by reminding them their privacy and anonymity in this study will be upheld throughout all testing phases. During the consent process, we will remind participants that there will be no commercial or government organization involvement in this study and that their data will be coded and de-linked to their personal information in the UIC database (name, home address, zip code). We will also explain our degree of security provided by the UIC database that includes password-protected access and encryption.

Only the PI and research team will have access to the sources of information about the subjects. Medical records or other external sources of information about the subjects will not be utilized for this study. All information about the subjects will be collected directly from the subject and generated from the study assessments and questionnaires. All hard copy documents, such as binders containing notes from coaching sessions with the behavioral coach and screening scripts will be kept in a locked drawer, and all electronic data collection copies including the online surveys, will be kept in password-protected databases. The PI and research team will have access to the drawer keys and passwords.

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