FEASIBILITY OF A COMMUNITY-BASED EXERCISE INTERVENTION FOR PERSONS WITH SPINAL CORD INJURY

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Feasibility of a Community-based Exercise Intervention for Persons with Spinal Cord Injury

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A Introduction

A1 Study Abstract

Persons with spinal cord injury (PwSCI) are at a greater risk for major health conditions and poorer health outcomes than persons without spinal cord injury. For PwSCI, habitual exercise is critical for both physiological and psychological well-being. Prior research indicates that exercise programs conducted in a controlled setting have positive effects on the physical and psychosocial fitness of PwSCI, but the efficacy and feasibility of these programs are not well understood in community-based settings. PwSCI will be randomized to a 12-week community-based exercise intervention (CBEI; n = 20) or an exercise education control group (EEG; n = 20). The proposed project aims to examine

potential health benefits in response to the intervention and identify the barriers and facilitators to successful implementation of a CBEI in PwSCI (N = 40).

A2 Primary Hypothesis

The community-based exercise group (CBEI) will have a 10% improvement in peak oxygen consumption (VO2peak), upper extremity strength, body fat, cardiovascular risk profile (fasting plasma HDL cholesterol, triglycerides, and insulin resistance), and psychological well-being (sleep, pain, fatigue, and depression) as compared to the exercise education control group (EEG) post-intervention.

A3 Purpose of the Study Protocol

The purpose of the study is to examine the impact of a community-based exercise intervention for persons with spinal cord injury on physiological and psychological well-being and identify barriers and facilitators to implementation.

B Background

B1 Prior Literature and Studies

Background:

SCI and exercise: Approximately 285,000 people in the US are living with an SCI.[1] PwSCI are at a greater risk for heart disease, high blood pressure, obesity, and diabetes than those without disabilities.[2-4] SCIs often result in various physiological alterations affecting multiple body systems, including blunted hemodynamics, altered sympathetic innervation, altered glycemic control, reduced active muscle mass, deteriorated circulatory vessels below level of injury, and impaired arterial compliance and function.[5] These pathophysiological alterations amplify the risk and prevalence of cardiovascular and metabolic diseases in PwSCI,[6-7] suggesting a great need for increased physical activity and fitness in this population. The typical daily routine of PwSCI does not stress the cardiorespiratory system enough to produce positive health-related changes; therefore, structured exercise activities are needed to enhance physical capacity and to reduce the likelihood of secondary complications.[8-10] Increased cardiorespiratory fitness in PwSCI promotes not only improved functional independence, but also improved cardiovascular and metabolic health.[7,11]

Exercise recommendations and barriers: Despite the widely recognized health benefits of regular physical activity,[12] PwSCI report the lowest levels of physical activity compared to other populations,[13-14] with fewer than 50% engaging in any physical activity, and only 15% engaging in physical activity sufficient to gain meaningful health benefits.[14-15] The most recent evidence-based exercise guideline for PwSCI recommends engagement in at least 30 minutes of moderate-to-vigorous-intensity aerobic exercise three times per week to achieve cardio-metabolic health benefits.[16] Because of decreased sympathetic innervation, muscle atrophy, and decreased cardiac reserves, it is difficult for PwSCI to achieve these intensity levels without proper support.[12,17] There is a considerable lack of accessible facilities, equipment, and support for PwSCI outside of rehabilitation,[18,22-25] and PwSCI also often lack knowledge of the types of exercise that will allow them to be successful in exercise. Typical exercise facilities (e.g., YMCA, 24 Hour Fitness) generally do not provide the types of support necessary for PwSCI to successfully exercise.[24,26] More evidence is needed to identify effective exercise

interventions implemented outside of the rehabilitation setting that improve health for PwSCI.[27]

Preliminary Work: We have conducted two related studies that support this proposed project. The first was a single-arm design that assessed 284 PwD (63 PwSCI) who joined the Paraquad Health and Wellness Center (PQHWC), an accessible gym with equipment and staff to support PwD. Participants were encouraged to work on strength and endurance exercises but were not monitored. We compared participants' weight, BMI, pain, endurance, and strength pre- and post- 12 weeks of participation in the PQHWC. Total group results showed significantly decreased average pain reported over the past 30 days and significant increases in four upper extremity strength exercises ($p <$ .05). No changes in body weight, BMI, or endurance were found. Limitations of this study were the lack of control group for comparisons, lack of rigorous assessments to identify changes at the cardiorespiratory or metabolic levels, and lack of structure to adequately meet the physical activity guidelines for PwSCI.[28-29,]

The second study was qualitative and involved interviews of seven active participants in the PQHWC and six staff members,[30] the purpose of which was to gather participant and staff perspectives about the impact of the program and suggestions for evaluation. Participants identified knowledgeable staff, options for adapted exercise equipment, and a positive social environment as critical program components. However, participants reported that although the supports were in place to exercise, their knowledge about how they should exercise was limited. Staff expressed the need for sound measures to identify whether participants were making changes. These two studies identified weaknesses of a community-based exercise program and the need for an exercise intervention that provides structure and education for PwSCI. Through the information learned in these studies, we developed the structured, 12-week CBEI proposed in this application.

B2 Rationale for this Study

Although a wealth of evidence exists regarding the benefits of exercise interventions for PwSCI, there is limited research on exercise interventions that are community-based and follow the recommend guidlelines.[31-32] Previous studies of community-based exercise programs have varied widely in their populations of focus, research designs, exercise protocols, and health outcomes. Many of these studies lack the rigorous designs, sample sizes, and testing needed to examine the effects of exercise on key health outcomes.[31,33] As a result, there is extensive variability in evaluation methods among published studies.[31,34] Additionally, metabolic measures are not often included in studies based in the community. The *proposed research is innovative* because it addresses factors that often impede successful implementation of exercise for PwSCI in the community, follows the recommended guidelines, and uses sound measures.

Cardiorespiratory-related diseases account for approximately 40% of mortality as the leading cause of death for PwSCI.[1, 35-36] For PwSCI, the decline in physical capacity and increased risk of secondary health conditions often result in reduced independence and participation in life activities. About 30% of PwSCI are re-hospitalized one or more times any given year following injury, with an average length of stay of 22 days.[37] PwSCI who are physically active tend to make fewer visits to physicians and experience fewer medical complications and hospitalizations than their sedentary counterparts.[38] Participating in recommended amounts of exercise may offer an effective method for

increasing cardiovascular fitness and metabolic health in PwSCI.[10] Therefore, it is imperative to build supports and resources outside of rehabilitation to promote health and well-being to improve physiological and psychosocial outcomes experienced by PwSCI. The *significance of this project* is its focus on a CBEI that uses accessible equipment and health professionals to implement multi-modal exercise programs that are individualized to each participant's needs and meet recommended guidelines. This study has the potential to establish a community-based model to be emulated in other settings.

C Study Objectives

C1 Primary Aim

Primary Aim: To estimate improvements in physical function, cardio-metabolic health, and psychological well-being of participants enrolled in a CBEI compared to an education-only control group.

Forty PwSCI will be randomized into either the CBEI group or the EEG receiving education only. We will measure physical function (cardiorespiratory fitness and strength), cardio-metabolic health (body composition, glucose tolerance, and cardiovascular risk profile), and psychological well-being (PROMIS). We hypothesize that the CBEI will have a 10% improvement in peak oxygen consumption (VO_2peak), upper extremity strength, body fat, cardiovascular risk profile (fasting plasma HDL cholesterol, triglycerides, and insulin resistance), and psychological well-being (sleep, pain, fatigue, and depression) as compared to the EEG post-intervention.

C2 Secondary Aim

Secondary Aim: To identify barriers, facilitators, and reasons for positive determinants for PwSCI to exercise in a community-based setting.

We will use a mixed methods approach to characterize key implementation outcomes: acceptability, feasibility, and fidelity. Information will be gathered during the intervention using activity monitors, heart rate monitors, and rating scales to identify whether exercise intensity rates were met. Participants will be interviewed for the purposes of comparing the experience of participants who experienced change and those who did not. This information will enable us to determine the degree to which the pilot intervention's success or failure was related to implementation outcomes and to inform the development of a future R01-funded clinical trial. We hypothesize that the intervention will be accepted among PwSCI, feasible to implement, and that delivery of the intervention will adhere to the exercise intervention protocol (fidelity).

C3 Rationale for the Selection of Outcome Measures

The primary outcome variables for this randomized controlled trial (RCT) include: cardiorespiratory fitness (VO_2peak and 6-minute push test), pain (Wong-Baker FACES), metabolic health (blood chemistries), body composition (dual-energy x-ray absorptiometry [DXA] scan, height, weight, BMI), vitals (heart rate and blood pressure), and psychosocial well-being (PROMIS-29 Profile). These variables are significantly impacted by physically inactive lifestyles, which are highly common among manual wheelchair users (MWUs) with SCI. MWUs with SCI also exhibit and report values of some of these variables below healthy range, potentially impacting physiological health and psychosocial well-being and overall quality of life. Secondary outcome variables

include qualitative perspectives of the research staff delivering the exercise intervention and of participants to assess the feasibility of the intervention protocol.

D Investigational Agent

Not applicable

D1 Preclinical Data

Not applicable

D2 Clinical Data to Date

Not applicable

D3 Dose Rationale and Risk/Benefits

Not applicable

E Study Design

E1 Overview or Design Summary

The proposed project utilizes a mixed-methods approach. An experimental strategy using an RCT (single-blinded) will be used. Forty participants (n = 40) will be randomized into the CBEI (n = 20) or the EEG (n = 20) by a research staff member who will not be involved in either conducting outcome assessments or implementation of the intervention. This design will assist in reducing variability and maximizing the effect size for powering a subsequent larger RCT.

The intervention for participants in the CBEI will consist of one-on-one, formally directed exercise sessions by trained staff in the PQHWC. The CBEI is based on the recent evidence-based exercise guideline for PwSCI,[14] American College of Sports Medicine's (ACSM) Physical Activity Recommendations for PwSCI,[29] best available evidence,[39-41] and preliminary work.[30] The intervention will include 36 60–90-minute sessions over 12 weeks (three sessions/week) with a goal of participants guiding their own exercise regimens by the end of the intervention. Personalized exercise sessions will be created for each participant based on fitness goal(s), preferred exercise equipment, and results from their initial assessment. Participants will be educated on how equipment works and what exercises are appropriate, and will be guided on intensity levels. At the beginning of each session, vitals and pain[42] will be assessed, and each participant will complete a minimum 5-minute warm-up. After the warm-up, each participant will complete cardiovascular training in bouts of at least 10 minutes. Staff will monitor the sessions to ensure that participants perform at least 30 minutes three times a week of moderate-to-vigorous exercise,[16,29] as determined by a report of 12 or higher on the Borg's Rate of Perceived Exertion (RPE) Scale (6–20).[43-44] Due to altered sympathetic innervation in PwSCI,[5] target heart rate may not be reliable; therefore, RPE will be the real-time determinate of intensity. Activity monitors (GT9X Actigraph, Pensacola, FL) will be donned to capture intensity data to be processed post hoc. Each participant will then complete a 3–5-minute cool-down. After cardiovascular training, each participant will complete strength training geared toward their goals, with guidance from PQHWC staff

to perform a comprehensive variety of strength exercises to promote fat-free mass, muscle endurance, and overall strength. Staff will set up and monitor strength training to ensure that, for each exercise, participants perform at least two to three sets of 10–15 repetitions (reps) at 50%–75% one-rep max (1RM) for each exercise targeting functioning muscle groups.[16,29] After strength training, participants will complete a 5–10 minute cool-down, and final heart rate, blood pressure, and pain will be assessed. Staff are occupational therapists and physical therapy assistants who have worked in an exercise setting with PwSCI. Staff will be taught the exercise guidelines[16,29] and exercise session protocols using written materials, demonstration, and practice sessions. Following each exercise intervention session, participants will describe what they liked and did not like, provide a rating (1–5) of how much they gained from the session, and answer an open-ended item requesting suggestions for improvement. At the end of each session, the trainer will rate the participant's perceived participation during the session (1–6) using the Pittsburgh Rehabilitation Participation Scale.[45]

The participants in the EEG will complete an intervention that consists of a one-on-one, hour-long educational session orienting participants to an online resource center, the National Center on Health, Physical Activity, and Disability (NCHPAD). NCHPAD promotes health and well-being for PwD through resources such as adapted exercise videos, information on accessible fitness equipment, personalized exercise videos tailored to PwD, and an individualized 14-week exercise program. Participants will be given an overview of NCHPAD and asked to identify resources of interest on the website. Each participant will be asked to use resources on NCHPAD to engage in physical activity for 12 weeks. Each participant will receive a weekly phone call to inquire about their physical activity, exercises engaged in, RPE during exercise, and whether any resources were used.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

1) Diagnosis of SCI
2) 18 years or older
3) Have written physician approval to participate in the study
4) Ability to use upper extremities to exercise
5) Participate in < 60 minutes of moderate-intensity exercise per week in the last month
7) Understand English at a sixth-grade level or higher
8) Be able to follow multi-step instructions
9) Independently provide informed consent
10) Willing to participate in three assessments and 36 intervention sessions

2.a Exclusion Criteria

1) Enrollment in a structured exercise program in the past six months.
2) Have had cardiovascular complications within the past year
3) Currently receive medical treatment for an acute upper extremity injury
4) Have a Stage IV pressure injury
5) Have a cognitive impairment that does not allow them to provide consent or follow multi-step directions.

2.b Ethical Considerations

Physical activity in healthy individuals and in people with varying pathologies is beneficial for physiological and psychological health and well-being, and these benefits are expected in people with SCI. Our previous studies have also shown that physical activity is safe and realistic for persons with SCI. There are no obvious ethical considerations.

2.c Subject Recruitment Plans and Consent Process

Potential participants may either be approached or identified by the PI from Paraquad's waiting list, or potential participants may contact us after viewing a study flyer posted within community and rehabilitation facilities. The study coordinator may describe the study with participants over the telephone or in person and, if they are interested, verbal consent will be obtained to continue with the screening document. This process will be the same for all populations, as the randomization does not occur until after the first assessment is completed. After the screening document is complete, the study coordinator will obtain medical referrals from the participant's physician(s); once permission from the participant's physician(s) is received, the participant will be contacted via phone by the study coordinator and scheduled for their first assessment appointment. Prior to the scheduled initial assessment, a copy of the written consent form may be mailed to the potential participants so they may have time to review it, become familiar with it, and prepare any questions they may have. The study coordinator may also contact potential participants via phone 24–72 hours prior to their scheduled initial assessment to remind potential participants of their upcoming initial assessment appointment. Upon arriving to their first assessment appointment, a research staff member will review the written consent form with the potential participant. Potential participants will be given time to review the form additionally on their own, discuss with family members if they wish, and have any and all questions addressed. Potential participants will then be asked to initial, sign, and date the form, as necessary, prior to participating further in the initial assessment.

2.d Randomization Method and Blinding

Randomization does not occur until after the initial assessment is completed. Immediately following completion of the initial assessment, each participant will be randomly assigned to either the CBEI (n = 20) or EEG (n = 20). To control for selection bias, stratified randomization will be used to ensure that the CBEI and EEG are balanced with respect to how long the participant has been injured (<2 years or ≥2 years), the participant's level of injury (below C7 or C7 and above), age (<40 years or ≥40 years of age), and gender. This will control for a large imbalance of participants allocated to one intervention. Research staff performing the assessments will be blinded to group randomization.

2.e Risks and Benefits

Risks:

A likely or common mild risk that may occur from participating in the testing sessions and/or participating in any exercise program for 12 weeks is that participants may experience muscle soreness or fatigue. Participants will have planned rest breaks, be allotted any unplanned rest breaks requested, and be encouraged to maintain hydration levels during exercise training. There is also a mild risk of emotional distress or discomfort in completing the questionnaires. Participants will complete questionnaires in

a private area and will be allowed to decline to answer any of the questions that make them uncomfortable.

An uncommon risk that may occur is an exercise-related injury, such as muscle strain or sprain. To help ensure that participants are safe to exercise, they will be required to have a physician's referral to participate in this study; in addition, a heart rate monitor and accelerometers will be worn during selected testing and exercise sessions (if assigned to the CBEI) to ensure accurate monitoring of their health status. They will also be educated about the proper and safe way to exercise before the study begins. For CBEI participants, trained research members will be present during all sessions to ensure participant safety. Proper precautions to avoid injury, including stretching and rest breaks, will be employed to reduce the risk of soft tissue damage.

Another risk to participants includes potentially dangerous conditions associated with SCI, such as autonomic dysreflexia, during assessments and exercise training. However, this is a very small risk. All research team members are familiar with serious conditions, such as autonomic dysreflexia, and medical precautions to monitor any life-threatening conditions will be taken during testing and training. In the highly unlikely event a participant experiences a medical emergency, immediate appropriate actions will be taken by research staff.

Benefits:

Participants may or may not benefit from being in this study. Participants may directly benefit by:

- Increasing their ability to exercise and function in the community
- Improving their cardiorespiratory and metabolic function
- Improving their psychological well-being
- Increasing their physical fitness
- Receiving new and valuable information about exercise recommendations and their health

2.f Early Withdrawal of Subjects

Participants (CBEI or EEG) will be withdrawn if they are non-compliant with the exercise program specific to their group assignment (miss >30% of visits in a particular month) or if they experience a medical complication that prohibits exercise.

2.g When and How to Withdraw Subjects

The research coordinator of the study is primarily responsible for scheduling testing and exercise sessions for participants. The research coordinator will also be in weekly contact with designated PQHWC staff to update the research team on the attendance/compliance of CBEI participants. If deemed that a participant is non-compliant with the exercise program protocol, the research coordinator will contact the participant and inform him/her of the withdraw policy. If the participant remains non-compliant over the following two weeks, he/she will be withdrawn by the research team and will be contacted via phone.

2.h Data Collection and Follow-up for Withdrawn Subjects

Whether participants withdraw voluntarily or are withdrawn by research staff, they may be asked to complete a close-out visit (in-person or on the phone) to provide the research team with feedback regarding why they decided to leave the study early/not comply with the program.

As this is a pilot RCT, if a participant is withdrawn, initial assessment data will be evaluated; however, no follow-up assessment will be conducted.

E3 Study Drug

The proposed study is not a drug-trial intervention, but rather an exercise intervention using a developed community-based exercise intervention program.

3.a Description

Not applicable, this is not a drug study.

3.b Treatment Regimen

Not applicable, this is not a drug study.

3.c Method for Assigning Subjects to Treatment Groups

Not applicable, this is not a drug study

3.d Preparation and Administration of Study Drug

Not applicable, this is not a drug study

3.e Subject Compliance Monitoring

Not applicable, this is not a drug study

3.f Prior and Concomitant Therapy

Not applicable, this is not a drug study

3.g Packaging

Not applicable, this is not a drug study

3.h Blinding of Study Drug

Not applicable, this is not a drug study

F Study Procedures

F1 Screening for Eligibility

Potential participants may either be approached or identified by the PI from Paraquad's waiting list; potential participants may also contact us after viewing a study flyer posted within community and rehabilitation facilities. The study coordinator may describe the study with participants over the telephone or in person and, if they are interested, verbal consent will be obtained to continue with the screening document. This process will be the same for all populations, as the randomization does not occur until after the first assessment is completed. After the screening document is complete, the study coordinator will obtain medical referrals from the participant's physician(s); once permission from the participant's physician(s) is received, the participant will be contacted via phone by the study coordinator and scheduled for their first assessment appointment.

F2 Schedule of Measurements

The research coordinator will primarily schedule all initial and post-assessments with participants over the phone once participants are deemed eligible for participation. Prior to the scheduled initial assessment, a copy of the written consent form may be mailed to the potential participants so they may have time to review it, become familiar with it, and prepare any questions they may have. The research coordinator may also contact potential participants via phone 24–72 hours prior to their scheduled initial assessment to remind potential participants of their upcoming initial assessment appointment.

F3 Visit 1

Upon arriving to their first assessment appointment, a research staff member will review the written consent form with the potential participant. Potential participants will be given time to review the form additionally on their own, discuss with family members if they wish, and have any and all questions addressed. Potential participants will then be asked to initial, sign, and date the form, as necessary, prior to participating further in the initial assessment. Once written consent is obtained, all participants will complete the initial assessment.

The initial assessment (T1) will be completed over two separate days, with the second day (D2) being completed within 10 days of the first assessment day (D1).

Procedures for Day 1 of Initial Assessment (T1D1):

T1D1 (90–120 minutes) will be completed at Washington University's EMC research laboratory, located within the Paraquad Health and Wellness Center building. During this appointment, participants will complete many self-report measures. These measures will assess: demographics (CORE), psychosocial factors (PROMIS–fatigue, depression, pain, sleep, and emotional support), physical activity (LTPAQA-SCI, ESES, and RM-4), and community participation (CPI). Participants will also be asked to perform functional mobility (6MPT), strength testing (BTE and Equalizer), and a cardiovascular fitness test (VO_2peak). Resting blood pressure and heart rate, height, weight, and body mass index will also be measured on T1D1. The participants may be asked to wear a heart rate monitor and accelerometers to measure their intensity levels during testing.

Self-Report Assessments:

Characteristics of Respondents (CORE): The following data will be collected via the CORE: demographics (age, gender, race, employment status, and highest level of education completed), diagnosis, neurological level of injury, time since onset of injury, general health status, secondary health conditions, medications, and mobility device used.[17]

PROMIS Measures: The PROMIS measures will be used to assess six different domains: emotional distress, emotional support, sleep, pain interference, pain intensity, and fatigue. Individuals respond to the items in each domain using a five-point Likert scale. The six domains are scored individually.

Leisure Time Physical Activity Questionnaire for People with SCI (LTPAQ-SCI): The LTPAQ-SCI is a self-report measure of leisure time physical activity that assesses minutes of mild, moderate, and heavy intensity activity over the previous seven days. The survey will be collected during screening to determine eligibility.

The SCI Exercise Self-Efficacy Scale (ESES): The ESES is a 10-item, SCI-

specific scale developed to measure perceived exercise self-efficacy for various types of physical activities. The scale requires individuals to self-report their confidence in performing physical activities and exercise. One dichotomous item asks whether the individual has exercised at home and/or in a gym in the past 12 months. Individuals respond to the 10 items using a four-point Likert scale (1: not at all true, 4: always true); the total score is then derived by summing the scores for the individual items; scores range from 10 to 40. Higher scores indicate greater perceived self-efficacy. The dichotomous item is used to estimate the participant's average exercise activity.

Community Participation Index (CPI): The CPI is a valid and reliable assessment of involvement in life situations and individual control over participation.[46-47] For each item, respondents rate frequency (either in days, hours, or times per week, depending on the activity), whether it was important (yes/no), and to what extent they do the item (too much, enough, or not enough). The measure is used as a categorical variable using validated scores. Participation will be assessed at baseline and both follow-up assessments to determine the level of change in participation for each MWU with SCI.

RM 4-FM: Motivation for Physical Activity and Exercise/Working Out: This questionnaire is designed to assess whether the participants are extrinsically or intrinsically motivated to engage in a physical activity. The questionnaire makes a statement of "I try, or would like to try, to be physical active regularly," and participants must rate themselves on a Likert scale between 1 (not true at all), to 7 (very true).

Physical Assessments:

VO_2peak: Measured using a standard computer-integrated, open-circuit, breath-by-breath metabolic measurement system (TrueOne 2400, Parvo Medics, Sandy, UT, US) while the participant performs a graded-exercise test on an arm crank ergometer (ACE), (SCIFIT PRO2, Life Fitness, Tulsa, OK, US). In addition, an H7 Heart Rate Sensor (Polar Electro Inc., Lake Success, NY, US) will be placed on each participant to monitor heart rate during testing. Each participant will be fitted with a silicone mask to cover his or her mouth and nose while performing the exercise test, which is typically completed in 8–12 minutes depending on the participant's fitness level.[8] The protocol involves a 3-minute warm-up at a workload of 8–10 watts (W) followed by a standard ACE ramp protocol. The ramp protocol requires participants to maintain 60 revolutions per minute (rpm) with incremental increases by 7 W every minute, until exhaustion.

Muscle Strength: The participants' muscle strength will be tested using Equalizer accessible exercise equipment to establish their one-repetition maximum (1-RM) on four upper-body exercises tested on each arm (left and right arm bicep curls, left and right arm chest press, left and right arm rowing, and left and right arm rickshaw triceps extension). Each exercise represents a different motion (pushing or pulling) in varying planes. For example, the rickshaw exercise involves pushing downward on straps connected to weights. Upon completion of one repetition during the strength assessment, the participants will report their arm movements as *easy*, *moderate*, or *hard*. The greatest amount of weight lifted for the complete range of motion for the lift will be recorded as the 1-RM. This will be used in determining the exercise routine for participants enrolled in the exercise intervention.

The 6-minute Push Test (6MPT): The 6MPT is a functional mobility and physical fitness test involving MWUs propelling a designated 30-meter loop. Participants are

asked to propel as far as possible on the course within 6 minutes. Total distance propelled is determined by tallying the number of completed 30-meter loops and measuring the partially completed final lap using a tape measure.[22]

Anthropometrics and Vitals: Body mass will be measured by height, weight (using a wheelchair accessible scale), and BMI. Resting and post-testing blood pressure and heart rate will also be taken at each testing session.

Qualitative Data: After completion of the 12-week sessions, participants will complete a 60-minute, semi-structured interview. Interviews will be conducted by applying general rules for qualitative research interviews.[48-50] A protocol for facilitating interviews will be developed with specific key questions. A sample question is, "Did this community-based exercise intervention support your ability to participate in a regular exercise routine?" Interviews will be recorded, and notes will be taken to assist in identifying main themes.

Procedures at for Day 2 of Initial Assessment (T1D2):

T1D2 (60 minutes) will be completed at the Center for Applied Research Sciences (CARS) Clinical Research Unit (CRU), which is established within the Institute of Clinical and Translational Sciences. T1D2 will consist of a blood draw (metabolic blood chemistries) and a DXA body scan (body composition). Prior to D2, participants will be instructed to fast the night before (8–10 hours). Trained CARS staff will conduct blood draws and DEXA scans and assist participants, as needed, during T1D2. Research staff may also be present during T1D2 at CARS to assist participants, as needed.

Body Composition:

Body compostion will be quantified by DXA (General Electric Lunar iDXA) located at the WUSM CRU. DXA is commonly used in research due to its precision and safety. Bone mineral density and whole-body, regional fat, and fat-free (i.e., lean) mass in kg and % will be calculated. Appendicular skeletal muscle mass will be estimated from these data as described and validated by Heymsfield et al.[51]

Metabolic Blood Chemistries:

Fasting blood values will be obtained for markers of inflammation (hsCRP), insulin resistance (HOMA-IR using fasting glucose and insulin concentrations), complete blood cell counts (CBC), fasting lipid/lipoproteins (triglycerides, total-, LDL-, HDL-cholesterol), and glycosylated hemoglobin (a marker of glycemic control) at T1 and T2. To explore neurogenesis mechanisms, we will quantify plasma BDNF, IGF-1, and VEGF using ELISA kits (R&D Systems, Minneapolis, MN).[52-54] Participants will be instructed to fast the night before (8–10 hours). Upon arrival to the CRU after the overnight fast, blood will be collected from the antecubital vein. Blood will be collected with preservatives and stored in Dr. Todd Cade's laboratory located in 1750 West Building on the Washington University School of Medicine Campus. Serum and plasma will be aliquoted into individual vials and frozen (−80° C) until all participants have completed the study intervention.

F4 Visit 2 etc.

All participants will complete a 12-week post-assessment within 10 days of completing their final intervention session, either CBEI or EEG. The post-assessment (T2) will also be completed over two separate days with the second day (D2) being completed within

10 days of the first assessment day (D1). T2D1 (120 minutes) and T2D2 (60 minutes) will be the same as the initial assessment (T1). In addition, at the T2D1 appointment, participants will complete a 30-minute, semi-structured qualitative interview regarding their experiences while participating in the study. The participants may also be asked to wear a heart rate monitor and accelerometers to measure their intensity levels during testing. T2D1 will take place at the EMC research laboratory, and T2D2 will be completed at the CARS CRU.

F5 Visit 3, etc.

Participants may complete a three-month post-assessment. The post-assessment (T3) will also be completed over one day. T3D1 (90 minutes) will be the same as the initial assessment (T1). The participants may also be asked to wear a heart rate monitor and accelerometers to measure their intensity levels during testing. T3D1 will take place at the EMC research laboratory.

F6 Safety and Adverse Events

6.a Safety and Compliance Monitoring

The research coordinator is the primary scheduler for initial and post-assessments and CBEI exercise sessions; therefore, she will daily monitor assessments and CBEI safety, compliance, and progress. The research coordinator will also be in weekly contact with designated PQHWC staff to update the research team on the safety and compliance of EEG participants.

Medical Monitoring:
There will be a physican who will provide medical monitoring of the body composition and metabolic blood chemistry appointments.

i Investigator only

ii Independent expert to monitor

Not applicable

iii Institutional Data and Safety Monitoring Board

To ensure that participants are medically stable and safe to participate in the project, physician's approval and a signed release will be required prior to the initial assessment. During assessment and exercise sessions, participants will be monitored for safety, pain, and any signs of distress. Heart rate monitors will be worn during the VO2 testing. Blood pressure will be taken at the beginning of all testing and intervention sessions. If a participant reports an 8/10 pain level prior to a session, the session will be canceled and rescheduled. If at the end of a session the participant reports pain 8/10 or higher, the rating will be documented in the study's adverse event tracking log. Participants may be dismissed from participation if they rate pain 8/10 or higher over three consecutive sessions. Trained research investigators will be present during all sessions to ensure participant safety. If a participant is uncomfortable with having their blood drawn for metabolic testing, they may choose to skip that portion and still continue within the study. All members of the research team are familiar with potentially dangerous conditions associated with SCI, such as autonomic dysreflexia, and will take appropriate actions if a

participant experiences a medical emergency. Adverse events will be reported to the IRB consistent with the IRB's reporting guidelines. We will take every precaution to ensure participant safety while avoiding risks.

Safeguarding of data: Researchers will assign participants a code to de-identify all data according to HIPAA policies. Data will be stored in a password-protected computer to guarantee participant privacy. To ensure quality of data collection, a research member will oversee each piece of equipment (i.e., Metabolic cart, heart rate monitor, and accelerometers) for immediate detection of technological malfunctions during sessions.

iv Independent Data and Safety Monitoring Board

Not applicable

6.b Definitions of Adverse Events

An adverse event will be defined as a musculoskeletal injury, episode of autonomic dysreflexia, or other medical event that is the result of the assessments or exercise training program.

6.c Classification of Events

i Relationship

ii Severity

Any event that requires medical care will be defined as an adverse event.

iii Expectedness

Adverse events are not expected as a result of the intervention.

6.d Data Collection Procedures for Adverse Events

Adverse events will be recorded in an adverse event tracking log and reported in publications resulting from data.

6.e Reporting Procedures

Adverse events will be reported to the IRB consistent with the IRB's reporting guidelines and will be reported to the National Institutes of Health upon annual progress reports.

6.f Adverse Event Reporting Period

Consistent with the IRB's reporting guidelines.

6.g Post-study Adverse Event

All adverse events will be examined at the completion of the study.

F7 Study Outcome Measurements and Ascertainment

G Statistical Plan

G1 Sample Size Determination and Power

This is a pilot study, with our primary interests in outcome variability and co-variability and estimates of feasibility and acceptability, which will aid in the planning of a larger trial. The sample size of 40 participants was selected to provide enough participants to assess the research protocol, determine trends in change, and provide data to calculate sample sizes for a larger RCT.

G2 Interim Monitoring and Early Stopping

The research coordinator is the primary scheduler for initial and post-assessments and CBEI sessions; therefore, she will daily monitor assessments and CBEI safety, compliance, and progress/stopping. The research coordinator will also be in weekly contact with designated PQHWC staff to update the research team on the safety and compliance of CBEI participants. Designated PQHWC staff will be present to supervise all CBEI participants to monitor safety.

G3 Analysis Plan

The proposed project utilizes a mixed method approach. The *Primary Aim* is an experimental strategy using an RCT method to estimate improvements in physical function, cardio-metabolic health, and psychological well-being of participants enrolled in a community-based exercise intervention compared to an education-only control group on people with SCI. This is a pilot study with the purpose of determining the feasibility of implementing an RCT intervention and developing methodology together with protocols for a larger study with longer-term follow-up assessments. The proposed project utilizes a mixed methods approach, with the ***Secondary Aim*** being both quantitative and qualitative in nature to evaluate the feasibility of the intervention and evaluate the methods of delivery from the perspective of the research staff conducting and monitoring exercise sessions and the participants regarding the enrollment, assessment, and acceptance, adherence, and tolerance of the intervention protocol.

G4 Statistical Methods

<u>*Aim 1:*</u> Data will be collected and managed using Research Electronic Data Capture (REDCap) and exported to SPSS for analysis. Descriptive statistics will be used to describe the CBEI and the EEG. The data will be examined for normality, outliers, and errors. To examine whether the datasets meet the assumptions of normality, a Shapiro-Wilks test will be conducted. The assumptions of homogeneity of variance and homogeneity of covariance will be examined with Box's M and Mauchly's W tests, respectively. To examine the presence of outliers, histograms will be used. The purpose of the analysis is to compare the post VO_2peak measures (primary outcome) between the two groups. First, a two sample t test (or non-parametric Wilcoxon test) will be used for unadjusted analyses. Then we will use a linear regression to compare VO_2peak between the CBEI and EEG, adjusting for pre-VO_2peak measures and other potential covariates. For other outcomes, based on the measurement scale, a similar analysis approach (unadjusted and adjusted) will be used. For binary outcomes, a Pearson Chi-square or fisher exact test will be used for unadjusted analyses, and a logistic regression model will be used for adjusted analyses. For continuous outcomes, we will perform

analyses similar to those of the VO_2peak outcome. Additionally, effect size (d) associated with the intervention will be calculated using Cohen's *d* and will be interpreted as small (d ≤ .2), moderate (d ~ .5), or large (d ≥ .8). We will explore whether results differ depending on level of SCI and length of time living with an SCI. We will use dummy variables for these two variables and test the interaction term (intervention-by-the-dummy) in the model.

Aim 2: We will use descriptive statistics to report on scales collected during and after sessions to further understand acceptability, feasibility, and fidelity. Our qualitative interviews will allow us to further explore whether patterns can be identified in participants who achieved improvement versus those who did not and those who dropped out of the study. Interview data will be transcribed, processed using NVivo, and analyzed using an adaptation of grounded theory analysis, which will include four steps to be employed iteratively: (1) open coding, in which particular concepts in the transcripts are identified and grouped into categories; (2) axial coding, in which categories are associated and related by conditions, actions/interactions, and consequences; (3) process coding, in which concepts and categories are examined in changing circumstances; and (4) selective coding, in which conceptual models and theories are developed, integrated, and refined.

G5 Missing Outcome Data

Only complete, valid data will be included in group analysis for each outcome measure for each participant. While missing outcome measure data will be excluded from group analysis, individual incomplete, invalid, or missing data may be analyzed on a case-by-case basis to potentially further inform the study process and explain participant outcomes.

G6 Unblinding Procedures

Not applicable

H Data Handling and Record Keeping

H1 Confidentiality and Security

All of the data will be treated confidentially, and the participants' names and identities will not be disclosed in any published reports. The participants will be informed orally and in writing that they are free to withdraw from the study at any time with no bias or prejudice. The data obtained from this study will be kept confidential. Researchers will assign participants a code to de-identify all data according to HIPAA policies. Electronic data that contain private health, medical, or research information will be stored in a password-protected computer behind firewalls, and will be maintained using the de-identified ID code to guarantee participant privacy. Only the PI, Dr. Kerri Morgan, and the research coordinator will have access to the code that matches the de-identified IDs to the patient identifiers. All hardcopy data records will be stored in locked file cabinets and kept in a locked office.

H2 Training

All research personnel will be HIPPA certified, and personnel at Washington University will be human subject research certified.

H3 Case Report Forms and Source Documents

Not applicable

H4 Records Retention

Not applicable

H5 Performance Monitoring

Not applicable

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

Not applicable

I2 Auditing and Inspecting

Ongoing monitoring will also be conducted to ensure fidelity. All interventionists have worked with people with SCI, understand the implications of SCI, and have extensive knowledge about wheelchairs. Dr. Morgan will train all interventionists on the CBEI and EEG protocols. Interventionists will be asked to complete a practice session. To ensure standardization of the intervention delivery and to reduce drift, Dr. Morgan will monitor the fidelity of the training sessions by completing a fidelity monitoring checklist on 20% of the CBEI and EEG participants during one of the sessions. The monitoring checklist will include aspects of the session and instructions given by the interventionist. The research coordinator will review all participant (CBEI and EEG) files weekly to ensure that the interventionists are completing all paperwork and documenting intervention sessions.

J Study Administration

J1 Organization and Participating Centers

Initial and post-assessments will be conducted at Washington University's EMC research lab, located within the PQHWC building, and at the WUSM CARS CRU. CBEI training sessions will be conducted at the PQHWC. Trained research staff will be present for all assessments, and PQHWC staff will be present for safety monitoring of CBEI training sessions.

J2 Funding Source and Conflicts of Interest

National Institutes of Health. No conflicts of interest.

J3 Committees

Not applicable

J4 Subject Stipends or Payments

Participants will be paid $50 for D1 of the initial assessment (T1) and $25 for D2 of the initial assessment. They will be paid $100 for D1 of the 12-week post-assessment (T2) and $25 for D2 of the 12-week post assessment. They will also be paid $50 for D1 of the follow-up assessment (T3). Participants in the CBEI will receive a free 12-week gym membership to the PQHWC ($165 value). Participants in the EEG will be receive a free 8-week gym membership to the PQHWC to be used after the intial 12 weeks. Participants will only be paid for sessions completed.

J5 Study Timetable

Project Activities	**Sept 2018**	**Oct-Dec 2018**	**Jan-Mar 2019**	**Apr-Jun 2019**	**Jul-Sept 2019**	**Oct-Dec 2019**	**Jan-Mar 2020**	**Apr-Jun 2020**	**Jul-Sept 2020**
IRB approval	x	X							
Recruit and screen		X	X	X	X	X	X		
Initial testing		X	X	X	X	X	X		
Intervention		X	X	X	X	X	X	X	X
Follow-up testing		X	X	X	X	X	X	X	X
Data analysis								X	X
Prepare manuscripts								X	X
Present at conferences		X	X			X	X		

K Publication Plan

Manuscript(s) will be written by Dr. Morgan and other research staff involved in the study and submitted for publication following the completion of the T1–T3 assessments, as well as following intervention completion.

L Attachments

L1 Tables

Not applicable

L2 Patient education brochures

Not applicable

L3 Special procedures protocols

Not applicable

L4 Questionnaires or surveys

Characteristics of Respondents (CORE) survey, PROMIS measures, Leisure Time Physical Activity Questionnaire for People with SCI (LTPAQ-SCI); The SCI Exercise Self-Efficacy Scale (ESES): Community Participation Index (CPI); RM 4-FM: Motivation for Physical Activity and Exercise/Working Out; 6-minute Push Test (6MPT)*;* and qualitative questions*.* Attachments of these are included in the IRB application.

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