RECOVER-NEURO: A Platform Protocol for Evaluation of Interventions for Cognitive Dysfunction 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 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 central Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to 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.

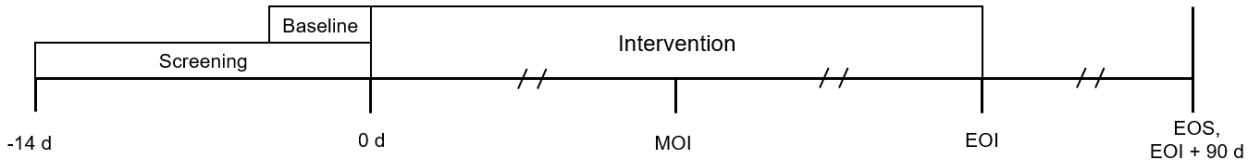
1.1 SYNOPSIS

Title:	RECOVER-NEURO: A Platform Protocol for Evaluation of Interventions for Cognitive Dysfunction in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
Study Description:	This platform protocol is designed to be flexible so that it is suitable for a wide range of settings within health care systems, for remote settings, and in community settings where it can be integrated into COVID-19 programs and subsequent treatment plans. This protocol is a prospective, multi-center, multi-arm, randomized, controlled platform trial evaluating potential interventions for symptoms of cognitive dysfunction that emerge in patients with PASC. The hypothesis is that PASC-associated dysfunction in cognitive domains, such as executive function and attention, may be improved by interventions that selectively focus on enhancing those domains.
Objectives:	Primary: 1. Evaluate the intervention's effect on self-reported cognitive function versus comparator Secondary: 1. Assess the intervention's effect on cognitive patient-reported outcomes (PROs) versus comparator 2. Compare the intervention's effect on an objective neurocognitive battery versus comparator 3. Evaluate the intervention's durable effect on self-reported cognitive function versus comparator

	4. Characterize the intervention's safety Exploratory: 1. Assess the intervention's effect on exploratory PROs versus comparator
Study Population:	Adults self-reporting cognitive dysfunction at least 12 weeks after a SARS-Cov-2 infection. The goal is to have a diverse population, including underserved communities and racial/ethnic populations frequently underrepresented in clinical research.
Phase:	Phase 2b
Description of Sites/Facilities Enrolling Participants:	Participants will be recruited from various acute COVID-19 trials and existing RECOVER initiatives including, but not limited to, the longitudinal cohort as well as other sites and research communities. Up to 45 sites in the US may participate. Though, the number and location of sites may differ among intervention appendices.
Description of Study Intervention:	Each intervention (fully described in each appendix) represents a different conceptual approach and control. In general, interventions will target enhancement of cognitive domains that present dysfunction following SARS-CoV-2 infection.
Participant Duration:	Participant duration will depend on the specific intervention appendix. After the intervention, participants will have one follow-up visit at 90 days.

1.2 SCHEMA

Figure 1. Overall protocol schema



Abbreviations: MOI, Middle of Intervention; EOI, End of Intervention; EOS, End of Study

1.3 KEY ROLES

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2 INTRODUCTION

2.1 STUDY RATIONALE

Post-Acute Sequelae of SARS-CoV-2 infection (PASC), also known as Long 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 number of PASC patients is escalating, and the personal and global impact of these long-term symptoms from SARS-CoV-2 infection can be debilitating. A prominent PASC symptom is cognitive dysfunction,[5] which can prevent patients' return to work.[6] Therefore, with the increasing number of people infected with SARS-CoV-2, an urgent and unmet clinical need exists to better understand the pathophysiology of PASC and to develop targeted interventions that restore patients' cognitive function. This platform protocol aims to investigate interventions with prior evidence of improving cognitive function. If successful, results will enable providers to treat PASC-related cognitive dysfunction.

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 (severe acute respiratory syndrome coronavirus 2, or SARS-CoV-2) as the etiological agent.[7] 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 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] Moreover, 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 healthcare costs and inability to work. Prolonged symptoms have kept individuals out of work, which has exacerbated poverty in the underserved, historically minoritized populations and worsened a decades-long mental health crisis. Considering these costs, identification of safe and effective methods to treat and prevent the occurrence of PASC represents an urgent, unmet public health need.

To address this need, the NIH has launched the RECOVER initiative across the nation (RECOVER: Researching COVID to Enhance Recovery) 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 women, and children. Data from the RECOVER initiative, as well as existing literature, highlight cognitive dysfunction as a frequently reported symptom that is substantially important to patients. Additionally, patients with PASC-related cognitive dysfunction express marked heterogeneity in symptomology and presentation.[8,9]

How COVID-19 induces cognitive dysfunction is not known. Postulated underlying mechanisms include neuroinflammation,[10,11] loss of hippocampal neurons,[10] microglial dysfunction,[11] and neuronal mitochondrial dysfunction.[11] What is known is that, in otherwise healthy adults, symptoms in the neuropsychiatric system cluster include persisting central fatigue,[12-14] central sensitization [15](myalgia,[16] headache[17]), emotional dysregulation[18,19] (depression,[20-22] anxiety[23,24]), and cognitive dysfunction ("brain fog").[5,25] Moreover, this cognitive dysfunction appears to persist for at least 7 to 12 months after acute SARS-CoV-2 infection.[26,27] This long-lasting impact contributes to functional disability, poor quality of life, and psychological morbidity.[28-31] This platform protocol focuses on treating PASC-mediated cognitive dysfunction.

No trials studying interventions directly addressing PASC-related cognitive dysfunction have reported results. One study intervening with olfactory training for olfactory dysfunction in PASC patients did observe memory improvements,[32] supporting the hypothesis that elements of cognitive dysfunction are reversible.

Furthermore, objective and subjective measures evaluating cognition in a PASC population are not well characterized. Objective measures are preferred for analyzing treatment effects on cognition; however, per the RECOVER initiative, only a portion of patients reporting cognitive problems truly have objective dysfunction through assessment. Therefore, to capture patients with objective deficits and those who do not but are still suffering in daily life with cognitive dysfunction, this platform protocol will use a subjective measure, the Everyday Cognition 2 (ECog2), to evaluate the interventions' effects on cognitive dysfunction (see Section 4.2 for detail).

The absence of data, heterogeneity and novelty of PASC, discordance between reported symptoms and objective findings,[8,9,33] and lack of validated measures and endpoints specific to this disease process highlight the importance of studying interventions in the context of well-controlled clinical trials to ensure that optimal and appropriate therapies are made rapidly available for patients. Additionally, clinical trials performed in the PASC population will test the utility of endpoints and outcome measures previously well-established in other disease processes.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks of this trial include those associated with the specific intervention (refer to appendices for details), blood draws, nasal swabs, 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 unlikely.

Risks associated with nasal swabs include mild irritation, insignificant local pain, and minor bleeding.

Loss of confidentiality is a risk. However, coding all participant data with a unique identification number will minimize this risk.

Participation in this study may induce post exertional malaise (PEM) in those prone to PEM or worsen symptoms in those who already have PEM. PEM may be triggered by travel to appointments, extended neurocognitive testing, or active participation in the interventions.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may benefit directly from improved cognitive function.

Future individuals who acquire PASC-mediated cognitive dysfunction will benefit from knowing effective treatment options.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential benefits may outweigh potential risks. Post-acute sequelae of SARS-CoV-2 infection (PASC) is a significant health issue and can have consequences that impact quality of life. These consequences are extremely important for the individual and the society at large.

PEM will be assessed at multiple time points of the interventions.

3 OBJECTIVES AND ENDPOINTS

The objectives, outcome measures, and endpoints for the trial are listed in Table 1. Further details on outcome measures and endpoints are provided in Section 10 and the Statistical Analysis Plan (SAP).

Table 1. Summary of study objectives, outcome measures, and endpoints

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
Primary		
Evaluate the intervention's effect on self-reported cognitive function versus comparator	Everyday Cognition 2 (ECog2)	Change in average score from baseline to End of Intervention (EOI)
Secondary		
Assess the intervention's effect on cognitive patient-reported outcomes (PROs) versus comparator	PROMIS-cognitive function – short form 8a (PROMIS-Cog)	Change in total score from baseline to EOI and End of Study (EOS), defined as 90 days post-intervention
Compare the intervention's effect on an objective neurocognitive battery versus comparator	• Auditory Verbal Learning Tests • Symbol Digit Modalities Test • Verbal Fluency (lexical + semantic) • Digit Vigilance Test • Cogstate tests: Detection, Identification, One Back • NIH Toolbox Flanker Inhibitory Control and Attention Test	Change from baseline to EOI and EOS
Evaluate the intervention's durable effect on self-reported cognitive function versus comparator	ECog2	Change in average score from baseline to EOS
Characterize the intervention's safety	Serious Adverse Events (SAEs), Unanticipated Adverse Device Effects (UADEs), and/or Events of Special Interest (ESIs)	Proportion of SAEs, UADEs, and/or ESIs
Exploratory		
Assess the intervention's effect on exploratory PROs versus comparator	• PASC Symptom Questionnaire • Patient-reported Outcomes Measurement Information System (PROMIS)-29+2 • PROMIS-fatigue – short form 10 a (PROMIS-Fatigue) • PROMIS-8a sleep related impairment (PROMIS-SRI) • PROMIS-8b sleep disturbance (PROMIS-SD) • Modified DePaul Symptom Questionnaire Post Exertional Malaise (DSQ-PEM)	Change in total score from baseline to EOI and EOS

4 STUDY DESIGN

4.1 OVERALL DESIGN

The overall design is a platform protocol designed to be flexible so that it is suitable for a wide range of settings within healthcare systems, for remote settings, and in community settings, where it can be integrated into COVID-19 testing programs and subsequent treatment plans. This platform protocol is a prospective, multi-center, multi-arm, randomized, controlled trial evaluating treatment of PASC-mediated cognitive dysfunction in outpatients previously infected with SARS-CoV-2.

This protocol will recruit adults experiencing PASC symptoms for at least 12 weeks and reporting reduced cognitive function following acute COVID-19 infection. This protocol will enroll participants meeting patient reported outcome criteria for cognitive dysfunction. Participants will consent before being randomly assigned to one of the actively enrolling interventions.

Each appendix will describe an intervention that is sized to meet the platform protocol objectives. Participants will be randomized to one of the intervention appendices that are actively enrolling at the time of randomization. See Section 6.2 for randomization details. Intervention appendices may be added or removed according to adaptive design and/or emerging evidence. Various interventions will be studied; refer to the protocol appendices for further information on each intervention.

This protocol will leverage common data elements (CDEs) already collected as part of the RECOVER initiative as well as assess overall global health status and symptomatology. Organ-specific assessments, including PROs of symptoms and functional status, and objective assessments will also be done. Intervention duration will be specific to an intervention appendix, but all will include a final study assessment 90 days after the intervention. Follow-up will be a combination of in-person visits when necessary to obtain objective clinical assessments and phone calls to be mindful of the participant burden.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Each intervention appendix under this platform protocol will follow a randomized trial design to compare the intervention(s) to a comparator. Intervention appendices will target affected cognitive domains, such as executive functioning and attention. Additional interventions can be studied as new interventions are available or as knowledge of PASC-mediated cognitive dysfunction evolves.

Inclusion will be based on patient-reported complaints (PROMIS-Cog) to maximize inclusiveness, because over half of individuals in the RECOVER observational study who had cognitive complaints do not have objective evidence of cognitive dysfunction. The RECOVER-NEURO Working Group recognizes the concern that those participants without objective evidence of cognitive dysfunction may be phenotypically different from those with objective cognitive dysfunction. However, while this is an issue for the FDA, FDA approval is not a goal here.

The primary outcome for this study uses a subjective assessment for cognitive function, the ECog2, instead of or without the addition of an objective assessment for multiple reasons: (a) the inclusion criteria do not require objective criteria; (b) the sensitivity of standard cognitive tests for PASC-related cognitive dysfunction is unknown; and (c) the cognitive deficits of the population under study are still undefined.

Moreover, the original ECog was designed to measure specific aspects of everyday cognition related to memory, language, visuospatial functions, and executive functioning. The ECog2 is clinically relevant and has been validated in the setting of mild cognitive dysfunction, which may increase its sensitivity to the PASC population and to tracking functional outcomes longitudinally. Furthermore, the ECog2 is a robust measure of perceived cognition, spanning across cognitive domains, unlike the other PROs being used. Finally, it has been translated into several languages and validated in a wide range of ethnic/racial minority populations and across educational levels, which increased the likelihood of generalizability.

4.3 JUSTIFICATION FOR DOSE

The dose and duration of the intervention will be based on the specific intervention. Refer to the appendices for details.

4.4 END OF STUDY DEFINITION

The End of Study will occur when all participants have completed their End of Study Visit.

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. PROMIS-Cog T-score < 40
3. Previous suspected, probable, or confirmed SARS-CoV-2 infection, as defined by the Pan American Health Organization[34]

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

    A. Met clinical OR epidemiological criteria:

    a. 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;

    b. Epidemiological criteria: Contact of a probable or confirmed case or linked to a COVID-19 cluster;

B. Presented 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. Presented 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, defined as having met clinical criteria above AND was a contact of a probable or confirmed case or was linked to a COVID-19 cluster.

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

A. Presented with a positive nucleic acid amplification test, regardless of clinical criteria OR epidemiological criteria; or

B. Met clinical AND/OR epidemiological criteria (See suspected case A), with a positive professional use or self-test SARS-CoV-2 Antigen-Rapid Diagnostic Test.

** Suspected and probable cases will only be allowed if they occurred before May 1, 2021, and will be limited to 10% of the study population. Otherwise, confirmed cases are required.*

4. Cognitive dysfunction symptoms following a SARS-CoV-2 infection that have persisted for at least 12 weeks and are still present at the time of consent[35,◊]
5. Fluent in English or Spanish language
6. Willing and able to provide informed consent, complete the intervention, complete the intervention assessments, and return for all of the necessary follow-up visits

5.2 EXCLUSION CRITERIA

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

1. Prior or active unstable or progressive major psychiatric or neurologic condition that would not show improvement and could hide treatment effect , at the investigator's discretion, including, but not limited to, the following examples:
    a. Progressive neurodegenerative disease, such as Alzheimer's disease, Parkinson's disease, etc.
    b. Past traumatic brain injury occurrence still associated with active post-concussive symptoms
    c. Uncontrolled seizure disorder, such as having at least one seizure in the last year that is adjudicated by clinical judgment
    d. Post-stroke deficits that may interfere with assessment, such as language or communication difficulties, aphasia, etc.
    e. Formal thought disorders, such as schizophrenia, etc.
    f. Any neuropsychiatric or neurologic disorder uncontrolled for the previous six months or that may interfere with assessment, at discretion of the investigator
2. Known prior diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome, not related to SARS-CoV-2 infection
3. Known active acute SARS-CoV-2 infection ≤ 4 weeks from consent
4. Current use of medications listed in Table 2*
5. History of electroconvulsive therapy
6. Current use of any medication for treating PASC-related symptoms
7. Attention-deficit/hyperactivity disorder (ADHD) diagnosis following the onset of PASC**

8. Current diagnosis of alcohol and substance use disorders
    a. Prior use disorders acceptable if abstinence achieved and maintained for at least 12 months before study enrollment
9. Insufficient visual, auditory, and motor function to participate in intervention and assessments
10. Known pregnancy
11. Current or recent use (within the last 2 months) of the intervention***
12. Known allergy/sensitivity/hypersensitivity to components of the intervention or comparator***
13. Currently receiving/using intervention from another clinical trial, such as another RECOVER trial****
14. Any condition that would make the participant, in the opinion of the investigator, unsuitable for the study
    a. The site investigator has the discretion to determine whether a participant is too cognitively impaired to participate and should instead be referred for clinical evaluation.

** Participants who are currently taking prohibited medications (Table 2) or alternative therapies (Table 2, Section 6.4.2) may undergo a 30-day washout period, which will be determined by the site principal investigator based on standard of care practices. However, if the site principal investigator determines that the participants must continue taking their current medication regimens or alternative therapies, then the participants will be ineligible for enrollment.*

***Participants diagnosed with ADHD prior to PASC-related symptoms and who are compliant on stable doses of medication may participate per the investigator's discretion. Participants should agree to maintain a stable dose of their medication while in the trial.*

**** Relevant if only one intervention appendix is open at the time of enrollment, though exclusion may be qualified in the appendix. If multiple intervention appendices are open, a participant may be excluded from any intervention appendix based on contraindications listed in the intervention appendix, current use of intervention, or known allergy/sensitivity/hypersensitivity and still remain eligible for the remaining intervention appendices.*

*****Following another interventional trial's end-of-study visit, participants must wait 90 days before enrolling into NEURO.*

Exclusions specific to intervention appendices are listed in each appendix.

5.3 LIFESTYLE CONSIDERATIONS

Participants must agree not to begin, resume, or increase the dose of any form of cognitive training or cognitive-enhancing supplements until the end of the active intervention phase of the trial. Participants who stop taking a cognitive-enhancing supplement before being enrolled must complete 30 days of washout before beginning study procedures. Cognitive training is any non-pharmacological intervention that participants started intending to enhance their cognition. A cognitive-enhancing supplement is any non-prescription compound being taken by participants with the goal of enhancing their cognition. Beginning, resuming, or increasing the dose of cognitive training or cognitive-enhancing supplements will result in a protocol deviation.

Participants must agree not to change their current dose of stimulant, atypical stimulant, non-stimulant medication used to treat ADHD, or antidepressant medication while on-study, unless directed by their prescribing clinician, in which case the dose change will be recorded on the eCRF.

Participants capable of becoming pregnant are encouraged to use an effective method of contraception during study intervention administration and for at least 7 days after the final administration of study intervention. If this consideration is not required for a specific appendix, the appendix will expressly state that contraception is not required. Additionally, the appendix will state whether participants can remain in the study if they becomes pregnant.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. 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 demography, screen failure details, and eligibility criteria.

5.5 STUDY DEFINITION OF ENROLLMENT

For this study, enrollment is defined as signing consent and completing randomization.

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

The RECOVER Clinical Trial Data Coordinating Center (CT-DCC) will use 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 will be refined and utilized. The study team will develop a comprehensive communication strategy involving print and social media, as well as leveraging 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 outreach by participating sites. Site investigators, or their designees, may contact eligible participants to introduce the study and discuss study participation.

Participants may be recruited from other ongoing COVID-19 trials if they opted-in to be contacted about future research opportunities. However, after completing other trials' interventions, including other RECOVER trials, 90 days must lapse before screening for this trial.

Finally, to support participant referral to actively enrolling trials, a series of invitation algorithms based on appendix-specific inclusion/exclusion criteria and participant-entered data may be used. Automatic invitations will be generated for participants who appear eligible based on trial interest, demographics, and medical history. Once participants accept the invitation and adequate consent is obtained, their information will be shared with the applicable study team.

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

During the active study period, study sites will maintain close connections with study participants.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

See appendices for full descriptions.

6.1.2 DOSING AND ADMINISTRATION

See appendices for detailed description.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Since the form of each intervention may differ, the comparators also may differ. In general, the comparator will be a reference intervention against which the effectiveness or safety of an experimental intervention is assessed. To achieve blinding and an equitable randomization probability, a two-step randomization process will be used. The study will employ a simple (unstratified) randomization scheme.

At the first stage, each participant will be assigned with equal probability to one of the intervention appendices for which the participant is eligible, after applying any intervention-specific safety exclusions. At the second stage, each participant will be assigned according to the specific appendix's randomization procedure.

If open intervention appendices have the ability to pool comparators, randomization to either an intervention or comparator will occur at an m:1 ratio, where m equals the number of interventions currently active in the platform protocol and which the participant is eligible to receive. For example, if 3 interventions are active simultaneously with comparators that can be pooled, and if the participant meets the criteria to receive all 3 interventions, the allocation ratio at the first step will be 1:1:1 and the second step 3:1 (intervention vs comparator) for an overall randomization ratio of 1:1:1:1. If 3 interventions are available, but a participant is only eligible to receive 2 of them, the allocation ratio at the first step will be 1:1, and at the second step will be 2:1 (intervention vs comparator) for an overall randomization of 1:1:1. Inclusion of a comparator for each intervention enables masking of study participants and clinical personnel to intervention assignment at the second stage. Participants randomized to the control comparator will only be included in the analyses of the appendices for which they were eligible.

Participants assigned to comparator will be considered part of pooled analyses if the intervention was active at the time of their enrollment and they were eligible to receive that intervention. This will result in approximately a 1:1 allocation ratio for any intervention to pooled comparator. If comparators differ substantially, the comparators will not be pooled.

Sites will be informed to which intervention appendix participants are randomized, but, when applicable, not whether they are allocated to the active intervention arm or comparator arm within that appendix. The participants and investigators will be blinded throughout the study, when possible.

If open intervention appendices do not have the ability to pool comparators but have independent comparators, at the second stage participants will be randomized in a 1:1 ratio to intervention vs comparator inside the specific intervention appendix they were randomized to at the first stage of the randomization procedure.

6.2.1 UNBLINDING

The participants, treating clinicians, and study personnel will remain blinded to intervention versus comparator assignment, when possible, until after the database is locked and final analysis is completed. Only the biostatistical team preparing closed interim reports will be unblinded. Unblinding will occur only if required for participant safety or treatment, at the request of the treating clinician. Refer to the Manual of Procedures (MOP) for further details.

6.3 STUDY INTERVENTION ADHERENCE

Participants will be notified of the importance of adhering to the entire protocol. Adherence definitions and aids may be detailed in each appendix.

6.4 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 will include all concomitant therapies taken by the participant within 14 days of informed consent.

Categorized as concomitant therapies for this protocol are forms of cognitive training and cognitive-enhancing supplements, both of which are defined in Section 5.3.

6.4.1 PROHIBITED MEDICATIONS

Any medication used for symptomatic treatment of PASC is not permitted during the study.

Table 2 displays medications and therapies and their conditions for being allowed or prohibited for participation. If participants are on prohibited medications and interested in participating, they should be encouraged to discuss discontinuing medications with their clinicians. Additionally, Table 2 lists commonly encountered medication examples. Questions about the status of other medications presenting in these drug classes should be directed to the sponsor.

Table 2. Prohibited medications and therapies

Drug class/Therapy	Generic name (examples)	Brand name (examples)	Allowed	Prohibited	Notes
Stimulant	methylphenidate	Adhansia, Aptensio, Concerta, Cotempla, Daytrana, Jornay, Focalin, Metadate, Methylin, Quillichew, Quillivant, Relexxii, Ritalin	Participants who were on stable doses of stimulants used for ADHD *before* their PASC symptoms will not need to washout, can maintain their current dose regimen All other instances of stimulant use after a 30-day washout before randomization	All other instances of stimulant use	Dose should be stable ≥ 90 days before randomization and maintained for study duration. A necessary change in dose does not cause discontinuation, but the dose change must be documented in the EDC.
	amphetamine/ dextroamphetamine/ lisdexamphetamine	Adderall, Adzenys, Desoxyn, Dyanavel, Mydayis, Vyvanse			
Atypical stimulant	armodafinil	Nuvigil	Participants who were on stable doses of atypical stimulants used for ADHD *before* their PASC symptoms will not need to washout, can maintain their current dose regimen. All other instances of atypical stimulant use after a 30-day washout before randomization	All other instances of atypical stimulant use	Dose should be stable ≥ 90 days before randomization and maintained for study duration.
	modafinil	Provigil			
	bupropion	Aplenzin, Budeprion, Buproban, Forfivo, Wellbutrin, Zyban			
	amantadine	Gocovri, Osmolex, Symmetrel			
Non-stimulant medications used to treat ADHD	atomoxetine	Strattera	Participants who were on stable doses of non-stimulant medications used for ADHD *before* their PASC symptoms will not need to washout, can maintain their current dose regimen.	Participants on non-stimulant medications used to treat ADHD if the dose is *not* stable or if the ADHD occurred *after* the onset of PASC	Dose should be stable ≥ 90 days before randomization and maintained for study duration.
	viloxazine	Qelbree			
	clonidine	Catapres, Kapvay, Nexiclon			
	guanfacine	Intuniv, Tenex			
Therapies for cognitive dysfunction used for symptomatic treatment of PASC or premorbid cognitive symptoms	donepezil	Aricept	After a 30-day washout	Continued treatment	
	memantine	Namenda			
	rivastigmine	Exelon			
	galantamine	Razadyne			
Narcotics	hydromorphone	Dilaudid	Occasional use (1-2 times/week) of low-dose narcotics according to local standards. All other instances of narcotic use after a 30-day washout before randomization	All other instances of narcotic use are exclusionary, such as higher frequency and dose	use must be refrained within 48 hours prior to assessments; failure to refrain will require rescheduling of the assessments.
	methadone	Dolophine, Methadose			
	meperidine	Demerol, Meperitab			
	oxycodone	Dazidox, Oxaydo, OxyCONTIN, Oxydose, Oxyfast, Roxicodone, Roxybond, Xtampza, Endodan, Percodan, Combunox, Endocet, Magnacet, Narvox, Percocet, Perloxx, Primalev, Roxicet, Roxilox, Tylox, Xartemix, Xolox			
	fentanyl	Lazanda, Duragesic, Ionsys, Sublimaze			
	morphine				
	opium				
	codeine				
	hydrocodone				

Drug class/Therapy	Generic name (examples)	Brand name (examples)	Allowed	Prohibited	Notes
Benzodiazepines	diazepam	Valium	Occasional use (1-2 times/week) of low-dose benzodiazepines according to local standards. All other instances of benzodiazepine use after a 30-day washout before randomization	All other instances of benzodiazepine use are exclusionary, such as higher frequency and dose	Use must be refrained within 48 hours prior to assessments; failure to refrain will require rescheduling of the assessments.
	alprazolam	Niravam, Xanax			
	triazolam	Halcion			
	lorazepam	Ativan, Loreev			
	clonazepam	KlonoPIN			
Anticholinergics	atropine	Atropen	Non-systemically administered (eg, inhaled, topical) anticholinergics, like the inhaled agents for bronchospasm, regardless of frequency and dose	Systematically administered (eg, oral, IV, IM, etc.) anticholinergics are exclusionary, unless it is washed out for 30 days prior to randomization	
	scopolamine	Maldemar, Scopace, Transderm Scop			
	trihexyphenidyl	Artane, Trihexane, Tritane			
	benztropine	Cogentin			
Antidepressants	fluoxetine	PROzac, Rapiflux, Sarafem	Participants who were on stable doses of antidepressants *before* their PASC symptoms will not need to washout, can maintain their current dose regimen.	All other instances of antidepressant use *after* PASC diagnosis are exclusionary, unless it is washed out for 30 days prior to randomization.	Dose should be stable ≥ 90 days before randomization and maintained for study duration. A necessary change in dose does not cause discontinuation, but the dose change must be documented in the EDC.
	duloxetine	Cymbalta			
	citalopram	Celexa			
	sertraline	Zoloft			
	paroxetine	Paxil, Pexeva			
	escitalopram	Lexapro			
	mirtazapine	Remeron			
	bupropion	Wellbutrin			
Electroconvulsive therapy			None	Any history of use	
Transcranial magnetic stimulation therapy			After a 30-day washout	Continued treatment	

6.4.2 ALTERNATIVE THERAPY

Transcranial magnetic stimulation and electroconvulsive therapy are NOT permitted during the study period. Any lifetime use of electroconvulsive therapy is exclusionary, but previous use of transcranial magnetic stimulation is permitted as long as it has not been performed within 30 days of study initiation.

6.4.3 RESCUE MEDICINE

Participants who require a rescue medication to treat a non-study-related acute condition during the study period should proceed with treatment for the acute condition, as prescribed by their treating clinician. They may continue receiving the intervention regardless of the medication.

7 PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION FROM INTERVENTION

Discontinuation from an intervention does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (such as changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed.

An investigator may use his/her discretion to discontinue a participant from the intervention for any reason, including, but not limited to, one of the following:

- Significant study intervention non-compliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Confirmed new case of acute SARS-CoV-2

The reason for participant discontinuation from an intervention will be recorded on the CRF. Participants who are discontinued from the intervention, but who are not withdrawn from the study, will continue to be followed for all study procedures. If participants discontinue an intervention, but do not withdraw consent, they will be followed for safety for at least 28 days.

7.2 PARTICIPANT WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. The study team will attempt to determine a reason for withdrawal; however, participants are not obligated to provide a reason for withdrawal. If obtained, the reason for withdrawal will be recorded on the CRF. No further study procedures will be performed and no further data will be collected from the participant following study withdrawal. All of the data collected up until the time of withdrawal will be maintained in the study database and will be used as the participant's data are evaluable for analysis.

7.3 LOST TO FOLLOW-UP

Participants will be 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 for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant or next of kin (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, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.4 STUDY HALTING RULES

The Data and Safety Monitoring Board (DSMB) will review study data at a regular frequency. During DSMB review, study enrollment and intervention-specific activities will continue. However, if the DSMB recommends to discontinue study activities, study enrollment and intervention-specific activities will be temporarily suspended while the NIH and the study Co-Principal Investigators consider the DSMB recommendations prior to making decisions on study continuation or discontinuation.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCHEDULE OF PROCEDURES

This table displays the general activities schedule for all interventions; however, intervention-specific activities that differ will be listed in the intervention appendix.

Table 3. Schedule of study procedures

	Screening	Baseline[1]	Start of Intervention	Middle of Intervention	End of Intervention	End of Study
PROCEDURE	**Day -14 to 0**	**Day -4 to 0**	**Day 0 + 21 days**	**MOI ± 3 days**	**EOI ± 3 days**	**EOI + 90 days (±3 days)**
Informed consent	X					
Demographics	X					
Medical history	X					
COVID treatment		X				
Blood pressure, heart rate, weight		X			X	X
Height	X					
Concomitant medication/therapy	X	X		X	X	X
Appendix-level eligibility criteria	X					
PROMIS-Cog	X			X	X	X
ECog2		X		X	X	X
Neurocognitive battery		X			X	X
Exploratory PROs		X[2]		X[2]	X[2]	X[2]
Randomization		X				
Safety assessment		X	X	X	X	X[3]
DSQ-PEM, twice weekly			X	X	X	
Nasal swab		X				
Pregnancy test		X				
Biorepository collection		X[4]			X[4]	X[5]

[1] Baseline assessments may occur on the same day as Screening

[2] The DSQ-PEM will be performed the immediate next day after completing the neurocognitive battery (Baseline, EOI, EOS) or study visit (MOI).

[3] As needed per intervention

[4] Blood and stool collection

[5] Blood collection only, no stool

8.2 SCREENING (DAY -14 TO 0)

The trial's activities, benefits and risks, and other treatment options will be thoroughly explained to potential participants. After obtaining informed consent, the following assessments will be performed at screening to determine eligibility:

- Demographics
- Medical history
- Height
- Collection of concomitant medications/therapies taken/received within 14 days of informed consent
- PROMIS-Cog*
- Review appendix-level eligibility criteria, refer to appendices

*If Baseline activities do not begin within 7 days of the participant completing the PROMIS-Cog, the PROMIS-Cog must be re-completed, with an inclusive score, before Baseline activities begin.

Participants who fail screening may be re-screened one time. Re-screening more than once is at the site investigator's discretion.

8.3 BASELINE (DAY -4 TO 0)

Baseline assessments may occur on the same day as Screening. The following will occur at the Baseline visit:

- Blood pressure, heart rate, and weight
    - Blood pressure and heart rate measurements should be obtained in the supine and standing positions: Supine measurements will be taken after the participant lies supine for 5 minutes, and then standing measurements after the participant stands for 1 minute.
- COVID treatment, including infection dates, treatment history, and vaccine use
- Concomitant medication/therapy review
- ECog2
- Neurocognitive battery, including the World Health Organization-University of California Los Angeles Auditory Verbal Learning Test (WHO-UCLA AVLT), Symbol Digit Modalities Test, Verbal Fluency (lexical + semantic), Digit Vigilance Test, Cogstate tests (Detection, Identification, One Back), and NIH Toolbox Flanker Inhibitory Control and Attention Test
- Exploratory PROs, including PROMIS-29+2, PROMIS-Fatigue, PROMIS-8a SRI and 8b SD, PASC Symptom Questionnaire, and DSQ-PEM
    - The DSQ-PEM will be performed the immediate next day after completing the neurocognitive battery.
- Biorepository, blood and stool collection (frozen for retrospective analysis)
- Urine or blood pregnancy test

- Nasal Swab, for SARS-CoV-2 rapid antigen test
- Safety assessment, including Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs), and Events of Special Interest (ESIs)
- Randomization

Participants should take their medication relative to assessments at consistent intervals across all timepoints. Similarly, the time of day assessments are scheduled should be as consistent as possible across all time points for each participant.

8.4 START OF INTERVENTION (DAY 0 + 21 DAYS)

See appendices for details. Safety assessments, including SAEs, Unanticipated Adverse Device Effects (UADEs), SUSARs, and ESIs, will occur at the start of intervention and continue until EOI.

The DSQ-PEM will be given twice weekly during the intervention, from the Start of Intervention to EOI. The 2 weekly surveys must be separated by at least 48 hours. A DSQ-PEM administered 24 hours after the Baseline, MOI, and EOI visits will not count as one of the two weekly surveys, ie, 3 surveys will be administered in those weeks.

8.5 MIDDLE OF INTERVENTION (MOI ± 3 DAYS)

The Middle of Intervention visit is designed to be fully remote for all interventions. The following will occur:

- Concomitant medication/therapy review
- PROMIS-Cog
- ECog2
- Exploratory PROs, including PROMIS-29+2, PROMIS-Fatigue, PROMIS-8a SRI and 8b SD, PASC Symptom Questionnaire, and DSQ-PEM
    - The DSQ-PEM will be performed the immediate next day after completing the study visit. This does not count as one of the two weekly administrations.
- Safety assessment, including SAEs, UADEs, SUSARs, and ESIs
- DSQ-PEM, twice weekly, separated by at least 48 hours

8.6 END OF INTERVENTION (EOI ± 3 DAYS)

The End of Intervention visit will occur ± 3 days after completing the intervention requirements and duration (see Appendices). The following will occur at the End of Intervention visit:

- Blood pressure, heart rate, and weight
    - Perform blood pressure and heart rate per the procedure explained in the Baseline visit.
- Concomitant medication/therapy review
- PROMIS-Cog
- ECog2

- Neurocognitive battery, including the modified-Rey Auditory Verbal Learning Test (RAVLT), Symbol Digit Modalities Test, Verbal Fluency (lexical + semantic), Digit Vigilance Test, Cogstate tests (Detection, Identification, One Back), and NIH Toolbox Flanker Inhibitory Control and Attention Test
- Exploratory PROs, including PROMIS-29+2, PROMIS-Fatigue, PROMIS-8a SRI and 8b SD, PASC Symptom Questionnaire, and DSQ-PEM
    - The DSQ-PEM will be performed the immediate next day after completing the neurocognitive battery.
- Biorepository, blood and stool collection (frozen for retrospective analysis)
- Subjective Global Assessment Questionnaire
- Safety assessment, including SAEs, UADEs, SUSARs, and ESIs
- DSQ-PEM, twice weekly, separated by at least 48 hours

8.7 END OF STUDY (EOI + 90 DAYS (±3 DAYS))

The following will occur at the End of Study visit:

- Blood pressure, heart rate, and weight
    - Perform blood pressure and heart rate per the procedure explained in the Baseline visit.
- Concomitant medication/therapy review
- PROMIS-Cog
- ECog2
- Neurocognitive battery, including the WHO-UCLA AVLT, Symbol Digit Modalities Test, Verbal Fluency (lexical + semantic), Digit Vigilance Test, Cogstate tests (Detection, Identification, One Back), and NIH Toolbox Flanker Inhibitory Control and Attention Test
- Exploratory PROs, including PROMIS-29+2, PROMIS-Fatigue, PROMIS-8a SRI and 8b SD, PASC Symptom Questionnaire, and DSQ-PEM
    - The DSQ-PEM will be performed the immediate next day after completing the neurocognitive battery.
- Biorepository, blood collection (frozen for retrospective analysis)
- Subjective Global Assessment Questionnaire
- Safety assessment, including SAEs, SUSARs, and ESIs, as needed per appendix

8.8 CLINICAL LABORATORY ASSESSMENTS

Clinical laboratory assessments, such as Complete Blood Count and Comprehensive Metabolic Panel, may be required as part of Baseline assessments. If a participant has these laboratory assessments available within 3 months of study enrollment, they do not need to be repeated as part of the study. See the relevant appendix for requirements.

8.9 STUDY ASSESSMENTS

The following assessments will occur according to the Schedule of Procedures (Table 2). The objective assessments in the secondary outcome will be administered at each study site by at least one person, who will be required to receive training in measurement tool administration (see MOP for details).

8.9.1 EVERYDAY COGNITION 2 (ECOG2)

The ECog2 is a self-report, 41-item questionnaire used to measure the participant's perceived capacity to perform activities related to cognitive function, which could impact major activities of daily living and independence.[36] It has been used for patients with mild cognitive impairment,[37] Alzheimer's Disease,[38] and dementia.[39] It takes 5 minutes to complete.

8.9.2 PROMIS-COG

The PROMIS-Cog is the PROMIS short form for the cognitive function domain and is a self-report, 8-item questionnaire targeting cognitive function in the past seven days.[40] It is a reliable measure with normative data,[41] and takes 2 minutes to complete.

8.9.3 EXPLORATORY PROS

8.9.3.1 PROMIS-29+2

Patient-Reported Outcomes Measurement Information System (PROMIS-29) global health scale: The PROMIS was developed out of the "Roadmap for Medical Research" created by the NIH in 2002 as valid, generalizable items to standardize clinical research across NIH-funded research dealing with PROs. Multiple PROMIS scales have been validated across many clinical populations.[42] 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 scales has been correlated against the EuroQol EQ-5D.[43] Additionally, PROMIS scales have been used with PASC patients.[44]

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 HRQOL 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. It takes 8 minutes to complete.

8.9.3.2 PROMIS-FATIGUE

The PROMIS-Fatigue is the PROMIS short form for the fatigue domain and is a self-report, 10-item questionnaire that assesses a participant's fatigue on a scale of 1 (not at all fatigued) to 5 (very much). It targets fatigue and its impacts on daily living in the past seven days.[40] It is a reliable and valid measure of fatigue across diverse clinical populations.[45] It takes 2 minutes to complete.

8.9.3.3 PROMIS-8A SRI AND 8B SD

The PROMIS 8a SRI and 8b SD were developed as short forms from the PROMIS SD and SRI. The 8-item short forms are strongly correlated with the long forms and have greater precision than other commonly used sleep assessments such as the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale. The PROMIS 8b SD form includes a total of 8-items that ask participants to reflect on their sleep over the past 7 days with one question rated very poor to very good and the remaining questions rated not at all to very much. The PROMIS 8a SRI form includes a total of 8-items that ask participants to reflect on their sleep over the past 7 days with questions rated not at all to very much. They take 5 minutes to complete.

8.9.3.4 PASC SYMPTOM QUESTIONNAIRE

The PASC Symptom Questionnaire is a self-report measure for reporting multiple PASC-related symptoms across multiple systems. For this platform protocol, two additional sleep-focused questions will be included. It takes 3 minutes to complete.

8.9.3.5 MODIFIED DEPAUL SYMPTOM QUESTIONNAIRE POST EXERTIONAL MALAISE

The DSQ PEM is a subset of the DSQ that assesses PEM.[46] This scale assesses symptom frequency and severity over the previous 6-month period; however, for the purposes of this trial, the look-back period will be modified to "since the previous visit" when administered at Baseline, MOI, EOI, and EOS. When administered twice weekly, the look-back period will be "the past 7 days." This form was previously validated in patients with myalgic encephalomyelitis/chronic fatigue syndrome. It takes less than 5 minutes to complete.

8.9.3.6 SUBJECTIVE GLOBAL ASSESSMENT QUESTIONNAIRE

The Subjective Global Assessment Questionnaire asks participants to self-report whether the intervention helped their symptoms and whether they think they received an active intervention or active comparator. It takes 2 minutes to complete.

8.9.4 NEUROCOGNITIVE BATTERY

The neurocognitive battery includes measures of objective cognitive function utilizing well-validated, psychometrically robust tests of attentional capacity, executive skill, and memory function. These measures objectively characterize the following:

Learning and Memory:

- Verbal list learning over repeated trials, free recall, and recognition memory

Executive Attentional and Processing Speed Skills:

- Timed sequencing of two sets of stimuli according to a key
- Vigilance tasks: Stimuli identification among simple and complex distractors
- Verbal fluency
- Measures of attention:
    - Simple reaction time; respond when X happens

- Choice reaction time; respond only if X happens

Concentration/working memory; yes/no does new stimuli match previous stimuli

The neurocognitive battery includes the objective measures in the following subsections.

8.9.4.1 AUDITORY VERBAL LEARNING TESTS

The WHO-UCLA AVLT will be used at Baseline and EOS, while a modified-RAVLT will be used at EOI.

The RAVLT is a robust test for clinical assessment of learning and memory and has been validated in English and Spanish.[47,48] The recognition list will be modified to match the number of words in the WHO-UCLA AVLT word list.

Both the RAVLT and WHO-UCLA AVLTare auditory list-learning tests that assess learning and memory and is sensitive to cognitive dysfunction. The tests involve five free recall trials of 15 words, a short delayed recall, a long delayed recall, and a recognition trial.[49] The WHO-AVLT has also been validated in Spanish-speaking populations.[50]

For both AVLTs, the learning trials take 8 minutes to complete, and recall and recognition trials take 5 minutes. Other nonverbal tasks or subjective scales can be administered during the delay period.

8.9.4.2 SYMBOL DIGIT MODALITIES TEST

The Symbol Digit Modalities Test is a neuropsychological executive task measuring sequencing/coding and processing speed.[51] It takes 5 minutes to complete.

8.9.4.3 VERBAL FLUENCY

Verbal Fluency includes neuropsychological measures of lexical and semantic fluency.[52] Each take 3 minutes to complete.

8.9.4.4 DIGIT VIGILANCE

Digit Vigilance is a neuropsychological executive task measuring sustained attention, vigilance, and processing speed.[53] It takes 10 minutes to complete.

8.9.4.5 COGSTATE

Cogstate is a commercially available platform of objective neuropsychological tests for measuring distinct cognitive functions: the Detection Test targeting psychomotor function, the Identification Test targeting attention, and the One Back Test targeting working memory.[54] The Cogstate is validated for telehealth assessment[55] and cognitive impairment.[56] It takes 3-4 minutes to complete each test, about 12 minutes total.

8.9.4.6 NIH TOOLBOX FLANKER INHIBITORY CONTROL AND ATTENTION TEST

The Flanker Test measures both a participant's attention and inhibitory control.[57] The test requires the participant to focus on a stimulus while inhibiting attention to stimuli flanking the stimulus. Scoring is based on a combination of accuracy and reaction time. It takes 3 minutes to complete.

8.10 BIOREPOSITORY FOR FUTURE RESEARCH

The RECOVER Biorepository is designed to collect and store biospecimens, such as blood plasma and serum 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 will prove equally productive and important. This Biorepository will be 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 RECOVER Biorepository will provide the opportunity to devise new hypotheses, since blood collection techniques are standardized across all approved protocols, thereby allowing cross-protocol sample comparisons if scientifically justified.

Within this framework, the design of the Biorepository is to collect stool, plasma, and serum for storage in the Biorepository for future, as yet unspecified, analyses, and studies. At each time point including blood collection, eighty (80) mL of blood will be collected to prepare the aliquots for storage at -80 °C. For this protocol, blood will be collected at Baseline, EOI, and EOS. These samples will be stored at the Biorepository in a lab for up to 7 years. See the MOP for details of blood and stool collection.

9 SAFETY ASSESSMENTS AND REPORTING

9.1 SAFETY EVENTS

9.1.1 DEFINITION OF SAFETY EVENTS

An Adverse Event (AE) is any untoward medical occurrence in humans, whether or not considered drug- or intervention-related, which occurs during the conduct of a clinical trial. An AE can therefore be any change in clinical status, routine labs, x-rays, physical examinations, etc., that is considered clinically significant by the study investigator.

A Serious Adverse Event (SAE) or serious suspected adverse reaction (SAR) or serious adverse reaction, as determined by the investigator or the sponsor, is an AE that results in any of the following serious outcomes:

- Death

- Life-threatening AE ("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 above outcomes from occurring

An Adverse Device Effect (ADE) is an event related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. An ADE also includes any event resulting from a use error or intentional misuse.

- Device malfunction – the failure of a device to perform in accordance with the Instructions for Use or clinical investigative plan.
- User error or intentional misuse – a device is used in a manner that is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

An Unanticipated Adverse Device Effect (UADE) is any serious adverse effect, problem, or death caused by or associated with a device if that effect was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Unanticipated Adverse Device Effects will include events meeting either A or B as stated below:

A. Events meeting ALL of the following criteria:
    - Not included in the relevant appendices, product label, or Instruction for Use
    - Related to the investigational device per the site principal investigator and/or IND sponsor
    - Serious (meets any of the following criteria):
        - Is life-threatening illness or injury
        - Results in permanent* impairment of a body function or a body structure
        - Necessitates medical or surgical intervention to prevent permanent* impairment of a body function or a body structure
        - Results in hospitalization
        - Led to fetal distress, fetal death or a congenital abnormality or birth defect
        - Led to death

      **Permanent* means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

B. Any other unanticipated serious problem associated with the investigational device that relates to the rights, safety, or welfare of subjects.

Hospitalization for elective treatment of a preexisting 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.

An unexpected AE is defined as any AE or ADE, the specificity or severity of which is not consistent with the study drugs' package insert or devices' Instruction for Use.

An unanticipated problem involving risk to human subjects or others, including an environmental exposure and exposure to a breastfeeding infant, will be reported to the sponsor and the site IRB and central IRB, as appropriate. The event will not be entered into the electronic data capture (EDC) system. Refer to the MOP and/or Safety Management Plan (SMP) for details.

If an intervention includes study drug(s) and medication errors result in an SAE, the errors are reportable. The medication error will be captured as a protocol deviation and the SAE captured on the SAE electronic Case Report Form (eCRF).

9.1.2 COLLECTION PERIOD OF AE AND SAE INFORMATION

Safety event collection will occur at the pre-specified study visits, but all participants will be instructed to self-report concerns by calling the site.

Serious adverse events (SAEs), UADEs, or ESIs will be extracted by site personnel from the participant's medical record if the participant seeks medical care or if hospitalization occurs, each of which notifies the site to conduct follow-up.

Medical occurrences that begin before intervention procedures, but after obtaining informed consent, will not be considered an AE. The medical occurrence or condition will be captured on the Medical History eCRF.

Non-serious AEs may be reported by the participant, but will not be collected to the study database or further assessed by the site or study personnel. However, any non-serious AEs or ADEs that result in intervention discontinuation will be reported as an AE or ADE in the study database and identified as the reason for discontinuation in the study database, and these non-serious AEs and ADEs will be collected from the start of intervention administration through the end of intervention procedures.

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

Serious adverse events (SAEs) will be collected from the first study procedure through the End of Study visit [(EOI + 90 days) ± 7 days].

Adverse events (AEs) that qualify as an ESI, even if a non-serious AE, will be collected from the start intervention procedures through the End of Study visit [(EOI + 90 days) ± 7 days]. A UADE observed from

the time of start of intervention through the end of the intervention will be collected in the clinical database.

9.1.2.1 SEVERITY OF EVENT

For reportable events, the following guidelines will be used to describe severity.

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

9.1.2.2 RELATIONSHIP TO STUDY INTERVENTION

All reportable events must have their relationship to the study intervention assessed by the clinician, who examines and evaluates the participant based on temporal relationship and his or her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE or ADE is known to occur with the study intervention, a reasonable possibility exists that the study intervention caused the AE or ADE, 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 AE or ADE.
- **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.

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

The occurrence of an AE, ADE, ESI, or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All reportable events will be captured on the appropriate CRF. Information to be collected includes event description, date/time of onset, clinician's assessment of severity, relationship to intervention product (assessed only by those with the training and authority to make a diagnosis), action taken with intervention product (e.g. discontinuation), and date/time of resolution/stabilization of the event. All events occurring within the pre-specified reportable time windows must be documented appropriately regardless of relationship.

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

Changes in the severity of a safety event will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Safety events characterized as intermittent require documentation of onset and duration of each episode.

The investigator will follow all SAEs or UADEs until resolution, stabilization, or the event is otherwise explained. The DCRI Safety Surveillance Team will follow all SAEs or UADEs until resolution, stabilization, or until otherwise explained.

9.1.4 REPORTING AND MONITORING OF SAES AND UADES

When an intervention appendix comprises a study drug(s), the study drug(s) may be under an IND and subject to IND regulations in 21 CFR 312, especially if their investigational use for treatment of PASC is not an approved indication. In such a case, the IND sponsor, DSMB, or Study Medical Monitor will review aggregate safety data. The IND sponsor or designee will be responsible for determining if the safety reporting criteria are met per 21 CFR 312.32(c)(1)(i)(C) and 21 CFR 312.32(c)(1)(iv) and will notify the CT-DCC to prepare an aggregate report for submission to the US Food and Drug Administration (FDA). An aggregate safety report will be submitted to FDA as soon as possible, but in no case later than 15 calendar days after the IND sponsor determination. If the IND sponsor determines that an unexpected fatal or life-threatening SAR occurs markedly more frequently in a study drug arm than in the comparator arm, an aggregate safety report will be submitted to the FDA as soon as possible, but in no case later than 7 calendar days after the IND sponsor determination. Information on individual SAEs will be available upon request from the FDA following the submission of any aggregate reports.

Any UADE that the IDE sponsor determines is/are reportable will be submitted to the FDA, manufacturer, all reviewing IRBs, and all participating investigators within 10 working days of when the sponsor makes that determination. Any fatal or life-threatening UADE the IDE sponsor determines is reportable will be submitted to the FDA, manufacturer, all reviewing IRBs and all participating investigators within 5 working days of notice of the effect.

If the IDE sponsor determines the UADE presents an unreasonable risk to participants, all investigations or parts of investigations presenting that risk shall be terminated as soon as possible. Termination shall occur not later than 5 working days after the IDE sponsor makes this determination and no later than 15 working days after the sponsor first received notice of the effect.

Individual SAEs or UADEs must be entered into the data system within 24 hours of site awareness. The DCRI Safety Surveillance team will notify pharmaceutical partners of SAEs and device manufacturer of UADEs within 1 to 2 business days of their receipt that occur involving the specific appendix of the supplied study intervention/comparator, as required. Serious Adverse Events that are related and confirmed unlisted by the DCRI Safety Medical Monitor and IND sponsor will be reported to the FDA as SUSARs; as 7-day reports for unexpected fatal or life-threatening adverse reactions and 15-day reports for serious and unexpected adverse reactions. The SUSARs will be shared with the pharmaceutical partner of the supplied study drug according to the same timelines. If the IND sponsor, DSMB, or FDA

note a clinically important increase in the rate of a SUSAR, the IND sponsor or designee will notify investigators no later than 15 calendar days after determining that the information qualifies for reporting. The investigators will notify their local IRB according to local guidelines if applicable. The CT-DCC will notify the central IRB. Refer to the SMP for details regarding specific reporting timelines.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study (but before the study itself has ended), and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to the sponsor via EDC entry.

9.1.5 EVENTS OF SPECIAL INTEREST

Each intervention may have a unique list of ESIs. Refer to the relevant appendix.

9.1.6 REPORTING OF PREGNANCY

Pregnancies occurring after starting intervention activities and while on-study will be documented in the database. Pregnant participants will be advised to discontinue the intervention. Upon discovery of a pregnancy, the study team will ask pregnant participants to complete a pregnancy-specific consent form in order to follow the pregnancy to its outcome in the case the outcome is not reached while the participant is on-study (i.e., occurs after EOS). Male participants on-study who conceive a child should notify the study team, which will request consent of the mother to follow the pregnancy to its end result. Within 1 to 2 business days after learning of the pregnancy, the DCRI Safety Surveillance team will notify study-drug or device supplying partners of the pregnancy, as required. Lastly, any pregnancy-associated ESI or SAE should be reported if information can be collected and entered into the CRF. Any appendix-specific changes to these reporting requirements are expressly stated in the specific appendix.

10 STATISTICAL CONSIDERATIONS

10.1 GENERAL CONSIDERATIONS

All statistical analyses will be performed using SAS (SAS Institute, Inc. Cary, NC, USA) version 9.4 or higher. Baseline demographic and clinical data will be summarized by intervention arm. Descriptive statistics will include mean, standard deviation, median, 25th and 75th percentiles for continuous variables and frequency and percentage for categorical variables. Statistical comparisons will be performed using two-sided tests at 0.05 significance level. The primary analyses will not be adjusted for multiplicity of comparisons since each intervention appendix can be justified as a separate experiment, as opposed to a part of a family of related experiments (see Proschan and Waclawiw, 2000).[58] Analyses of the secondary endpoints will not be adjusted for multiplicity of comparisons and the results of these analyses will be considered exploratory. Additional details regarding statistical analyses will be provided in the SAP which will be finalized prior to the database lock.

10.2 STATISTICAL HYPOTHESES

Primary Endpoint:

1. Less dysfunction on ECog2 at the EOI compared to baseline in intervention in comparison to comparator condition

Secondary Endpoints:

1. Less dysfunction on the PROMIS-Cog at EOI and at EOS compared to baseline in intervention in comparison to comparator condition
2. Less dysfunction on neurocognitive battery assessments (AVLT, Symbol Digit, Verbal Fluency, Digit Vigilance, Cogstate, Flanker) at EOI and at EOS compared to baseline in intervention in comparison to comparator condition
3. Less dysfunction on ECog2 at EOS compared to baseline in intervention in comparison to comparator condition
4. Study interventions are safe in the PASC population

10.3 SAMPLE SIZE DETERMINATION

This study uses an adaptive platform trial design that will allow interventions to be added or dropped from consideration based on accruing evidence of futility or efficacy, whichever is appropriate to the intervention. In such a design, the required sample size depends on both the number of interventions tested and the ability to pool their comparator arms for analysis. Initial sample size estimates are based on a study with a single intervention and 1:1 allocation to active intervention or comparator. If additional interventions are added later that can contribute to pooled comparator, the sample size will be adjusted accordingly.

See the appendices for intervention-specific details of sample size determination.

10.4 POPULATIONS FOR ANALYSES

Population for effectiveness analyses: ITT. The primary efficacy analysis will be based on an intention-to-treat (ITT) population. All randomized participants will be included and will be analyzed according to their assigned intervention group.

Safety population. Safety analyses will be performed among participants in the ITT population who report completing at least one intervention activity, which is aimed at addressing a study outcome, in the intervention or comparator. Participants will be analyzed according to their assigned intervention groups.

10.5 STATISTICAL ANALYSES

This section describes analysis methods for the primary, secondary, and safety outcomes. Full details will be provided in the SAP.

10.5.1 ANALYSIS OF THE PRIMARY ENDPOINT

The primary endpoint analysis will be performed using a linear regression model with change of ECog2 from baseline to EOI as an outcome. The analysis model will include intervention arm indicator variables and will be adjusted for baseline ECog2, age, sex, education level, and primary language (English vs. Spanish). The normality assumption for the outcome distribution will be evaluated. If this assumption is not met, outcome transformations or regression models with different distributional assumptions may be utilized.

10.5.2 ANALYSES OF THE SECONDARY ENDPOINT(S)

PROMIS-Cog. The PROMIS-Cog is a continuous measure. Changes in total score from baseline to EOI and to EOS will be analyzed using similar methods as those outlined for the primary endpoint.

Neurocognitive dysfunction: Neurocognitive battery (AVLT, Symbol Digit, Verbal Fluency, Digit Vigilance, Cogstate, Flanker). Each of the neurocognitive assessments results in a continuous score. Changes from baseline to EOI and to EOS for each neurocognitive outcome will be analyzed using similar methods as those outlined for the primary endpoint.

ECog2 at EOS. Change in ECog2 from baseline to EOS will be analyzed using similar methods as those outlined for the primary endpoint.

Safety endpoints. Safety endpoints include the proportion of participants who experience individual SAEs/UADEs and the proportion who experience any one or more SAEs/UADEs. These will be analyzed in the safety population. Events of Special Interest (ESIs) will be summarized by intervention appendix. Incidence of AEs/SAEs/UADEs leading to discontinuation will also be summarized.

10.5.3 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

PROMIS-29+2, PROMIS-Fatigue, PROMIS-SRI, PROMIS-SD, DSQ-PEM, and PASC Symptom Questionnaire. These PROs are continuous measures. Changes from baseline to EOI and to EOS will be analyzed using similar methods as those outlined for the primary endpoint.

10.5.4 MISSING DATA

The primary and secondary analyses will be performed without missing data imputation. Additional sensitivity and supplementary analyses with adjustments for missing data will be described in the SAP.

10.5.5 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 performance of the trial. The primary objective of these interim analyses will be to ensure the safety of the participants enrolled in the trial. 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.

This protocol does not have planned early stopping rules for efficacy. 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 intervention risks and benefits based on important secondary effectiveness and safety outcomes. Stopping early would also limit the collection of data that are critical for planning future trials in similar patient populations.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

11.1.1 INFORMED CONSENT PROCESS

11.1.1.1 INSTITUTIONAL REVIEW BOARD (IRB)

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

11.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

All consenting will occur either via an electronic consent process or a paper process. Consent forms describing in detail the intervention/comparator, study procedures, and risks will be 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 will be provided to the participants. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The participant will be provided contact information in the event they have questions about study participation. This will allow them to communicate with the investigators (or their delegate), for further explanation of the research study and to answer any questions that may arise, as necessary. Participants will have the opportunity to carefully review the consent form and ask questions prior to signing.

Participants should have the opportunity to discuss the study and think about it before agreeing to participate. Participants will sign the informed consent document before performing any study procedures. Participants may withdraw consent at any time throughout the course of the study. A copy of the informed consent document will be provided to participants for their records. The rights and welfare of participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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

11.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the sponsor to study participants, site investigators, the central IRB, and the US FDA, as applicable. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

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

11.1.3 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 will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The study participant's contact information will be securely stored in the clinical study database.

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

11.1.4 KEY ROLES AND STUDY GOVERNANCE

The RECOVER program is overseen by the RECOVER Executive 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 CT-DCC, the NIH, the FDA, and academic and subject matter experts.

The CT-DCC is overseen by a Principal Investigator. The 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 will oversee the safety and welfare of trial participants as well as provide recommendations for continuation, discontinuation, or revision of the trial.

11.1.5 DATA AND SAFETY MONITORING BOARD

Safety oversight will be under the direction of the RECOVER DSMB composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet 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 arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the NIH.

11.1.6 CLINICAL MONITORING

This study will employ a centralized, remote, 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 will facilitate regular communication through training sessions, teleconferences, videoconferencing, email, etc. Using quality-by-design principles, steps will be taken at the study design stage to foresee and limit significant problems that might occur during the study conduct.

11.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

The study team will work in tandem 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 will be implemented:

1. **Training.** Prior to the start of enrollment, the clinician investigators and key study personnel at each site will be trained with the clinical protocol and data collection procedures, including how to use the EDC system. Follow-up training and training for new study personnel or new versions of the protocol will be conducted as needed.

2. **Monitoring.** The RECOVER CT-DCC will ensure that data collection is handled properly, will provide in-service training, and will address questions from site investigators and coordinators. Electronic review of data quality and completeness will occur on a regular and ongoing basis. Any issues will be addressed.

3. **Managing data.** After the data have been transferred for statistical summarization, data description, and data analysis, further crosschecking of the data will be performed with discrepant observations being flagged and appropriately resolved through a data query system.

4. **Reviewing data.** Data regarding events of interest will be reviewed to ensure appropriate documents are collected for DSMB review. The CT-DCC will monitor study data and contact site study teams when events comprising the primary endpoint are not complete.

11.1.8 DATA HANDLING AND RECORD KEEPING

11.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Streamlining research activities and conducting the trial in a pragmatic manner will increase the ability to complete the trial in the face of 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 will be collected directly from participants using REDCap through text messaging or email with a survey link, or a site-based computer, or phone call as back up. The process for using text messaging and email is Health Insurance Portability and Accountability Act (HIPAA) compliant.

Site personnel or participants will enter study data into a secure online database. Data will be maintained in a secure online database until the time of study publication. At the time of publication, the CT-DCC will generate a de-identified version of the database for archiving (see Section 11.1.10). All source documents at the sites should be completed in a neat, legible manner to ensure accurate interpretation of data.

11.1.8.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of six years after the study has ended. However, if required by local regulations or the US FDA, these documents should be retained for a longer period. No records will be destroyed without the written consent of the sponsor. The sponsor is responsible for informing the investigator when these documents no longer need to be retained.

11.1.9 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(s) 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 IRB and local IRB per their guidelines, recorded in source documents, and reported to the coordinating center. Major protocol deviations will be tracked. For this study, any missed or delayed survey completion will not be considered a major protocol deviation, unless the survey is required for the primary endpoint.

11.1.10 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. The Policy requires scientists to submit final peer-reviewed

journal manuscripts, which arise from NIH funds, to the digital archive PubMed Central upon acceptance for publication.

11.1.11 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 must be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11.2 ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
ADHD	Attention-deficit/hyperactivity disorder
CDE	Common Data Element
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CoRE	Cognitive Recovery
COVID-19	Coronavirus Disease of 2019
CRF	Case Report Form
CT-DCC	Clinical Trial – Data Coordinating Center
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
ECog2	Everyday Cognition 2
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EOI	End of Intervention
EOS	End of Study
ESI	Events of Special Interest
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board

ITT	Intention-To-Treat
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
PASC	Post-acute Sequelae of SARS-CoV-2 Infection
PI	Principal Investigator
PRO	Patient Reported Outcome
PROMIS	Patient-reported Outcomes Measurement Information System
PROMIS-Cog	PROMIS-Cognitive Function – short form 8a
PROMIS-Fatigue	PROMIS-Fatigue – short form 10a
PROMIS-SD	PROMIS-8a Sleep Disturbance
PROMIS-SRI	PROMIS-8a Sleep Related Impairment
RAVLT	Rey Auditory Verbal Learning Test
RECOVER	Researching COVID to Enhance Recovery
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SMP	Safety Management Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
tDCS	Transcranial Direct Current Stimulation
UADE	Unanticipated Adverse Device Effect
US	United States
WHO-UCLA AVLT	World Health Organization-University of California Los Angeles Auditory Verbal Learning Test

11.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change
1.0	01MAY2023	None, original protocol
2.0	09JUN2023	• Added risk posed to participants with post-exertional malaise (Section 2.3.1) • Replaced the Rey Auditory Verbal Learning Test with the WHO-UCLA Verbal Learning Test (Section 8.9.4.1) • Added sub-exclusion to exclusion 12 to convey an investigator has discretion to determine whether a participant is too cognitively impaired to participate and should be referred for clinical evaluation (Section 5.2) • Added rationale for the neurocognitive battery (Section 8.9.4) • Changed use of PROMIS 8a SD to 8b SD

		• Added time burden to PASC Symptom Questionnaire (Section 8.9.3.4) • Added pregnancy requirement for female partners of male participants to platform protocol (Section 9.1.6) • Added pregnancy and contraception considerations to Appendix A that are different than those in the platform (Appendix A) • Added stool to blood collection (Section 8.10) • Added Subjective Global Assessment Questionnaire at End of Intervention and End of Study (Section 8.9.3) • Defined cognitive training, cognitive-enhancing supplement (Section 5.3) • Added anticholinergics as allowable except within 48 hours of assessments (Section 5.3) • Added that "Failure to refrain from [benzodiazepine, anticholinergic, narcotic] their use in this time frame will require rescheduling of the assessments." (Section 5.3) • Added concomitant medication/therapy review at MOI (Section 8.1) • Changed “control” to “comparator” throughout platform • Added “±3 Days” to EOS visit • Added unanticipated adverse device effects to a secondary outcome • Clarified that Clinical laboratory assessments will not be required as part of Baseline assessments. (Section 13.4.5) • Added twice weekly DSQ-PEM assessments throughout the intervention (Section 8.1) • Other administrative changes, such as grammar and punctuation
3.0	10JAN2024	• Added NCT numbers to the cover page for the platform protocol and to Appendix A • Edited the primary endpoint from change in total score to change in average score (Section 3) • Added the exclusion of ADHD diagnosis treated with stimulants that cannot be discontinued (Section 5.2) • Added the exclusion of lifetime use of electroconvulsive therapy (Section 5.2) • Edited exclusion #4 to direct the reader to prohibited medications in Table 2 (Section 5.2) • Added a footnote to exclusion #4 that allows for a washout period of prohibited medications (Section 5.2) • Edited exclusion #6 from any stimulant treating PASC to any medication treating PASC (Section 5.2) • Added Table 2 for prohibited medications and therapies • Edited section 6.4.1 to be for prohibited medications

		• Added a 30-day washout requirement for participants who stop taking a cognitive-enhancing supplement before being enrolled (Section 5.3) • Moved and edited language from Section 5.3 about occasional use of drugs to Section 6.4.1 with Table 2 • Added 21-day buffer to Start of Intervention due the potential time required for forming PASC-CoRE groups (Section 8.1) • Added blood pressure and heart rate collection to the Baseline, EOI, and EOS visits (Section 8.1)Added that participants cannot change their stimulant dose while on-study (Section 5.3) • Added that 90 days must lapse after completing another trial before screening for this one (Section 5.6) • Added statements to clarify randomization (Section 6.2) • Added alternative therapy instructions (Section 6.4.2) • Removed that participants may be replaced (Section 7.1) • Added that "Participants who fail screening may be re-screened one time." (Section 8.2) • Separated COVID treatment from medical history and moved COVID treatment to Baseline (Section 8.3) • Made the term "cognitive dysfunction" consistent throughout • Edited the look-back periods for the DSQ-PEM (Section 8.9.3.5) • Rey Auditory Verbal Learning Test added as an AVLT with the WHO-UCLA AVLT, with corresponding changes made throughout (Section 8.9.4.1) • Added that pregnancy testing is not required for female participants who self-report menopause, have no menstrual cycle for at least 12 months, or are surgically sterile (Section 13.7) • Added pregnancy considerations to Appendix A (Section 13.7) • Updated the primary comparisons in Appendix A (Section 13.8.2) • Made punctuation changes throughout

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13 APPENDIX A

This intervention is registered on clinicaltrials.gov as NCT05965739.

13.1 INTERVENTION RATIONALE

The interventions below comprise this appendix.

13.1.1 BRAINHQ

BrainHQ is an online cognitive training program developed by Posit Science Corporation, and has been used to improve cognitive function among persons with cognitive impairment based on principles of neuroplasticity. It targets memory, attention, and brain speed. BrainHQ has 29 training exercises and a total of 800 training levels. Exercises focus on speed and accuracy of neural information processing with a reward system when exercises are performed correctly. BrainHQ is a fully remote training system delivered through an application on an electronic device, such as a tablet or computer.

BrainHQ is established for research use and has been used in brain-injured populations. It provides a portal that research teams can use to specialize the challenges that are presented to participants. BrainHQ continuously challenges participants by using algorithms that adapt to each participant's initial cognitive impairment and learning rate. Moreover, BrainHQ exercises are visually appealing and responsive in order to maintain user engagement.

BrainHQ platform provides a set of cognitive activities, like puzzles and games, that are cognitively stimulating and actively engage participants but do not continuously and adaptively challenge them. These activities are designed to be a face-valid, active comparison approach to cognitive therapy, thus participants are blinded, attention time is matched, and overall user experience is identical to the active arms.

13.1.2 PASC-COGNITIVE RECOVERY

PASC-Cognitive Recovery (PASC-CoRE) is a manualized cognitive rehabilitation intervention with demonstrated efficacy in improving attention and executive functions, among other cognitive domains.[59-61] PASC-CoRE comprises 3 essential training components: 1) attention regulation using a mindfulness-based approach; 2) training in goal management; and 3) managing cognitive fatigue.

Attention regulation training uses mindfulness to emphasize redirection of cognitive processes towards tasks that are salient. Participants are taught to use these principles in a range of personally relevant situations. Training takes place virtually through one-on-one or group sessions. Additionally, homework is assigned for more practice in applying these attention-regulation principles. Goal management training encourages participants to identify, select, and execute self-generated, personally relevant, and functional goals.

Fatigue management training teaches participants strategies for managing cognitive fatigue, including "brain breaks," planning ahead, and avoiding overstimulation.

PASC-CoRE is cognitive rehabilitation targeting improvements in executive function and attention. It is a therapy based on an understanding of brain-behavior relationships and may even be capable of inducing neuroplasticity-related brain changes.[62]

13.1.3 TRANSCRANIAL DIRECT CURRENT STIMULATION

Transcranial direct current stimulation (tDCS) will use a device developed by Soterix Medical, Inc. specifically for home-based use (Soterix 1x1 mini-CT). This device delivers a weak electrical current of 2.0 mA passed through two electrodes placed on the scalp to target the dorsolateral prefrontal cortex region of the brain. The electrodes are single-use for each session and can be attached to a headset by snapping into place.

The device has a user-friendly interface and a large-button keypad, making it is easy to use at home. It has many built-in safety features, and the user can easily abort any session if needed. tDCS is FDA-approved for investigational use in the US and has an excellent safety and tolerability profile (i.e., no serious AE reported in human clinical trials to date).[63,64]

tDCS has demonstrated efficacy for many symptoms in the neuropsychiatric cluster, including cognitive dysfunction, central fatigue, central sensitization, and emotional dysregulation. Possible mechanisms of tDCS include increases in neuronal activity and blood flow.[65,66] When paired with a cognitive training activity, it may potentiate and strengthen the learning process.[67] tDCS targeted to brain regions engaged in the cognitive training activity increases brain activity and the corresponding rate of learning during training, thus enhancing its therapeutic outcomes. Pairing with cognitive training may increase learning and performance outcomes, and targeting the dorsolateral prefrontal cortex may lead specifically to improvement in measures of processing speed.[68-71] Repeated application of tDCS has been reported to improve cognitive function.[72]

13.2 EXCLUSION CRITERIA (APPENDIX LEVEL)

1. Presence of metal objects in the head or neck
2. Skin disorders or skin-sensitive areas near tDCS stimulation locations that would interfere with electrode placement or increase the risk of stimulation-induced damage, at the investigator's discretion

13.3 STUDY DESIGN

These interventions will comprise a five-arm design implemented over 10 weeks:

1. Active Comparator (video games)
2. BrainHQ
3. BrainHQ + PASC-CoRE
4. BrainHQ + tDCS-active
5. BrainHQ + tDCS-sham

13.3.1 DESIGN RATIONALE

This design seeks to evaluate each intervention relative to the Active Comparator. The BrainHQ (alone) arm is important because the intervention is commercially available, accessible, relatively inexpensive, and does not require trained personnel to administer. The BrainHQ + PASC-CoRE arm and the BrainHQ + tDCS arms are suspected to provide cognitive improvements beyond BrainHQ alone through different mechanisms. Both PASC-CoRE and tDCS have extensive prior use. This design does not control for PASC-CoRE; doing so would require a second control group, which would reduce power for observing differences among the primary comparisons. Further, this design positively compromises study-design purity for reduced patient burden and affords analysis of incremental value of intervention combinations most likely to be implemented clinically.

This study design is unique compared to other ongoing or forthcoming clinical trials: It is the only trial investigating BrainHQ alone or BrainHQ paired with PASC-CoRE in a PASC population. Conversely, this study uniquely complements three trials that are or will be recruiting to investigate tDCS with or without cognitive training in patients with PASC. Table 3 summarizes these studies primary outcomes and interventions.

Table 4. Comparison studies for Appendix A

NCT#	Status	Primary Outcome	Intervention Arms	tDCS Dose	Estimated Enrollment
5092516	Recruiting	Change in inhibitory control and processing speed	tDCS-active tDCS-sham	2.0 mA, 4 wk, 7 d/wk, 30 min/d	40
5589272	Not yet recruiting	Change in working memory	tDCS-active + CT (4 wk) tDCS-sham + CT (4 wk) tDCS-active + CT (5d) tDCS-sham + CT (5d)	4 wk: 2.0 mA, 4 wk, 4 d/wk, 20 min/d 5 d: 2.0 mA, 5 d consecutive, 13 min/d	60
5389592	Not yet recruiting	Change in neuropsychological assessments of memory, attention, executive functions, and mood	tDCS-active + CT (BrainHQ) tDCS-sham + CT (BrainHQ)	2.0 mA, 4 wk, 5 d/wk, 20 min/d	60

Abbreviations: tDCS, transcranial direct current stimulation; CT, cognitive training

This study complements those in Table 3 because it is investigating BrainHQ alone and is dosing tDCS for a longer duration and session time, while using the same intensity. Further, this study is evaluating neuropsychological changes, though in a larger population. Together, these studies will offer observations on the efficacy of tDCS, particularly tDCS combined with cognitive training, on enhancing cognitive domains in the PASC population.

13.3.2 RANDOMIZATION

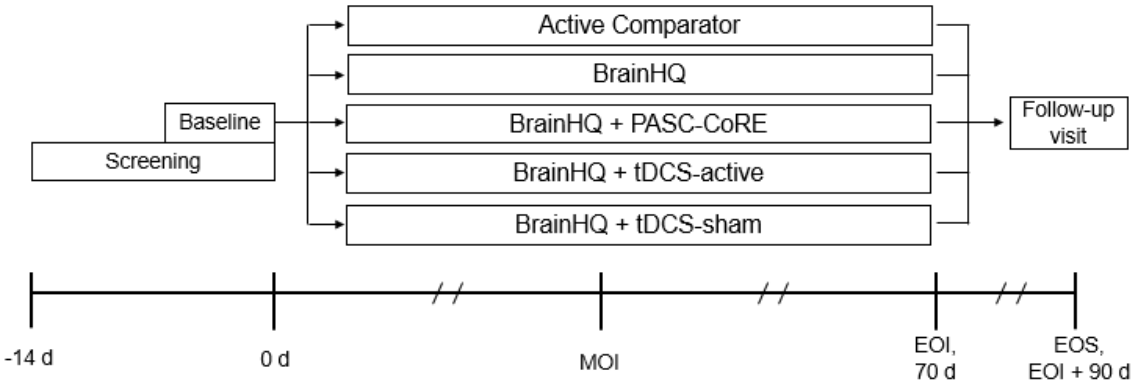
Participants will be randomized equally across the five arms, i.e., the randomization probability will be 0.2 for each arm.

13.3.3 BLINDING

Participants, investigators, study personnel, and analysts will be blinded to whether participants are in (a) the BrainHQ or Active Comparator arms and (b) the BrainHQ + tDCS-active and BrainHQ + tDCS-sham arms.

13.3.4 SCHEMA

Figure 2. Schematic of Appendix A intervention



13.3.5 CONTROL/COMPARATOR

The control group is an active comparison group, i.e., not inactive like a waitlist control. The Active Comparator group will receive non-adaptive training or video games, such as word puzzles and visual search games, delivered through the same BrainHQ research portal.

13.4 INTERVENTION PROCEDURES

All intervention procedures will be performed remotely, which requires accessing a device with internet connection. However, limited technology access will not preclude participation. All participants will receive an electronic device preloaded with the relevant BrainHQ configuration and videoconferencing software. Participants without internet access will be provided a hotspot. Additionally, participants in the tDCS groups will be mailed the necessary hardware (see Section 13.4.3). After the intervention, participants will return all materials.

13.4.1 BRAINHQ

BrainHQ and Active Comparator sessions will number 50 over the 10-week period at 5 sessions/week and 30 min/session. In each of the four active intervention arms using BrainHQ, participants will receive active cognitive training. The BrainHQ research portal will be configured for the active cognitive training condition (BrainHQ arms), or the control cognitive training condition (Active Comparator arm), in advance of delivering the device to participants.

Before and after each BrainHQ or Active Comparator session, participants will be prompted to complete a questionnaire, which will document session completion and highlight session interruptions.

Participants will be monitored by a study technician during the entirety of the first 3 sessions. Afterward, participants will be briefly monitored, at startup and the initial few minutes.

13.4.2 PASC-COGNITIVE RECOVERY

PASC-CoRE components will be delivered by trained interventionists during weekly virtual sessions, totaling nine 1.5-hour group sessions and three 30-minute individual sessions (see Table 4 for session content). Individual sessions will occur at the beginning, middle, and end of training series to allow for group session review and one-on-one participant feedback. Group sessions will include two to five participants and one interventionist. The small groups will empower participants to be more active and afford easier scheduling. All sessions will be scheduled to maximize convenience for participants, and will include evenings and weekends. Further, participants will only be required to move through the sessions by scheduled sequence, but they will not be restricted to the same group of participants.

A training manual divided by session will be mailed to participants, who will be instructed to open each session-specific manual at the beginning of the relevant session by the session interventionist. Participants will receive an overview of materials and training in Session #1.

Table 5. PASC-CoRE session content

Session	Content
Group #1	Introduction and overview
Group #2	Progressive information maintenance and mindfulness exercises
Individual #1	*Individualized assessment and strategy building*
Group #3	Goal selection: options for group and individual projects
Group #4	Breaking down projects into sub-tasks, creating timeline; apply to group and individual projects
Group #5	Execution and dealing with procrastination
Individual #2	*Individualized progress monitoring*
Group #6	Staying on tasks, error correction, and adjustments
Group #7	Project progress review and adjustments
Group #8	Individual project presentation
Group #9	Group project presentation, discussion of maintenance, and graduation celebration
Individual #3	*Individual wrap-up*

13.4.3 TRANSCRANIAL DIRECT CURRENT STIMULATION

tDCS devices, headgear, and electrodes displayed in Figure 3 will be mailed directly to participants. tDCS devices used in the active arm will be pre-programmed to deliver the direct electrical current at 2.0 mA for 30 minutes. tDCS devices used in the sham arm will be pre-programmed to deliver the same ramp up/down at the beginning/end of the 30-minute period as the active arm, except with no current

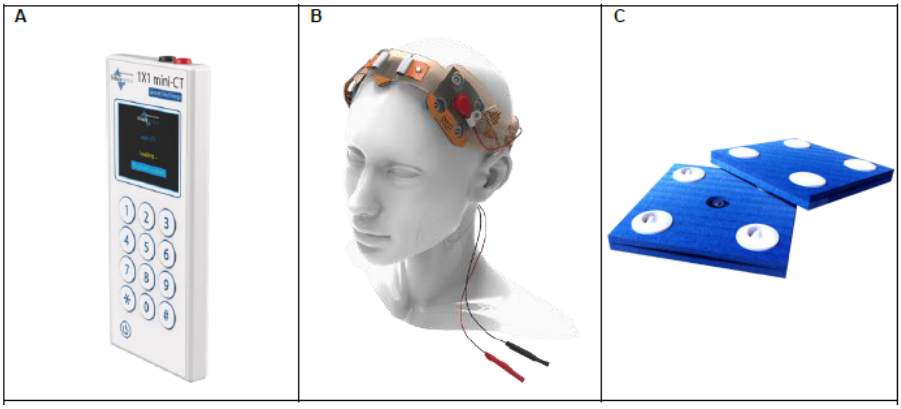
otherwise delivered during the session. For both arms, time of day and consistency of electrode placement will be held as constant as possible; however, given the real-world nature of this study, flexibility will be allowed.

To begin each live online session, a study technician will check for safety and visually confirm correct headset placement and adequate contact quality. Then, the study technician will confirm that the participant is ready to start the session and guide the participant to unlock the device using the one-time use unlock code. At the end of each session, participants will dispose of the single-use electrodes. The study technician will monitor the entire tDCS session for compliance at each daily session during the first week; thereafter, only one session per week will be entirely monitored, while the other four will be briefly monitored for headset placement and contact quality.

tDCS use will be paired with BrainHQ engagement. Participants will engage BrainHQ and then position and power on the headgear. After 30 minutes, participants will disengage from BrainHQ and remove the headgear.

After the intervention, participants will return the devices and headgear in a prepaid container that came with the original package.

Figure 3. Equipment for tDCS intervention



(A) 1x1 Mini-CT tDCS device; (B) SNAPstrap Headgear; (C) EASYpad Electrodes.

13.4.4 DOSING

In summary, the dosing of these intervention arms are as follows:

- Active Comparator: 5 sessions/week at 30 min/session
- BrainHQ: 5 sessions/week at 30 min/session
- BrainHQ + PASC-CoRE: BrainHQ plus 9 group sessions at 1.5 hr/session and 3 individual sessions at 30 min/session
- BrainHQ + tDCS-active: 2.0 mA stimulation delivered for 30 min during each BrainHQ session
- BrainHQ + tDCS-sham: inactive stimulation delivered for 30 min during each BrainHQ session

13.4.5 SCHEDULE OF PROCEDURES (APPENDIX-LEVEL DIFFERENCES)

Clinical laboratory assessments will not be required as part of Baseline assessments, in contrast to Section 8.8.

13.4.6 ADHERENCE

High adherence is expected given the remote nature of the intervention and the study team-participant engagement. Further, tDCS sessions will be monitored regularly; adherence will be captured by the device per session completion. Moreover, the study's cloud database will alert participants when they are to complete their daily session. Finally, the study team will provide remote computer support and technical assistance to ease any technical barriers participants may encounter. Although, participants are encouraged to complete every BrainHQ and tDCS session, one 3-day pause is allowed and will not trigger non-adherence.

13.5 SAFETY

BrainHQ and PASC-CoRE have no obvious risks and have been designated non-significant risk devices by the FDA. Minor AEs associated with BrainHQ are wrist soreness and headache.[73]

tDCS has also been designated non-significant risk with no known risk of SAEs, though common side effects include warmth, itching, or tingling under the electrodes. tDCS will be remotely supervised and within safety limits established by previous research. The tDCS device affords dose and usage control by employing a one-time use-code provided by the study team to unlock the device for each stimulation session (i.e., the device cannot be used outside this window). Additional built-in safety features include automatic shutoff and a manual abort button. Furthermore, the study team trains participants on headgear placement and overall device use. Importantly, tDCS poses no risk of worsening headache in patients with migraines and is not associated with seizure activity in patients with epilepsy.[74]

13.6 EVENTS OF SPECIAL INTEREST

None.

13.7 PREGNANCY AND LIFESTYLE CONSIDERATIONS

Contraception is *not* required.

Relative to the reporting requirements in Section 9.1.6, the following are altered: (a) Pregnancies occurring after starting intervention activities and while on-study will be documented in the database, but pregnant participants will *not* be advised to discontinue the intervention; (b) mothers who conceived a child with a male participant on-study will *not* be required to consent to having their pregnancies followed, and their pregnancies will not be followed through completion; and (c) the DCRI Safety Surveillance team will *not* need to notify device supplying partners of the pregnancy.

Related to these alterations: Pregnancy testing is *not* required at each study visit; thus, participants' self-report is acceptable. Additionally, pregnancy testing is *not* required for female participants who self-

report menopause, have no menstrual cycle for at least 12 months, or are surgically sterile (such as hysterectomy, bilateral tubal ligation, bilateral oophorectomy).

13.8 STATISTICAL CONSIDERATIONS (APPENDIX LEVEL)

13.8.1 SAMPLE SIZE DETERMINATION

No existing published data are available to evaluate the minimal clinically meaningful effect size in the PASC population. As a reference, a study of 33 patients with traumatic brain injury who were randomized to 5 weeks of an intervention using similar approaches to PASC-CoRE versus 5 weeks Brain Health Education found improvements with effect sizes of 0.48 to 0.71 on the Mayo-Portland Adaptability Inventory-4.[75]

A sample size of 50 participants per group will provide 90% power to detect an effect size of 0.655 for a comparison of any two arms, using a two-sample t-test and assuming 1:1 randomization and a two-sided type I error rate of 0.05. Assuming 20% loss to follow-up, 63 participants per arm would need to be randomized. Table 6 provides effect sizes that can be detected with 80 and 90% power under various assumptions for sample size per arm and percent loss to follow-up.

Table 6. Effect sizes that can be detected with 80% and 90% power under various scenarios for enrollment and loss to follow-up

Power	Number of patients per arm	Number of patients needed per arm assuming 10% loss to follow up	Number of patients needed per arm assuming 20% loss to follow up	Effect size
80%	50	56	63	0.57
80%	75	83	94	0.46
80%	100	111	125	0.40
90%	50	56	63	0.66
90%	75	83	94	0.53
90%	100	111	125	0.46

13.8.2 PRIMARY AND SECONDARY COMPARISONS

The current interventions and design afford evaluation of the following primary comparisons:

A. BrainHQ versus Active Comparator
B. BrainHQ + PASC-CoRE versus Active Comparator
C. BrainHQ + tDCS-active versus BrainHQ + tDCS-sham
D. BrainHQ + PASC-CoRE versus BrainHQ

The following secondary comparisons will be evaluated:

E. BrainHQ + tDCS-active versus Active Comparator
F. BrainHQ + tDCS-active versus BrainHQ