The Effect of an Adaptive Exercise Program on Chronic Inflammation in Spinal Cord Injury.

Protocol Number: Version 5

National Clinical Trial (NCT) Identified Number: NCT05376449

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Site/Sponsor: HealthPartners Neuroscience Center/HealthPartners Institute

Institutional Review Board Number: A21-006

Funded by: Minnesota Office of Higher Education

Date: August 14th, 2023

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the terms of the award.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name: Amanda A. Herrmann, PhD
Title: Research Associate

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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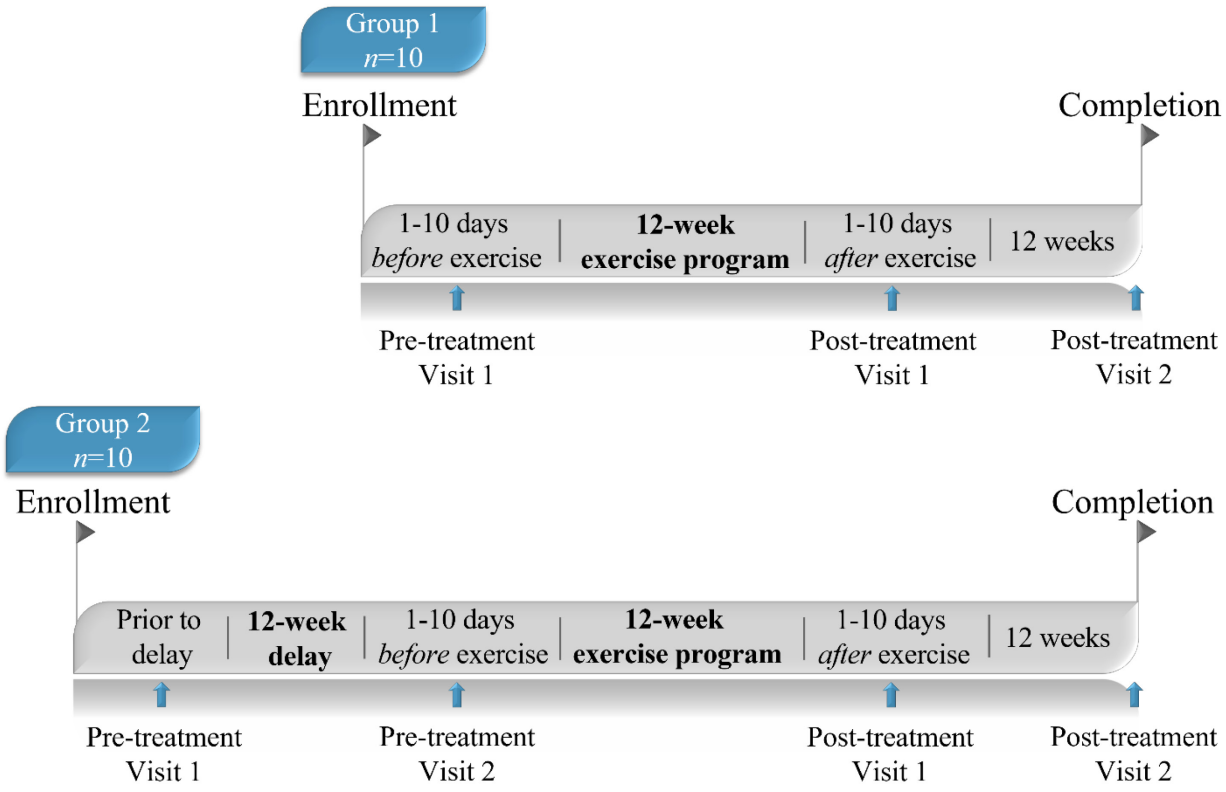
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	The Effect of an Adaptive Exercise Program on Chronic Inflammation in Spinal Cord Injury.
IRB Number:	A21-006
Study Description:	Long lasting inflammation in the body is related to cardiovascular and respiratory disease, which are the two most common causes of death in people living with spinal cord injury (SCI). Individuals with SCI have been reported to have higher levels of inflammation when compared to healthy individuals. Exercise is a well-known method to reduce inflammation; however, people with SCI are often inactive. The main goal of this study is to determine whether a 12-week adaptive exercise program can reduce inflammation in people with SCI. Participants will be randomized to start exercise immediately or after a 12-week delay.
Specific Aims:	Specific Aim 1: To examine the effect of a 12-week exercise program on inflammation in individuals with SCI. Specific Aim 2: To examine the effect of a 12-week exercise program on strength and cardiovascular health in individuals with SCI. Specific Aim 3: To observe the impact of a 12-week exercise program on quality of life (QOL) in individuals with SCI.
Endpoints:	Primary Endpoint: Change in inflammatory biomarkers: CRP, IL-6, TNF-α Secondary Endpoint: Strength: 1-repitition maximum, Cardiovascular: 6-minute submaximal exercise test. Tertiary Endpoint: Spinal Cord Injury-Quality of Life short forms
Study Population:	25 individuals aged 18-70 with a diagnosis of SCI will be recruited for this study.
Description of Sites/Facilities Enrolling Participants:	For in-person visits, participants will attend the exercise program at the HealthPartners Neuroscience Center, located at 295 Phalen Blvd., St. Paul, MN 55130.
Description of Study Intervention/Experimental Manipulation:	The exercise program will be administered by exercise physiologists and physical therapists 3 times per week for a duration of 12 weeks.
Study Duration:	The duration of this study is 2 years.
Participant Duration:	We anticipate that participants will complete all study-related tasks within approximately 6-9 months.

1.2 SCHEMA


Group 1
n=10
Enrollment
Completion
1-10 days
before exercise
12-week
exercise program
1-10 days
after exercise
12 weeks
Pre-treatment
Visit 1
Post-treatment
Visit 1
Post-treatment
Visit 2
Group 2
n=10
Enrollment
Completion
Prior to
delay
12-week
delay
1-10 days
before exercise
12-week
exercise program
1-10 days
after exercise
12 weeks
Pre-treatment
Visit 1
Pre-treatment
Visit 2
Post-treatment
Visit 1
Post-treatment
Visit 2

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening	Consent	Pre-treatment 1	Pre-treatment 2	Study Intervention	Post-treatment 1	Post-treatment 2	Early Withdrawal Visit
Group 1: Immediate Start	*Visit 0*	*Visit 1*	*Visit 2*	*N/A*	*Visit 3-38*	*Visit 39*	*Visit 40*	
Group 2: Delayed Start				*Visit 3*	*Visit 4-39*	*Visit 40*	*Visit 41*	
Review Eligibility	X							
Informed Consent		X						
Randomization		X						
Demographics		X						
Medications		X	X	X	X	X	X	X
Blood Draw- *in person*			X	X		X	X	X
Strength & Cardiovascular Testing- *in person*			X	X		X	X	X
SCI-QOL- *e-mail survey*			X	X		X	X	X
Adverse Events (AE) Reporting					X	X	X	X
Treatment Adherence					X			

VISIT SCHEUDULE DESCRIPTION

All in-person visits will take place at: **HealthPartners Neuroscience Center, 295 Phalen Boulevard, St. Paul, MN, 55130.**

1. Pre-screening Phone/Video Call (Groups 1 & 2)

- Duration: Approximately 30 minutes
- Research staff will:
  - Provide potential participants information about the study and ask whether they are interested in participating.
  - Determine whether they meet the inclusion/exclusion criteria for the study.
  - Ask participants for permission to communicate through e-mail for the study and assist them in setting up an account if they do not have one (e.g. send them study documents, QOL survey).
  - Schedule Consent Visit if the person is eligible for the study and e-mail the person the Informed Consent, Health Insurance Portability and Accountability Act (HIPAA), and HealthPartners non-discrimination forms.

2. Consent Phone Call (Groups 1 & 2)

- Duration: Approximately 1 hour via phone
- Research staff will:
    - Review the Informed Consent and HIPAA documents with potential participants.
    - Answer any questions of potential participants and ensure they understand the expectations of the study.
    - Ask participants to electronically sign the Informed Consent and HIPAA documents via REDCap and provide them electronic copies for their records.
    - Complete the Demographics short form in the relevant electronic case report forms (eCRFs) in Research Electronic Data Capture (REDCap), a secure web-based system.
    - Randomize the participant and schedule the Pre-treatment visit(s).

3. Pre-treatment Visit 1 (Groups 1 & 2)

- Duration: Approximately 1 hour in person
- Research staff will:
    - Complete the Medication review in REDCap.
    - Have the laboratory staff obtain a blood sample from the patient.
    - Take the patient to the rehabilitation gym for strength and cardiovascular testing (described in detail below)
- Patient will be asked to complete the Spinal Cord Injury-Quality of Life (SCI-QOL) short forms via e-mail survey within 3 days (approximately 30 minutes).

4. Pre-treatment Visit 2 (Group 2 only)

- Duration: Approximately 1 hour in person
- Research staff will:
    - Complete the Medication review in REDCap.
    - Have the laboratory staff obtain a blood sample from the patient.
    - Take the patient to the rehabilitation gym for strength and cardiovascular testing.
- Patient will be asked to complete the SCI-QOL short forms via e-mail survey within 3 days (approximately 30 minutes).

5. Study Intervention (Groups 1 & 2)

- Duration: Each visit approximately 1 hour
- The exercise physiologists will:
    - Complete the Adverse Events (AE) Reporting, Medication Review, and Treatment Adherence in the relevant eCRFs in REDCap.
    - Provide exercise instruction as described in more detail below.

6. Post-treatment Visit 1 (Groups 1 & 2)

- Duration: Approximately 1 hour in person
- Research staff will:
    - Complete the Medication review in REDCap.
    - Have the laboratory staff obtain a blood sample from the patient.

- Take the patient to the rehabilitation gym for strength and cardiovascular testing.
- Patient will be asked to complete the SCI-QOL short forms via e-mail survey within 3 days (approximately 30 minutes).

7. Post-treatment Visit 2 (Groups 1 & 2)

- Duration: Approximately 1 hour in person
- Research staff will:
  - Complete the Medication review in REDCap.
  - Have the laboratory staff obtain a blood sample from the patient.
  - Take the patient to the rehabilitation gym for strength and cardiovascular testing.
- Patient will be asked to complete the SCI-QOL short forms via e-mail survey within 3 days (approximately 30 minutes).

8. Early Withdrawal Visit (For patients who begin the intervention and then withdraw from the study.)

- Duration: Approximately 1 hour in person
- Research staff will:
  - Complete the Medication review in REDCap.
  - Have the laboratory staff obtain a blood sample from the patient.
  - Take the patient to the rehabilitation gym for strength and cardiovascular testing (if medically able).
- Patient will be asked to complete the SCI-QOL short forms via e-mail survey within 3 days (approximately 30 minutes).

2 INTRODUCTION

2.1 BACKGROUND & STUDY RATIONALE

Two of the most common causes of death in people living with spinal cord injury (SCI), cardiovascular and respiratory disease, have been linked to chronic low-grade inflammation.[1] Inflammation has also been linked to obesity, pulmonary issues, diabetes, and poor wound healing.[2] Although some levels inflammation in the body can be considered "good" (e.g. inflammation occurs during injury repair), chronic inflammation can have negative consequences. Fortunately, chronic inflammation after a SCI could likely be reduced through modifiable risk factors, as described below.

Higher levels of inflammatory biomarkers are observed in SCI when compared to healthy individuals. Biomarkers are measurable substances from the body (e.g. blood serum). C-reactive protein, which is a marker of both inflammation and cardiovascular disease, was reported to be higher in adults with chronic SCI.[3] Proinflammatory cytokines (signaling molecules that promote inflammation) interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), and the IL-1 receptor agonist (IL-1RA) (produced in response to infection or inflammation) are also increased.[4] Finally, Antiganglioside (anti-GM_1) immunoglobulin (IgG), which are antibodies that are typically also present in autoimmune diseases (e.g. Guillain–Barré syndrome), have also been shown to be elevated.[4] Not only are these inflammatory biomarkers elevated

in individuals with SCI, they are even more elevated in those with medical complications (e.g. urinary tract infection, pressure ulcers).[4]

A well-known method to reduce inflammation is through exercise; however, due to limitations in mobility, individuals with SCI are among the most sedentary and inactive in the world.[5] Muscle atrophy, damaged muscle innervation, and reduced muscle activation create barriers for individuals with SCI to exercise. In addition, exercise conditioning in persons with SCI is complicated, because its benefits can be potentially counterbalanced by both ineffective exercise activities and the consequences of imprudent exercise, lending to further injury and accelerated musculoskeletal decline. Individuals with SCI also frequently encounter challenges and barriers when navigating a typical gym space. Therefore, individuals with SCI may be limited in their ability to achieve anti-inflammatory benefits through exercise.

While exercise has been shown to reduce biomarkers of inflammation[6,7] and increase the release of anti-inflammatory proteins[7] in healthy individuals, it has not been extensively examined in individuals with SCI. In one study, CRP, IL-6, and TNF-α were all reduced in individuals with SCI after participation in a 10 week cycling exercise program.[8] In another study, CRP and erythrocyte sedimentation rate (ESR; test to detect inflammation) were both reduced in individuals with SCI following a 6-week body weight supported treadmill training program.[9] However, these studies included small sample sizes (18 and 14, respectively), did not include a control group, examined biomarkers immediately after the program, and included only cardiovascular exercise. In another study that included both individuals with SCI and multiple sclerosis (MS), there was a significant decrease in TNF-α after one exercise session.[10] However, these results included both patients with SCI and MS and only a single exercise session. Thus, the generalization of the results, the long-term effects, and the effects of strength training are not yet known.

While there is limited evidence that an exercise program can reduce inflammation in individuals with SCI, exercise has been shown to have other important beneficial effects. A recent review found evidence that exercise can improve fitness (cardiorespiratory fitness, power output, muscle strength) and cardiometabolic health (body composition, cardiovascular risk) of individuals with SCI.[11] Another review reported evidence that exercise can greatly improve the physical and psychosocial well-being of individuals with SCI.[12] As the result, if the barriers to exercise participation after a SCI can be overcome, individuals may have multiple positive health benefits. For this study, we anticipate that a 12-week adaptive exercise program will reduce chronic inflammation and improve overall health in individuals with SCI.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

Exercise
Potential risks of exercise in individuals with SCI include autonomic dysreflexia, musculoskeletal injury, hypotension, thermal dysregulation,[13] pain, fatigue, and skin breakdown. The exercise program will be supervised by exercise physiologists to reduce these risks.

Blood Draw
Potential risks of blood draws include pain, bruising, dizziness, and local infection.

Assessments/Questionnaires (SCI-QOL)

The Spinal Cord Injury-Quality of Life short forms are standardized questionnaires that will measure personal perception of life. The questions on these assessments may make participants feel uncomfortable because some parts may be easy to answer, while some parts may be difficult or tiring. Filling out the questionnaires may also cause individuals to feel uncomfortable or upset.

Loss of Confidentiality
There may be a slight possibility of breach of confidential information that was collected. However, the following procedures will be implemented to reduce this risk:

- Data collection and reporting tools will be developed and stored internally.
- Data collected and stored electronically will remain confidential and secure (e.g. secured server and password protected files [REDCap]).
- Study binders will be stored in a locked file cabinet within a locked office.
- After the study is closed, all subject identifiers and blood samples will be destroyed.

2.2.2 KNOWN POTENTIAL BENEFITS

Exercise has been shown to reduce inflammation in other populations, but has not been studied much in people with SCI. Therefore, exercise may reduce inflammation in the SCI population, however this is not guaranteed. In addition, there will be no cost for individuals to participate in the exercise program, while enrolled in the study.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We believe the potential risks to the participants in this study are minimal and that the benefit of understanding whether exercise can reduce chronic inflammation and improve strength, cardiovascular health, and quality of life in patients with SCI outweighs the potential risks.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To examine the effect of a 12-week exercise program on inflammation in individuals with SCI.	Change in inflammatory biomarkers: CRP, IL-6, TNF-α
Secondary	
To examine the effect of a 12-week exercise program on strength and cardiovascular health in individuals with SCI.	Strength: 1-repitition maximum, Cardiovascular: 6-minute submaximal exercise test.
Tertiary	
To observe the impact of a 12-week exercise program on QOL in individuals with SCI.	SCI-QOL

4 STUDY DESIGN

4.1 OVERALL DESIGN

Study Design:

This study is an unblinded, randomized, 2-arm clinical trial.

Hypotheses:
Primary Hypothesis: We hypothesize that exercise will reduce inflammatory biomarkers.
Secondary Hypothesis: We hypothesize that exercise will improve strength and cardiovascular health.
Tertiary Hypothesis: We hypothesize that exercise will improve QOL.

Randomization:
At the consent visit, participants will be randomized into one of two treatment groups. Randomization is explained in **Section 6.3**.

Treatment Groups:

Group 1: 10 participants will begin the exercise program immediately (3x per week for 12 weeks = 36 total).
Group 2: After a 12-week delay, 10 participants will begin the exercise program (3x per week for 12 weeks = 36 total).

Study Intervention:
Exercise sessions will last approximately 1 hour and will be lead by exercise physiologists and therapists. Additional details are discussed in **Section 6.1**.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Justification for an unblinded study: Because it will be clear to both study personnel and participants who will have a delayed start and who will start immediately, neither will be blinded in this study. This will be reported as a limitation of the study.

Justification for an uncontrolled study with no control group: N/A

4.3 JUSTIFICATION FOR INTERVENTION

Exercise is well known to have positive health effects, such as reducing inflammation and improving fitness and cardiometabolic health. For this study, we anticipate that a 3-month adaptive exercise program will reduce chronic inflammation and improve overall health in individuals with SCI.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed study treatment visits and assessments. The end of the study is defined as completion of the last post-treatment visit for each group.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Ability to provide and provision of signed and dated informed consent form
- Age 18-70
- Diagnosis of SCI and post injury ≥ 6 months
- Able to achieve adequate active range of motion at the elbow and wrist (flexion/extension) and able to achieve at least 90° active shoulder flexion, in order to complete study activities

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

- Non-English speaking
- Exercise program participation ≤1 month from study enrollment or any other exercise participation during the duration of the study
- Patients with significant cognitive impairment of any etiology that prevents them from being able to participate
- Patients that were given sternal or spinal precautions that would prevent excessive twisting, bending, overhead reaching and lifting over 10 pounds
- Patients with a history heart failure, chronic lung disease, angina or any other condition that causes unreasonable shortness of breath on exertion
- Has been diagnosed with autonomic dysreflexia that is severe, unstable, and uncontrolled
- Requires ventilator support
- Spasms that limit the ability of the subjects to participate in the study training as determined by the Investigator
- Pregnant, planning to become pregnant
- Any other medical conditions that could affect their ability to participate in the exercise program (as determined by study investigators)
- Active participation or past participation ≤3 months in any other interventional study.
- Unwilling to participate in all study related activities

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Pre-screening Phone Call:
All potential participants will undergo a pre-screening phone call to determine whether they meet the inclusion/exclusion criteria. Patients will be considered ineligible if they do not meet one or more of the inclusion/exclusion criteria during pre-screening. We will collect information on why participants are ineligible or decide not to move forward with the trial.

Pre-treatment Visit:
Screen failures are defined as participants who are considered eligible during the pre-screening phone call, but it was subsequently determined that they do not meet one or more of the inclusion/exclusion criteria at or after the Pre-treatment (baseline) visit. We will collect information on why participants screen fail or decide not to move forward with the trial.

Rescreening Patients:
Individuals who do not meet the criteria for participation in this trial (ineligible or screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened up to one time. Examples include: patient no longer has sternal or spinal precautions; exercise program participation ≤ 1 month from study enrollment; or participation in an interventional study ≥3 months prior. Rescreened participants will be assigned a new participant number.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment: Individuals with SCI will be recruited by physician and therapist referrals from HealthPartners' clinics. We will also advertise our research study by distributing flyers to HealthPartners' physicians and throughout HealthPartners' and Park Nicollet clinics. Recruitment flyers will also be provided to our community partners, for example, the Minnesota Spinal Cord Injury Association and the Get Up Stand Up to Cure Paralysis Foundation. If we encounter difficulties with recruitment, we plan to submit an amendment to the IRB to contact HealthPartners patients and members and invite them to participate. To reach our target enrollment, we anticipate that we will need to screen 60 people, of those 25 individuals will sign the informed consent and will be randomized to treatment groups.

Remuneration: Participants will be provided gift cards totaling $20 per person for completing certain time points of the research study. Group 1: Will receive a $20 gift card at each of the pre- and post-treatment visits (3 visits x $20 = $60 total). Group 2: Will receive a $20 gift card at each of the pre- and post-treatment visits (4 visits x $20 = $80 total).

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The study intervention for both groups is an adaptive exercise program. The exercise program is described next in more detail.

6.1.2 ADMINISTRATION AND/OR DOSING

Exercise Program:
Twenty individuals with a SCI will participate in a 12-week strength and endurance adaptive exercise program. They will be enrolled into our already existing NeuroWell program, which is an exercise program geared toward individuals with neurological disorders or injuries run by the Regions Hospital Rehabilitation department at the HealthPartners Neuroscience Center. Prior to participating in the exercise program, the prospective participant will provide a medical clearance by their physician. Certified Clinical Exercise Physiologists will supervise the program. Therapists will also assist with the program as needed. The exercise programming will be designed by the exercise physiologists and adapted to individuals' abilities. Exercise prescriptions will be designed based on established guidelines, level and completeness of injury, individual functional ability, individual goals, and baseline exercise assessments.

The American College of Sports Medicine recommends that those with an SCI participate in 2-3 exercise sessions per week consisting of moderate intensity (40-59% Heart Rate Reserve) aerobic exercise, light to moderate intensity (20 RM to 10 RM) resistance training, and daily flexibility training. Therefore, participants will exercise 3 times a week during the 12-week program, following these guidelines. Each session will consist of 20-30 minutes of endurance exercise, 20 minutes of resistance training, and 10 minutes of flexibility, core exercises, and seated balance training. Types of exercise and equipment utilized are described in Table 1. The program will allow individuals who have suffered a SCI to access an exercise program that is adaptive to their current function and tailored to their individual fitness goals.

Table 1. *Exercise Session Components*

Endurance/Aerobic	Strength/Resistance	Flexibility, Core, Balance
FES Cycle (Restorative Therapies, Inc) (Figure 1a)	IncludeStrength (IncludeHealth) (Figure 1d)	Passive
Upper Body Ergometer (SCIFIT) (Figure 1b)	Resistance Machines (leg press, chest press, lat pulldown, rowing machine, CanDo Rickshaw)	Active
Wheelchair Ergometer (Wheelers' Paramill) (Figure 1c)	Resistance Bands (Theraband)	Active-Assisted
	Ankle/wrist cuff weights	Functional Activities (e.g. mat exercises)

Improvements in fitness and health outcomes will be optimized through the utilization of adaptive equipment and expert exercise programming. Novel, adaptive equipment and technology is integrated into the exercise program to accommodate varying levels of abilities. The RT300 Functional Electrical Stimulation (FES) Leg | Core cycle (Figure 1a; Restorative Therapies, Inc) transmits electrical pulses through surface electrodes, which allows individuals with little or no lower limb voluntary movement to pedal. The Pro1 upper body ergometer (Figure 1b; SCIFIT) is a versatile arm exerciser that includes a removable seat and wheelchair platform for easy wheelchair access. The wheelchair ergometer (Figure 1c; Wheelers' Paramill) is a treadmill designed to fit all manual wheelchairs and allows for backward and forward motion. The IncludeStrength (Figure 1d; IncludeHealth, Inc) machine includes movable seating for wheelchair access, the ability to secure a wheelchair, and dexterity-free handles. Finally, the exercise program will have access to specialty equipment to offer further adaptive support such as gripping aids (Active Hands) and leg stabilizers (NuStep, Inc).

Figure 1. *Adaptive Equipment*

Biomarker Quantification (Aim 1): The primary outcome for Aim 1 will be change in inflammatory biomarkers: CRP, IL-6, TNF-α, as these were the primary biomarkers shown to be higher in individuals with SCI compared to healthy individuals in previous studies. Patients in Group 1 will undergo 3 blood draws and patients in Group 2 will undergo 4 blood draws. Patients will give approximately 2.5 teaspoons of blood for each blood draw. Blood samples will be collected by the HealthPartners Neuroscience Center laboratory staff. CRP will be analyzed through Regions Hospital Central Laboratory. IL-6 and TNF-α will be analyzed using the MAGPIX® by Millipore Sigma™, a multiplex ELISA, allowing the quantification of multiple analytes from a single sample by combining magnetic and fluorescent technology. After collection, blood will be allowed to clot for at least 30 minutes before centrifuging for 10 minutes at 1000xg. Serum will be removed, aliquoted and stored in sterile cryo-preservation tubes in -80°C freezers onsite in a secured location with temperature tracking until time of analysis. At the time of analysis samples will be thawed and diluted 1:2 in Assay Buffer provided by a custom Milliplex® kit: HCTYA-60K-03 (IL6, TNFa, IL1RA). The beads provided by the kit will also be added and the plate will be incubated on a plate shaker following the kit protocol. After incubation the plate will be placed on a magnet and washed, then incubated with a secondary antibody provided by the kit. Once the secondary incubation is completed the plate will be again placed on a magnet and washed before being run by the MAGPIX®. Data quantification will be acquired using the xPonent® software provided by Millipore Sigma™.

Strength and Cardiovascular Health (Aim 2): Participants will undergo a strength and cardiovascular test during the pre-treatment and first post-treatment visits. The strength test will consist of a 1-repetition maximum chest press test. This test quantifies the amount of weight that participants can possibly lift during the one repetition. The cardiovascular test will consist of a 6-minute submaximal exercise test using an arm ergometer following previously published methods.[14] Heart rate (HR) and blood pressure will be

measured before and after the test. Rate of perceived exertion (RPE), a measure of physical activity intensity, will be measured after the test.

Spinal Cord Injury-Quality of Life (Aim 3): Participants will be asked to complete the Spinal Cord Injury-Quality of Life (SCI-QOL) short forms at the pre-treatment and post-treatment visits. The SCI-QOL includes the following domains: basic mobility, fine motor, manual/power wheelchair, self-care, ability to participate in social roles and activities, anxiety, bladder complications, bladder/bowel management difficulties, depression, grief/loss, independence, pain behavior, pain interference, positive affect and well-being, pressure ulcer, resilience, satisfaction with social roles and activities, self-esteem, stigma, and trauma. The SCI-QOL has strong reliability and validity.[15]

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Training and Tracking:
The PI will train research staff on data collection using REDCap. All training will be documented on a training log. This will include dates and times of the trainings, and printed names and signatures of the trainees and PI.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization:
Randomization will be performed with a 1:1 allocation ratio. Balanced treatment assignments will be achieved using permuted block randomization with random block sizes. The study biostatistician will generate a randomization schedule using the SURVERYSELECT procedure in SAS. Assignments will not be seen by other study personnel in advance and will not be changed after randomization.

Blinding:
Study personnel will be unblinded to the randomization, as it will be clear the number of participants who have a 12-week delay and those who do not. In addition, it will be clear to participants which treatment group they are in and it will be impossible to blind them from this information.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participants will be asked to adhere to study visits and to complete study assessments. Participants will remain active unless withdrawn from the study (see **Section 7**). We will track participants' adherence to study visits, as well as completion of the assessments. These will be documented in the relevant eCRF.

6.5 CONCOMITANT THERAPY

Participants may use over-the-counter medications, dietary supplements, and prescribed medications. Medications will be assessed at each study visit and documented in the relevant eCRF.

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

When a participant who signed the consent form chooses to discontinue participation in the study after beginning the study intervention, or if the principal investigators (PIs) and co-investigators determine that a participant should discontinue participation, they will be withdrawn from the study. A withdrawal will either be defined as 'Patient Withdrawal' or 'PI Withdrawal'. The participant will be asked to complete an early withdrawal visit within 14 days from the date the intervention was discontinued. The purpose of the visit will be to obtain study outcome data and to record any AEs or serious adverse events (SAEs) that may have occurred after the discontinuation of the intervention. Research staff will attempt to call the participant up to 3 times to set up an in person visit.

The data that will be collected at the time of study withdrawal will include the following:

- The reason(s) for discontinuation of the study intervention

The data that will be collected during the early withdrawal visit will include the following:

- Blood sample
- Strength and cardiovascular testing (if medically able)
- Medication review
- AEs or SAEs that occurred since the time of withdrawal
- SCI-QOL via e-mail survey

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

1. Participant has not completed a intervention treatment session for > 10 days, unless a participant has an illness, such as COVID-19. In this case, additional time may be allowed, as determined by the investigator.
2. Significant study intervention non-compliance during exercise sessions
3. Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
4. Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
5. The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the relevant eCRF. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and

receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to attend any scheduled study visit and study staff are unable to contact the participant after at least 5 attempts, while maintaining the 10 day maximum between visits.

The following actions must be taken if a participant fails to attend any required study visit:

- Study staff will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, telephone calls or e-mail – if no answer leave a voicemail on the first and last attempt). These contact attempts will be documented.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Demographics: Demographic information will be collected, including: gender, age, race, ethnicity, language, height, zipcode, weight, marital status, employment status, medical history, and medications.

Injury, Illness, & Life Events: At all pre- and post-treatment visits, patients will be asked over the last 7 days whether they have had any injuries, illnesses, or major life events to report. This information will be tracked as it may likely impact inflammatory biomarkers.

Treatment Adherence: The participant's treatment adherence will be measured to determine tolerability of the intervention. We will record the number of attended sessions. We will also record participants' ability to complete the entire session.

Quality of Life: Participants will be asked to complete the SCI-QOL short forms, which include questions regarding quality of life, such as mobility, self-care, pain, and independence.

8.2 SAFETY ASSESSMENTS

Assessment of Adverse and Serious Adverse Events:
AEs and SAEs will be monitored by study staff throughout the study. Staff will immediately notify the PIs and utilize the eCRF to record any AEs or SAEs. The PIs will review and categorize all AEs or SAEs and report them accordingly, as discussed below.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of AE from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

This protocol uses the definition of SAE from 21 CFR 312.32 (a): An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or study clinician, it results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

1. **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
2. **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3. **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All AEs will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

The physician PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Study staff will record AE/SAEs with start dates occurring any time after the first intervention treatment session until the last post-treatment visit for each group. All reported events will be monitored until the

last post-treatment visit for each group. Any reported event that is definitely or probably related to the intervention will be followed until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

In consultation with the PIs, a trained member of the study team will be responsible for conducting an evaluation of an AE and shall report the results of such evaluation to the reviewing IRB either at the time of continuing review or within 10 working days of becoming aware of the event if the event is considered to be serious or meets the definition of an unanticipated problem involving risks to study subjects or others.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI and the study clinician, a trained member of the study team will be responsible for conducting an evaluation of a SAE and shall report the results of such evaluation to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Following IRB review of any AEs or SAEs, the PI will follow the IRB's recommended actions. This may include, but is not limited to, modifying the informed consent document or process, re-consenting current participants, providing information to past or current participants (e.g. whenever the information may relate to the participant's willingness to continue participants), and modifications to the protocol/research plan.

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

Women who are currently pregnant or planning to become pregnant during the study are excluded from this study. This is because it would be considered a high-risk pregnancy. If any participant who is undergoing exercise expectedly or unexpectedly becomes pregnant while active in the trial, the participant will be withdrawn from the study by the PI. The participant will be asked to complete an early withdrawal phone call in 7-14 days from the date the intervention was discontinued for safety follow-up.

If any participant who has completed all exercise sessions expectedly or unexpectedly becomes pregnant, the participant may remain in the study until study completion.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The PIs will report unanticipated problems (UPs) to the reviewing IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB as soon as possible, but no later than 10 working days after the investigator first learns of the event

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Following IRB review of any unanticipated problems, the PI will follow the IRB's recommended actions. This may include, but is not limited to, modifying the informed consent document or process, re-consenting current participants, providing information to past or current participants (e.g. whenever the information may relate to the participant's willingness to continue participants), and modifications to the protocol/research plan.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- **Primary:**
  We hypothesize that exercise will reduce inflammatory biomarkers.

- **Secondary:**
  We hypothesize that exercise will improve strength and cardiovascular health.

- **Tertiary:**
  We hypothesize that exercise will improve QOL.

9.2 SAMPLE SIZE DETERMINATION

The primary analysis is an superiority test of means on data from a parallel-group design. Assuming a standard deviation of 2.0 units for CRP, 1.0 units for IL-6, and 0.5 units for TNF-α,[8] and a true difference between means of 0, 10 subjects in each study group achieves 80% power at a 5% significance level to detect a 1.3 SD difference in mean change in inflammatory biomarkers between groups (PASS 2019 software). No interim analysis is planned. The potential effect on our power if our estimates for the effect size are displayed on the table below.

Power for N = 20 (10/arm) α = 0.05		
CRP (σ=2.0)		
Δ	**δ/σ**	**Power**
2.3	1.2	0.70
2.6	1.3	0.80
3.1	1.5	0.90
IL-6 (σ = 1.0)		
Δ	**δ/σ**	**Power**
1.2	1.2	0.70
1.3	1.3	0.80
1.5	1.5	0.90
TNF-α (σ=0.5)		
Δ	**δ/σ**	**Power**
0.6	1.2	0.70
0.7	1.3	0.80
0.8	1.5	0.90

Based on preliminary estimates, we do not anticipate difficulty recruiting 25 participants. Physical Medicine and Rehabilitation physicians see approximately 25 individuals with SCI per month at the Neuroscience Center. Therefore we will need a 10% enrollment rate to reach our recruitment goal in the allotted time frame.

9.3 POPULATIONS FOR ANALYSES

All analyses will be performed on an intention-to-treat basis. If poor attendance is observed and/or patients choose to withdraw early, we will perform a per-protocol analysis as a sensitivity analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Discrete variables will be summarized using frequencies and percentages, while continuous variables will be summarized by means and standard deviations. If the continuous variables are found to be skewed, we will instead report medians and interquartile ranges. Statistical significance will be determined using p-values less than 0.05 and 95% confidence intervals, unless otherwise indicated. All inferential tests will be two-sided. For descriptive statistics (means, SDs, proportions) where no inferential statistics were conducted, we will refrain from making confirmative statements. All covariates will be pre-specified in the sections below. Any additional analyses will be described as post-hoc and exploratory.

Distribution of the outcome variables will be assessed prior to conduct of our analyses to determine if the planned tests are appropriate and to identify outliers. If variables are found to be non-normally distributed and/or outliers are present we will explore the use of log-transformations or non-parametric tests such as the Kruskal-Wallis test.

Patients who do not complete all assessments required for a given analysis will be excluded from the model/test and described separately. If missingness > 10% within the full analytic dataset, a comparison of participants with and without missing values will be performed and used to inform possible next steps (imputation, feasibility assessment of program, etc.). Reports of injury, illness, and life events occuring during the data collection period will be summarized and compared between arms. These summaries will be used to inform possible sensitivity analysis as described in section 9.4.10. All analysis will be performed in SAS 9.4 using two-sided alphas of 0.05 to determine significance.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary outcome, change in inflammatory biomarker (CRP, IL-6, TNF-α), will be measured using a series of blood draws as described in **Section 6.1**. For our primary analysis, we are interested in the change over the course of the first 3 months, during which group 1 completes the exercise program and group 2 acts as a control. The change in inflammatory biomarker will be calculated by measuring the difference between the first and second measurement for each pariticipant. We will then present the mean change by group with corresponding standard deviations. Analysis of covariance (ANCOVA) will be used to compare the change in each of the 3 inflammatory biomarkers between groups: An unadjusted model will account for a participant's baseline biomarker measurement while an adjusted model will include the set of covariates identified in **Section 9.4.6**. If these analyses identify a significant difference in change of inflammatory biomarkers associated with participation in the exercise program, next steps will assess if this change is still present three months after completing the exercise program. Using data from both groups in aggregate, paired t-tests will be used to compare the inflammatory marker level directly after participation in the exercise program and inflammatory marker levels three months afterward.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Similarly structured ANCOVA models will be used to evaluate the change in secondary outcome measures (HR, RPE, and maximal weight) associated with participation in the intervention. Data from the first 3 months from both groups will be compared in both unadjusted and adjusted analyses. This maintains the

benefits of including control data when estimating the intervention effect on strength and cardiovascular health. If there is a significant change in secondary outcome measures after participation in the intervention, participants' measurements directly post-exercise program will be compared to those taken 12-weeks later to determine if the effect persists. These measurements will be compared using paired t-test or Wilcoxon signed rank tests, as appropriate, with no group comparisons.

9.4.4 ANALYSIS OF THE TERTIARY ENDPOINT(S)

To evalulate the effect of the exercise program on QOL, SCI-QOL scores will be analyzed similarly to the primary and secondary endpoints.This includes exploration of any observed effects on QOL in the 12-weeks after program completion.

9.4.5 SAFETY ANALYSES

AE/SAEs will be reported as described in **Section 8.3** of this document. They will be classified by severity, relationship to study procedures, and expectedness. No other formal safety analyses will be conducted.

9.4.6 BASELINE DESCRIPTIVE STATISTICS

Baseline variables will be compared between groups to ensure randomization achieved balanced treatment assignments. This will include demographics (e.g. gender, age, race). All such variables are listed in **Section 8.1** of this document. Variables will be summarized using descriptive statistics (e.g. mean and SD, or frequency and proportion) and compared inferentially. Continuous variables will be compared using two-sample t-tests or Wilcoxon rank tests and discrete variables will be compared using chi-square tests for independence or Fisher's exact tests. Variables that are unbalanced between the groups, as identified with $p<0.1$ due to small sample size, will be included as covariates in adjusted analysis.

9.4.7 PLANNED INTERIM ANALYSES

N/A

9.4.8 SUB-GROUP ANALYSES

Both primary and secondary outcomes will be descriptively summarized based on gender. Our sample size is unlikely to allow for other meaningful sub-group analyses.

9.4.9 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.10 EXPLORATORY ANALYSES

Exploratory outcomes (e.g. treatment adherence) will be compared between groups with Student's t-test, Chi-square test, and Mann-Whitney-U test and mixed-model ANOVAs, as appropriate.

Planned sensitively analysis includes per-protocol analyses to accompany the main intent-to-treat results. Patients who choose to withdraw early and complete the early withdrawal assessment will analyzed separately from those who complete the intervention as planned. If the results from the per-protocol analysis demonstrate inconsistent findings from the main intent-to-treat analysis, the interpretation of any observed intervention effects will be qualified in all future presentation of the results. If necessary, we will conduct a sensitivity analysis in which we exclude participants that had protocol deviations (e.g. large delays between treatments) and those that report any injury, illness, or life events during the data collection period.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol:

- Study Participant Informed Consent Form
- Study Participant HIPAA Authorziation Form
- Recruitment Brochure
- Recruitment Flyer

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

At the end of the Pre-screening phone call, all eligible patients will be provided a copy of the consent and HIPAA forms via e-mail. Patients will also be provided an electronic copy of HealthPartners' statement of non-discrimination form. During the Consent phone call, research staff will review the consent and HIPAA forms with the patients. Patients will be allowed time to review all documents and ask any questions prior to signing electronically. Research staff will confirm that the patients understand the information in the forms and answer any questions. To obtain signature, the e-consent framework in REDCap will be utilized. This framework allows the patient initials, date, time to be stamped in the footer as extra identity as to who is completing the consent and HIPAA documents. Following the consent conversation, the staff member will sign and e-mail the consent and HIPAA electronically to the patient. The patient will electronically sign, certify, and submit the consent and HIPAA in REDCap. A fully executed PDF copy of the consent and HIPAA will be provided electronically to the patient for their records as well as saved via the auto-archiver function in REDCap. Research staff will complete this process during the Consent phone call, to ensure completion and assist if there are any questions.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, the funding agency, the IRB and regulatory authorities. If the study is prematurely terminated or suspended, the PIs will promptly inform study participants, the IRB, and the funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to participants
2. Demonstration of efficacy that would warrant stopping
3. Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
4. Data that are not sufficiently complete and/or evaluable
5. Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, IRB, or other relevant regulatory or oversight bodies.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

All study regulatory binders will be stored in a locked file cabinet within a secure office. The internal study monitor, representatives of the IRB, or regulatory agencies, may inspect all documents and records required to be maintained by the investigators, for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be password-protected and stored on REDCap, a secure web-based system. Only research study staff will have access to the data. Individual participants and their research data will be assigned a unique study identification number. While the study is active, subject identifiers (e.g. name, MRN) will be stored in REDCap, however, after the study is closed all subject identifiers will be removed.

The PIs will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be

thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

After the study is completed, any stored blood samples will be destroyed and the de-identified data will be stored in REDCap for use in future research. Permission to keep the de-identified data will be included in the informed consent.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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10.1.6 SAFETY OVERSIGHT

There is no Data Safety Monitoring Board for this study, as exercise has been previously shown to be safe and have minimal risks. During team meetings, the PI and study will regularly review a rolling report of adverse events and report them appropriately.

10.1.7 CLINICAL MONITORING

N/A, refer to next section.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Study staff will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process and 10% of the completed consent documents. Feedback will be provided to study staff to ensure proper consenting procedures are followed.

Source documents and the electronic data --- The majority of data will be directly entered into eCRFs in REDCap. To ensure accuracy for data not directly entered in REDCap, study staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review documented protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PIs will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research study staff under the supervision of the PIs. The PIs will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All data will be entered directly into eCRFs in REDCap. The data system includes password protection and internal quality checks by study staff to identify data that appear inconsistent, incomplete, or inaccurate.

10.1.9.2 STUDY RECORDS RETENTION

Investigator records will be retained in accordance with regulatory, organizational and sponsor or grantor requirements, but no less than 6 years following the completion of the research. All records will be maintained securely with limited access. Disposal of investigator records will be done in such a manner that no identifying information can be linked to research data.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol. The noncompliance may be either on the part of the participant, the investigators, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It will be the responsibility of the PIs to use continuous vigilance to identify, document, and report deviations as soon as possible, but no later than 10 working days after identification of the protocol deviation. Minor deviations, which do not impact participant safety, compromise the integrity of study data and/or affect the participant's willingness to participate in the research are to be reported at the time of continuing review. Protocol deviations will be addressed in study source documents and sent to the reviewing IRB per their policies. The PIs will be responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with HealthPartners Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

COVID-19: This study will align with the HealthPartners' policies regarding COVID-19 for in-person visits. This will be done to ensure the safety of patients and study staff. Appropriate COVID-19 screening procedures and personal protective equipment (PPE) will be utilized for all in person visits. Participants will be screened for COVID-19 on the day of each clinic visit. If a patient screens positive for COVID-19, study visits will be postponed for the appropriate amount of time per current guidance, and we will follow the current clinic site process for COVID-19 positive screens, as defined by the medical group.

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANOVA	Analysis of Variance
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Forms
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability
ICH	International Council on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
OHRP	Office for Human Research Protections
PI	Principal Investigator
QOL	Quality of Life
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SCI	Spinal Cord Injury
UP	Unanticipated Problem

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	03/02/22	Response to RRC & IRB Review	
3.0	06/30/22	Expand window for pre-tx visit	Scheduling conflicts
4.0	08/03/22	Update blood amount for accuracy	Due to protocol deviation for amount of blood that was drawn, wanted to make it clear to patients.
5.0	08/14/23	Increase enrollment to 25	Replace participants who withdrew prior to intervention

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