RECOVER-ENERGIZE: A Platform Protocol for Evaluation of Interventions for Exercise Intolerance in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference 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)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials should have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the single Institutional Review Board (sIRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study. In addition, all changes to the consent form 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. Changes to the protocol will be approved by the Data and Safety Monitoring Board (DSMB) and NIH.

1.1 SYNOPSIS

Title:	RECOVER-ENERGIZE: A Platform Protocol for Evaluation of Interventions for Exercise Intolerance in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
Study Description:	This is a platform protocol designed to be flexible so that it is suitable for a range of interventions and settings within diverse health care systems and community settings with incorporation into clinical COVID-19 management programs and treatment plans if results achieve key study outcomes. This protocol is a prospective, multi-center, multi-arm, randomized, controlled platform trial evaluating interventions to address and improve exercise intolerance and post-exertional malaise (PEM) as manifestations of Post-Acute Sequelae of SARS-CoV-2 Infection (PASC). The focus of this protocol is to assess interventions that can improve exercise capacity, daily activities tolerance, and quality of life in patients with PASC.
Purpose and Objectives:	The purpose of this platform study is to address PASC-related exercise activity intolerance and PEM by evaluating interventions in a randomized, multi-center trial. The objectives, outcome measures, and endpoints for each intervention in the study are provided in the Appendices.
Study Population:	Please refer to each Appendix for details regarding applicable study population and sample size. Overall enrollment depends upon the specific intervention, the ability to pool control groups for analysis, and sample size based on the intervention. The goal is to have a diverse population representative of those who develop PASC, including underserved communities and racial/ethnic populations frequently underrepresented in clinical research.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Participants are recruited from various sources including, but not limited to, acute COVID-19 trials, RECOVER initiatives including the longitudinal cohort, and other sites and research communities. The number of sites depends upon the intervention, the number of sites with resources to participate, the number of PASC patients at each site, site experience and expertise in clinical trials, ability to enroll the requisite number of participants, ability to enroll a diverse population of participants, and ability to rapidly enroll participants. It is possible that up to 100 sites in the US may participate.
Description of Study Intervention:	Each study Appendix describes a different intervention.
Participant Duration:	Participation ends after the End of Study phone or video call, which occurs 6 months after Baseline for all Appendices. Participants may be contacted

	after the End of Study to determine interest in taking part in additional research.

1.2 SCHEMA

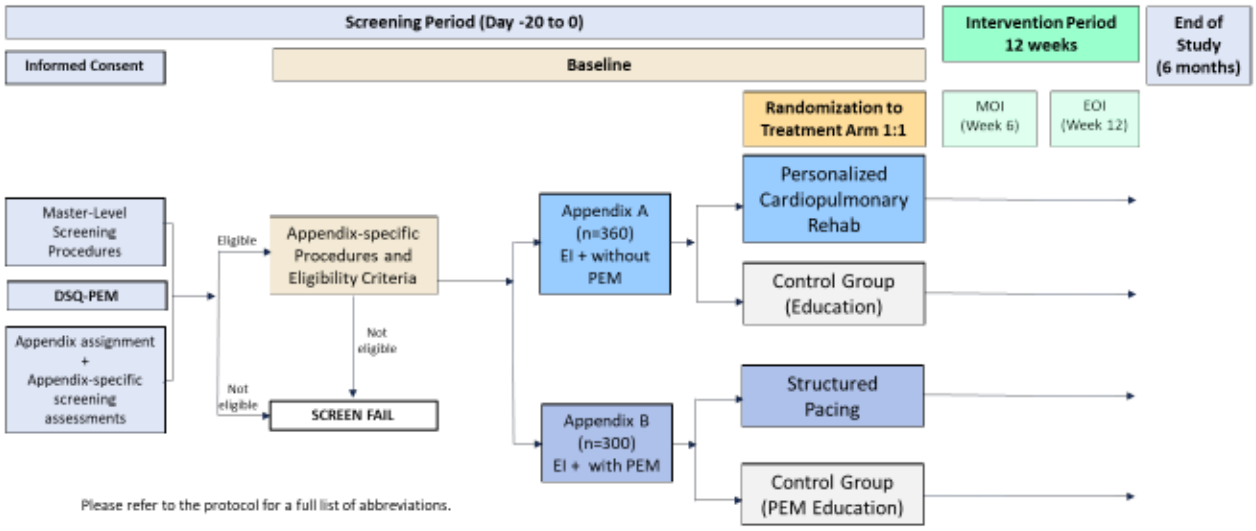


Figure 1. Overall Study Schema

2 INTRODUCTION

2.1 STUDY RATIONALE

Post-Acute Sequelae of SARS-CoV-2 infection (PASC), also known as Long COVID or Post COVID, is a chronic condition present in up to 80% of SARS-CoV-2-infected, hospitalized patients and 40% to 70% of non-hospitalized patients with COVID-19.[1-4] The personal impact of these long-term symptoms from SARS-CoV-2 infection can be debilitating, and the number of patients with PASC is growing. Given the overall number of people infected with SARS-CoV-2, its emerging variants, and the continued impact on public health, an urgent and unmet clinical need exists to better understand the pathophysiology of PASC and to develop targeted therapeutics to resolve the disease more rapidly and restore patients' health. The focus of this protocol is to assess the impact of targeted interventions on the PASC-related symptoms of exercise intolerance and PEM. If successful, this trial will provide tools that providers can rapidly use to combat such symptoms in patients diagnosed with PASC.

Individualized, supervised, cardiopulmonary rehabilitation is considered a safe and effective intervention for most cardiac and pulmonary conditions. It has also been effectively utilized in previously hospitalized and non-hospitalized patients with severe COVID-19 to gradually improve function. While this traditional approach appears helpful in some situations, the exercise intolerance experienced by many with PASC may require a different approach, especially when attempts to exercise result in PEM. This apparently common manifestation of PASC has been compared to the activity intolerance and PEM known to occur in another post-viral syndrome, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The pathophysiology is not well understood, but some type of disturbance of energy metabolism at the cellular level is suspected. There are no major studies that have examined

the efficacy of either carefully supervised, individualized physical conditioning, taking PEM and other illness symptoms into account, or the effectiveness of activity pacing in either Long COVID or ME/CFS. RECOVER aims to carefully investigate these questions in the Long COVID population.

As data on exercise intolerance and PEM related to PASC emerges, different interventions may be explored including pharmaceutical or other interventions. The platform design provides consistency in study population and outcomes while allowing additional interventions to be tested and quickly operationalized.

2.2 BACKGROUND

In 2019, a novel coronavirus disease (COVID-19) emerged in Wuhan, China. A month later, the Chinese Center for Disease Control and Prevention identified a new beta-coronavirus (SARS coronavirus 2, or SARS-CoV-2) as the etiological agent.[5] The clinical manifestations of COVID-19 range from asymptomatic infection or mild, transient symptoms to severe viral pneumonia with respiratory failure, and other serious, life-threatening complications.

COVID-19 has led to the death of more than 6 million people worldwide; however, this disease has affected even more lives through often-debilitating symptoms lingering long after acute SARS-CoV-2 infection. Post-Acute Sequelae of SARS-CoV-2 infection, also known as PASC, is a chronic condition present in up to 80% of infected, hospitalized patients and 40% to 70% of non-hospitalized patients.[1-4,6] It affects nearly every organ system, with more than 200 individual symptoms, ranging from new-onset anxiety, depression, and cognitive difficulties to shortness of breath, dizziness, and arrhythmias.[6] PASC can occur regardless of severity of acute COVID-19 disease, and it impacts across socioeconomic, racial and ethnic, and age strata. These prolonged symptoms open the door for substantial short- and long-term individual and societal costs, including inability to work and healthcare costs. Prolonged symptoms have kept individuals out of work, which has exacerbated poverty in the underserved, historically minoritized populations, worsening a decades-long mental health crisis. Considering these costs, identification of safe and effective methods to prevent and treat PASC and PASC-related symptoms represents an urgent, unmet public health need.

To address this need, the NIH has launched the Researching COVID to Enhance Recovery (RECOVER) initiative across the nation to better understand the disease. The RECOVER initiative brings together patients, caregivers, clinicians, community leaders, and scientists from across the nation to understand, prevent, and treat PASC. The RECOVER Consortium represents and supports researchers who are leading studies on PASC at more than 200 sites around the country. These studies have a diverse group of participants, including adults, pregnant people, and children. Data from the RECOVER initiative, as well as existing literature, have highlighted three predominant symptom clusters – exercise intolerance, cognitive dysfunction, and autonomic dysfunction – that are frequently reported and of substantial importance to patients. In addition, data have identified substantial heterogeneity in symptomology and presentation, even among those within a specific symptom cluster, and a lack of consistent concordance between objective findings and reported symptoms.[7,8]

Emerging research is also beginning to identify risk factors for PASC. Women are disproportionately impacted by PASC relative to men at an approximately 3:1 ratio, with this sex difference appearing to fade in older individuals 60 to 70 years of age.[9-11] Longitudinal, multi-omic profiling of COVID patients

has revealed several risk factors for PASC at the time of diagnosis, including type 2 diabetes, SARS-CoV-2 viremia, Epstein-Barr Virus viremia, and autoantibodies.[12]

Exercise intolerance, a common symptom of PASC, is described as the limitation of the capacity to do physical activity due to the presence of symptoms such as dyspnea and fatigue during exercise. Exercise intolerance can have long-term effects on the health and quality of life of patients with PASC. As such, it is important to address and resolve exercise intolerance in PASC patients. Another common symptom of PASC is post-exertional malaise (PEM), the worsening of both symptoms and function following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks. Patients with PEM experience the inability to exercise or to do routine activities of daily living following physical, mental, cognitive, or emotional activity.[13] Additionally, patients with PEM report cognitive dysfunction, changes in mood, and sleep disturbance following exertion.[14] These symptoms are similar to those reported for patients diagnosed with ME/ME/CFS.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks of this study include those associated with the specific study intervention (refer to Appendices for details), outcome measures, blood draws, nasal swabs, performance measures, and loss of confidentiality.

Risks associated with blood draws include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although uncommon.

Risks associated with nasal swabs include mild irritation, insignificant local pain, and minor bleeding. Possible side effects of the electrocardiogram (ECG) are skin irritation, itching and redness from the ECG electrode pads.

Participation in this study may induce or worsen PEM in those prone to PEM. PEM may be triggered or worsened by travel to appointments, physical and/or cognitive exertion, or active participation in the interventions.

Risks associated with collection of stool samples include contamination of skin from the collection container.

There is also a risk of loss of confidentiality. However, coding all participant data with a unique identification number will minimize risk to loss of participant confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

It is possible that participants may benefit from improvement in symptoms of exercise intolerance, PEM, and other PASC symptoms, as well as an overall improvement in quality of life. However, it is not known whether these potential benefits outweigh the risks described above in Section 2.3.1.

Society in general and future patients infected with SARS-CoV-2 will benefit from the study's results, which will provide a better understanding of the benefits/risks of treatments for PASC-related exercise

intolerance and PEM. Participants are able to keep activity trackers (Fitbit®) for personal health monitoring after the study ends.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential benefits are considered to outweigh potential risks. Post-acute Sequelae of SARS-CoV-2 infection (PASC) are a significant health issue and can have consequences that impact quality of life. These consequences are extremely important for the individual and also impact society at large. The risks from the study interventions as designed are low and the potential benefit in improvements in exercise tolerance and quality of life are high. Potential risks are minimized by careful monitoring (please refer to Appendices for intervention-specific details).

3 OBJECTIVES AND ENDPOINTS

The objectives, outcome measures, and endpoints for each intervention in the study are provided in the Appendices. Further details on outcome measures and endpoints are provided in the Statistical Analysis Plan (SAP).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a platform protocol designed to be flexible so that it is suitable for a range of interventions and settings within health care systems and community settings with eventual incorporation into clinical COVID-19 programs and treatment plans if results achieve key study outcomes. The purpose of this platform study is to address PASC-related exercise activity intolerance and post-exertional malaise by evaluating interventions in a randomized, multi-center trials. The platform protocol enrolls participants who meet study eligibility criteria. Each Appendix describes a study intervention that is designed to meet the protocol objectives. Eligible patients are assigned to one of the study intervention Appendices that are actively enrolling. Study intervention Appendices may be added or removed according to adaptive design and/or emerging evidence. Once assigned to an Appendix, participants are randomized to either the study intervention arm or a control arm.

This platform protocol is a prospective, multi-center, multi-arm, randomized, controlled trial evaluating treatment of PASC-related exercise and activity intolerance. Various interventions are being studied; refer to the protocol Appendices for further information on each study intervention.

This protocol leverages common data elements (CDEs) already collected as part of the RECOVER initiative, as well as assesses overall global health status and symptoms. Organ-specific assessments, including patient-reported outcomes (PROs) of symptoms, functional status and objective assessments are also being done. Follow-up is a combination of in-person visits when necessary to obtain performance measures and remote visits to minimize participant burden.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Each study intervention under this platform protocol follows a randomized trial designed to compare the study intervention to control. As data on exercise intolerance related to PASC emerges, other interventions, including pharmaceuticals, may be explored. The platform design provides consistency in study population and outcomes while allowing additional interventions to be quickly tested and operationalized.

4.3 JUSTIFICATION FOR DOSE

Not applicable for this platform protocol.

4.4 END OF STUDY DEFINITION

The End of Study occurs when all participants have completed their End of Study follow-up.

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:

1. ≥ 18 years of age at the time of enrollment
2. Previous suspected, probable, or confirmed SARS-CoV-2 infection, as defined by the Pan American Health Organization[15ϕ]

   ϕ Suspected or probable SARS-CoV-2 infection will only be allowed if it occurred before May 1, 2021, and will be limited to no more than 20% of the study population. Otherwise, confirmed cases are required. Refer to the Manual of Procedures (MOP) for details.

   Suspected case of SARS-CoV-2 infection - Three options, A through C:

   A. *A person who meets the clinical OR epidemiological criteria. Clinical criteria: Acute onset of fever AND cough (influenza-like illness) OR Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general, weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, nausea, diarrhea, anorexia. Epidemiological criteria: Contact of a probable or confirmed case or linked to a COVID-19 cluster; or*
   B. *Acute respiratory infection with history of fever or measured fever of ≥ 38°C; and cough; with onset within the last 10 days; and who requires hospitalization; or*
   C. *With no clinical signs or symptoms, NOR meeting epidemiologic criteria with a positive professional use or self-test SARS-CoV-2 Antigen-Rapid Diagnostic Test.*

   Probable case of SARS-CoV-2 infection:

   A. *A patient who meets clinical criteria above AND is a contact of a probable or confirmed case or is linked to a COVID-19 cluster.*

   Confirmed case of SARS-CoV-2 infection - Two options, A through B:

   A. *A person with a positive nucleic acid amplification test, regardless of clinical criteria OR epidemiological criteria; or*
   B. *Meeting clinical criteria AND/OR epidemiological criteria (See suspected case A above for criteria). With a positive professional use or self-test SARS-CoV-2 Antigen-Rapid Diagnostic Test.*

3. Self-reported limitation to physical activity due to the presence of symptoms such as fatigue, shortness of breath, and/or PEM following a SARS-CoV-2 infection, that has persisted for at least 12 weeks and is present at the time of consent.
4. Willing, able, and agree to provide informed consent, complete questionnaires and outcome assessments, and participate in the study, including assigned intervention or control and study visits whether remote, hybrid, or in-person.

5.2 EXCLUSION CRITERIA

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

1. Known active acute SARS-CoV-2 infection ≤ 4 weeks prior to the consent.
2. Known prior diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), not related to SARS-CoV-2 infection.
3. Current or recent use (within the last 14 days) of a formal program utilizing one or more of the current study intervention(s) or similar intervention(s) to treat the underlying condition, unless a washout period is permitted per Appendices.
4. Participation in another interventional clinical trial.[1]
5. Any condition that would make the participant, in the opinion of the investigator, unsuitable for the study.

5.3 SCREEN FAILURES

Screen failures are defined as individuals who consent to participate in the clinical trial after reviewing and signing the informed consent, but who are not subsequently assigned to a study arm for randomization or not entered in the study. If a prospective participant signs informed consent, they undergo initial study screening. Initial screening determines which arm (i.e., Appendix) of the study is most appropriate for the participant. The informed consent provides general details of all study arm interventions, procedures, and risks; specific details about study schedules are provided to participants in supplemental materials. There may be additional screening assessments once a participant is assigned to a study arm. If a participant ultimately screen fails for a given arm, they may be eligible for another study arm (e.g., participants who do not meet eligibility for Appendix A may be eligible for Appendix B) or may be eligible for re-screening at a later date.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, eligibility criteria assessment and screen failure details.

5.4 STUDY DEFINITION OF ENROLLMENT

For this study, enrollment is defined as signing the study informed consent and being randomized.

[1] Please note that, following another interventional trial's end of intervention visit, participants must wait 90 days before enrolling on RECOVER-ENERGIZE.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The RECOVER Clinical Trial Data Coordinating Center (CT-DCC) uses an integrated strategy of coordinating with community organizations, the public, and clinical trial sites to identify and retain study participants. To ensure a diverse population is enrolled, strategies from prior successful initiatives are refined and utilized. The study team develops a comprehensive communication strategy involving print and social media and leverages existing organizational structures where possible to educate the public on concerns about PASC and opportunities for clinical trial participation. Interested members of the public will be provided with information to contact a local site for potential participation.

Participants can be recruited and identified through participating site outreach. Associated with prescreening activities (e.g., review of existing registries and electronic records), site investigators, or their designee(s), can contact potentially eligible participants to introduce the study and discuss study participation.

Participants may be recruited from other ongoing COVID-19 studies if they opt-in to being contacted about future research opportunities.

Patient advocates that represent a diverse PASC community are engaged in the study at every step. Patient advocates serve as consultants to inform study design, protocol development, and recruitment and retention strategies.

During active study, study sites should maintain close contact with study participants.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

See Appendices.

6.1.2 STUDY INTERVENTION ADMINISTRATION

See Appendices.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

If applicable per Appendix, receipt and use of materials is handled, tracked by the sites when applicable, and stored in safe and secure locations to which only the investigator and designated personnel have access.

Adherence to study intervention will be recorded by the participants and tracked by the sites. Refer to the MOP for details.

If applicable per Appendix, participants may be asked to bring any unused materials with them to their End of Intervention Study Visit.

See Appendices for further details.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

See Appendices.

6.2.3 PRODUCT STORAGE AND STABILITY

See Appendices.

6.2.4 PREPARATION

See Appendices.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Since administration of each study intervention (i.e., Appendix) in the platform may differ, the controls may also differ per platform. Blinding is applied, as possible, and detailed in relevant Appendices.

Each participant is assigned to the study Appendix for which they are eligible, after applying any Appendix-specific eligibility criteria. Within each Appendix, unless specified otherwise in the Appendix, each participant is assigned to either the active study intervention arm or control arm in a 1:1 ratio.

6.3.1 BLINDING

Please refer to the Appendices for blinding information for each study intervention and to the MOP for further details.

6.4 STUDY INTERVENTION ADHERENCE

Participants are notified of the importance of completing the full course of intervention, and adherence to the intervention is assessed wherever possible. Refer to the MOP for details.

6.5 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are relevant concomitant prescription medications, over-the-counter medications, and supplements.

Baseline concomitant medications include all concomitant therapies taken by the participant within 14 days of informed consent.

7 PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION FROM STUDY INTERVENTION

Discontinuation from study intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol.

An investigator may discontinue a participant from a study intervention at their discretion, for any reason including, but not limited to, one of the following:

- Significant study intervention non-compliance
- If any clinical abnormality, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study intervention would not be in the best interest of the participant
- Worsening symptoms of PEM (refer to Sections 12.9 and 13.6 for appendix-specific details)

The reason for participant discontinuation from study intervention will be recorded on the CRF.

Participants who are discontinued from the study intervention, but who are not withdrawn from the study, should continue to be followed for all study assessments.

7.2 PARTICIPANT WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time. The study team should attempt to determine a reason for withdrawal; however, participants are not obligated to provide a reason for withdrawal. If obtained, the reason for withdrawal should be recorded on the CRF. No further study procedures are performed and no further data is collected from the participant following study withdrawal. All of the data collected up until the time of withdrawal is maintained in the study database and used as the participant's data are evaluable for analysis. Please also refer to appendices for further details (Sections 12.9 and 13.6).

7.3 LOST TO FOLLOW-UP

Participants are considered lost to follow-up if they fail to return for any scheduled visit *and* if they are unable to be contacted after multiple attempts and methods by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site should attempt to contact the participant on multiple occasions and by multiple methods (e.g., phone, text, email, next of kin/secondary contacts provided by the participant) to reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule if needed. Study staff should also ascertain if the participant wishes to continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee should make every effort to regain contact with the participant or next of kin/secondary contacts (where possible, telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, after exhausting all methods, the participant is considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 STUDY HALTING RULES

There are no overall study halting rules. Please refer to Section 11.1.6 for a description of monitoring by the DSMB.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCHEDULE OF PROCEDURES

See Appendices for Schedule of Events tables.

8.2 SCREENING (DAY -20 TO 0)

Information about the study is presented to potential participants and questions are asked to determine potential eligibility. The informed consent must be signed by the prospective participant before any overall study screening procedures take place. Screening procedures may be done over one or two calendar days based on patient preference and lack of patient fatigue from the assessments.

After signing the informed consent, the following procedures are performed at study screening to determine eligibility for the study:

- Demographics
- Eligibility criteria assessment
- Medical History, including SARS-CoV-2 test result date (if available), SARS-CoV-2 vaccination status and dates, other acute respiratory illnesses/infections in the past 3 months, signs and symptoms, and treatment (including hospitalization, Intensive Care Unit [ICU] status, supplemental O_2 status), and PASC history (symptoms and duration)
- Height and weight
- Clinical blood collection for the following evaluation:
  - Complete blood count (Refer to Section 8.10.5)
- mDSQ-PEM, completed at the beginning of the visit (3-month lookback period)
- Activity tracker, distributed for participants to wear during study

If eligible after initial screening procedures, the mDSQ-PEM from initial screening also determines which arm (i.e., Appendix) of the study is appropriate for the participant. Please refer to the Appendices for additional screening tests and procedures for each study Appendix.

8.3 BASELINE PERIOD (DAY -13 TO 0)

Baseline assessments occur from Day -13 to Day 0. During the Baseline Period for each Appendix, participants wear an activity tracker (e.g., Fitbit®) for ≥ 7 days prior to the Baseline Visit to establish baseline metrics.

Please refer to Appendices for details about the wash-in period for each study intervention.

8.4 INTERVENTION PERIOD (DAY 1 TO END OF INTERVENTION [EOI])

The Intervention Period occurs from Day 1 until the EOI with Day 1 being the first day of either intervention or control (i.e., Day 0 is the day the participant is randomized). Participants in the intervention arm have up to 30 days from randomization to start Day 1 of the intervention. Interventions are defined in the Appendices. The EOI is defined per Appendix and occurs at the End of Study intervention administration. Refer to Appendices for specific outcome assessments during the Intervention Period.

8.5 INTERVENTION PERIOD MIDPOINT STUDY VISIT (WEEK 6)

There is one in-person study visit during the Intervention Period, unless otherwise specified in the Appendices. This visit collects interim outcome measures and occurs approximately halfway through the Intervention Period (± 7 days). For example, if the Appendix defines an Intervention Period of 12 weeks, the Intervention Period Study Visit occurs at 6 weeks. Please refer to Appendices for specific outcome assessments during the Intervention Period midpoint.

8.6 END OF INTERVENTION STUDY VISIT (WEEK 12)

The EOI Study Visit occurs at Week 12 from start of intervention, after the participant has completed the study intervention administration period (+ 7 days). Please refer to Appendices for specific assessments at the EOI visit.

8.7 EARLY DISCONTINUATION STUDY VISIT

If a participant discontinues the study early (i.e., no longer wishes to participate), the participant should be asked to complete an Early Discontinuation Study Visit (refer to Appendices for details).

8.8 END OF STUDY

The EOS follow-up is applicable to all Appendices and occurs remotely via phone or video call 183 days (± 14 days) after randomization. Please refer to Appendices for specific assessments at this visit.

8.9 UNSCHEDULED VISITS

Unscheduled visits not directly described in the protocol may be conducted at the site investigator's discretion. Participants may be asked to return to the study site for an unscheduled visit to complete an activity required for the study. Please refer to the MOP for details.

8.10 STUDY OUTCOME ASSESSMENTS

Outcome assessments occur according to the Schedule of Procedures in each Appendix. Procedures should preferably be completed by research study coordinators. However, outcome assessments performed as part of the RECOVER observational study may be used as intervention study outcomes. Training to standardize these assessments will be provided to participating sites by the RECOVER CT-DCC and protocol study teams. Please refer to the MOP for more details.

8.10.1 PATIENT-REPORTED OUTCOMES (PROS)

The following PROs may be utilized in Appendices for this platform study. Please refer to the outcome assessments in each Appendix.

8.10.1.1 PROMIS-29+2

Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29) v.2.1 global health scale. PROMIS measures were developed as part of the "Roadmap for Medical Research" created by the NIH in 2002. These assessments are valid, generalizable items designed to standardize clinical research across NIH-funded research dealing. Multiple PROMIS scales have been validated across many clinical populations.[16] The PROMIS-29 consists of 29 items that assess general domains of health and functioning, including overall physical health, mental health, social health, pain, fatigue, and overall perceived quality of life. The PROMIS global health scale has been correlated against the EuroQol EQ-5D.[17] Additionally, PROMIS scales have been used with PASC patients.[18]

The PROMIS-29+2 is used to calculate a preference score (PROPr) by the addition of two Cognitive Function Ability items. Preference-based scores provide an overall summary of health-related quality of life on a common metric. Preference-based scores summarize multiple domains on a metric ranging from 0 (as bad as dead) to 1 (perfect or ideal health). Scores can be used in comparisons across groups and for cost-utility analyses.[19]

8.10.1.2 PROMIS SF-COGNITIVE FUNCTION 8A

The PROMIS Short Form v.2.0 – Cognitive Function 8a (PROMIS-Cog) is the PROMIS Short Form to assess cognitive function and is a self-report, 8-item questionnaire targeting cognitive function in the past seven days.[16] It is a reliable measure with normative data.[20]

8.10.1.3 PROMIS SF-PHYSICAL FUNCTION 8B

The PROMIS Short Form v2.0 – Physical Function 8b (PROMIS-PF) consists of 8 items. The PROMIS Physical Function instruments measure self-reported capability rather than actual performance of

physical activities. The form assesses current function and includes the functioning of the participant's upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands. The questionnaire is universal rather than disease-specific and appropriate for the adult general population and adults with chronic health conditions.[21]

8.10.1.4 EQ-5D-5L

The EQ-5D is a standardized measure of health status that was developed by the EuroQoL Group to provide a simple descriptive profile and single index value for health status that is undemanding and quick to complete.[22] The EQ-5D-5L includes five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 levels (no problems, slight, moderate, severe, and extreme problems). It also includes an EQ Visual Analogue Scale (EQ-VAS).

8.10.1.5 MMRC DYSPNEA SCALE

The Modified Medical Research Council Dyspnea Scale (mMRC) is a measure of shortness of breath. The symptom severity scale has a grade range of 0 (not breathless except on strenuous exercise) to 4 (too breathless to leave the house or breathless when dressing/undressing).[23,24]

8.10.1.6 PASC SYMPTOM QUESTIONNAIRE

Participants are asked to complete a 33-question survey that asks about the presence of a wide variety of PASC symptoms. This questionnaire was developed by the RECOVER initiative and is used in the RECOVER observational study (NCT05172024) and adapted in other RECOVER treatment studies. The PASC Symptom Questionnaire is a measure for self-reporting multiple PASC-related symptoms across multiple systems.

8.10.1.7 MODIFIED DEPAUL SYMPTOM QUESTIONNAIRE – POST-EXERTIONAL MALAISE

With permission from the authors, the DePaul Symptom Questionnaire – Post-Exertional Malaise (DSQ-PEM) PRO has been adapted by using different lookback durations to assess PEM in this study (mDSQ-PEM).[25] The published scale assesses symptom frequency and severity over a 6-month look back period. For the purposes of this study, the lookback period has been modified as described in the Appendices and the MOP (e.g., over the past 3 months, the past 7 days, or since your last visit). The DSQ-PEM was previously validated in patients with ME/CFS. Frequency is rated on a 5-point Likert scale: 0 = none of the time, 1 = a little of the time, 2 = about half the time, 3 = most of the time, and 4 = all of the time. Severity is rated on a 5-point Likert scale: 0 = symptom not present, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

8.10.1.8 MODIFIED ORTHOSTATIC HYPOTENSION QUESTIONNAIRE

The Orthostatic Hypotension Questionnaire (OHQ) is a measure of orthostatic intolerance, which has been the primary presentation of patients with PASC-related autonomic dysfunction.[26] The modified OHQ (mOHQ) measure used in this study includes a total of ten items related to daily activities and symptoms. Prior data in patients with PASC suggests that this measure well-discriminates those with symptoms compared to healthy controls.[27]

8.10.1.9 HOURS OF UPRIGHT ACTIVITY

Hours of Upright Activity (HUA) is defined as hours with feet on the ground (i.e., activities such as walking, standing, or sitting with feet on the floor, as long as feet are not elevated) captured per 24-hour period.[27] It is a self-reported estimate by the participant that will collected by a study team member. Please refer to the MOP for details.

8.10.1.10 PATIENT GLOBAL IMPRESSION OF CHANGE

The Patient Global Impression of Change (PGIC) from the National Institute of Mental Health (NIMH) is a single-item measure of global improvement related to a treatment that uses a 7-point scale ranging from 1=very much improved to 7=very much worse.[28,29] The anchor point for this public domain scale is "since the start of the study."

8.10.2 INCREMENTAL SHUTTLE WALK TEST (ISWT)

The ISWT evaluates peak exercise capacity and was originally intended for those with chronic obstructive pulmonary disease (COPD).[30-33] It is conducted along a 10-meter course with walking speed increasing every minute until the patient is too breathless or fatigued to continue or cannot maintain speed.

8.10.3 ENDURANCE SHUTTLE WALK TEST (ESWT)

The ESWT consists of timed walking on a 10m course.[34] The result is expressed as total walking time after an initial 2-minute warm-up. In order to determine walking speed, the baseline ESWT will be performed in combination with the ISWT.[35] Walking speed for the ISWT is increased every minute until the participant is too breathless or fatigued to continue walking at the required speed. The ESWT is then performed as 85% of the maximum walking speed achieved on the ISWT.[34] The ESWT is completed twice; the initial ESWT occurs at least 30 minutes prior to the second ESWT. The maximum of the two ESWTs is used for statistical analyses. The ESWT is an outcome measure of exercise capacity for this platform protocol.

8.10.4 CARDIOPULMONARY EXERCISE TESTING (SELECT SITES)

Cardiopulmonary Exercise Testing (CPET) (exploratory performance measure) is completed at select sites to assess the cause and mechanism of exercise limitation and response to intervention. The CPET is an exercise test that measures exercise abilities. The test involves a 2 to 3-minute warm-up, followed by 8 to 12 minutes of progressively harder work on a treadmill or stationary cycle. The goal is to exercise until the participant is no longer able to continue. The final outcome for this measure is the maximum rate of oxygen consumption (VO_2 max).

8.10.5 CLINICAL LABS

A complete blood count is completed as a local laboratory assessment at screening. If a participant has this laboratory assessment available within 3 months of study enrollment, it does not need to be repeated as part of the study.

At Baseline and at EOI, blood is collected from participants and sent to a central lab for biomarkers assessment (refer to Section 8.11). Any additional clinical labs that are required are defined per Appendix, as needed.

8.10.6 ELECTROCARDIOGRAM

A screening electrocardiogram (ECG) may be done as part of screening for a study Appendix due to the intervention (please refer to Appendices). If a screening ECG is performed, it also serves as a pre-intervention baseline, if needed.

8.10.7 RESEARCH BLOOD AND STOOL SAMPLES

Research blood and stool samples are collected for assessments of biomarkers and stored in the Biorepository at timepoints provided in the Schedule of Procedures tables in the Appendices. Refer to Section 8.11 and the MOP for further details regarding specimen collection, preparation, shipment, and storage in the Biorepository.

8.10.8 ACTIVITY TRACKER

The activity tracker (e.g., Fitbit®) captures participants' activity metrics, like step count and minutes spent at different activity levels. Participants are given their activity tracker after providing informed consent at Screening. Participants are asked to wear the tracker for ≥ 7 days before the start of the Baseline Visit for the collection of baseline metrics. Participants are encouraged to wear the tracker throughout the study. Seven days prior to study outcome visits and before the EOS visit, the study team checks in with the participant to make sure the activity tracker is being worn. Please refer to Appendices and the MOP for additional details.

8.11 BIOREPOSITORY FOR FUTURE RESEARCH

The RECOVER Biorepository is designed to collect and store blood plasma, serum samples, and stool samples for future research related to the various studies of the RECOVER program. Such research might include developing diagnostic and/or prognostic tests, improving our understanding of the underlying pathophysiology of PASC, and developing new therapeutic targets. Samples from biorepositories have proven to be enormously important in the last 20 years, as information on the components of blood has expanded rapidly. Important insights have been gained from biorepository samples from clinical trials and the stored samples from the RECOVER program should prove equally productive and important. This biorepository is conducted under the coordination of the Duke Clinical Research Institute (DCRI), which serves as the CT-DCC for all RECOVER clinical trials.

The existence of the biorepository provides the opportunity to devise new hypotheses, since blood and stool collection techniques are standardized across all approved RECOVER protocols thereby allowing cross-protocol sample comparisons if scientifically justified.

Within this framework, the design of the biorepository is to collect additional research blood and prepare EDTA plasma samples and serum samples to be stored in the Biorepository for future, as yet unspecified, analyses and studies. A serologic test of COVID-19 infection is done as part of the

biorepository for all participants. At each blood collection time point, 80 mL of blood is collected to process local labs (as applicable, per Appendix) and to prepare the biorepository sample aliquots for storage at -80 °C. These samples are stored at the biorepository in a lab for up to 7 years. Refer to the MOP for biorepository sample collection instructions.

9 SAFETY ASSESSMENTS AND REPORTING

9.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1.1 DEFINITION OF ADVERSE EVENTS (AES) AND SERIOUS ADVERSE EVENTS (SAES)

An AE is any untoward medical occurrence, whether or not considered intervention-related, which occurs during the conduct of a clinical trial. An AE can therefore be a change in clinical status, routine labs, ECGs, etc. that is considered clinically significant by the study investigator.

A serious adverse event (SAE), as determined by the investigator or the sponsor, is an AE that results in any of the following serious outcomes:

- Death
- Life-threatening ("life-threatening" means that the study participant was, in the opinion of the investigator or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization
- Congenital abnormality or birth defect
- Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline does not meet the definition of an SAE. Hospitalization is defined as a stay in the hospital exceeding 24 hours.

9.1.2 COLLECTION PERIOD FOR SAFETY EVENT INFORMATION

Adverse event (AE) collection is limited as part of this trial to SAEs (see Section 9.1.1 and Appendices) and Events of Special Interest (ESIs) (see Sections 9.1.4 and Appendices). Collection of SAEs and ESIs occur at the pre-specified study visits, but all participants are instructed to self-report concerns by communicating with their site. Additionally, SAEs and ESIs are extracted by site personnel from the participant's medical record if the participant seeks medical care or if hospitalization occurs.

Medical occurrences that begin before the first invasive study procedure (blood collection), but after obtaining informed consent, are not considered a safety event. The medical occurrence or condition is captured on the medical history electronic Case Report Form (eCRF).

Non-serious AEs may be reported by the participant but are not recorded in the study database or further assessed by the site or study personnel. Any non-serious AE that results in study intervention discontinuation is identified as the reason for study intervention discontinuation in the study database.

Any AEs that are also classified as symptoms associated with PASC and collected during the study are not collected as safety events in the study database or further assessed by the site or study personnel, because they are collected as part of the PASC symptom dataset.

Serious Adverse Events (SAEs) and ESIs are collected from the first invasive study procedure (blood collection or nasal swab) to EOS and are followed until resolution, stabilization, or the event is otherwise explained. If additional information becomes available, follow-up information is recorded using the same reporting process as the initial event.

9.1.3 REPORTING AND MONITORING OF SAES

All SAEs should be assessed for reportability based upon standard criteria (i.e., considered serious, unanticipated, and related or possibly related to the research). The determination of adverse event severity rests on medical judgement of a medically-qualified investigator. Serious AEs are standardly defined as incapacitating with inability to do usual activities or significantly affecting clinical status and warranting intervention.

An unexpected SAE is defined as any SAE for which the specificity or severity is not consistent with the study interventions' package inserts, if applicable, and/or the risks identified within the protocol (see Appendices for risks of each study intervention).

The relationship of an SAE to the study intervention should be assessed by the investigator or their designee and should be based on both temporal relationship and clinical judgement. The degree of certainty about causality will be graded using the categories below.

- Related – The SAE is known to occur with the study intervention, a reasonable possibility exists that the study intervention caused the SAE, or a temporal relationship subsists between the study intervention and event. Reasonable possibility means that evidence suggests a causal relationship between the study intervention and the SAE.
- Not Related – No reasonable possibility exists that the administration of the study intervention caused the event, no temporal relationship subsists between the study intervention and event onset, or an alternate etiology has been established.

Final attribution or relatedness of an SAE is assessed by the site Principal Investigators (PIs). Any SAEs deemed related by site PIs should be reported to the Study Chairs (please refer to the MOP for reporting procedures and timelines).

For reportable events, the following guidelines are used to describe severity grades, described in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published November 27, 2017.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 Moderate: minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living
- Grade 3 Severe or medically significant, but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4 Life-threatening consequences: urgent intervention indicated
- Grade 5 Death related to AE.

9.1.4 EVENTS OF SPECIAL INTEREST (ESIS)

Each study intervention may have a unique list of additional ESIs that are also collected and documented, as indicated above. Refer to the relevant Appendix (Sections 12.11 and 13.11).

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

Hypotheses are addressed in Appendices.

10.2 SAMPLE SIZE DETERMINATION

Please refer to separate Appendices for sample size calculations.

10.3 POPULATIONS FOR ANALYSES

Any primary efficacy and safety analyses are based on a modified intention-to-treat (mITT) population, consisting of all randomized participants who begin either study intervention or control. Participants are analyzed according to their randomly assigned treatment group. Please refer to Appendices for details.

10.4 STATISTICAL ANALYSES

Please refer to Appendices and the SAP for details.

10.4.1 OVERALL STATISTICAL DESIGN

Please refer to Appendices for a brief description of the overall statistical design for each study intervention.

Any changes to the overall statistical design of this platform study should occur prior to database lock and be detailed in the SAP.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT

Please refer to Appendices.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Please refer to Appendices.

10.4.4 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

Please refer to Appendices and the SAP for details. Of note, exploratory analysis may be presented with consideration to subgroups by baseline symptoms, racial and ethnic subgroup, sex, acute COVID-19 severity, and timing after acute infection.

10.4.5 PLANNED INTERIM ANALYSES

Please refer to Appendices.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 SINGLE INSTITUTIONAL REVIEW BOARD (SIRB)

The protocol, informed consent form(s) (ICF[s]), recruitment materials, and all participant materials are submitted to the sIRB of record for review and approval. This approval must be obtained before any participant is enrolled. Any amendment to the protocol requires review and approval by the sIRB before being implemented in the study. All changes to the consent form are also sIRB-approved and a determination is made regarding whether previously consented participants need to be re-consented.

11.1.2 INFORMED CONSENT PROCESS

11.1.2.1 CONSENT PROCEDURES AND DOCUMENTATION

Consent for the study will either be obtained in-person or remotely (e.g., via an electronic consent [eConsent]) as approved by the sIRB. The remote consent process is described in the MOP. Consent forms describing in detail the study intervention/control, study procedures, and risks are given to the participant and documentation of informed consent is required prior to starting study procedures.

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. A description of risks and possible benefits of participation is provided to the participants. Participants who screen fail for a study Appendix after Appendix-level screening may be eligible for a different study Appendix or may be eligible for re-screening at a later date. Consent forms and consent form addenda are IRB-approved and the participant is asked to read and review the document(s). The participant is provided contact information in the event they have questions about study participation. This allows them to communicate with the

investigators (or their delegates) for further explanation of the research study and to answer any questions that may arise, as necessary. Participants have the opportunity to carefully review the consent form and/or consent form addenda and ask questions prior to signing. Please refer to the MOP for details of the consent process.

The participants have the opportunity to discuss the study and think about it prior to agreeing to participate. The participant signs the informed consent document prior to any procedures being done specifically for the study. A copy of the informed consent document is provided to the participants for their records. The rights and welfare of the participants are protected by emphasizing to them that the quality of their medical care is not adversely affected if they decline to participate in this study. The participants may withdraw consent at any time throughout the course of the study.

The study team distinguishes between the desire to discontinue study intervention and the desire to withdraw consent for study follow-up.

11.1.3 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. In such instances, written notification that documents the reason for study suspension or termination will be provided by the sponsor to study participants, site investigators, the central IRB, and the US Food and Drug Administration (FDA), as applicable. 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:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or FDA, as applicable.

11.1.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical and private information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated is held in strict confidence. No information concerning the study or the data is to be released to any unauthorized third party without prior written approval of the sponsor. The study participant's contact information is securely stored in the clinical study database.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, is transmitted to and stored at the RECOVER CT-DCC. The study data entry and study management systems used by clinical sites and by research staff are secured and password-protected. At the end of the study, all study-related data storage systems will be archived according to local processes.

11.1.5 KEY ROLES AND STUDY GOVERNANCE

The RECOVER program is overseen by the RECOVER CT-Steering Committee. The RECOVER program also includes a Clinical Trial Steering Committee, which is a multi-stakeholder committee that oversees the study and includes patients, the RECOVER CT-DCC, the NIH, and academic and subject matter experts.

The RECOVER CT-DCC is overseen by the overall RECOVER Principal Investigator. The RECOVER CT-DCC is responsible for study coordination, site management, communication, financial administration, treatment allocations, receipt and processing of data, quality control programs, and statistical analysis and reporting.

The DSMB oversees the safety and welfare of trial participants, as well as provides recommendations for continuation, discontinuation, or revision of the trial.

The Study PIs are responsible for the overall conduct of the study, including enrollment, data collection, interventions, regulatory compliance, and protection of the rights, safety, and welfare of study participants.

11.1.6 DATA AND SAFETY MONITORING BOARD

Safety oversight is under the direction of the RECOVER DSMB composed of individuals with the appropriate expertise. Members of the DSMB are selected by NIH, are independent from the study conduct, as feasible, and are either free of conflict of interest or have measures put into place to minimize perceived conflict of interest. The DSMB meets at least semi-annually to approve protocols, assess safety and efficacy data, and, at appropriate intervals, to meet requirements for the interim analyses on each Appendix of the study, if applicable. The DSMB operates under the rules of an approved charter that have been written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess is clearly defined. The DSMB provides its input to the NIH.

11.1.7 CLINICAL MONITORING

This study employs a centralized risk-based approach to monitoring with routine and periodic review of site-submitted data to review the informed consent process, select eligibility criteria, medical history, identify and follow-up on missing data, inconsistent data, data outliers, etc. and ensure completion of administrative and regulatory processes. The study team facilitates regular communication through training sessions, teleconferences, videoconferencing, email, etc. Using quality-by-design principles, steps are taken at the study design stage to foresee and limit significant problems that might occur during the study conduct.

11.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The study team works to ensure that the data collected in this study are as complete and correct as possible. A four-step, multi-functional approach to quality control has been implemented:

- Site Selection: The RECOVER CT-DCC ensures that selected sites have the appropriate staff training and experience to conduct this research study according to Good Clinical Practice.

Further, sites may be evaluated for Appendix participation based upon access to specialized services or equipment as required by the protocol.

- Training: Prior to the start of enrollment, the clinician investigators, study research coordinators and other key study personnel at each site are trained with the clinical protocol and data collection procedures, including how to use the electronic data capture (EDC) system. Follow-up training and training for new study personnel or new versions of the protocol is conducted as needed.
- Monitoring: The RECOVER CT-DCC ensures that data collection is handled properly, provides in-service training, and addresses questions from site investigators and coordinators. Electronic review of data quality and completeness occurs on a regular and ongoing basis. Any issues found will be addressed in a timely manner.
- Managing data: After the data have been transferred for statistical summarization, data description and data analysis, as well as further crosschecking of the data is performed with discrepant observations being flagged and appropriately resolved through a data query system.
- Reviewing data: Data regarding events of interest are reviewed to ensure appropriate documents are collected for DSMB review. The RECOVER CT-DCC monitors study data and contacts site study teams when events comprising the primary endpoint are not complete.

11.1.9 DATA HANDLING AND RECORD KEEPING

11.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Streamlining research activities and conducting the trial in a pragmatic manner facilitates completion of the trial despite strained clinical and research resources. Data may be collected by electronic methods, supplemented by telephone or videophone follow-up, and from the electronic health record.

Data are collected directly from participants at study visits, using email with a survey link, via an electronic application, or by phone/videophone call. These processes are Health Insurance Portability and Accountability Act (HIPAA) compliant.

Site personnel or participants enter study data into a secure online database. Data is maintained in a secure online database until the time of study publication. At the time of publication, the RECOVER CT-DCC generates a de-identified version of the database for archiving (see Section 11.1.11). All source documents at the sites should be completed in a neat, legible manner to ensure accurate interpretation of data.

11.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of six years after the study has ended. However, if required by local, state, or federal regulations, these documents will be retained for a longer period. No records will be destroyed without the written consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.1.10 PROTOCOL DEVIATIONS

A protocol deviation is defined as non-compliance with the clinical study protocol or GCP requirements. The non-compliance may be on the part of the participant, site investigator, or the site staff.

A major protocol deviation is a significant divergence from the protocol that may have significant effect on the participant's safety, rights, or welfare and/or on the integrity of the study data. Major protocol deviations must be sent to the study sIRB and local IRBs per their guidelines, recorded in source documents, and reported to the coordinating center. Major protocol deviations are tracked. For this study, any missed or delayed survey completion or clinical assessment is not to be considered a major protocol deviation, unless it is a study procedure that is required for the primary endpoint.

11.1.11 PUBLICATION AND DATA SHARING POLICY

This study complies with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

11.1.12 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 are disclosed and managed. Furthermore, persons who have a perceived conflict of interest are 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 the NIH, has established policies and procedures for all study group members to disclose all conflicts of interest and has established a mechanism for the management of all reported dualities of interest.

11.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BP	Blood Pressure
CDE	Common Data Element
CFR	Code of Federal Regulations
CFS	Chronic Fatigue Syndrome
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease of 2019
CPET	Cardiopulmonary Exercise Testing
CRF	Case Report Form
CT	Clinical Trial
CT-DCC	Clinical Trial – Data Coordinating Center
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
DSQ-PEM	DePaul Symptom Questionnaire Post-Exertional Malaise
ECG	Electrocardiogram
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
EOI	End of Intervention
EQ-VAS	EuroQol-Visual Analogue Scale
ESI	Events of Special Interest
ESWT	Endurance Shuttle Walk Test
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HIPAA	Health Insurance Portability and Accountability Act
HUA	Hours of Upright Activity
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IRB	Institutional Review Board
ISWT	Incremental Shuttle Walk Test
ME	Myalgic Encephalomyelitis
mDSQ-PEM	Modified DePaul Symptom Questionnaire Post-Exertional Malaise
mITT	Modified Intention-To-Treat
mMRC	Modified Medical Research Council
mOHQ	Modified Orthostatic Hypotension Questionnaire
MOI	Midpoint of Intervention
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIMH	National Institute of Mental Health

OHQ	Orthostatic Hypotension Questionnaire
OI	Orthostatic Intolerance
OHDAS	Orthostatic Hypotension Daily Activity Scale
OHSA	Orthostatic Hypotension Symptom Assessment
PASC	Post-acute Sequelae of SARS-CoV-2 Infection
PEM	Post-Exertional Malaise
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PRO	Patient-Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMIS SF	Patient-Reported Outcomes Measurement Information System Short Form
PROPr	Patient-Reported Outcomes Measurement-Preference Score
RECOVER	Researching COVID to Enhance Recovery
RPD	Rate of Perceived Dyspnea
RPE	Rate of Perceived Exertion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sIRB	Single Institutional Review Board
SLV	Since Last Visit
SD	Standard Deviation
US	United States

11.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change
1.0	12JAN2024	None, original protocol
2.0	01MAR2024	• Overall study schema corrected – Appendix B n changed from 360 to 300 (Figure 1, Section 1.2) • Revisions made to the bulleted list of reasons why an investigator may discontinue a participant from a study intervention (Section 7.1). Specifically, confirmed new case of acute SARS-CoV-2 during the Intervention Period has been removed in favor of appendix-specific guidelines should a participant test positive during the study. In addition, worsening symptoms of PEM has been shortened to remove inapplicable participant withdrawal language. • Baseline Period correction to add ≥ prior to 7 days for the activity tracker (Section 8.3) • Changes made to Early Discontinuation Study Visit information in Section 8.7 to remove mention of being followed per study visit timeline. • New section added for Unscheduled Visits (Section 8.9) • Minor fixes throughout protocol to acronyms and expansion of acronyms • Section **Error! Reference source not found.** language about the 2nd study nasal swab has been modified for consistency with newly added appendix-level language regarding new SARS-CoV-2 infection. • Timing of activity tracker distribution revised in Section 8.10.8. Additional language also added regarding when the tracker is worn. • Timing of when SAEs and ESIs are collected changed from the time of informed consent to the 1st invasive study procedure (Section 9.1.2). • Updates to Abbreviations table (Section 11.2) • Appendix A Schema (Figure 2, Section 12.1.1) has been revised: o 'mDSQ-PEM+1day*' has been changed to 'mDSQ-PEM SLV*' to align with timing of remote mDSQ-PEM per Footnote 10. o Abbreviations updated o mOHQ at Baseline moved to Screening as it is part of Appendix A – Level Exclusion Criteria (Section 12.4). See also Section 12.5.1. • Table 1. Appendix A Objectives, Outcome Measures, and Endpoints (Section 12.1.2) has been revised: o mOHQ pulled out of the 1st exploratory outcome measure and endpoint and into a new exploratory objective that compares mOHQ from screening to study timepoints. See also Sections 12.5.4.1, 12.5.4.2, 12.5.5.1, 12.5.5.2. • Table 1. Appendix A Objectives, Outcome Measures, and Endpoints (Section 12.1.3) has been revised: o New language added to Footnote 5 regarding activities that should occur prior to randomization. o Row added for mOHQ o New sentence added to Footnote **Error! Bookmark not defined.** to e xplain why mOHQ is at Screening (i.e., why it is at a different timepoint than other PROs)

		○ Additional language included in Footnote **Error! Bookmark not defined.** to allow for completion of other PROs at Early Discontinuation after the prioritized PROs (see also Section 12.5.5.1) ○ New row added to depict Activity Tracker Distribution timing ○ New row added to depict Physical Therapy Assessment timing for the Intervention Arm, along with a new Footnote 16 further describing the assessment. See also Section 12.5.4. ○ Footnote 17 modified to remove last sentence and replace with new sentence regarding in-person, remote synchronous, and remote asynchronous sessions. • Exercise assessments re-termed physical therapy assessments throughout Appendix A (Section 12) • Added Short Physical Performance Battery Protocol and Score Sheet as part of physical therapy assessment (Section 12.7.2) • New section added for Modifications for COVID-19 (Section 12.8) • Location of ESI-specific form removed from Section 12.11 • Statistical treatment of exploratory objectives revised in Section 12.12.3.4 • Appendix B Schema (Figure 4, Section 13.1.1) has been revised: ○ Abbreviations updated ○ mOHQ at Baseline moved to Screening to align with timing needed in Appendix A. See also Section 13.7.1. • Table 4. Appendix B Objectives, Outcome Measures, and Endpoints (Section 13.1.2) has been revised: ○ mOHQ pulled out of the 1st secondary outcome measure and into a new secondary objective that compares mOHQ from screening to study timepoints. See also Sections 13.7.4.1, 13.7.4.2, 13.7.5.1, 13.7.5.2. • Table 5. Schedule of Study Procedures in Appendix B (Pacing) (Section 13.1.3) has been revised: ○ Row added for mOHQ ○ New sentence added to Footnote **Error! Bookmark not defined.** to explain why mOHQ is at Screening (i.e., why it is at a different timepoint than other PROs) ○ Additional language included in Footnote **Error! Bookmark not defined.** to allow for completion of other PROs at Early Discontinuation after the prioritized PROs (see also Section 13.7.5.1) ○ Footnote 25 corrected to remove sentence about weekly mDSQ-PEMs (see also Section 13.7.4) ○ New row added to depict Activity Tracker Distribution timing ○ New row added to depict Structured Pacing Assessment timing for the Intervention Arm, along with a new Footnote 28 further describing the assessment. See also Section 13.7.4. ○ Footnote 28 deleted as information is now incorporated in Footnote 28 • Clarification made to Appendix B – Level Inclusion Criteria #2 (Section 13.3) • New section added for Modifications for COVID-19 (Section 13.5) • 'Structured' added before 'pacing' and 'coaching' added before 'sessions' in various sections of Appendix B (Section 13)

		• Statistical treatment of exploratory objectives revised in Section 13.12.3.4
3.0	27SEP2024	• Face page of protocol updated to remove "Pending" from National Clinical Trial (NCT) Numbers and the following NCT numbers added: o Platform: NCT06404047 o Appendix A: NCT06404060 o Appendix B: NCT06404073 • Appendix-level eligibility related to the mDSQ-PEM clarified in Sections 12.4 and 13.3
4.0	09APR2025	• Overall Study Schema in Section 1.2 revised to remove timeframe of Baseline "(Day -10 to 0)" and extend Screening Period box over Baseline, in order to clarify timing. Abbreviations removed to make figure less cluttered. • Reference to a webpage removed in Section 2.2 as it is no longer active. • Change made to inclusion criteria regarding the percentage of the study population allowed to have suspected or probable SARS-CoV-2 infection, not confirmed (Section 5.1) • Wording correction made to inclusion criterion about confirmed case of SARS-CoV-2 infection (Section 5.1) • Footnote added to an exclusion criterion (Section 5.2) indicating that participants must wait 90 days after the end of another interventional trial before enrolling in RECOVER-ENERGIZE • Cross-reference to other relevant sections added to Section 7.2 • Timing of End of Study corrected to count from randomization (Sections 8.8, Table 2, 12.5.5.2, Table 5, and 13.7.5.2) • Nasal swab for COVID-19 testing removed from screening and from subsequent "as needed" repeat testing. If participant is symptomatic, testing should occur as part of standard clinical care (see Sections 8.2, removal of previous version's Section 8.10.7, 9.1.2, 11.2, Figure 2, Table 2, 12.5.2.1, Figure 4, Table 5, and 13.7.3). • Moved CBC from baseline to main platform Screening (Sections 8.2, 8.10.5, Table 2, 12.5.2.1, Table 5, and 13.7.3) • Clarification added to Section 8.10.5 to add timing • Corrections or clarifications made to headings of Sections 8.3, 8.5, 8.6, 12.5.2, 12.5.2.1, 13.7.2, and 13.7.3 to better describe the time periods • Clarified timing of when tracker should be worn at start of study (to align with Section 8.10.8) in Section 8.3, Table 2, Section 12.5.2, Table 5, and Section 13.7.2. • Clarify that participants in the intervention arm have up to 30 days from randomization to start Day 1 of the intervention (Sections 8.4, 12.5.4, 13.7.4, and footnotes in Table 2 and Table 5) • Correct timing of the EOI study visit (Section 8.6) • Correct timing of the EOS study visit (Section 8.8, Table 2, Section 12.5.5.2, Table 5, and 13.7.5.2) • Clarify timing of blood collection for biomarkers assessment (Section 8.10.5) • Wording improvement in Section 9.1.2 • Schemas for Appendix A (Figure 2) and Appendix B (Figure 4) modified to align with other changes in the protocol • Table 1: o 2nd bullet under Primary Endpoint deleted

		○ "Step Count" added to clarify "Actigraphy" under the Secondary Efficacy Outcome Measure ○ Exploratory Endpoint evaluating healthcare utilization re-worded for clarity ○ Exploratory Endpoint evaluating effects on exercise capacity re-worded for clarity ○ New Exploratory Objective added using Actigraphy-Heart Rate as Outcome Measure • Revision to Early Discontinuation footnotes in Table 2 and Table 5 • Clarification of timing of randomization in footnote of Table 2 • "Clinical Laboratory Test – Blood Collection" changed to "Clinical Laboratory Test – Complete Blood Count" and associated footnotes removed in Table 2 and Table 5 • Exploratory PROs expanded in Table 2 and Table 5 to include new rows for each PRO separately (includes changes to footnotes) • mDSQ-PEM expanded into separate rows for each lookback period (e.g., 3-month, SLV, 7-Day) in Table 2 and Table 5 with corresponding changes to footnotes, as well as in Section 12.5.4.1 • Education Session separated from Weekly Touch-in phone calls in Table 2 to make a new row with corresponding changes to footnotes • Correction to made to footnote describing the Physical Therapy Assessment in Table 2 • Removed fuzzy 'X' and footnote in cells for the intervention arm assessment row/Baseline Study Visit 1 column to avoid confusion in Table 2 and Table 5. • Clarification made to 1st sentence of Section 12.2 • Exclusion criterion correction in Section 12.4 • Revisions in Section 12.5 to align with changes made to Table 2 • Clarifications made regarding the Intervention Group in Appendix A (Section 12.7.2) • Clarifications made regarding the Control Group in Appendix A (Sections 12.10.1 and 12.10.2) • 2nd bullet removed from Primary Endpoint, PASC Symptom Questionnaire removed from 1st Secondary Outcome Measure, and new Exploratory Objective created for Appendix B (Table 4) • Inclusion criterion correction in Section 13.3 • "Usual Care" removed from control arm in Table 5 • "material" added to sentence describing basic PEM education (Sections 13.10 and 13.10.1) • Revisions and updates made to the statistical sections of Appendix B (13.12.3.2 and 13.12.3.3)

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12 APPENDIX A (CARDIOPULMONARY REHABILITATION)

12.1 STUDY DESIGN AND RATIONALE

Exercise intolerance is described as the limitation of the capacity to do physical activity due to the presence of symptoms such as dyspnea and fatigue during exercise. Exercise intolerance may impair functional capacity, activities of daily living, and quality of life. Impaired exercise tolerance has also been associated with reduced survival in patients with chronic diseases[36], as well as in healthy individuals.[37] Exercise intolerance is among the most common symptom complexes in patients with PASC, and as such is an important target for the RECOVER program. As noted below (Section 12.7.1), rehabilitation approaches combining endurance exercise, strength training, and education have shown promising initial data in patients with PASC. We have designed a randomized controlled trial to evaluate the effect of a 12-week personalized cardiopulmonary rehabilitation intervention on exercise tolerance and other PROs.

12.1.1 APPENDIX A SCHEMA

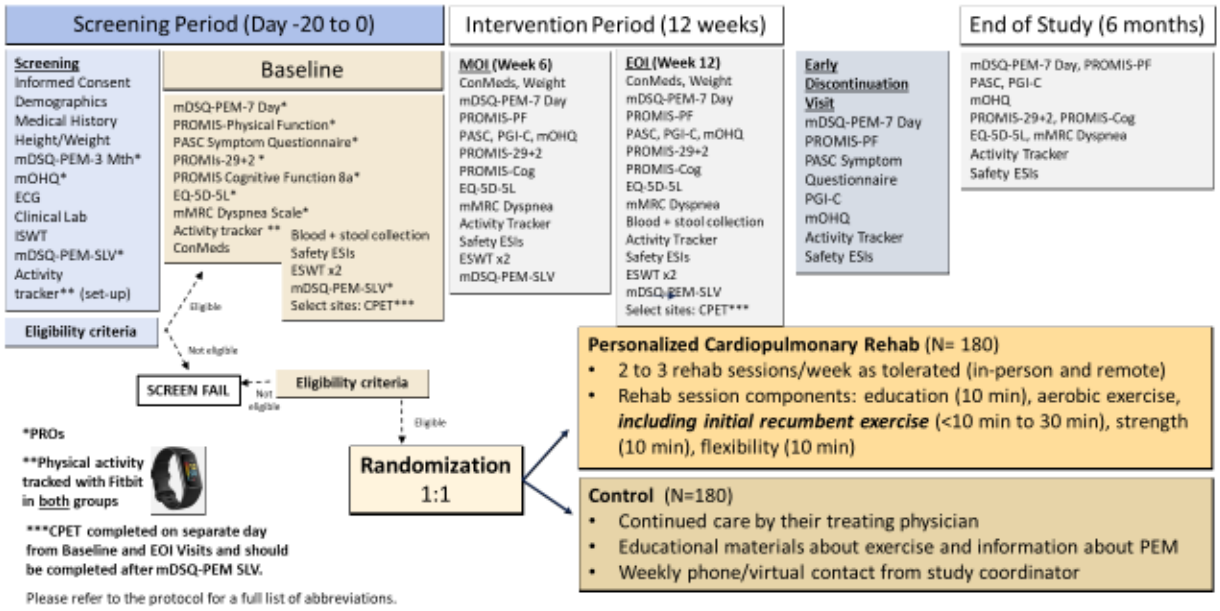


Figure 2. Appendix A Schema

12.1.2 OUTCOME MEASURES AND ENDPOINTS

Specific Appendix A objectives, outcome measures, and endpoints are provided below in Table 1.

Table 1. Appendix A Objectives, Outcome Measures, and Endpoints

OBJECTIVE	OUTCOME MEASURE	ENDPOINT
Primary		
Evaluate the effect of study intervention on exercise tolerance versus control	Endurance Shuttle Walk Test (ESWT)	Change from baseline in the treatment group compared to control group at the EOI on the ESWT
Secondary		
Efficacy – Evaluate the effect of study intervention on physical function versus control	• PROMIS SF-Physical Function (PROMIS-PF) • Actigraphy – Step Count	Change from baseline to the middle of intervention, EOI, and End of Study (EOS) in the treatment group compared to control group
Safety – Evaluate the effect of study intervention on PEM symptoms (frequency, severity, and duration) versus control	Modified DePaul Symptom Questionnaire – Post-Exertional Malaise (mDSQ-PEM)	Change from baseline to the middle of intervention, EOI, and EOS in the treatment group compared to control group
Exploratory		
Evaluate the effect of study intervention on shortness of breath, cognitive function, Quality of Life (QoL), and PASC symptoms versus control	• Modified Medical Research Council (mMRC) Dyspnea Scale • PROMIS SF-Cognitive Function 8a (PROMIS-Cog) • PROMIS-29+2 • EQ-5D 5L • PASC Symptom Questionnaire	Change from baseline to the middle of intervention, EOI, and EOS in the treatment group compared to control group on mMRC, PROMIS-Cog, PROMIS-29 + 2, EQ-5D 5L, and PASC Symptom Questionnaire

OBJECTIVE	OUTCOME MEASURE	ENDPOINT
Evaluate the effect of study intervention on orthostatic hypotension versus control	• Modified Orthostatic Hypotension Questionnaire (mOHQ)	Change from screening to the middle of intervention, EOI, and EOS in the treatment group compared to control group on mOHQ
Evaluate the effect of study intervention on relevant biomarkers versus control	• Viral biomarkers • Immune biomarkers	Change in biomarker(s) from baseline to EOI in the treatment group compared to control group
Evaluate the effect of study intervention on healthcare utilization versus control	Healthcare utilization – medical visits and hospitalizations	• Cumulative medical visits from baseline to EOI or EOS • Cumulative hospitalizations from baseline to EOI or EOS
Describe the effects of study intervention on exercise capacity *(at select sites)*	Cardiopulmonary Exercise Testing (CPET)	Change from baseline compared to EOI in physiological responses to CPET (i.e., incremental cycle ergometer or treadmill exercise)
Compare the effect of study intervention on physical function versus control	Actigraphy – Heart Rate	Change from baseline to the middle of intervention, EOI, and End of Study (EOS) in the treatment group compared to control group

12.1.3 SCHEDULE OF APPENDIX A PROCEDURES

The full Schedule of Procedures for Appendix A is shown below in Table 2.

Table 2. Schedule of Study Procedures in Appendix A (Cardiopulmonary Rehabilitation)

	Screening Period		Baseline Period		Study Period (6 months)				
					Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	Screening (before assignment to Appendix)	Appendix A Screening	Baseline Study Visit 1	Baseline Study Visit 2 *(selected sites)*	Intervention Period Study Visit 1	Intervention Period Study Visit 2	End of Intervention (EOI) Study Visit	Early Discontinuation Study Visit[2]	End of Study (EOS)
Weeks					1	6	12	N/A	24
Days	Day -20 to 0				Day 1[3]	Midpoint of Intervention Period (MOI) ± 7 Days	EOI Day + 7 Days	N/A	Randomization + 183 days ± 14 days
General Evaluations									
Informed Consent[4]	X								
Appendix-Level Eligibility Criteria		X							
Randomization *(Day 0)*			X[5]						
Demographics	X								
Medical History	X								
Height and Weight	X					X[6]	X[6]		

[2] Early Discontinuation Visits should prioritize completion of PROs in this order: mDSQ-PEM, PROMIS-SF Physical Function, PASC Symptom Questionnaire, PGIC, and mOHQ.
[3] Participants in the intervention arm have up to 30 days from randomization to start Day 1 of the intervention.
[4] The informed consent process should occur prior to any screening activities. Please refer to MOP for specifics of the consent process.
[5] Randomization occurs after confirmation of eligibility for Appendix A and prior to initiating intervention. All baseline activities should occur prior to randomization with the exception of the 2nd mDSQ-PEM obtained remotely 48-72 hours after the in-person Baseline Visit.
[6] Weight only

	Screening Period		Baseline Period		Study Period (6 months)				
					Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	**Screening (before assignment to Appendix)**	**Appendix A Screening**	**Baseline Study Visit 1**	**Baseline Study Visit 2 *(selected sites)***	**Intervention Period Study Visit 1**	**Intervention Period Study Visit 2**	**End of Intervention (EOI) Study Visit**	**Early Discontinuation Study Visit[2]**	**End of Study (EOS)**
Weeks					1	6	12	N/A	24
Days	Day -20 to 0				Day 1[3]	Midpoint of Intervention Period (MOI) ± 7 Days	EOI Day + 7 Days	N/A	Randomization + 183 days ± 14 days
Concomitant Medications			←==========Continuous==========→						X
Laboratory and Safety Evaluations									
ECG		X[7]							
Clinical Laboratory Test – Complete Blood Count	X								
Biorepository – Blood & Stool Collection[8]			X				X		
SAEs and Safety ESIs		←==========Continuous==========→							
HRQOL Evaluations									
ISWT		X							
ESWT			X[9]			X[9]	X[9]		
PROMIS SF-Physical Function			X			X	X	X	X
mMRC Dyspnea Scale			X			X	X	X	X

[7] Prior to ISWT
[8] Two 1.0 mL aliquots of EDTA plasma and two 1.0 mL aliquots of serum to be frozen and stored for future research, as well as stool collection per MOP (see Sections 8.10.7 and 8.11)
[9] The ESWT is completed twice; the initial ESWT occurs at least 30 minutes prior to the second ESWT.

	Screening Period		Baseline Period		Study Period (6 months)				
					Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	**Screening (before assignment to Appendix)**	**Appendix A Screening**	**Baseline Study Visit 1**	**Baseline Study Visit 2 *(selected sites)***	**Intervention Period Study Visit 1**	**Intervention Period Study Visit 2**	**End of Intervention (EOI) Study Visit**	**Early Discontinuation Study Visit[2]**	**End of Study (EOS)**
Weeks					**1**	**6**	**12**	**N/A**	**24**
Days	**Day -20 to 0**				**Day 1[3]**	**Midpoint of Intervention Period (MOI) ± 7 Days**	**EOI Day + 7 Days**	**N/A**	**Randomization + 183 days ± 14 days**
PROMIS SF-Cognitive Function			X			X	X	X	X
PROMIS-29+2			X			X	X	X	X
EQ-5D 5L			X			X	X	X	X
PASC Symptom Questionnaire			X			X	X	X	X
PGIC						X	X	X	X
mDSQ-PEM-3 Month[10]	X								
mOHQ		X				X	X	X	X
mDSQ-PEM-SLV		X[11]	X[12]			X[12]	X[12]		
mDSQ-PEM-7 Day			X[12]			X[12]	X[12]	X	X
CPET *(select sites only)*				X			X		
Activity Tracker	X								

[10] Completed first at study screening to determine appendix assignment with a lookback period of 3 months.
[11] mDSQ-PEM-SLV is completed remotely (via phone or electronic survey) 48-72 hours after the Appendix A screening visit to assess PEM post ISWT. SLV allows us to assess the effect of study procedures at in-person visits on exacerbation or development of PEM in a population who may be particularly vulnerable to this condition.
[12] There are two mDSQ-PEMs completed at Baseline, MOI, and EOI. The 1st is at the in-person visit when the lookback period is 7 days. The 2nd is obtained remotely 48-72 hours after the in-person visit and is SLV. The mDSQ-PEM at Early Discontinuation and EOS is last 7 days.

	Screening Period		Baseline Period		Study Period (6 months)				
					Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	**Screening (before assignment to Appendix)**	**Appendix A Screening**	**Baseline Study Visit 1**	**Baseline Study Visit 2 *(selected sites)***	**Intervention Period Study Visit 1**	**Intervention Period Study Visit 2**	**End of Intervention (EOI) Study Visit**	**Early Discontinuation Study Visit[2]**	**End of Study (EOS)**
Weeks					**1**	**6**	**12**	**N/A**	**24**
Days	**Day -20 to 0**				**Day 1[3]**	**Midpoint of Intervention Period (MOI) ± 7 Days**	**EOI Day + 7 Days**	**N/A**	**Randomization + 183 days ± 14 days**
Distribution									
Activity Tracker[13]	X		X		X			X	X
Intervention									
Education Sessions *(control arm only)*[14]					X				
Weekly Touch-in phone calls *(control arm only)*[15]						X			

[13] The activity tracker is distributed for participants to wear during the study. Participants are asked to wear the tracker for ≥ 7 days before the start of the Baseline Visit for the collection of baseline metrics. Participants are encouraged to wear the tracker throughout the study. Participants are also asked to wear the tracker for 7 days prior to study outcome visits and before the EOS visit.

[14] The control arm will receive 2 general education sessions during the Intervention Period. The 1st general education session is at the start of the Intervention Period, and the 2nd is 2 – 3 weeks later.

[15] The control arm will receive weekly touch-in phone calls during the Intervention Period.

	Screening Period		Baseline Period		Study Period (6 months)				
					Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	**Screening (before assignment to Appendix)**	**Appendix A Screening**	**Baseline Study Visit 1**	**Baseline Study Visit 2 *(selected sites)***	**Intervention Period Study Visit 1**	**Intervention Period Study Visit 2**	**End of Intervention (EOI) Study Visit**	**Early Discontinuation Study Visit[2]**	**End of Study (EOS)**
Weeks					**1**	**6**	**12**	**N/A**	**24**
Days	**Day -20 to 0**				**Day 1[3]**	**Midpoint of Intervention Period (MOI) ± 7 Days**	**EOI Day + 7 Days**	**N/A**	**Randomization + 183 days ± 14 days**
Physical Therapy Assessment *(intervention arm only)*					X[16]				
Cardiopulmonary Rehabilitation *(intervention arm only)*[17]					X	X	X		

Abbreviations: MOI – Midpoint of Intervention, EOI – End of Intervention, EOS – End of Study, ECG – Electrocardiogram, SAE – Serious Adverse Event, ESI – Event of Special Interest, HRQOL – Health-Related Quality of Life, EDTA - Ethylenediaminetetraacetic acid, MOP – Manual of Procedures, ISWT – Incremental Shuttle Walk Test, ESWT – Endurance Shuttle Walk Test, PROs – Patient-Reported Outcomes, mDSQ-PEM – Modified DePaul Symptom Questionnaire – Post-Exertional Malaise, CPET – Cardiopulmonary Exercise Training, mMRC – Modified Medical Research Council, PROMIS – Patient-Reported Outcomes Measurement, PASC – Post-acute Sequelae of SARS-CoV-2 Infection, OHQ – Orthostatic Hypotension Questionnaire, PGIC – Patient Global Impression of Change, PEM – Post-Exertional Malaise

[16] The intervention arm undergoes an in-person physical therapy assessment on Day 1 to determine the appropriate starting level for the cardiopulmonary rehabilitation intervention. Potentially, participants may have the physical therapy assessment after randomization on the same day as Baseline, instead of at the beginning of Day 1 of the Intervention Period. Timing of the assessment can be determined at the site level based upon what works best for the participant.

[17] X's indicate cardiopulmonary rehabilitation session timepoints (1st and last week should be in person). Based on participant and rehabilitation program factors, the remaining sessions may include a combination of in-person, remote synchronous, and remote asynchronous sessions.

12.2 BLINDING

Primary outcome measures (ESWTs) are conducted by research study staff who are blinded to the individual participant's intervention assignment. Specifically, the participants and the study personnel who are conducting the Appendix A study intervention with the participants are not blinded; however, the study personnel who are obtaining outcome measures are blinded. Refer to the MOP for details.

12.3 ADDITIONAL APPENDIX A – LEVEL INCLUSION CRITERIA

Not applicable.

12.4 ADDITIONAL APPENDIX A – LEVEL EXCLUSION CRITERIA

1. Known pre-existing postural orthostatic tachycardia syndrome, not related to SARS-CoV-2 infection
2. Known uncontrolled hypertension (blood pressure [BP] ≥ 160/100 mmHg at rest)
3. Any of the following within 4 weeks of enrollment – acute myocardial infarction, unstable angina, uncontrolled arrhythmias causing symptoms or hemodynamic compromise, acute myocarditis or pericarditis, uncontrolled acutely decompensated heart failure (acute pulmonary edema), acute pulmonary embolism, suspected dissecting aneurysm, severe hypoxemia at rest, thromboembolic event(s), any acute or chronic disorder that may affect exercise capacity or be aggravated by exercise (e.g., infection, exercise induced syncope, thyrotoxicosis, unable to cooperate)
4. Score of 2 or greater for both frequency **and** severity for any of the first 5 questions on the Screening mDSQ-PEM **AND** answer of 'YES' to either item 7 or 8 on the Screening mDSQ-PEM, **AND** response of ≥ 14 hours in item 9
   OR
   Score of 3 or greater on any severity question (regardless of frequency) **AND** answer of 'YES' to either item 7 or 8 on the Screening mDSQ-PEM, **AND** response of ≥ 14 hours in item 9
   OR
   Any new score of 3 or greater on any of the severity questions on the mDSQ-PEM 48-72 hours following the Screening ISWT test
5. A selection of ≥ 8 on question 1 or ≥ 9 on question 3 of the OH Activity Scale from the mOHQ
6. Engaged in purposeful moderate or greater intensity exercise with the intent to improve one's health 2 or more times per week over the 30 days prior to informed consent
7. Inability to walk

12.5 STUDY ASSESSMENTS AND PROCEDURES

Please also refer to Table 2.

12.5.1 APPENDIX A SCREENING (DAYS -20 TO 0)

Participants who sign informed consent and are eligible for Appendix A of the study have the following additional screening procedures for eligibility.

- Review of Appendix-level eligibility criteria (see Sections 12.3 and 12.4)
- mOHQ (Refer to Section 8.10.1.8)
- ECG (should occur prior to ISWT) (Refer to Section 8.10.6)
- Clinical blood collection for the following evaluation:
  - Complete blood count (Refer to Section 8.10.5)
- ISWT (Refer to Section 8.10.2)
- mDSQ-PEM-SLV[11] (Refer to Section 8.10.1.7)
- SAEs and ESIs (Refer to Section 9.1 and 12.11)

12.5.2 BASELINE PERIOD (DAYS -13 TO 0):

The Baseline Period begins 13 days before starting the Intervention Period. The participant begins using their activity tracker ≥ 7 days before the Baseline Visit to establish baseline metrics.

12.5.2.1 BASELINE VISIT 1

Refer to Appendix A Table 1 for summary of all outcome measures specific to change from baseline.

The following baseline procedures are completed at Baseline Study Visit 1:

- Randomization must occur after confirmation of eligibility and prior to initiating intervention, but can occur at any time during the baseline window (day of randomization is Day 0)
- Collection of concomitant medications taken within 14 days of signing informed consent
- Blood and stool collection for biorepository (frozen for retrospective analysis) (Refer to Sections 8.10.7 and 8.11)
- SAEs and ESIs (Refer to Section 9.1 and 12.11)
- ESWT, completed twice at least 30 minutes apart (Refer to Section 8.10.3)
- PROMIS SF-Physical Function (Refer to Section 8.10.1.3)
- mMRC Dyspnea Scale (Refer to Section 8.10.1.5)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- EQ-5D 5L (Refer to Section 8.10.1.4)
- PASC Symptom Questionnaire (Refer to Section 8.10.1.6)
- mDSQ-PEM[12] (Also refer to Section 8.10.1.7)
- Activity tracker check-in

12.5.3 BASELINE VISIT 2 AT SELECT SITES ONLY (DAY -6 TO 0):

- CPET (Refer to Section 12.5.6.1)

12.5.4 INTERVENTION PERIOD (12 WEEKS)

The beginning of the 12-week Intervention Period is Day 1. Participants in the intervention arm have up to 30 days from randomization to start Day 1 of the intervention. On Day 1, the intervention arm of the study has their first cardiopulmonary rehabilitation intervention visit (should be in-person) and the control arm of the study has the first of their two general education sessions. The frequency of exercise sessions in the intervention arm during the Intervention Period should be a minimum of two sessions per week, increasing to 3 sessions per week, as tolerated. Please refer to Section 12.7.2 and the MOP for more details.

- Concomitant Medication review
- SAEs and ESIs (Refer to Section 9.1 and 12.11)
- Activity tracker check-in
- *Physical Therapy Assessment (Intervention Arm only)*[16]
- *Intervention Arm only: Cardiopulmonary rehabilitation intervention*
  - *Note: The frequency of cardiopulmonary rehabilitation exercise sessions during this period should be a minimum of two sessions per week, increasing to 3 sessions per week, as tolerated.*
- *Control Arm only: Participants in the control arm receive 2 general education sessions and weekly phone call follow-ups during the Intervention Period. The 1st general education session is at the start of the Intervention Period, while the 2nd is 2 – 3 weeks later.*

12.5.4.1 INTERVENTION PERIOD – MIDPOINT (APPROXIMATELY 6 WEEKS ± 7 DAYS)

Refer to Appendix A Table 1 for summary of all outcome measures specific to change from baseline to Midpoint.

- Weight
- Concomitant medication review
- SAEs and ESIs (Refer to Section 9.1 and 12.11)
- ESWT, completed twice at least 30 minutes apart (Refer to Section 8.10.3)
- PROMIS SF-Physical Function (Refer to Section 8.10.1.3)
- mMRC Dyspnea Scale (Refer to Section 8.10.1.5)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- EQ-5D 5L (Refer to Section 8.10.1.4)
- PASC Symptom Questionnaire (Refer to Section 8.10.1.6)
- PGIC (Refer to Section 8.10.1.10)
- mOHQ (Refer to Section 8.10.1.8)
- mDSQ-PEM[12] (Also refer to Section 8.10.1.7)
- Activity tracker check-in
- *Intervention Arm only: Cardiopulmonary rehabilitation intervention*
  - *Note: The frequency of exercise sessions during this period should be a minimum of two sessions per week, increasing to 3 sessions per week, as tolerated.*
- *Control Arm only: Participants in the control arm receive weekly phone call follow-ups during the Intervention Period.*

12.5.4.2 END OF INTERVENTION (+ 7 DAYS)

Refer to Appendix A Table 1 for summary of all outcome measures specific to change from baseline to EOI.

- Weight
- Concomitant Medication review
- Blood and stool collection for biorepository (frozen for retrospective analysis) (Refer to Sections 8.10.7 and 8.11)
- SAEs and ESIs (Refer to Section 9.1 and 12.11)
- ESWT, completed twice at least 30 minutes apart (Refer to Section 8.10.3)
- PROMIS SF-Physical Function (Refer to Section 8.10.1.3)
- mMRC Dyspnea Scale (Refer to Section 8.10.1.5)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- EQ-5D 5L (Refer to Section 8.10.1.4)
- PASC Symptom Questionnaire (Refer to Section 8.10.1.6)
- PGIC (Refer to Section 8.10.1.10)
- mOHQ (Refer to Section 8.10.1.8)
- mDSQ-PEM[12] (Also refer to Section 8.10.1.7)
- *Select Sites only: CPET (Refer to Section 12.5.6.1)*
- Activity tracker check-in
- *Intervention Arm only: Cardiopulmonary rehabilitation intervention (should be in-person)*
- *Control Arm only: Participants in the control arm receive weekly phone call follow-ups during the Intervention Period.*

12.5.5 FOLLOW-UP PERIOD (12 WEEKS)

12.5.5.1 EARLY DISCONTINUATION

If a participant discontinues the study early (i.e., no longer wishes to participate), the participant should be asked to complete an Early Discontinuation Visit. The following procedures should occur at an Early Discontinuation Visit if the participant is willing:

- SAEs and ESIs (Refer to Section 9.1 and 12.11)
- PROMIS SF-Physical Function (Refer to Section 8.10.1.3)
- mMRC Dyspnea Scale (Refer to Section 8.10.1.5)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- EQ-5D 5L (Refer to Section 8.10.1.4)
- PASC Symptom Questionnaire (Refer to Section 8.10.1.6)
- PGIC (Refer to Section 8.10.1.10)
- mOHQ (Refer to Section 8.10.1.8)
- mDSQ-PEM (7-day lookback period) (Refer to Section 8.10.1.7)
- Activity tracker check-in

The order that PROs listed above for Early Discontinuation should be completed by the participant, based upon importance to the study, is mDSQ-PEM, PROMIS SF-Physical Function, PASC Symptom Questionnaire, PGIC, and mOHQ. Reason for discontinuation should be collected when possible.

12.5.5.2 END OF STUDY (± 14 DAYS)

Refer to Appendix A Table 1 for summary of all outcome measures specific to change from baseline to EOS.

The following procedures occur during the EOS visit 183 days (± 14 days) after randomization, which is remote by phone or videophone call for Appendix A:

- Concomitant Medication review
- SAEs and ESIs (Refer to Section 9.1 and 12.11)
- PROMIS SF-Physical Function (Refer to Section 8.10.1.3)
- mMRC Dyspnea Scale (Refer to Section 8.10.1.5)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- mOHQ (Refer to Section 8.10.1.8)
- mDSQ-PEM (7-day lookback period) (Refer to Section 8.10.1.7)
- Activity tracker check-in

12.5.6 ADDITIONAL APPENDIX A ASSESSMENTS

Please refer Section 8.10 of the master protocol for descriptions of platform assessments used in Appendix A per Section 12.5 and Table 2.

12.5.6.1 CARDIOPULMONARY EXERCISE TESTING (SELECT SITES)

Cardiopulmonary exercise testing (exploratory performance measure) is completed at select sites. This is an exercise test that measures exercise abilities. The test involves a 2 to 3-minute warm-up, followed by 8 to 12 minutes of progressively harder work on a treadmill or stationary bike. The goal is to exercise until the participant is no longer able to continue. The final outcome for this measure is the maximum rate of oxygen consumption (VO_2 max).

12.6 PRECAUTIONS

Cardiac rhythm should be monitored for participants with underlying heart conditions.

12.7 CARDIOPULMONARY REHABILITATION INTERVENTION

Cardiopulmonary rehabilitation is a hybrid intervention that includes elements of cardiac rehabilitation and pulmonary rehabilitation, both of which are used as part of standard clinical care. The heterogeneous combination of symptoms in the PASC population that results in exercise intolerance necessitates an approach that addresses both cardiac and pulmonary causes of exercise intolerance. This intervention is not exclusively cardiac or pulmonary focused; instead, it tailors aspects of both

standard clinical programs to address the unique needs of the PASC population to improve exercise tolerance. Depending upon a participant's screening and baseline assessments and recommendations by trained staff, cardiopulmonary rehabilitation may start with recumbent exercise (i.e., exercise while in a semi-reclined seated position).

Clinical sites are chosen that have an existing pulmonary or cardiac rehabilitation program with trained, experienced staff and a Medical Director.

12.7.1 SCIENTIFIC RATIONALE FOR INTERVENTION

Ongoing trials have evaluated exercise rehabilitation in patients with acute COVID-19 and set the precedence for use in the PASC population. In a recently completed study (NCT04368845), investigators evaluated a 6-month tele-rehabilitation program in adults hospitalized due to COVID-19. The intervention included endurance exercises, low intensity aerobic exercises, upper and lower extremity strength training, breathing exercises, and video conferencing with a physiotherapist three times per month. Another study evaluated 37 patients who participated in an 8-week in-person rehabilitation program within 6 months of confirmed COVID-19 diagnosis.[38] The rehabilitation program included 80-minute sessions twice a week of aerobic exercise on a treadmill at moderate intensity (60 to 75% of the reserve heart rate calculated by the Karvonen method and perceived exertion of 4 to 6 on the modified Borg scale), resistance exercises (intervals of 1 to 2 minutes between 3 sets of 10 repetitions for the trunk and upper and lower limbs), and trained muscle stretches at the end of the session. The primary outcome for exercise capacity was the greatest distance covered after two tests with an interval of 30 minutes on the ISWT. The study showed an increase in exercise capacity by an average of 100.8 ± 86.1 m ($p<0.001$) in those who participated in the in-person rehabilitation and an average increase of 65.9 ± 61.9 m ($p=0.001$) in those who participated in remote rehabilitation.[38]

Both cardiac and pulmonary rehabilitation are highly effective and scalable, as demonstrated in clinical practice. Pulmonary rehabilitation has been explored and evaluated in other chronic respiratory disorders, such as SARS-CoV-1 and Middle East Respiratory Syndrome. Given the similarity of symptoms (exercise intolerance and dyspnea) overlapping presentation of PASC and COPD, evidence from pulmonary rehabilitation research could provide helpful insights to the post-acute rehabilitation needs of patients with PASC.[39,40]

12.7.2 INTERVENTION DETAILS AND ADMINISTRATION

Initial Physical Assessment. All participants undergo an in-person baseline physical therapy assessment on Day 1 to determine the appropriate starting level for lower extremity aerobic exercise. Additionally, an assessment by a trained physical, occupational, rehabilitation, respiratory, exercise, or similar therapist includes testing muscle strength, balance, range of motion and flexibility with the goal of increasing functional capacity, as appropriate, for each individual. These assessments help the trained therapist to develop an appropriate cardiopulmonary rehabilitation program that is specific for an individual participant, which may begin with recumbent exercise. Trained therapists will utilize the Short Physical Performance Battery Protocol and Score Sheet[41] to complete the initial physical assessment. Site staff who are providing cardiopulmonary rehabilitation also receive study-specific education about PEM.

Rehabilitation sessions. The frequency of cardiopulmonary rehabilitation sessions should be a minimum of two sessions per week, increasing to 3 sessions per week, as tolerated. The duration of the cardiopulmonary rehabilitation program is 12 weeks. The first week and at least one of the three sessions during Week 12 must occur in-person. Based on participant and rehabilitation program factors, the remaining sessions may include a combination of in-person, remote synchronous, and remote asynchronous sessions. Remote sessions start only once the participant is deemed to sufficiently understand the training program and be independent in exercise performance. The participant is queried as to their choice of in-person or remote sessions, in order to maintain adherence to the requisite number and frequency of training sessions. Participant factors that indicate the need for remote sessions include, but are not limited to, transportation to an in-person site and work schedules. Rehabilitation program factors that determine remote sessions include, but are not limited to, the prior use of remote sessions, rehabilitation staff familiarity and comfort with remote sessions, rehabilitation program resources, and ability to monitor participant exercise remotely. Participants are provided with instructions on continuing therapy exercises on their own at home. Refer to the MOP for details.

Each cardiopulmonary rehabilitation session includes social support and may include monitoring of heartrate, oxygen saturation, and blood pressure, as appropriate for each individual participant. The following components are generally included with each rehabilitation session, although the actual duration and intensity is adjusted based on the participant's baseline assessment, symptoms, and progress:

- Education, including topics such as fundamentals of exercise and PEM, self-management strategies, management of stress, anxiety, and depression, and nutrition and weight management;
- Aerobic exercise, progressing up to 30 minutes or more, as the participant is able. Note that if a participant is not able to perform 10 minutes of aerobic exercise, per their baseline assessment, the starting duration should be tailored to their abilities. Aerobic intensity should achieve Borg rate of perceived exertion (RPE)/rate of perceived dyspnea (RPD) of 5 to 6 and a heartrate > 60% of predicted maximum (modified based on RPE/RPD). Modes of possible lower extremity aerobic exercise training include, but are not limited to, walking, treadmill, and cycling (recumbent or upright) depending on participant clinical factors such as arthritis, strength, and balance and equipment availability;
- Strength training; and
- Flexibility training.

Rehabilitation sessions are provided by respiratory therapists, exercise physiologists, physical therapists, nurses, or others who have experience and training in either pulmonary or cardiac rehabilitation.

12.7.3 RISK ASSESSMENT

Both supervised and home-based cardiac rehabilitation programs have been shown to have a very low risk of adverse events even in high risk cardiac patients[42] with no difference in safety for in-person versus remote cardiac rehab.[43]

Potential risks associated with the incremental and endurance shuttle walk tests (ISWT/ESWT) include PEM, tiredness, shortness of breath, or palpitations during the test. The cardiopulmonary exercise test may result in fatigue, shortness of breath, possible bronchospasm, cardiac arrhythmia, and/or syncope.

Risks associated with cardiopulmonary rehabilitation are highly dependent on exertion and include increased blood pressure and heart rate and decrease in oxygen saturation. Exertion is monitored via RPE and RPD. During each session, if the RPE and/or RPD are indicated as being in the 7 to 10 range on the Borg scale, exercise stops if needed and further exercise intensity is reduced. In cases where the participants are unable to continually exercise for the designated time according to the protocol, participants are allowed to take a break and restart exercise or cease exercise for that session.

Indications for stopping cardiopulmonary rehabilitation include, but are not limited to, chest pain, syncope, dizziness, palpitations, cardiac arrhythmia, respiratory distress, inability to continue and persistent oxygen desaturation (oxygen saturation < 86% for ≥ 2 minutes) or severe oxygen desaturation (oxygen saturation < 82% for any duration).

12.8 MODIFICATIONS FOR COVID-19

If a participant tests positive for COVID-19 during the Intervention Period, the investigator or designee may modify the participant's schedule and assessments as needed, including temporary interruption of study intervention, if applicable. Information regarding the new COVID-19 infection will be collected, including date of positive test, any prescription medications started, and any associated symptoms or sequelae.

12.9 PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant begins to develop worsening PEM while taking part in the Intervention Period, study staff will review PEM education with them. The participant will not resume the study intervention until PEM symptoms return to baseline. Once PEM symptoms are back to baseline, participants may resume the study intervention at a lower duration or intensity as recommended by trained staff. Participants should continue the lowered duration/intensity for at least two sessions without worsening PEM before gradually increasing duration/intensity. If the participant is unable to resume the study intervention due to continued worsening PEM symptoms after more than 2 weeks, the study intervention should be discontinued and follow-up assessments completed through EOS at 6 months. Please refer to Section 11.1.6 for a description of monitoring by the DSMB.

12.10 CONTROL INFORMATION

General education is used as a control for the cardiopulmonary rehabilitation intervention. Education includes two sessions at start of the Intervention Period with weekly phone call follow-ups coordinated by site study staff.

12.10.1 SCIENTIFIC RATIONALE FOR CONTROL

Education on topics like exercise and nutrition is used as a retention strategy for participants randomized to the control arm. Education that is provided by a study team member is not expected to significantly increase exercise capacity.

12.10.2 CONTROL DETAILS AND ADMINISTRATION

Weekly phone calls from site study staff will include education on topics of interest, including, but not limited to, fundamentals of exercise, self-management strategies, management of stress, anxiety, and depression, and nutrition and weight management.

12.11 EVENTS OF SPECIAL INTEREST (ESIS)

The following ESIs are collected:

- New cardiovascular events
  - Myocardial infarction
  - Cerebrovascular event
  - Hospitalization for heart failure
- New or worsening PEM

12.12 STATISTICAL CONSIDERATIONS (APPENDIX A)

12.12.1 SAMPLE SIZE DETERMINATION

The power and sample size calculations for analyzing the effects of the intervention on ESWT was based upon comparing the mean change in ESWT between the treatment groups with adjustment for ESWT measured at baseline. The regression model is:

$$E[ESWT_1 - ESWT_0 \mid Trt, ESWT_0] = \beta_0 + \beta_1 Trt + \beta_2 ESWT_0$$

where $E[ESWT_1 - ESWT_0]$ is referred to as the mean change in ESWT, Trt is the treatment assignment indicator with $(Trt = 1)$ for the exercise intervention and $(Trt = 0)$ for the control group; $ESWT_0$ is ESWT collected at baseline. The model parameter, β_1, is the mean change in ESWT between the two treatment groups, given that they have comparable baseline ESWT values. The parameter, β_1, represents the "treatment effect" for this primary endpoint.

For our sample size determinations, we considered a variety of plausible effect sizes for the treatment effect based upon the statistical summaries from Daynes et al.[44] Specifically, for the sample (N=30) of participants with lasting symptoms of COVID-19 [mean age 58 (standard deviation [SD]=16) years], the researchers observed a pre-rehabilitation mean (SD) ESWT of 292 (216) seconds and post-rehabilitation ESWT of 873 (406) seconds. The absolute change difference was approximately 544 seconds.

The following conservative assumptions were made for the sample size calculation:

- Overall baseline ESWT mean of 300 seconds, and
  - Absolute improvements of 150 (small), 225 (moderate) and 300 seconds (large)
  - For the assumed baseline ESWT (300 sec), this corresponds to percent change improvements of 50%, 75% and 100%
- Standard deviation of ESWT of 400 (medium), 450 (large) and 500 (very large) seconds
- Number of ESWT measurements collected at follow-up (i.e., one or two)
- Correlation between baseline and follow-up ESWT scores of r = 0.3 (low), 0.5 (moderate), and 0.7 (high)
  - *Note:* the higher the correlation, the more precision gained for change comparisons

- Our sample size projections below incorporate 20 percent attrition or drop out. These adjusted sample sizes have the form: Adjusted N = Original N / (1 – dropout rate).

Table 3 provides the minimum adjusted sample sizes necessary to achieve 80 or 90 percent power for the nine (3x3) combinations of effect sizes (Δ) and variability of ESWT (SD) for having 1 or 2 follow-up ESWT measurements.

Table 3. Minimum Adjusted Sample Sizes

		Standard Deviation (SD) of ESWT					
		SD = 400		SD = 450		SD = 500	
Mean Difference (Δ)	*Power*	*Follow-up ESWT measurements*		*Follow-up ESWT measurements*		*Follow-up ESWT measurements*	
		1	*2*	*1*	*2*	*1*	*2*
Δ = 150	*80%*	128	79	162	100	199	123
	90%	170	105	215	133	267	164
		1	*2*	*1*	*2*	*1*	*2*
Δ = 225	*80%*	58	35	73	45	89	55
	90%	77	48	97	60	119	74
		1	*2*	*1*	*2*	*1*	*2*
Δ = 300	*80%*	33	20	42	25	50	32
	90%	43	27	55	34	68	42

Shaded area shows the minimum sample size (per group) required for 80% and 90% statistical power.
The calculations account for 20% attrition & assume the missing data mechanism is non-informative.

We provided power and sample size curves (Figure 3[44]) for only small and moderate improvements in ESWT at follow-up. (Statistical power estimates for ESWT changes of 300 seconds was at least 97.8 percent for all combinations of SD's at 1 or 2 follow-up measures.) For Figure 3[44], the adjusted sample sizes were varied from N = 75 up to N=325 per group.

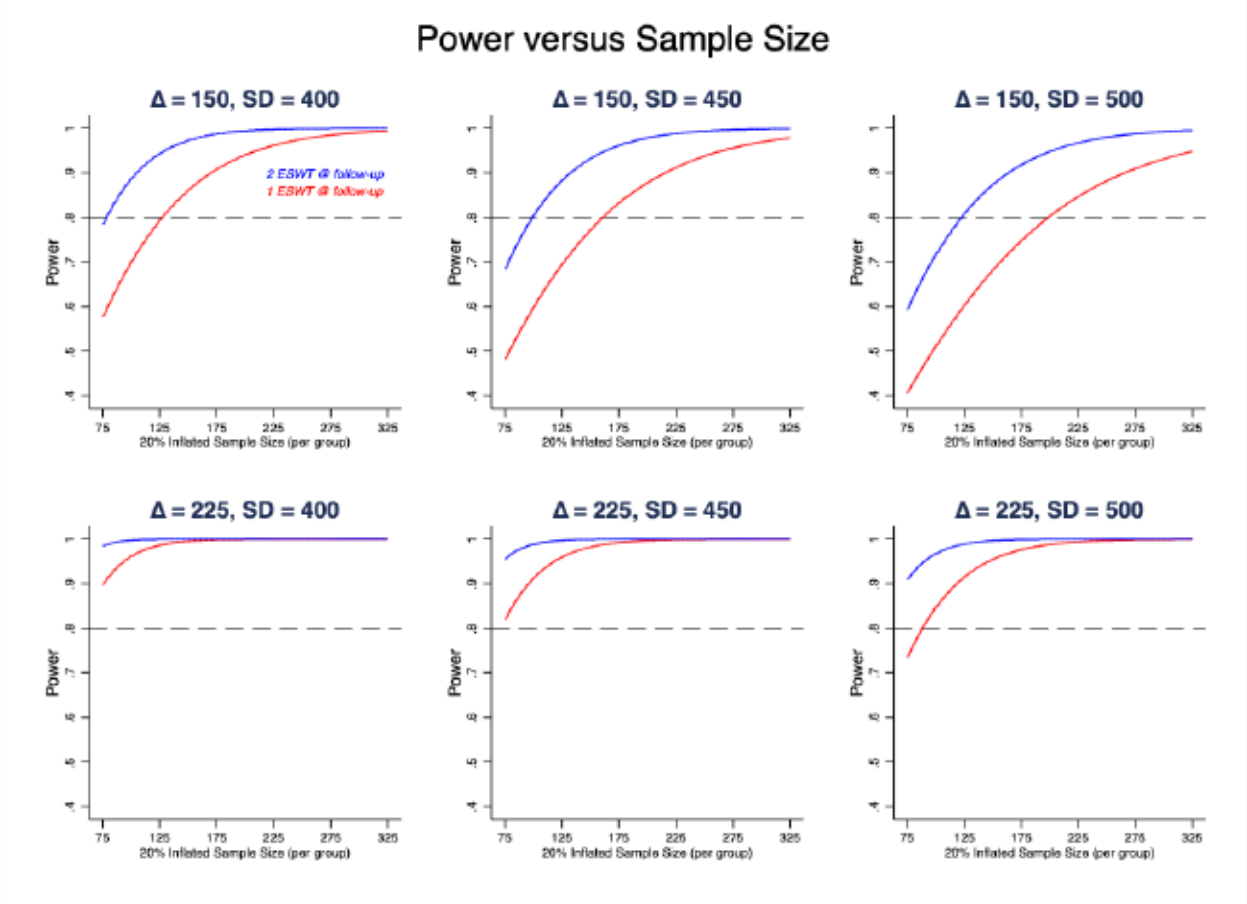


Figure 3. Sample size calculations

The symbol, Δ, represent the absolute improvements (i.e., mean differences in ESWT between the treatment groups). The blue lines correspond to using the average of ESWT measurements at follow-up; the red lines correspond to using a single ESWT measurement at follow-up in the analysis. We restricted our display the lowest intra-patient correlation of r=0.3. The two higher correlations investigated (r= 0.5, 0.7) yielded uniformly higher statistical power.

For the targeted sample size of N=360 per Appendix, randomized 1:1 study intervention to control, and using the average of two ESWT measurements at follow-up, statistical power will exceed 87 percent for all scenarios considered. If we consider using only a single ESWT follow-up measurement in our analysis, statistical power would exceed 80 percent except for the two most conservative scenarios (i.e., the smallest mean difference [150 seconds] at the two highest levels of variability of ESWT [SD=450 and 500 seconds]). In those scenarios, we would require adjusted sample sizes of N=162 if the SD were 450 seconds, and N=199 if the SD were 500 seconds. The sample size estimates are per treatment group, respectively. Please see Table 3 for additional information.

12.12.2 POPULATIONS FOR ANALYSES

Modified Intention-to-Treat (mITT) – Efficacy and safety analyses will be based on the mITT population. All enrolled participants who receive the control intervention or treatment intervention will be included in the analyses and will be analyzed according to their assigned treatment.

12.12.3 STATISTICAL ANALYSES

This section describes the analytical methods for the endpoints in Appendix A. The analytic approach to evaluate the primary and secondary outcomes will be independent data and correlated data regression analysis. Both regression methods will employ robust (sandwich) variance estimates for statistical testing and estimating confidence intervals. Full details will be provided in the SAP.

12.12.3.1 OVERALL STATISTICAL DESIGN

For this study, data from all enrolled participants who receive the control intervention or treatment intervention will be included in the analyses. Between group comparisons of the primary study endpoint, the change from baseline to EOI in ESWT, and quantitative secondary endpoints will be analyzed using linear regression, adjusting for the baseline ESWT as a concomitant variable and possibly pre-specified baseline characteristics (details to be provided in the SAP). Comparisons of the treatment groups for repeated measures outcomes (e.g., ESWT, mDSQ-PEM) will be investigated using Generalized Estimating Equations (GEE) regression models. Comparisons between the treatment groups and binary secondary outcomes will be tested using chi-square tests (of homogeneity).

Analyses of the primary endpoint, ESWT, require both the baseline and follow-up measurements. Participants that are missing one or both of their respective ESWT measurements will not be included in the analysis of the endpoint. Values will not be imputed for missing data in the confirmatory analyses. However, multiple imputation will be used to perform sensitivity analyses to investigate the conclusions of the study's findings. All hypothesis tests and (confidence) interval estimates will be two-sided. A Type I error rate of 0.05 will be used to investigate the hypothesis of the primary objective.

12.12.3.2 ANALYSIS OF APPENDIX A PRIMARY ENDPOINT

The mean difference between the treatment groups for the primary endpoint will be compared for the mTT population. Participants that complete the ESWT at baseline and at EOI will be included in the analysis for the primary aim. A between (treatment) group comparison for the mean difference in change from baseline to EOI in ESWT, adjusting for baseline ESWT as a concomitant variable and possibly pre-specified baseline characteristics (details to be provided in the SAP), will be conducted as

$$E[ESWT_1 - ESWT_0 | Trt, ESWT_0] = \beta_0 + \beta_1 Trt + \beta_2 ESWT_0$$

where the $ESWT_1$ is the measurement at the EOI study visit and $ESWT_0$ is the measurement at baseline. We will test the mean difference in the change of ESWT from baseline to EOI, between the two treatment groups, adjusting for the baseline ESWT by testing the null hypothesis that the regression parameter for the treatment variable, Trt, is statistically different from zero. The parameter, β_1, is interpreted as $\beta_1 = E[ESWT_1 - ESWT_0 | Treatment, ESWT_1] - E[ESWT_1 - ESWT_0 | Control, ESWT_0]$. We will test,

$$H_0: \beta_1 = 0.$$

12.12.3.3 ANALYSIS OF APPENDIX A SECONDARY ENDPOINTS

PROMIS SF – Physical Function. The PROMIS SF – Physical Function outcome is an ordinal variable and has eight items used to score a participant's level of physical function. The composite t-score ranges

from a low of 1 (cannot do/unable to do) to 5 (without any difficult/not at all). The mean t-scores will be compared between the treatment groups using GEE linear regression. The GEE accounts for intra-participant repeated measurements correlation and will be used to consistently test whether there is a treatment effect.

mDSQ-PEM Safety Endpoint. Post-exertional malaise (PEM) is defined as having no symptoms of moderate or greater severity with 50% or more frequency as determined by the mDSQ-PEM short form at EOI. Outcome differences by treatment group will be compared using GEE regression with a logit link. GEE is a natural extension to logistic regression to account for repeated measures in PEM scores. Modeling PEM severity with adjustment for baseline PEM severity (as determined by the mDSQ-PEM) will yield incidence odds ratio. The null hypothesis of no difference in the PEM incidence odds between treatment and controls will be investigated. An odds ratio less than one will be indicative of "better" for the active treatment.

Safety endpoints include the proportion of participants who experience individual ESIs and the proportion who experience any one or more ESIs (see Section 12.11). These will be analyzed in the safety population. ESIs will be summarized by study intervention Appendix and duration. Incidence of AEs/SAEs leading to discontinuation will also be summarized.

12.12.3.4 EXPLORATORY ENDPOINTS

Exploratory endpoints will be summarized with descriptive statistics. Continuous variables will be presented as n (with number of non-missing observations), mean, standard deviation, median, Q1, Q3, and minimum and maximum. Binary and categorical variables will be presented as counts and percentages (among non-missing values).

12.12.3.5 PLANNED INTERIM ANALYSES

Interim examination of clinical endpoints and key safety events will be performed at regular intervals during the course of the trial. An independent, NIH-appointed, DSMB will monitor participant safety and review participant enrollment and performance of the trial. The primary objective of these interim analyses will be to ensure the safety of the participants enrolled in the trial and evaluate the accumulating endpoint data by treatment group. In addition, interim monitoring will involve a review of participant recruitment, compliance with the study protocol, status of data collection, and other factors which reflect the overall progress and integrity of the study.

There are no planned early stopping rules for efficacy in this protocol. Because PASC presentations and outcomes are highly varied, an important study objective is to estimate the effect of treatment on a wide range of participant-relevant outcomes. If the study were to be stopped early with less than the full sample size, it would decrease precision and reduce the study's ability to characterize treatment risks and benefits based on important secondary effectiveness and safety outcomes. It would also limit the collection of data that are critical for planning future trials in similar patient populations.

13 APPENDIX B (PACING)

13.1 STUDY DESIGN AND RATIONALE

Post-exertional malaise (PEM) is defined as the worsening of both symptoms and function after even minor physical or mental exertion with symptoms typically worsening 12 to 48 hours after the activity and lasting from days to weeks.[45] It is a condition where patients experience the inability to exercise or to do routine activities of daily living at some point after earlier physical activity or even other forms of exertion (e.g., mental, cognitive, or emotional). Additionally, patients with PEM report cognitive dysfunction, changes in mood, and sleep disturbance following the exertion. PEM is experienced by people with PASC and is similar to the PEM experienced by patients diagnosed with ME/CFS in both onset and duration.[46] However, the experience of PEM (e.g., the symptoms and methods of recovery) differs between the patient groups.[46]

We are including an intervention known as pacing in this platform trial to determine whether it is effective in reducing the symptoms of PEM in patients suffering from PASC. Pacing is a management strategy for PEM that begins with determining individual limits for mental and physical activity with the goal of staying within these limits (also known as the "energy envelope") so PEM flare-ups can be mitigated. Pacing is an established therapy for patients diagnosed with PEM due to ME/CFS.[47,48] Since the emergence of SARS-CoV-2 and the identification of PASC[1-4,6], pacing has been identified as a possible therapy for PEM in patients who suffer from PASC.[49]

13.1.1 APPENDIX B SCHEMA

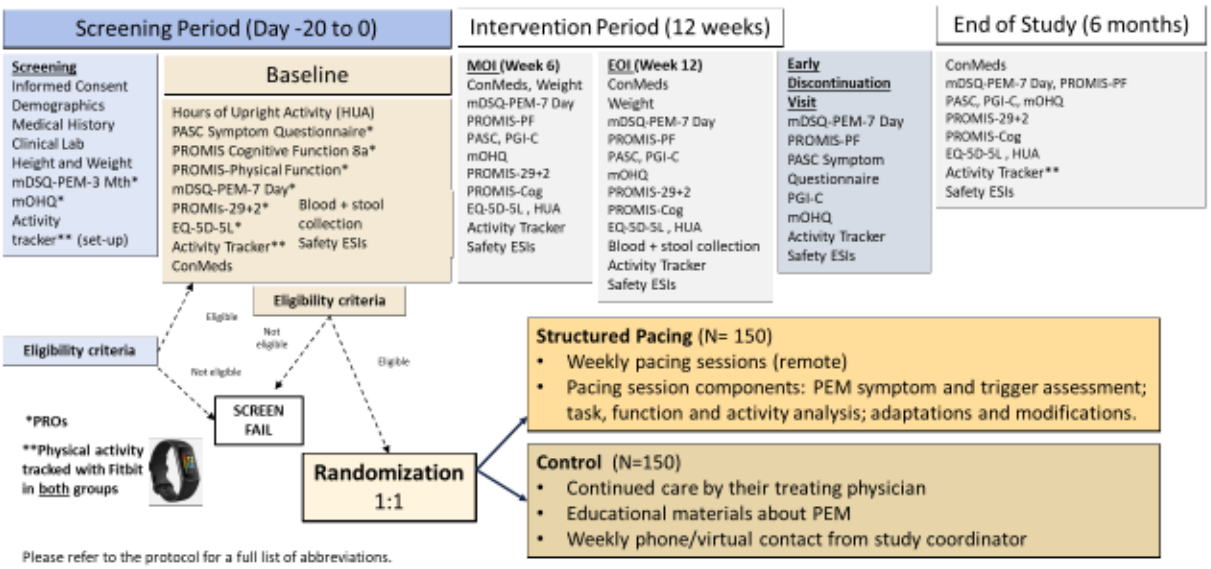


Figure 4. Appendix B Schema

13.1.2 OUTCOME MEASURES AND ENDPOINTS

Specific Appendix B objectives, outcome measures, and endpoints are provided below in Table 4.

Table 4. Appendix B Objectives, Outcome Measures, and Endpoints

OBJECTIVE	OUTCOME MEASURE	ENDPOINT
Primary		
Evaluate the effect of study intervention on PEM symptoms (frequency, severity, and duration) versus control	Modified DSQ-PEM	Change from baseline to EOI in the treatment group compared to control group
Secondary		
Evaluate the effect of study intervention on PASC symptoms versus control	PROMIS-Cog	Change from baseline to the middle of intervention, EOI, and EOS in the treatment group compared to control group
Evaluate the effect of study intervention on QoL versus control	• PROMIS-29+2 • EQ-5D 5L	Change from baseline to the middle of intervention, EOI, and EOS
Evaluate the effect of study intervention on physical activity versus control	• Actigraphy (Fitbit®) • PROMIS SF-Physical Function (PROMIS-PF)	Change from baseline to the middle of intervention, EOI, and EOS in the treatment group compared to control group
Evaluate the effect of study intervention on orthostatic hypotension versus control	• Modified Orthostatic Hypotension Questionnaire (mOHQ)	Change from screening to the middle of intervention, EOI, and EOS in the treatment group compared to control group on mOHQ
Exploratory		
Evaluate the effect of study intervention on physical activity versus control	Hours of Upright Activity (HUA) on Best Day and on Worst Day in last week	Change from baseline to the middle of intervention, EOI, and EOS in the treatment group compared to control group
Evaluate the effect of study intervention on relevant biomarkers versus control	• Viral biomarkers • Immune biomarkers	Change in biomarker(s) from baseline to EOI in the treatment group compared to control group
Evaluate the effect of study intervention on healthcare utilization versus control	Healthcare utilization – medical visits and hospitalizations	Change from baseline to the EOI in the treatment group compared to control group: • Cumulative medical visits • Cumulative hospitalizations
Evaluate the effect of study intervention on PASC symptoms versus control	PASC Symptom Questionnaire	Change from baseline to the middle of intervention, EOI, and EOS in the treatment group compared to control group

13.1.3 SCHEDULE OF APPENDIX B PROCEDURES

The full Schedule of Procedures for Appendix B is shown below in Table 5.

Table 5. Schedule of Study Procedures in Appendix B (Pacing)

	Screening Period		Baseline Period	Study Period (6 months)				
				Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	**Screening (before assignment to Appendix)**	**Appendix B Screening**	**Baseline Study Visit**	**Intervention Period Study Visit 1**	**Intervention Period Study Visit 2**	**End of Intervention (EOI) Study Visit**	**Early Discontinuation Study Visit[18]**	**End of Study (EOS)**
Weeks				1	6	12	N/A	24
Days	Day -20 to 0			Day 1[19]	Midpoint of Intervention Period (MOI) ± 7 Days	EOI Day + 7 Days	N/A	Randomization + 183 days ± 14 days
General Evaluations								
Main Informed Consent[20]	X							
Appendix-Level Eligibility Criteria		X						
Randomization *(Day 0)*			X[21]					
Demographics	X							
Medical History	X							

[18] Early Discontinuation Visits should prioritize PROs in the following order: mDSQ-PEM, PROMIS-SF Physical Function, PASC Symptom Questionnaire, and PGIC.
[19] Participants in the intervention arm have up to 30 days from randomization to start Day 1 of the intervention.
[20] The informed consent process should occur prior to any screening activities. Please refer to the MOP for details regarding the consent process.
[21] Randomization occurs after confirmation of eligibility and prior to initiating intervention.

	Screening Period		Baseline Period	Study Period (6 months)				
				Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	**Screening (before assignment to Appendix)**	**Appendix B Screening**	**Baseline Study Visit**	**Intervention Period Study Visit 1**	**Intervention Period Study Visit 2**	**End of Intervention (EOI) Study Visit**	**Early Discontinuation Study Visit[18]**	**End of Study (EOS)**
Weeks				1	6	12	N/A	24
Days	Day -20 to 0			Day 1[19]	Midpoint of Intervention Period (MOI) ± 7 Days	EOI Day + 7 Days	N/A	Randomization + 183 days ± 14 days
Height and Weight	X[22]				X[23]	X[23]		
Concomitant Medications			←==========Continuous==========→					X
Laboratory and Safety Evaluations								
Clinical Laboratory Test – Complete Blood Count	X							
Biorepository – Blood and Stool Collection[24]			X			X		
SAEs and ESIs		←==========Continuous==========→						
HRQOL Evaluations								
PASC Symptom Questionnaire			X		X	X	X	X
PROMIS-Cog			X		X	X	X	
PROMIS 29+2			X		X	X	X	

[22] To be done any time before randomization
[23] Weight only
[24] Two 1.0 mL aliquots of EDTA plasma and two 1.0 mL aliquots of serum to be frozen and stored for future research, as well as stool collection per MOP (see Sections 8.10.7 and 8.11)

	Screening Period		Baseline Period	Study Period (6 months)				
				Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	**Screening (before assignment to Appendix)**	**Appendix B Screening**	**Baseline Study Visit**	**Intervention Period Study Visit 1**	**Intervention Period Study Visit 2**	**End of Intervention (EOI) Study Visit**	**Early Discontinuation Study Visit[18]**	**End of Study (EOS)**
Weeks				1	6	12	N/A	24
Days	Day -20 to 0			Day 1[19]	Midpoint of Intervention Period (MOI) ± 7 Days	EOI Day + 7 Days	N/A	Randomization + 183 days ± 14 days
EQ-5D 5L			X		X	X	X	
PROMIS-SF Physical Function			X		X	X	X	
Hours of Upright Activity			X		X	X	X	
PGIC					X	X	X	
mDSQ-PEM-3 Month[25]	X							
mOHQ		X			X	X	X	X
mDSQ-PEM-7 Days[26]			X		X	X	X	X
Activity Tracker Distribution	X							
Activity Tracker[27]	X		X		X			X

[25] The lookback period for the mDSQ-PEM at Screening is 3 months.
[26] The lookback period for the mDSQ-PEM at Baseline and during the Intervention Period and the Follow-up Period is 7 days.
[27] The activity tracker is distributed for participants to wear during the study. Participant will be asked to wear the tracker for ≥ 7 days before the start of the Baseline Visit for the collection of baseline metrics. Participants are encouraged to wear the tracker throughout the study. Participants are also asked to wear the tracker for 7 days prior to study outcome visits and before the EOS visit.

	Screening Period		Baseline Period	Study Period (6 months)				
				Intervention Period (3 months)			Follow-up Period (3 months)	
Timepoint	**Screening** (before assignment to Appendix)	**Appendix B Screening**	**Baseline Study Visit**	**Intervention Period Study Visit 1**	**Intervention Period Study Visit 2**	**End of Intervention (EOI) Study Visit**	**Early Discontinuation Study Visit**[18]	**End of Study (EOS)**
Weeks				1	6	12	N/A	24
Days	Day -20 to 0			Day 1[19]	Midpoint of Intervention Period (MOI) ± 7 Days	EOI Day + 7 Days	N/A	Randomization + 183 days ± 14 days
Intervention								
Weekly Touch-in Phone Calls *(control arm only)*				X				
Structured Pacing Assessment *(intervention arm only)*				X[28]				
Structured Pacing sessions *(intervention arm only)*				X	X	X		

Abbreviations: MOI – Midpoint of Intervention, EOI – End of Intervention, EOS – End of Study, SAE – Serious Adverse Event, ESI – Event of Special Interest, HRQOL – Health-Related Quality of Life, PROs – Patient-Reported Outcomes, mDSQ-PEM – Modified DePaul Symptom Questionnaire – Post-Exertional Malaise, EDTA — Ethylenediaminetetraacetic acid, MOP – Manual of Procedures, PASC – Post-acute Sequelae of SARS-CoV-2 Infection, PROMIS – Patient-Reported Outcomes Measurement

[28] An initial assessment with a pacing coach establishes an individualized pacing program for each participant (see Section 13.9.2). Potentially, participants may have the initial assessment after randomization on the same day as Baseline, instead of at the beginning of Day 1 of the Intervention Period. Timing of the assessment can be determined at the site level based upon what works best for the participant.

13.2 BLINDING

Not applicable.

13.3 ADDITIONAL APPENDIX B – LEVEL INCLUSION CRITERIA

1. Participant identifies new PEM following a SARS-CoV-2 infection that has persisted for at least 12 weeks and is still present at the time of consent.
2. Score of 2 or greater for both frequency **and** severity for any of the first 5 questions on the Screening mDSQ-PEM **AND** answer of 'YES' to either item 7 or 8 on the Screening mDSQ-PEM, **AND** response of ≥14 hours in item 9
   OR
   Score of 3 or greater on any severity question (regardless of frequency) **AND** answer of 'YES' to either item 7 or 8 on the Screening mDSQ-PEM, **AND** response of ≥ 14 hours in item 9

13.4 ADDITIONAL APPENDIX B – LEVEL EXCLUSION CRITERIA

1. Inability to attend in-person screening visit or participate in weekly visits (in-person [≥ 1] and remote)
2. Participant was previously enrolled in Appendix A of this protocol and has NOT completed the full study follow-up period of Appendix A

13.5 MODIFICATIONS FOR COVID-19

If a participant tests positive for COVID-19 during the Intervention Period, the investigator or designee may modify the participant's schedule and assessments as needed, including temporary interruption of study intervention, if applicable. Information regarding the new COVID-19 infection will be collected, including date of positive test, any prescription medications started, and any associated symptoms or sequelae.

13.6 PARTICIPANT DISCONTINUATION/WITHDRAWAL

It is not anticipated that participants will develop worsened PEM from the pacing intervention, but if they do or if they are too ill to participate in the weekly communications with the pacing coach, any particular visit can be shortened or cancelled and deferred until the participant is well enough to continue. Once PEM symptoms are back to baseline, participants may resume the study intervention at a lower duration or intensity as recommended by trained staff. If the participant is unable to resume the study intervention due to continued worsening PEM symptoms after more than 2 weeks, the study intervention should be discontinued and follow-up assessments completed through EOS at 6 months. Please refer to Section 11.1.6 for a description of monitoring by the DSMB.

13.7 STUDY ASSESSMENTS AND PROCEDURES

Please also refer to Table 5.

13.7.1 APPENDIX B SCREENING (DAYS -20 TO 0)

Participants who sign informed consent for the study and enroll on Appendix B have the following additional screening procedures for eligibility.

- Review of Appendix-level eligibility criteria (see Sections 13.3 and 13.4)
- SAEs and ESIs (Refer to Section 9.1 and 13.11)
- mOHQ (Refer to Section 8.10.1.8)
- Blood collection for the following evaluations:
  - Complete blood count (Refer to Section 8.10.5)

13.7.2 BASELINE PERIOD (DAYS -13 TO 0):

The Baseline Period begins 13 days before starting the Intervention Period. The participant begins using their activity tracker ≥ 7 days before the Baseline Visit to establish baseline metrics.

13.7.3 BASELINE STUDY VISIT

Refer to Appendix B Table 4 for summary of all outcome measures specific to change from baseline.

The following baseline procedures are completed at Baseline Study Visit 1 following study informed consent:

- Randomization must occur after confirmation of eligibility and prior to initiating intervention, but can occur at any time during the baseline window (day of randomization is Day 0)
- Collection of concomitant medications taken within 14 days of study informed consent
- Blood and stool collection for biorepository (frozen for retrospective analysis) (Refer to Sections 8.10.7 and 8.11)
- SAEs and ESIs (Refer to Section 9.1 and 13.11)
- PASC (Refer to Section 8.10.1.6)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- EQ-5D 5L (Refer to Section 8.10.1.4)
- PROMIS SF-Physical Function (Refer to Section 8.10.1.3)
- Hours of Upright Activity (Refer to Section 8.10.1.9)
- mDSQ-PEM[26] (Refer to Section 8.10.1.7)
- Activity tracker check-in

13.7.4 INTERVENTION PERIOD (12 WEEKS)

The beginning of the 12-week Intervention Period is Day 1. Participants in the intervention arm have up to 30 days to start Day 1 of the intervention. On Day 1, the intervention arm of the study has their first structured pacing intervention visit. The frequency of pacing coaching sessions during this period should be weekly. Please refer to Section 13.9.2 and the MOP for more details.

- Concomitant Medication review
- SAEs and ESIs (Refer to Section 9.1 and 13.11)
- Activity tracker check-in
- Structured Pacing Assessment *(intervention arm only)*[28]
- *Intervention Arm only: Participants in the intervention arm receive weekly structured pacing coaching sessions (See Section 13.9.2 and refer to the MOP for details).*
- *Control Arm only: Participants in the control arm receive weekly phone call follow-ups during the Intervention Period (see Section 13.10.2).*

13.7.4.1 INTERVENTION PERIOD – MIDPOINT (APPROXIMATELY 6 WEEKS ± 7 DAYS)

Refer to Appendix B Table 4 for summary of all outcome measures specific to change from baseline to Midpoint.

- Weight
- Concomitant Medication review
- SAEs and ESIs (Refer to Section 9.1 and 13.11)
- PASC (Refer to Section 8.10.1.6)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- EQ-5D 5L (Refer to Section 8.10.1.4)
- PROMIS SF-Physical Function (Refer to Section 8.10.1.3)
- Hours of Upright Activity (Refer to Section 8.10.1.9)
- PGIC (Refer to Section 8.10.1.10)
- mOHQ (Refer to Section 8.10.1.8)
- mDSQ-PEM[26] (Refer to Section 8.10.1.7)
- Activity tracker check-in
- *Intervention Arm only: Participants in the intervention arm receive weekly structured pacing coaching sessions (See Section 13.9.2 and refer to the MOP for details).*
- *Control Arm only: Participants in the control arm receive weekly phone call follow-ups during the Intervention Period (see Section 13.10.2).*

13.7.4.2 END OF INTERVENTION (+ 7 DAYS)

Refer to Appendix B Table 4 for summary of all outcome measures specific to change from the start of the intervention period to EOI.

- Weight
- Concomitant Medication review
- Blood and stool collection for biorepository (frozen for retrospective analysis) (Refer to Sections 8.10.7 and 8.11)
- SAEs and ESIs (Refer to Section 9.1 and 13.11)
- PASC (Refer to Section 8.10.1.6)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- EQ-5D 5L (Refer to Section 8.10.1.4)

- PROMIS SF-Physical Function (Refer to Section 8.10.1.3)
- Hours of Upright Activity (Refer to Section 8.10.1.9)
- PGIC (Refer to Section 8.10.1.10)
- mOHQ (Refer to Section 8.10.1.8)
- mDSQ-PEM[26] (Refer to Section 8.10.1.7)
- Activity tracker check-in
- *Intervention Arm only: Participants in the intervention arm receive weekly structured pacing coaching sessions (See Section 13.9.2 and refer to the MOP for details).*
- *Control Arm only: Participants in the control arm receive weekly phone call follow-ups during the Intervention Period (see Section 13.10.2).*

13.7.5 FOLLOW-UP PERIOD (12 WEEKS)

13.7.5.1 EARLY DISCONTINUATION

If a participant discontinues the study early (i.e., no longer wishes to participate), the participant should be asked to complete an Early Discontinuation Visit. The following procedures should occur at an Early Discontinuation Visit if the participant is willing:

- SAEs and ESIs (Refer to Section 9.1 and 13.11)
- PASC Symptom Questionnaire (Refer to Section 8.10.1.6)
- PROMIS SF-Cognitive Function (Refer to Section 8.10.1.2)
- PROMIS-29+2 (Refer to Section 8.10.1.1)
- EQ-5D 5L (Refer to Section 8.10.1.4)
- PROMIS SF – Physical Function (Refer to Section 8.10.1.3)
- Hours of Upright Activity (Refer to Section 8.10.1.9)
- PGIC (Refer to Section 8.10.1.10)
- mOHQ (Refer to Section 8.10.1.8)
- mDSQ-PEM[26] (Refer to Section 8.10.1.7)
- Activity tracker check-in

An Early Discontinuation Visit should include, if possible, the PROMIS SF-Physical Function and PASC Symptom Questionnaire. However, the mDSQ-PEM is first priority. PROMIS SF – Physical Function is 2nd priority, and PASC Symptom Questionnaire is 3rd priority.

13.7.5.2 END OF STUDY (EOS) (± 14 DAYS)

Refer to Appendix B Table 4 for summary of all outcome measures specific to change from baseline to EOS.

The following procedures occur during the EOS visit 183 days (± 14 days) after randomization, which is remote by phone or videophone call for Appendix B:

- Concomitant Medication review
- SAEs and ESIs (Refer to Section 9.1 and 13.11)
- PASC Symptom Questionnaire (Refer to Section 8.10.1.6)

- mOHQ (Refer to Section 8.10.1.8)
- mDSQ-PEM[26] (Refer to Section 8.10.1.7)
- Activity tracker check-in

13.7.6 ADDITIONAL APPENDIX B ASSESSMENTS

Please refer Section 8.10 of the master protocol for descriptions of platform assessments used in Appendix B per Section 13.7 and Table 5.

13.8 PRECAUTIONS

Participants should be monitored for exacerbation of PEM.

13.9 STRUCTURED PACING INTERVENTION

Pacing is a personalized management strategy with the intent to prevent or reduce PEM. Typically, people who have PEM attempt normal activity and then experience symptom worsening that requires rest. These fluctuations alternate as a push-crash cycle that is not compatible with normal productivity. The concept of pacing begins with recognition of PEM occurrences, followed by an assessment of what may have caused the PEM. The triggers might be physical, orthostatic, or cognitive/emotional stressors that occurred one or even 2 days before the PEM symptoms. The next step is determining individual limits for activity, with the goal of staying within these limits (also known as the "energy envelope") so PEM flare-ups can be mitigated.[50] Pacing includes finding a balance of activity and rest so episodes of PEM can be prevented or diminished. The person may not achieve the highest level of activity desired, but successful pacing results in a more stable level of day-to-day activity with fewer illness symptom flares that makes productivity and quality of life more predictable.

Clinical sites are chosen that have an existing physical therapy, occupational therapy, rehabilitation therapy, or equivalent staff and services.

13.9.1 SCIENTIFIC RATIONALE FOR INTERVENTION

PEM is a challenging condition for those diagnosed with PASC.[46,51] Small interventional and observational studies of patients with PASC have shown benefits of structured pacing as a tool to ameliorate PEM.[49,52] However, larger efficacy studies are needed to learn whether structured pacing has a measurable impact on PEM in the PASC population.

13.9.2 INTERVENTION DETAILS AND ADMINISTRATION

Each participant will meet with a provider who has received study-specific education about PEM and how to create and manage pacing strategies for participants. These trained providers are called pacing coaches for the purpose of this study. Please refer to the MOP for details on pacing training for providers. The ideal trained provider would be an occupational therapist as the concepts align with their therapeutic practices. However, provider types may vary from occupational or physical therapists to rehabilitation therapists or home health nurses depending upon staffing at site locations. Once an initial

pacing strategy is created, the pacing coach speaks with the participant weekly to make appropriate, ongoing adjustments to their individualized pacing strategy.

13.9.3 RISK ASSESSMENT

The primary risk of the structured pacing intervention is exacerbation of PEM symptoms or feeling too ill to actively participate in the study. Pacing coaches work with participants closely, in order to make quick determinations of worsening PEM.

13.10 CONTROL INFORMATION

Usual care (i.e., care that the participant receives by their clinical team) is used for patients randomized to the control group. Participants in the control group receive basic education material about PEM and a weekly call for support and communication, but do not receive detailed guidance about pacing to prevent PEM. All study participants should be informed about the importance of adherence to study protocols and how participation, regardless of the intervention, is a contribution to the advancement of scientific knowledge.

13.10.1 SCIENTIFIC RATIONALE FOR CONTROL

Basic PEM education is used as a retention strategy for participants randomized to the control group of Appendix B. Basic PEM education material provided by a study team member is not expected to significantly increase effective pacing, the primary outcome of this study.

13.10.2 CONTROL DETAILS AND ADMINISTRATION

Usual care is any care (i.e., instruction, education, testing, etc.) provided by a participant's clinical care team.

13.11 EVENTS OF SPECIAL INTEREST (ESIS)

No ESIs are anticipated for Appendix B.

13.12 STATISTICAL CONSIDERATIONS (APPENDIX B)

13.12.1 SAMPLE SIZE DETERMINATION

For the targeted sample size of N=300 for Appendix B, randomized 1:1 study intervention to control, and using the arithmetic mean of the five symptom questions for frequency of the mDSQ-PEM questionnaire as the primary endpoint, statistical power will exceed 85 percent if there is a mean difference of 0.4 points between the treatment groups. Statistical power was estimated using an independent two-sample t-test. We assume a two-sided 5 percent alpha-level of significance (or a one-sided test with a 2.5 percent alpha). The estimates were determined conservatively using statistical summaries from recently published work on the DSQ-PEM (Jason et al., 2023).[53] Jason et al.[53] collected a sample of more than 2600 subjects with ME/CFS and controls and observed sample SD's that ranged between 1.08 and 1.11 for the mean of the five frequency questions. We conservatively assumed a SD of 1.15 points for our power calculations.

13.12.2 POPULATIONS FOR ANALYSIS

Modified Intention-to-Treat (mITT) – Efficacy and safety analyses will be based on the mITT population. All enrolled participants who receive the control intervention or treatment intervention will be included in the analyses and will be analyzed according to their assigned treatment.

13.12.3 STATISTICAL ANALYSES

This section describes the analytical methods for the endpoints in Appendix B. Full details will be provided in the SAP.

13.12.3.1 OVERALL STATISTICAL DESIGN

Data from all randomized participants who receive the control intervention or pacing intervention will be included in the analyses. We will make between group comparisons of the primary study endpoint, the change from baseline to EOI in the modified DSQ-PEM score, and also all quantitative secondary endpoints using linear regression, adjusting for pre-treatment outcomes as concomitant variables and possibly pre-specified baseline characteristics (details to be provided in the SAP) for each analysis performed. For secondary outcomes that include repeated measures outcomes (e.g., PASC Symptom Questionnaire, actigraphy, PROMIS-PF), we will use GEE regression models to evaluate treatment differences. Analyses of the primary endpoint, the modified DSQ-PEM score, require both the baseline and follow-up measurements. Participants that are missing one or both of their respective modified DSQ-PEM score will not be included in the analysis of the endpoint. Values will not be imputed for missing data in the confirmatory analyses. However, multiple imputation will be used to perform sensitivity analyses to investigate the conclusions of the study's findings. All hypothesis tests and (confidence) interval estimates will be two-sided. A Type I error rate of 0.05 will be used to investigate the hypothesis of the primary objective.

13.12.3.2 ANALYSIS OF APPENDIX B PRIMARY ENDPOINT

Modified DSQ-PEM Endpoint. The primary endpoints are the change from baseline to EOI in arithmetic mean for the five symptom questions for frequency, severity, and duration of the mDSQ-PEM questionnaire.

For frequency and severity, the mean differences between the treatment groups will be compared using linear regression with robust (sandwich) variance estimates. The frequency scores range from none of the time (0) to all of the time (4), and the severity scores range from symptom not present (0) to very severe (4). We will the model mean change of the scores in frequency, and severity of the mDSQ-PEM questionnaire from baseline to EOI, adjusting for the baseline outcome as a concomitant variable and possibly pre-specified baseline characteristics (details to be provided in the SAP). The regression model will have the form:

$$E[DSQPEM_1 - DSQPEM_0 \mid Trt, DSQPEM_0] = \beta_0 + \beta_1 Trt + \beta_2 DSQPEM_0$$

We will test whether there is a difference in the mean of the change in modified DSQ-PEM from baseline to EOI, between the two treatment groups, adjusting for the baseline mDSQ-PEM by testing the null hypothesis that the regression parameter for the treatment variable, Trt, is statistically different from

zero. The parameter, β_1, is interpreted as the mean difference between the treatment groups, given their baseline modified DSQ-PEM scores are the same. We will test, H_0: $\beta_1 = 0$, to formally evaluate whether there is an effect of the pacing intervention.

For duration, we will analyze it using a proportional odds or ordered logit regression model:

$$log\ odds[Duration \leq j \mid Trt] = \alpha_j + \beta_1 Trt, \quad j = 0,1,2,3,4$$

where *j* corresponds to one of the first five duration categories: 0: <1 hour, 1: 2–3 hours, 2: 4–10 hours, 3: 11–13 hours, 4: 14–23 hours, and 5: ≥24 hours; α_j are ordered intercept terms; β_1 is the coefficient for the treatment effect, where exp(β_1) represents the odds of being in a higher duration category (i.e., longer duration feeling worse) for the treatment group compared to the control group. A negative coefficient (i.e., $\beta_1 < 0$) is indicative of the pacing intervention lowering the duration of feeling worse. We will test, H_0: $\beta_1 = 0$ versus H_0: $\beta_1 < 0$, to formally evaluate whether the pacing intervention is beneficial for duration.

13.12.3.3 ANALYSIS OF APPENDIX B SECONDARY ENDPOINTS

All secondary endpoints: PASC Symptom Questionnaire, PROMIS-Cog, mOHQ, PROMIS-29+2, EQ-5D 5L, PROMIS-PF Physical Function, and the actigraphy measures obtained from the Fitbit® devices, will all be analyzed using GEE linear regression. The GEE approach accounts for intra-participant repeated measurements correlation. We will investigate whether there is an effect of the pacing intervention by testing whether the regression coefficient for the treatment indicator is statistically different from zero. mOHQ will be analyzed descriptively.

13.12.3.4 ANALYSIS OF APPENDIX B EXPLORATORY ENDPOINTS

Exploratory endpoints will be summarized with descriptive statistics. Continuous variables will be presented as n (with number of non-missing observations), mean, standard deviation, median, Q1, Q3, and minimum and maximum. Binary and categorical variables will be presented as counts and percentages (among non-missing values).

13.12.3.5 PLANNED INTERIM ANALYSES

No interim analyses are planned.