RECOVER-SLEEP: A Platform Protocol for Evaluation of Interventions for Sleep Disturbances in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

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** To ensure the integrity of the study's randomization and data collection process, some material has been condensed or removed from this public version of the protocol. If you have any questions, please email recoverresearch@duke.edu.

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-SLEEP: A Platform Protocol for Evaluation of Interventions for Sleep Disturbances in Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
Study Description:	This platform protocol is a prospective, multi-center, multi-arm, randomized controlled platform trial evaluating potential interventions for PASC-mediated sleep disturbances. The hypothesis is that symptoms of sleep and circadian disorders that emerge in patients with PASC can be improved by phenotype-targeted interventions. Specific sleep and circadian disorders addressed in this protocol include sleep-related daytime impairment (referred to as hypersomnia) and complex PASC-related sleep disturbance (reflecting symptoms of insomnia and sleep-wake rhythm disturbance). The platform protocol is designed to be flexible so that it is suitable for a range of study settings and intervention types. Therefore, the platform protocol provides a general protocol structure that can be shared by multiple interventions and allows comparative analysis across the interventions. For example, objectives, measures, and endpoints are generalized in the platform protocol, but intervention-specific features are detailed in separate appendices. Interventions will be added to the platform protocol as appendices. Each appendix will leverage all elements of the platform protocol, with additional elements described in the individual appendix.

Objectives:	Primary: 1. Evaluate the efficacy of study intervention versus control on sleep-related daytime impairment, sleep disturbance, and/or sleep-wake rhythm disturbance Secondary: 1. Evaluate the effect of study intervention versus control on fatigue 2. Assess the effect of study intervention versus control on cognitive function 3. Evaluate the effect of study intervention versus control on PASC-related symptoms 4. Evaluate the effect of study intervention versus control on insomnia symptoms 5. Compare the effect of study intervention versus control on sleep duration, efficiency and timing 6. Compare the effect of study intervention versus control on sleep-wake patterns Exploratory: 1. Describe the effect of study intervention versus control on rebound symptoms 2. Describe the effect of study intervention versus control on change in other patient-reported outcomes 3. Describe the effect of study intervention versus control on relevant biomarkers 4. Describe the effect of study intervention versus control on rebound sleep-wake patterns 5. Describe patterns of positive airway pressure device (PAP) device adherence and the association of PAP device adherence on study outcomes (among participants using study-provided continuous PAP devices) 6. Evaluate the effect of study intervention versus control on participants' impression of their change in health status
Study Population:	Each study intervention appendix may require a different sample size depending on the number of groups within the appendix and the design of the appendix. This platform will enroll adult participants who have persistent symptoms of various sleep disturbances. Overall enrollment will depend on the number of screen failures, the number of study intervention appendices that are added, the ability to pool their control groups for analysis, and adjustments to sample size based on study data. The goal is to have a diverse population, including underserved communities and racial/ethnic populations frequently underrepresented in clinical research.
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. The number of sites for each appendix will depend upon the intervention and the

	appendix design. Approximately 25 to 100 sites in the United States may participate.
Description of Study Intervention:	Each study intervention appendix describes different study intervention(s) and control.
Participant Duration:	The duration of each intervention will be appendix-specific. An End of Study visit will occur for all interventions approximately 30 days after the end of the intervention. Study participation will last for the pre-randomization period, the duration of the intervention, and until the End of Study visit.

1.2 SCHEMA

The overall protocol design is illustrated in Figure 1. The workflow of home sleep apnea testing (HSAT) and sleep-related breathing disorder (SRBD) screening is detailed in Figure 2, and the phenotype assessment is exhibited in Figure 3.

Figure 1. RECOVER-SLEEP Protocol Overall Workflow

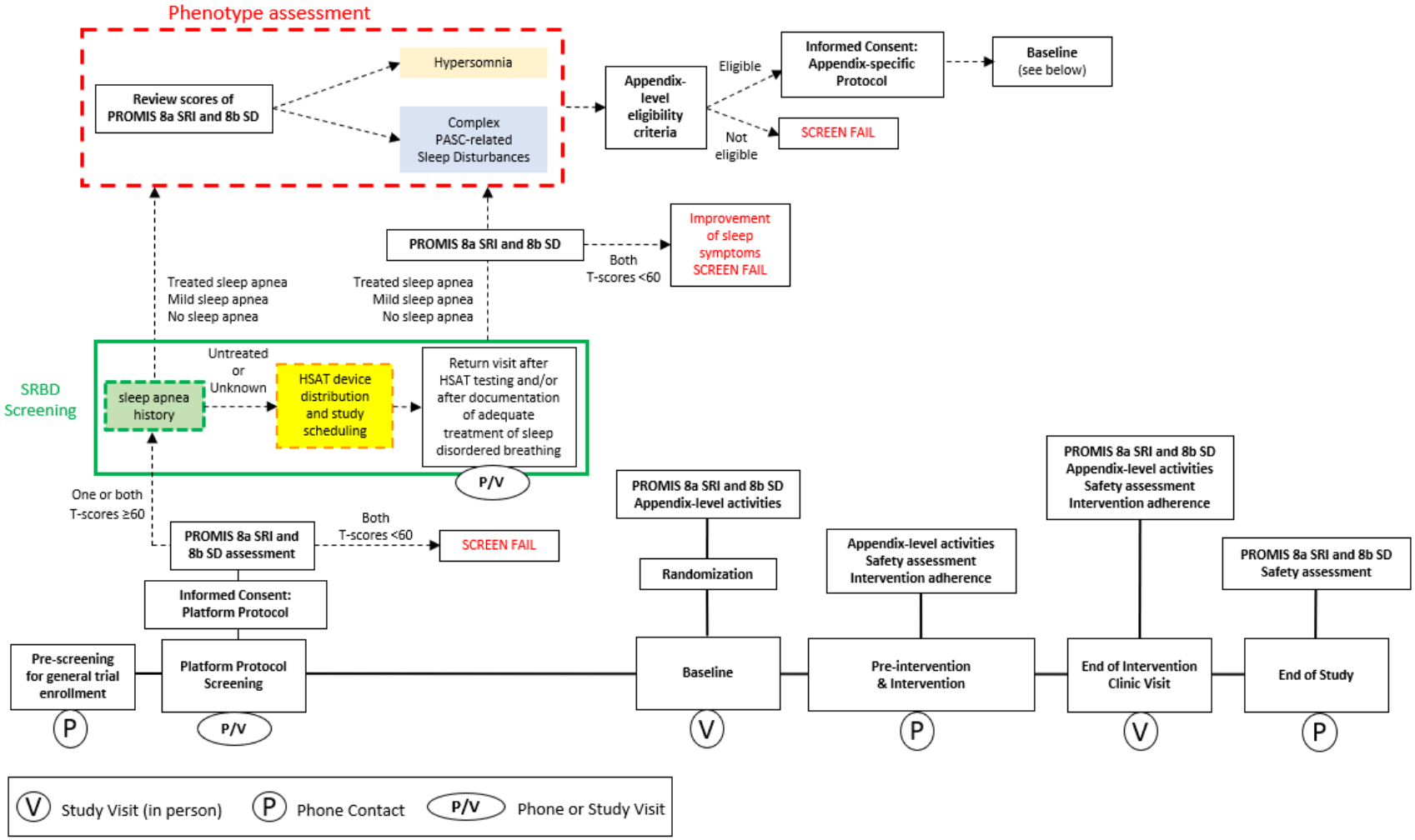

Figure 1. Abbreviations: SD – sleep disturbance; SRI – sleep-related impairment; SRBD – sleep-related breathing disorder; HSAT – home sleep apnea testing.

Participants will be initially pre-screened for trial entry over the phone. If they pass this screening, participants will undergo informed consent for the platform protocol, followed by assessment with both the PROMIS 8a SRI and 8b SD. Participants with adjusted T scores less than 60 on both assessments will be considered screen failures, but those scoring 60 or greater on either will proceed to SRBD screening (green box). Participants who have documentation within the past 6 months verifying they have adequately treated, mild, or no sleep apnea will proceed to the phenotype assessment (red box). Participants will be marked as untreated or unknown if they do not have documentation within the past 6 months verifying they have adequately treated, mild, or no sleep apnea; unknown can also refer to being treated with non-PAP treatments. These participants will be referred for HSAT (yellow hatched box). After completing HSAT, participants will need to follow-up for another in-person visit or phone call to review sleep apnea test results and determine continued trial eligibility. Participants identified with untreated moderate or severe Obstructive Sleep Apnea (OSA) or inadequately treated OSA will be referred to clinical care for initiation or modification of OSA treatment. Assuming testing and treatment for sleep apnea are adequate after clinical intervention, participants will retake the PROMIS 8a SRI and 8b SD and, if still eligible, proceed to phenotype assessment (red box); however, if their sleep symptoms improve after diagnosis and treatment of OSA (both T scores <60), they will be ineligible for study participation. The participants' phenotype – hypersomnia or complex PASC-related sleep disturbance – will be determined by their PROMIS 8a SRI and 8b SD scores coupled with several simple, self-reported sleep-symptom questions. Based upon their phenotypes, participants will be assigned to a specific trial appendix. Appendix-level exclusion criteria will be applied to classify participants as screen failures or eligible for Baseline assessments. Eligible participants will consent to the appendix before starting Baseline activities. At the Baseline visit, participants will complete the appendix-level activities and be randomly assigned to an intervention group. Participants will proceed to pre-intervention and intervention activities. Then, they will return for an EOI clinic visit comprising the listed activities. Finally, participants will be contacted by phone on or around 30 days after the End of Study Clinic Visit for a final safety assessment. For greater workflow detail, see Section 8.

Figure 2. Sleep-Related Breathing Disorder Screening Schema

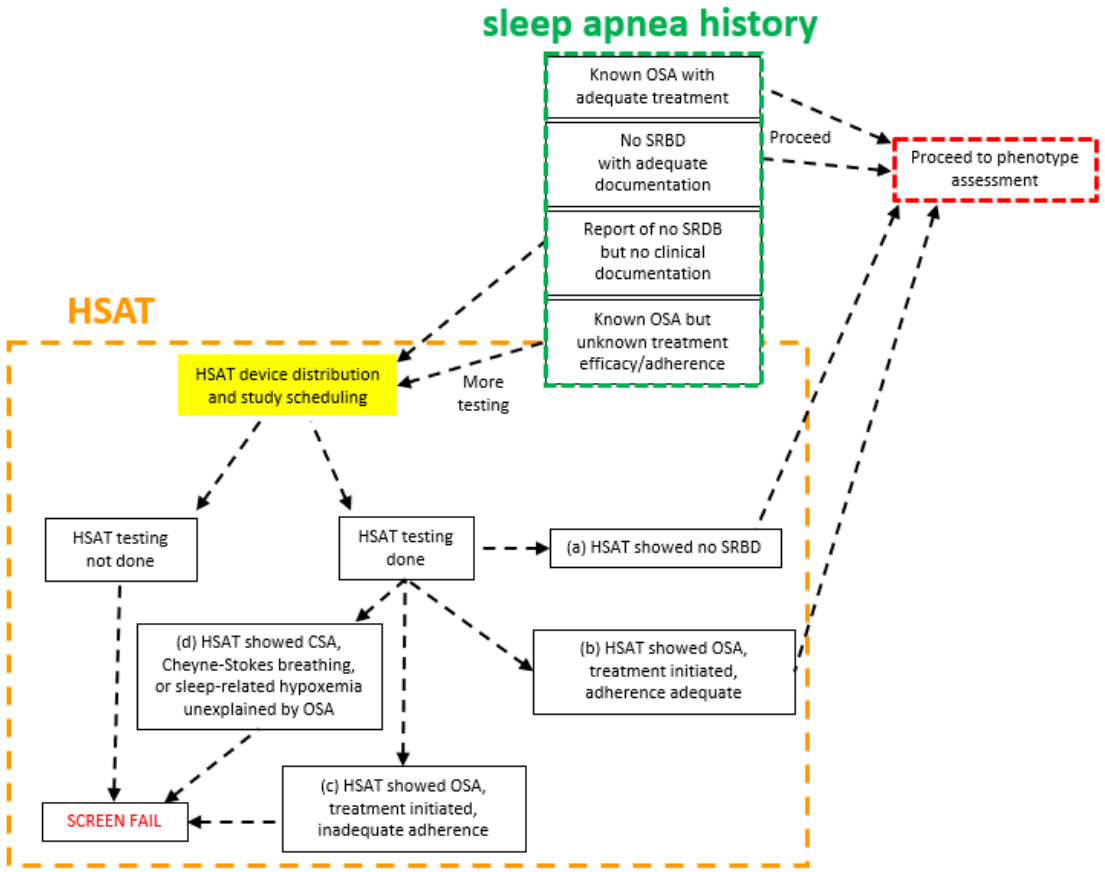

Figure 2. Abbreviations: OSA – obstructive sleep apnea; SRBD – sleep-related breathing disorder; HSAT – home sleep apnea testing; CSA – central sleep apnea.

This schematic represents how SRBD is screened based on history and available documentation (green hatched box). Some participants will require additional testing and will be referred for HSAT (yellow hatched box). Participants referred for HSAT will be scheduled for testing and/or clinical treatment. Participants who choose not to complete testing or who are found to have moderate-severe OSA and choose not to be treated will be ineligible. Participants who complete testing will proceed to the phenotype assessment if testing reveals (a) participants do not have SRBD or (b) participants have OSA but they adequately adhere to treatment. Participants will be ineligible if testing reveals they (c) have OSA but do not adequately adhere to treatment or (d) have an SRBD that is not OSA.

Figure 3. Phenotype Assessment Schematic

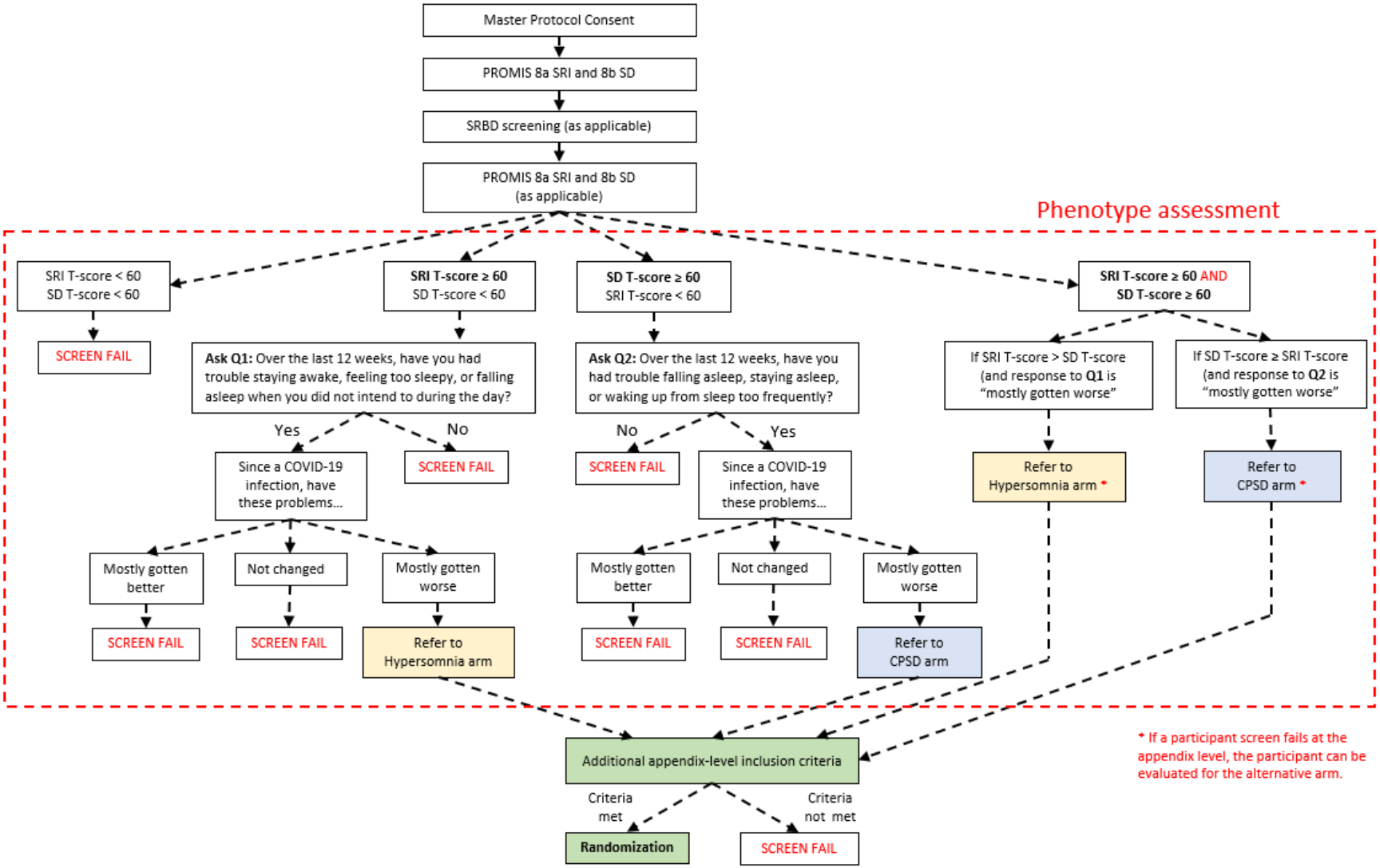

Figure 3. Abbreviations: SD – sleep disturbance; SRI – sleep-related impairment; CPSD – Complex PASC-related Sleep Disturbance.

Participants' scores on the PROMIS 8a SRI and 8b SD will determine their allocation to one of four phenotype pathways, leading to the Hypersomnia arm or the CPSD arm, or to screen failure. Applying appendix-level eligibility criteria will determine if participants proceed to Baseline assessments and randomization or if they screen fail. Note that screen failures may be re-evaluated for other phenotypes for which their PROMIS 8a SRI or 8b SD score matches.

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 that develops in up to 80% of SARS-CoV-2-infected, hospitalized patients and in 40% to 70% of non-hospitalized patients with COVID-19.[1-4] The number of individuals with PASC is rising, and the personal and global impact of PASC symptoms can be debilitating. Individuals with PASC can experience extensive symptoms, including dyspnea, autonomic dysfunction, exercise intolerance, anxiety, depression, cognitive impairment, and a wide range of sleep disturbances. Insufficient sleep, excessive daytime sleepiness, and sleep-wake disturbances can markedly impact quality of life, energy and vitality, and overall health – directly or indirectly affecting other PASC symptoms. 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' sleep health. This platform protocol aims to investigate interventions with prior evidence of improving disordered sleep and its daytime symptoms. If successful, results will enable providers to treat PASC-emergent symptoms of sleep and circadian rhythm disturbances.

2.2 BACKGROUND

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

COVID-19 has led to the deaths of more than 6 million people worldwide, and it has affected even more lives through often-debilitating symptoms lingering long after acute SARS-CoV-2 infection. Post-Acute Sequelae of SARS-CoV-2 infection, also known as PASC, is a chronic condition that affects nearly every organ system, with more than 200 individual symptoms.[6] PASC can occur regardless of the 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 underserved, historically minoritized populations and worsened a decades-long mental health crisis. Considering these costs, identifying 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 (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 people, and children. Data from the RECOVER initiative, as well as existing literature, have highlighted three predominant symptom clusters, including exercise intolerance, cognitive dysfunction, and autonomic dysfunction, which are frequently reported and also of substantial importance to patients. In addition, data have identified substantial heterogeneity in symptomology and

presentation, even among those within a specific symptom cluster, as well as poor concordance between objective findings and reported symptoms in many cases.[6,7]

Emerging research is also beginning to identify risk factors for PASC. Women are disproportionately impacted by PASC relative to men at an approximately 3:1 ratio, with this sex difference appearing to fade in older individuals 60 to 70 years of age.[8-10] Longitudinal, multi-omic profiling of COVID patients has revealed several anticipating risk factors for PASC at the time of diagnosis, including type 2 diabetes, SARS-CoV-2 RNAemia, Epstein-Barr Virus viremia, and autoantibodies.[11]

Healthy sleep and circadian rhythms are fundamental and integrative physiological processes that are critical for physical and mental health, immune function, longevity, and well-being.[12-14] In the general population, disturbed sleep and circadian physiology increase the prevalence and/or incidence of cardiovascular disease, renal disease, diabetes, and interstitial lung disease and are associated with mood disturbances, cognitive impairment, and risk of Alzheimer's Disease (including memory encoding/retrieval and alertness/executive functioning).[15-21] Underlying mechanisms for these adverse outcomes include perturbations of autonomic function, inflammation, oxidative stress, metabolism, neurodegeneration, neuroinflammation, amyloid β production and clearance, synaptic plasticity, hematopoiesis, and atherosclerosis.[19,22-24] Sleep is also associated with antigen-specific immune defense, consistent with a close inter-relationship between sleep and both the adaptive and innate immune systems, highlighting sleep's specific relevance to PASC.[25]

Symptoms of sleep-related disorders are the third most common PASC symptom after fatigue and shortness of breath.[26,27] Recent international surveys studying PASC that included detailed sleep measures suggested that long-lasting sleep symptoms are at the "core of post-acute sequelae of Covid-19".[28] Several mechanisms likely contribute to the occurrence of a wide spectrum of sleep disturbances following SARS-CoV-2 infection. PASC-related neuroinflammation may directly affect central brain centers that regulate sleep-wake patterns and circadian rhythmicity leading to disorders characterized by insomnia (difficulty falling asleep or maintaining sleep), hypersomnia (excessive daytime sleepiness and difficulty staying alert), and variability in sleep timing (delayed sleep onset or highly variable sleep patterns). Novel presentations of sleep disturbances also have been reported in individuals with PASC, such as within-person transitions from insomnia to hypersomnia (suggesting instability in hypothalamic and other sleep-wake brain centers), nightmares and REM behavioral disorder (a potential harbinger of neurodegeneration), and restless leg syndrome (implicating abnormalities in iron and dopamine-related pathways). Sleep-wake patterns are also influenced by physical and mental health conditions common after SARS-CoV-2 infection, providing reciprocal, amplifying inter-relationships between disordered sleep and poor health. Untreated sleep disturbances in PASC may not only directly impact quality of life, mood, alertness, and daily function, but also contribute to the pathogenesis of PASC and its multiple symptom clusters through effects on autonomic nervous dysfunction, inflammation, oxidative stress, metabolism, neurodegeneration, neuroinflammation, amyloid β production and clearance, synaptic plasticity, hematopoiesis, and immune dysfunction.[24,25,29-32]

Evidence-based treatments for sleep disorders reduce sleep symptoms and improve quality of life and health. However, scant data specifically address their utility in patients with PASC. Therefore, treatment of PASC-related sleep disturbances provides an attractive intervention target. Given that sleep disturbances and disorders disproportionately affect low-income and minoritized populations, clinical trials should target sleep disturbance symptoms for improving PASC and appropriately represent minority groups in the sample population.[33]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks of this study include those associated with the specific study intervention (refer to appendices for details), sleep apnea testing, blood draws, nasal swabs, and loss of confidentiality.

Risks associated with sleep apnea testing include skin irritation associated with sensors taped to the skin and temporary disturbance of sleep.

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

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

Additional risks associated with interventions will be defined in the appendices.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants may benefit from improvement in PASC symptoms and quality of life. Because many of the sleep-specific interventions are placebo controlled, participants may not derive any direct benefit from participation. However, society in general and future patients infected with SARS-CoV-2 will benefit from the study's results, which will provide a better understanding of the benefits and risks of sleep disturbance treatment for PASC and alleviation of PASC symptoms. The participants who undergo sleep apnea testing as part of the initial trial screening process will receive these study results, which can guide further evaluation and treatment. Participants who screen positive for OSA may receive a study-provided Positive Airway Pressure (PAP) device. Participants may be able to keep activity trackers and/or portable blood pressure monitors for personal health monitoring after the study ends.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential benefits may outweigh potential risks. PASC is a significant health issue and can have consequences that impact quality of life. These consequences affect the individual and society at large.

3 OBJECTIVES AND ENDPOINTS

The objectives, outcome measures, and endpoints listed in Table 1 are shared across all intervention appendices. Further details on outcome measures and endpoints are provided in Sections 8.8 and 10 and the Statistical Analysis Plan (SAP).

Table 1. Summary of Study Objectives, Outcome Measures, and Endpoints

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
Primary		
Evaluate the efficacy of study intervention versus control on sleep-related daytime impairment, sleep disturbance, and/or sleep-wake rhythm disturbance	See each appendix for which measure(s) is/are used: • PROMIS 8a SRI (Sleep-Related Impairment) • PROMIS 8b SD (Sleep Disturbance) • (only Complex PASC-Related Sleep Disturbance) Activity tracker	Primary endpoint: change in total score from baseline to End of Intervention (EOI) of either 8a SRI or 8b SD • The other measure becomes a secondary endpoint. Primary endpoint (only for Appendix B: Complex PASC-Related Sleep Disturbances): change in sleep onset variability from baseline to EOI
Secondary		
Evaluate the effect of study intervention versus control on fatigue	PROMIS 10a Fatigue	Change from baseline to EOI on PROMIS 10a Fatigue
Assess the effect of study intervention versus control on cognitive function	• Everyday Cognition 2 (ECog2) • Neurocognitive Battery	Change from baseline to EOI on cognitive function
Evaluate the effect of study intervention versus control on PASC-related symptoms	• PASC Symptom Questionnaire	Change from baseline to EOI on PASC-related symptoms
Evaluate the effect of study intervention versus control on insomnia symptoms	Insomnia Severity Index (ISI)	Change in total score from baseline to EOI on the ISI
Compare the effect of study intervention versus control on sleep duration, efficiency, and timing	Sleep diary	Change from baseline to EOI in sleep onset variability, average nocturnal and 24-hour sleep duration, and absolute sleep midpoint
Compare the effect of study intervention versus control on sleep-wake patterns	Activity tracker	Change from baseline to EOI in average nocturnal and 24-hour sleep duration, sleep efficiency, and sleep midpoint

OBJECTIVES	OUTCOME MEASURES	ENDPOINTS
Exploratory		
Describe the effect of study intervention versus control on rebound symptoms	• PROMIS 8a SRI • PROMIS 8b SD	Change in total score of either 8a SRI or 8b SD from EOI to End of Study
Describe the effect of study intervention versus control on change in other patient-reported outcomes (PROs)	• Orthostatic Hypotension Questionnaire (OHQ) • Modified DePaul Symptom Questionnaire Post-exertional Malaise (DSQ-PEM)	Change from baseline to EOI on PROs
Describe the effect of study intervention versus control on relevant biomarkers	Biomarker levels in biosamples	Change in biomarker(s) from baseline to EOI
Describe the effect of study intervention versus control on rebound sleep-wake patterns	Activity tracker	Change from EOI to End of Study in average nocturnal and 24-hour sleep duration, sleep efficiency, and sleep midpoint
Describe patterns of PAP device adherence and the association of PAP device adherence on study outcomes (among participants using study-provided continuous PAP devices)	Hours of PAP use from the PAP device output	Average nightly PAP use over the study period
Evaluate the effect of study intervention versus control on participants' impression of their change in health status	Patient Global Impression of Severity (PGIS)	Change in total score from baseline to EOI on the PGIS

4 STUDY DESIGN

4.1 OVERALL DESIGN

This platform protocol is a prospective, multi-center, multi-arm, randomized, controlled trial evaluating possible treatments for sleep disturbance in PASC. It includes trials of different designs using different interventions examining several symptoms of sleep disturbance (sleep phenotypes). Each appendix describes a study intervention or interventions that target(s) a different symptom of sleep disturbance with an adequate sample size to meet the platform protocol objectives. Refer to the protocol appendices for further information on each study intervention.

Participants will provide informed consent for the platform protocol, which includes general screening procedures and an assessment of their sleep phenotype. Based on their sleep phenotype, participants will be assigned to an appendix intervention and provide informed consent for that appendix. Within the assigned appendix, participants will be randomized to an intervention group based on that appendix's study design.

This protocol will leverage common data elements already collected as part of the RECOVER initiative. The protocol will also collect patient-reported outcomes related to symptoms directly or indirectly impacted by sleep disturbances, such as fatigue and cognition. Follow-up will include 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

As part of the platform design, all participants will be screened for sleep-related breathing disorders (SRBD), including OSA, central sleep apnea (CSA), Cheyne-Stokes breathing, and sleep-related hypoxemia unexplained by OSA. These SRBDs are either exclusion criteria (CSA, Cheyne-Stokes breathing, unexplained hypoxemia) or, for OSA, a significant co-morbidity that must be assessed and managed before assessing eligibility for a specific sleep phenotype arm.[34] OSA, the most common SRBD, occurs in 9% to 38% of adults and leads to nightly, recurring acute hypoxemic episodes that can trigger a cascade of pathophysiological responses, including inflammation, autonomic and endothelial dysfunction, and oxidative stress. This cascade of responses can promote adverse physiology and symptom clusters relevant to PASC, including cardiometabolic disease, excessive daytime sleepiness, neurocognitive impairment (including "brain fog" as reported by patients with sleep apnea), and possibly lung injury.[15,16,35,36] Although data are scant on OSA in PASC, among patients with acute SARS-CoV-2 infection, OSA is associated with an approximately 50% increased mortality rate in analyses adjusted for demographic factors; notably, no evident increased risk was observed in patients with treated OSA.[34] Importantly, and relevant to this clinical trial, untreated severe sleep apnea can negatively impact the efficacy of treatments for all other sleep disorders. In using wake-promoting medications, it is important to exclude untreated OSA or only use these medications in patients with hypersomnia who do not tolerate or fail primary treatment of OSA. Therefore, to test interventions targeting PASC-emergent sleep disturbances like insomnia and hypersomnia, it is important to screen for and exclude individuals with moderate or severe, untreated OSA and other severe SRBDs.

Each appendix will detail a different study intervention and design that targets the complex symptoms of PASC-emergent sleep disturbance. Study interventions may include pharmaceutical agents, hormones, behavioral interventions, light therapy, or non-traditional interventions. Additional study interventions may be added as new agents/interventions are proposed to address sleep disturbance issues in PASC.

4.3 JUSTIFICATION FOR DOSE

The dose and duration of the study 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 the End of Study visit which is to be scheduled approximately 30 days after the participant has completed the study intervention period.

5 STUDY POPULATION

The following inclusion and exclusion criteria are the basic criteria for the platform protocol. Some appendices may have variations or criteria specific to their intervention. See appendices.

5.1 INCLUSION CRITERIA

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

1. ≥18 years of age at the time of enrollment
2. Previous suspected, probable, or confirmed SARS-CoV-2 infection, as defined by the Pan American Health Organization:[37]

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

   A. *Met the 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; or*

   B. *Presented with acute respiratory infection with a history of fever or measured fever of ≥38 °C (100.4 °F) and cough, with onset within the last 10 days, and required 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 the clinical criteria above AND was a contact of a probable or confirmed case or is linked to a COVID-19 cluster; or*
   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 criteria 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.*

3. New/worse sleep problems following a SARS-CoV-2 infection that have persisted for at least 12 weeks[38] and are still present at the time of consent
4. PROMIS 8a SRI or 8b SD T score ≥60
   A. If the PROMIS 8a SRI is ≥60, participants must also self-report symptoms of trouble staying awake, feeling too sleepy, or falling asleep unintentionally during the day over the preceding 12 weeks, and these symptoms either started after a SARS-CoV-2 infection, or if they preceded a SARS-CoV-2 infection, must have mostly worsened since the infection. These PRO outcomes and patient responses suggest a hypersomnia phenotype.
   B. If the PROMIS 8b SD is ≥60, participants must also self-report symptoms of trouble falling asleep, staying asleep, or frequently waking from sleep over the preceding 12 weeks, and these symptoms either started after a SARS-CoV-2 infection, or if they preceded a SARS-CoV-2 infection, must have mostly worsened since the infection.

These PRO outcomes and patient responses suggest an insomnia or circadian rhythm disorder phenotype.

5. Willing and able to provide informed consent, complete the surveys and clinical assessments, and return for all of the necessary follow-up visits
6. Adequate method of birth control for participants of child-bearing potential

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study (though participants may be re-screened at the site investigator's discretion):

1. Known active acute SARS-CoV-2 infection ≤4 weeks from consent
2. Known pregnancy, breastfeeding, or contemplating pregnancy during the study period
3. Untreated SRBDs
    a) OSA (apnea hypopnea index/respiratory event index ≥15)
    b) CSA (central apnea index ≥10)
    c) Cheyne-Stokes breathing >10 minutes)
    d) percentage estimated sleep time at an oxyhemoglobin saturation <88% (T88) >10% unexplained by an elevated apnea hypopnea index
4. Current night or rotating shift work
5. Known history of narcolepsy prior to SARS-CoV-2 infection
6. Any non-marijuana illicit drug use within 30 days of informed consent
7. Known history of severe mental disorder, such as psychotic disorders and bipolar disorder
8. Current or recent use (within the last 14 days) of study intervention or similar intervention to treat the underlying condition, unless a washout period is permitted per appendix*
9. Known allergy/sensitivity or any hypersensitivity to components of the study intervention or control*
10. Known contraindication(s) to study intervention including prohibited concomitant medications and without the ability to safely hold prohibited concomitant medications (see appendices)*
11. Currently receiving/using intervention from another clinical trial that could impact or mask treatment effect
12. Any condition that would make the participant, in the opinion of the site investigator, unsuitable for the study

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

5.3 LIFESTYLE CONSIDERATIONS

Participants capable of becoming pregnant must agree to use an effective method of contraception during study intervention administration and for at least 7 days after the final administration of the study intervention. Effective methods include any of the following: abstinence, partner vasectomy, bilateral tubal ligation, intrauterine device, progestin implants, oral contraceptive pills, or barrier (condom, diaphragm, cervical cap) plus spermicide.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the platform protocol but are not subsequently randomly assigned to an appendix study intervention. 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. Individuals who screen fail may be referred to other RECOVER protocols.

5.5 STUDY DEFINITION OF ENROLLMENT

For this study, enrollment is defined as signing the platform and appendix consents 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 designee, may contact eligible participants to introduce the study and discuss study participation.

Participants may be recruited from other ongoing trials (eg, COVID-19 trials) if they opted-in to be contacted about future research opportunities. Co-enrollment in other trials must be approved by RECOVER-SLEEP leadership.

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 recruitment and retention strategies.

During the active study, 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.

6.1.2 DOSING AND ADMINISTRATION

See appendices.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The use of study intervention will be tracked by the sites. The sites will call participants at least once during the intervention period to monitor compliance with study intervention administration.

For appendices with a study drug, receipt and use will be handled, tracked by the sites, and stored in a safe and secure location to which only the site investigator and designated personnel have access. Participants will also be asked to bring any unused study drug with them to the End of Intervention Clinic Visit, as applicable.

For appendices with a study device, receipt and use will be accounted for by the sites. Additionally, some devices may have accountability measures built in.

See appendices for further details.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

See appendices.

6.2.3 PRODUCT STORAGE AND STABILITY

See appendices.

6.2.4 PREPARATION

See appendices.

6.2.5 DESTRUCTION

Used and unused study drug can be destroyed at the site according to accepted pharmacy practice and both local and national guidelines, using the site's destruction procedure. A copy of the drug destruction procedure should be maintained in the pharmacy section of the regulatory binder.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This platform protocol is designed to allocate participants into an intervention appendix based on their symptoms of sleep disturbance (see Figure 3). Within the appendix, participants will be randomly assigned based on the appendix study design. Site investigators and personnel will be informed as to which study intervention appendix participants are assigned, but they will be blinded to whether participants are receiving the active study intervention or control, when possible. Similarly, participants will be blinded to active intervention or control, when possible. Randomization will be stratified by the study site; other stratification factors may be considered per appendix.

6.3.1 UNBLINDING

As applicable per appendix, the participant, treating clinicians, and study personnel will remain blinded to study intervention versus control assignment until after the database is locked and blinded analysis is completed. Only the biostatistical team who is preparing closed-session 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.

6.4 STUDY INTERVENTION ADHERENCE

Participants will be notified of the importance of completing the full course of intervention.

6.5 CONCOMITANT THERAPY

Concomitant therapies to be reported in the Case Report Form (CRF) are relevant concomitant prescription medications, over-the-counter medications, and supplements taken by the participant within 14 days of the time point of interest. Note the following:

- Prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.
- Baseline concomitant medications will include all concomitant therapies taken by the participant within 14 days of informed consent.

6.5.1 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. If they are in a *blinded appendix*, they may continue to receive study intervention as long as the rescue medication is not listed as a contraindication to *any* of the interventions within the appendix in which they are participating. If they are in an *unblinded appendix*, they may continue to receive study intervention as long as the rescue medication is not listed as a contraindication to the intervention group they are in. If the rescue medication is contraindicated, participants will discontinue the use of the study intervention but will continue to be followed according to the Schedule of Procedures (per each appendix). If the rescue medication is stopped before the intervention is finished (ie, the EOI Clinic Visit has not been completed), participants may resume receiving the intervention, per the discretion of the site investigator (see MOP for details). All participants who started receiving the intervention but discontinued due to a rescue medication requirement will be considered evaluable for the analysis.

Of note, after starting an intervention, if an event interrupts participation but the interruptive event ends before the intervention is finished (ie, the EOI Clinic Visit has not been completed), participants may resume receiving the intervention, per the discretion of the site investigator (see MOP for details).

7 PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION FROM STUDY INTERVENTION

Discontinuation from study intervention does not mean discontinuation from the entire study; thus, the remaining study procedures should be completed as scheduled by the study protocol. Participants will be asked to complete Early Termination Clinic Visit (Section 8.6). If a clinically significant finding is identified (such as changes from baseline) after enrollment, the site investigator or qualified designee will determine if any change in participant management is needed.

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

- Significant study intervention non-compliance
- Occurrence of any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation such that continued participation in the study or study intervention would not be in the best interest of the participant

The reason for participant discontinuation from the study intervention will be recorded on the CRF. Participants who are discontinued from the study intervention, but who are not withdrawn from the study, will continue to be followed through all study procedures.

7.2 PARTICIPANT WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from study participation at any time upon request. The study team will attempt to determine a reason for withdrawal; however, participants are not obliged to provide a reason. 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 participants following study withdrawal. All data collected until the time of withdrawal will be maintained in the study database and used as participants' data are evaluable for analysis.

7.3 LOST TO FOLLOW-UP

Participants will be deemed lost to follow-up if they fail to return for any scheduled visit *and* cannot be contacted after multiple attempts and methods by the study site staff and/or a central search company.

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

- The site will attempt to contact the participant and 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 site investigator or designee will make every effort to regain contact with the participant or next of kin via telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent. 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

See appendices.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCHEDULE OF PROCEDURES

See the appendices.

8.2 PRE-RANDOMIZATION VISITS (WK -6 TO -1)

8.2.1 PRE-SCREENING

Interested patients who call a study site may be asked a series of questions to help determine if the study is a good fit for them and to reduce unnecessary physical and temporal effort and burden coinciding with a study visit. Patients who appear eligible may be scheduled for the Screening visit. Patients who are not eligible may be referred to another RECOVER study or re-screened based on the site investigator's discretion.

8.2.2 SCREENING

Information about the study will be presented to potential participants and questions will be asked to determine potential eligibility. *Study-specific screening procedures will begin only after informed consent for the platform protocol is obtained*. Informed consent may be obtained via paper or online forms.

The PROMIS 8a SRI and 8b SD will be the first procedure completed after obtaining consent. The PROMIS 8a SRI and 8b SD may be administered over the phone, by mail, in-person, or electronically. Both the 8a SRI and 8b SD will be administered, but which one serves the primary endpoint is defined in each appendix. Moreover, both will be completed as the first study procedure so that participants who score below 60 on both the 8a SRI and 8b SD (screen failure) will not be required to complete the remaining screening procedures. Conversely, participants who score 60 or greater on either the 8a SRI or 8b SD (eligible) will complete the Sleep-screening questions, which are several self-reported sleep-symptom questions. Based on their answers, they will screen fail or proceed to a sleep apnea history examination and the other screening procedures, which include the following:

- Demographics
- Concomitant medications, review of the previous 14 days
- Medical history, including SARS-CoV-2 infection history and PASC symptoms and duration

- Pregnancy test, urine or serum, for individuals of childbearing potential
- Nasal swab for SARS-CoV-2, using rapid antigen test or PCR test
- Screening blood labs, dependent on PROMIS 8a SRI and 8b SD scores

Screening procedures may be performed over 1 or 2 calendar days. Baseline assessments, specimen collection, and the initial study intervention administration can occur on the same calendar day. For some participants, SRBD[1] screening will reveal the need for further testing and treatment. This process (including HSAT device delivery, data collection, device return, data analysis, and treatment) may take 6 weeks or more.

All participants will undergo SRBD screening.

8.2.2.1 SLEEP APNEA HISTORY – TREATED, MILD, NONE

Participants who have documented treated, mild, or no OSA may not be required to complete HSAT testing. Documentation must be valid, such as a participant's medical record or information from a positive airway pressure (PAP) device app; ascertainment of OSA status cannot be based only on participant self-report. With documentation of adequately treated, mild, or no OSA, participants may proceed to the evaluation of their sleep phenotype based on their PROMIS 8a SRI and 8b SD scores (see Figure 3). In some instances, the investigator may need to adjudicate OSA status. Appendix-level eligibility criteria will be applied to determine if participants will progress to Baseline assessments (Section 8.3) or be re-evaluated for another phenotype. Participants eligible for Baseline assessments will first sign an informed consent form for their respective phenotype appendix.

If documentation of sleep apnea testing and/or treatment was more than 6 months prior or documentation does not exist, participants may be required to complete HSAT testing pending investigator discretion (see Section 8.2.2.2).

8.2.2.2 SLEEP APNEA HISTORY – UNTREATED, UNKNOWN

Participants who have untreated or unknown sleep apnea or have not completed sleep apnea testing within 6 months of informed consent will be required to complete HSAT testing. Similarly, participants who have their OSA treated prior to screening with a therapy other than a PAP therapy, such as an oral appliance, hypoglossal stimulation, bariatric surgery, or other conservative treatment, will be referred to HSAT testing using the device or therapy that had been previously prescribed. Participants will receive a HSAT device with use instructions, access to an instructional video, and discussion of HSAT results. Participants will be required to return their HSAT device.

If the participants' HSAT data reveal they have no or mild OSA (an apnea hypopnea index <15) and no evidence of other significant SRBD (central apnea index <10; duration of Cheyne-Stokes breathing <10 minutes; percentage estimated sleep time at an oxyhemoglobin saturation <88% [T88] <10%;), they will retake the PROMIS 8a SRI and 8b SD and, providing an eligible score, proceed to the other screening procedures listed below.

If the participants' HSAT data reveal they have CSA, Cheyne-Stokes breathing, or hypoxemia, then participants will be considered a screen failure and referred to routine clinical care.

[1] includes evaluation of OSA and CSA, Cheyne-Stokes breathing, and hypoxemia unexplained by OSA

If they are found to have OSA that is moderate or severe (an apnea hypopnea index/respiratory event index >15), then PAP treatment is required for further study participation. Participants will be referred to local health care providers for review of the HSAT results and other relevant clinical information. If PAP treatment is determined to be appropriate and prescribed, participants may receive a study-issued, auto-titrating PAP device. Participants will be counseled on treatment and adherence (Section 8.2.2.3). Adequate adherence is necessary for continued study participation. PAP devices that are study-issued do not have to be returned.

This evaluation and treatment process may take 6 weeks or more. Participants who do not seek, initiate, or adhere to treatment will be ineligible to proceed. If 7 or more days elapse since the PROMIS 8a SRI and 8b SD were last assessed, participants will retake the PROMIS 8a SRI and 8b SD. If they provide an eligible score, they may proceed to the other screening procedures, which include the following:

- Concomitant medications, review of the previous 14 days
  - Only if the Screening review occurred more than 14 days prior
- Pregnancy test, urine or serum, for individuals of childbearing potential
  - Only if the Screening test occurred more than 3 days prior
- Nasal swab, for SARS-CoV-2 using rapid antigen test or PCR test
  - Only if the Screening test occurred more than 3 days prior
- Screening blood labs, dependent on PROMIS 8a SRI and 8b SD scores

Appendix-level eligibility criteria will be applied to determine if participants will progress to Baseline assessments (Section 8.3) or be re-evaluated for another phenotype. Participants eligible for Baseline assessments will first sign an informed consent form for their respective phenotype appendix.

8.2.2.3 TREATMENT ADHERENCE

See the MOP for definitions on adequate adherence.

8.3 BASELINE (DAY 0)

Baseline assessments may occur on the same day as Screening, depending on each patient's time availability and tolerance. If not on the same day, Baseline assessments may be divided into home and in-person assessments in order to reduce in-person burden time. For example, the PROMIS 8a SRI and 8b SD, secondary outcome measures, and exploratory PROs could be administered at home before the in-person visit, which would be used for completing the remaining assessments and procedures. Regardless of their order or location, the following assessments and procedures comprise the Baseline visit:

- Concomitant medications, collected for medications taken in the past 14 days, and alternative therapies
  - Only if the Screening review occurred more than 14 days prior
- Pregnancy test, urine or serum, for individuals of childbearing potential
  - Only if the Screening test occurred more than 3 days prior
- Nasal swab, for SARS-CoV-2 using rapid antigen test or PCR test
  - Only if the Screening test occurred more than 3 days prior
- PROMIS 8a SRI and 8b SD
  - Only if the Screening test occurred more than 7 days prior

    - If multiple assessments are performed, the most recent score is used for inclusion.
- Height and weight
    - Height may be obtained by self-report for participants who are unable to stand or by medical record.
    - Weight must be obtained from a scale.
- Sleep Phenotype questionnaire
- PROMIS 10a Fatigue
- Neurocognitive Battery
- ECog2
- PASC Symptom Questionnaire
- Insomnia Severity Index (ISI)
- Orthostatic Hypotension Questionnaire (OHQ)
- Modified DePaul Symptom Questionnaire-Post-Exertional Malaise (DSQ-PEM)
- Patient Global Impression of Severity (PGIS)
- SASS-Y, only for the Complex PASC-Related Sleep Disturbance appendix
- Sleep diary, distributed for participants to complete during pre-intervention
- Activity tracker, distributed for participants to wear during pre-intervention
- Blood collection, for clinical labs; timing and type may differ for each appendix
- Biorepository, for blood and stool; see Section 8.9
- Safety assessment, including serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs)

See each appendix for additional procedures. Refer to the MOP for details of these procedures.

After completing Baseline assessments, participants will be randomized to an intervention group within their assigned appendix, which is based on their sleep phenotype.

After randomization, pre-intervention activities must begin within 48 hours of completing Baseline assessments, as applicable per appendix.

8.4 PRE-INTERVENTION AND INTERVENTION

8.4.1 PRE-INTERVENTION

Participants will complete the sleep diary and wear the activity tracker for 7 days. The activity tracker should be worn at all times during the 7 days except when charging. Other activities may occur according to each appendix.

8.4.2 INTERVENTION

The Intervention type and duration are specific to each appendix. See appendices for necessary in-person visits.

Wearing the activity tracker during the entire intervention is optional, but doing so should be encouraged. Not wearing the activity tracker during the entire intervention will not prompt a deviation.

Additionally, the following will occur by phone call. Refer to appendices for intervention-specific timing of this phone call.

- Safety assessment including SAEs, SUSARs, and events of special interest (ESIs)
- Intervention adherence evaluation, see appendices
- Healthcare Encounter survey

At each patient contact during the intervention, safety assessments will be assessed and the Healthcare encounter survey will be administered.

The final week of the intervention period will include the EOI Clinic Visit.

8.5 END OF INTERVENTION CLINIC VISIT (EOI ±3 DAYS)

The EOI Clinic Visit will occur in the last week of the intervention. The earliest it can occur is the first day of the last week, and the latest it can occur is the last day of the last week. However, data collection with the activity tracker and sleep diary should begin 7 days before the scheduled EOI. Note that the same flexibility of data collection suggested for the Baseline visit also applies to this visit. The following activities will occur at the EOI Clinic Visit:

- PROMIS 8a SRI and 8b SD
- Concomitant medication (and alternative therapies)
- Weight
- PROMIS 10a Fatigue
- Neurocognitive Battery
- ECog2
- PASC Symptom Questionnaire
- Insomnia Severity Index (ISI)
- Orthostatic Hypotension Questionnaire (OHQ)
- Modified DePaul Symptom Questionnaire-Post-Exertional Malaise (DSQ-PEM)
- Patient Global Impression of Severity (PGIS)
- Patient Global Impression of Change (PGIC)
- Sleep diary, to be completed for 7 days before EOI
- Activity tracker, to be worn for 7 days before EOI at all times except when charging
- Biorepository, for blood and stool (Section 8.9)
- Safety assessment including SAEs, SUSARs, and ESIs
- Intervention adherence evaluation
- Healthcare Encounter (separate form from the safety assessment)

See each appendix for additional procedures. Refer to the MOP for details of these procedures.

8.6 EARLY TERMINATION CLINIC VISIT

Participants who discontinue the study intervention early will be asked to complete an Early Termination Clinic Visit. The Early Termination Clinic Visit should occur as soon as possible after study intervention discontinuation, preferably within ±3 days of discontinuation. Note that the same flexibility of data collection timing suggested for the Baseline visit also applies to this visit. The visit assessments match those in the End of Intervention Clinic Visit.

8.7 END OF STUDY (EOI +30 (±3) DAYS)

The End of Study timepoint is applicable for all appendices and will assess persistence or rebound of primary sleep outcomes. It will be a phone call 30 (±3 days) after the EOI or Early Termination Clinic Visit and will comprise the following activities:

- PROMIS 8a SRI and 8b SD
- Patient Global Impression of Change (PGIC)
- Safety assessment including SAEs, SUSARs, and ESIs
- Activity tracker, to be worn for 7 days before End of Study at all times (except when charging)

8.8 STUDY ASSESSMENTS

8.8.1 PRIMARY OUTCOME MEASURES

The primary outcome measure will be determined per appendix; however, all participants will complete both outcome measures, PROMIS 8a SRI and 8b SD, at each visit that requires them.

Patient-Reported Outcomes Measurement Information System (PROMIS) 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.[39] The PROMIS 8a SRI and 8b SD were developed as short forms from the PROMIS SD and SRI. The 8-item short forms strongly correlate 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. They take 5 minutes to complete.

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-related daytime impairment over the past 7 days with questions rated not at all to very much.

An activity tracker will be used as an objective measure to assess sleep onset variability as a primary outcome, along with PROMIS 8b SD, only in Appendix B.

8.8.2 SECONDARY OUTCOME MEASURES

8.8.2.1 PROMIS 10A FATIGUE

The PROMIS 10a Fatigue is a 10-item questionnaire that assesses a participant's fatigue on a scale of 1 (not at all fatigued) to 5 (very much). It takes 2 minutes to complete.

8.8.2.2 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:
    - o Stimuli identification among simple distractors
    - o Stimuli identification among more complex distractors
- Verbal fluency
- Measures of attention:
    - o Simple reaction time; respond when X happens
    - o Choice reaction time; respond only if X happens

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

8.8.2.3 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.[40] It has been used for patients with mild cognitive impairment,[41] Alzheimer's Disease,[42] and dementia.[43] It takes 5 minutes to complete.

8.8.2.4 PASC SYMPTOM QUESTIONNAIRE

Participants will be asked to complete a questionnaire asking about the presence of PASC symptoms at Baseline and at follow-up visits. This questionnaire includes symptoms that have been associated with PASC.

8.8.2.5 INSOMNIA SEVERITY INDEX

The ISI is a 7-item, self-report questionnaire that assesses the nature, severity, and impact of insomnia, on a 5-point Likert scale (eg, 0 = not at all, 4 = extremely; scores: from 0 to 28). The ISI asks patients to recall their insomnia symptoms over the past 2 weeks, assesses various dimensions of insomnia under the DSM-V criteria[44] and has been validated as an outcome measure for insomnia research.[45] A reduction of 6 ISI points is associated with improvements in patient-reported quality of life, productivity, and fatigue and represents a clinically meaningful within-patient improvement in individuals with insomnia.[46] It takes about 3 minutes to complete.

8.8.2.6 SLEEP DIARY

The sleep diary will request participants to log characteristics of their sleep, including bed time, sleep time, wake time, sleep quality, nap counts, nap periods, and unintended sleep. The sleep diary log presents sleep definitions to help participants complete the log.

8.8.2.7 ACTIVITY TRACKER

The activity tracker will capture participants' activity metrics, like step count, and sleep metrics, such as average nocturnal and 24-hour sleep duration, sleep efficiency, and sleep midpoint. Participants will be required to wear the activity tracker on their wrists for 7 days before and at the end of the intervention.

8.8.3 EXPLORATORY PROS

8.8.3.1 ORTHOSTATIC HYPOTENSION QUESTIONNAIRE (OHQ)

The OHQ is a measure of orthostatic intolerance, which has been the primary presentation of patients with PASC-related autonomic dysfunction. The OHQ can accurately evaluate the severity of symptoms and the functional impact of orthostatic intolerance.[47] This measure includes the Orthostatic Intolerance Daily Activity Scale and the Orthostatic Intolerance Symptom Assessment, and prior data in patients with PASC suggests that this measure discriminates well those with symptoms compared to healthy controls. It takes less than 5 minutes to complete.

8.8.3.2 MODIFIED DEPAUL SYMPTOM QUESTIONNAIRE POST EXERTIONAL MALAISE

The Modified DePaul Symptom Questionnaire Post-exertional Malaise (DSQ-PEM) is a short form of the DSQ that assesses PEM.[48] This scale assesses symptom frequency and severity over the previous 6-month period; however, for this trial, the look-back period will be modified to the previous 7 days. This short form was previously validated in patients with myalgic encephalomyelitis/chronic fatigue syndrome. It takes less than 5 minutes to complete.

8.8.3.3 PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS)

The PGIS asks participants to describe the severity of their overall status over the past week. The survey takes less than 1 minute to complete.

8.8.4 SPLIT WEEK SELF-ASSESSMENT OF SLEEP SURVEY (FOR CPSD APPENDIX)

The SASS-Y is an 18-item survey that asks participants to self-report their sleep characteristics from the previous week.[49] It takes 2 minutes to complete.

8.8.5 PATIENT GLOBAL IMPRESSION OF CHANGE

The PGIC asks participants to describe their overall status since the beginning of the study. The survey takes less than 1 minute to complete.

8.8.6 BIOMARKERS

Blood and stool samples will be collected from participants for biomarkers assessment. Biospecimens will be stored in a biorepository. Refer to the MOP for further details regarding specimen collection, preparation, and shipment.

8.9 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 focus on 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 future, as yet unspecified, analyses and studies. At each blood collection time point, 80 mL of blood will be collected to prepare the aliquots for storage at -80 °C. These samples will be stored at the Biorepository in a lab for up to 7 years. See MOP for details.

9 SAFETY ASSESSMENTS AND REPORTING

9.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1.1 DEFINITION OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

An AE is any untoward medical occurrence in humans, whether or not considered 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 site investigator.

An SAE or serious suspected adverse reaction 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
- An important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of a serious event

For those interventions that include a device, the following additional definitions will apply.

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, operation, or any malfunction of the investigational medical device. This also includes any event that is a result of 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 a principal investigator and/or a platform protocol principal investigator
    - Serious (meets any of the following criteria):
        - Is a 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, the specificity or severity of which is not consistent with the interventions' package insert or directions for use.
The DCRI Safety Medical Monitor will determine expectedness/listedness for SAEs and UADEs.

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 (per appendix) 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 the first invasive study procedure (blood collection or nasal swab), but after obtaining informed consent, will not be considered an AE. The medical occurrence or condition will be captured on the Medical History electronic case report form (eCRF).

Non-serious AEs may be reported by the participant, but will not be collected into the study database as an AE or further assessed by the site or study personnel. Non-serious AEs that result in study intervention discontinuation will be identified as the reason for study intervention discontinuation in the study database and reported separately as an AE, and they will be collected from the start of study intervention administration through the end of the intervention.

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 invasive study procedure (blood collection or nasal swab) through the End of Study for all appendices that use a study drug and through the EOI Clinic Visit for all appendices that include other interventions.

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

Adverse events (AEs) that qualify as an ESI, even if a non-serious AE, will be collected from the start of the study intervention through the End of Study (30 ±3 days after EOI) for all appendices that use a study drug and through the EOI Clinic Visit for all appendices that include non-drug interventions.

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 site investigator, who will evaluate the event based on its 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 intervention must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship 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, ESI, UADE, 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 study intervention (assessed only by those with the training and authority to make a diagnosis), action taken with study intervention (eg, 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 the relationship.

Any medical condition that is present at the time the participant is screened will be considered a baseline condition and not reported as a safety event. However, a deterioration of the condition at any time during the study 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 the onset and duration of each episode.

The site 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 otherwise explained.

9.1.4 REPORTING AND MONITORING OF SAES FOR STUDY DRUG(S) OR UADES FOR DEVICE(S)

Study drugs used in this platform protocol are not approved for the indication for the treatment of PASC. The DSMB will review aggregate safety data according to the DSMB Charter.

Any UADE(s) that a platform protocol principal investigator determines is/are reportable will be submitted to the manufacturer, all reviewing IRBs, and all participating site investigators within 10 working days of when the platform protocol principal investigator makes that determination.

If the platform protocol principal investigator determines that a 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 no later than 5 working days after the 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. After receiving that data, within 1 to 2 business days the DCRI Safety Surveillance team will notify pharmaceutical partners of SAEs (if applicable) and device manufacturers of UADEs that occur involving the specific appendix of the supplied study drug/control or supplied device, as required.

Serious adverse events (SAEs) that are related to the study drug and confirmed unlisted by the DCRI Safety Medical Monitor and platform protocol principal investigator will be reported to the central IRB 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 applicable. If the DSMB notes a clinically important increase in the rate of a SUSAR, the platform protocol principal investigator will notify site investigators no later than 15 calendar days after determining that the information qualifies for reporting. The site investigators will notify their local IRBs according to local guidelines, if applicable. Refer to the Safety Management Plan for details regarding specific reporting timelines.

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

9.1.5 EVENTS OF SPECIAL INTEREST

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

9.1.6 REPORTING OF PREGNANCY

Pregnancies that occur in participants following study intervention initiation and while on-study will be recorded in the database, and participants will be discontinued from the study intervention (see Section 7.1 for discontinuation definition). 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 case the outcome is not reached while the participant is on-study. Additionally, within 1 to 2 business days after learning of the pregnancy, the DCRI Safety Surveillance team will notify study-drug 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.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

Primary Endpoint:

1. Improvement in the EOI outcome measure(s) from the EOI compared to baseline in study intervention(s) vs control

Secondary:

1. Improvement in fatigue in the study intervention(s) vs control
2. Improvement in cognitive function in the study intervention(s) vs control
3. Reduction in PASC-related symptoms in the study intervention(s) vs control
4. Reduction in insomnia symptoms in the study intervention(s) vs control
5. Improvement in sleep duration, efficiency, and timing in the study intervention(s) vs control
6. Improvement in sleep-wake patterns in the study intervention(s) vs control

10.2 SAMPLE SIZE DETERMINATION

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

Appendix-level sample size calculations are fully described within each appendix.

10.3 POPULATIONS FOR ANALYSES

Population for effectiveness analyses: mITT. The primary efficacy analysis will be based on a modified intention-to-treat (mITT) population, consisting of all randomized participants who were administered the study intervention or control at least once. All participants in the mITT population will be included and analyzed according to their randomly assigned treatment group.

Safety population. Safety analyses will be performed among participants in the mITT population who report administering study intervention or control at least once. Participants will be analyzed according to their actual treatment received.

10.4 STATISTICAL ANALYSES

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

10.4.1 OVERALL STATISTICAL DESIGN

This study is a platform protocol designed to be flexible and consists of distinct symptoms of sleep disturbance using different interventional designs integrated into COVID-19 programs and subsequent treatment plans. For this study, data from all enrolled participants that receive the control intervention or treatment intervention will be included in the analyses. Between-group comparisons of the primary study endpoint, change from baseline in PROMIS SRI/SD T-scores (and sleep onset variability for Complex PASC-Related Sleep Disturbance), and clinically important secondary endpoints (eg, PROMIS 10a Fatigue, Neurocognitive Battery, etc.) will be analyzed using ANCOVA models. For endpoints that are categorized into binary secondary outcomes, logistic regression models will be utilized. Comparisons of the treatment groups for repeated measures outcomes over time will be investigated using mixed-

effect linear models with Generalized Estimating Equations (GEE) to account for correlated data within-participant.

Analyses of the primary endpoint measures, PROMIS SRI/SD T-scores (and sleep onset variability for Complex PASC-Related Sleep Disturbance), will require both the baseline and follow-up measurements. Participants missing one or both of their respective PROMIS SRI/SD measurements (or sleep onset variability) will not be included in the primary analysis cohort, ie, missing data on the primary endpoint will not be imputed in the primary analyses. However, sensitivity analyses will be conducted using imputation methods (eg, single or multiple imputation) to investigate the robustness of study findings. All testing hypotheses and estimated confidence intervals will be two-sided at a .05 significance level. The type I error rate of .05 for the secondary endpoints will be controlled using the Hochberg method.[50]

Changes to the overall statistical design that occur prior to locking the study database will be detailed in the final SAP.

10.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary efficacy analysis for the comparison of study intervention versus control will be based on the mean change in the primary endpoint among at-risk populations. Participants who complete the PROMIS SRI/SD T-scores at baseline and at EOI will be included in the primary analysis. Change from baseline comparison between groups for the PROMIS SRI/SD T-scores is defined as,

ABSOLUTE CHANGE = PROMIS SRI/SD [EOI] – PROMIS SRI/SD [Baseline],

where the EOI measurement is collected at the End of Intervention Clinic Visit. ANCOVA linear regression models will be implemented with change from baseline as the response variable and baseline PROMIS 8a T-scores as a covariate.

A similar analytic approach will be applied to sleep onset variability. The primary outcome(s) measure(s) will be defined per appendix. The outcome measure that is not chosen will be analyzed as a secondary outcome to the primary objective. Refer to the SAP for details.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints listed below will be analyzed using ANCOVA linear regression models similar to the approach used in the primary endpoint:

- PROMIS 10a Fatigue total score
- Neurocognitive Battery total score
- ECog2 total score
- PASC Symptom Questionnaire total score
- ISI total score
- Sleep diary
    - Average nocturnal and 24-hour sleep duration and sleep efficiency
    - Within-individual standard deviation of sleep onset
- Activity tracker
    - Within-individual standard deviation of sleep onset timing
    - Average nocturnal and 24-hour sleep duration and efficiency

Comparisons of the treatment groups for endpoints with repeated measures outcomes over time will be investigated using mixed-effect linear models with GEE to account for correlated data within-participant.

If the null hypothesis is rejected for the primary outcome, then testing of the above secondary outcomes will be performed using the Hochberg method to control the type I error rate at 0.05. However, if the null hypothesis for the primary outcome is not rejected, then inferences on the secondary endpoints will be considered exploratory.

Safety endpoint. Safety endpoints include the proportion of participants who experience individual SAEs and the proportion who experience at least one or more SAEs. These will be analyzed in the safety population defined as the subset of mITT participants who confirm at least one administration of study intervention/control. Events of Special Interest (ESIs) will be summarized by the study intervention appendix and duration. The incidence of AEs/SAEs leading to discontinuation will also be summarized.

Other endpoints. Other secondary endpoints are either binary or continuous. Binary endpoints will be analyzed by logistic regression models to estimate the odds ratios [95% confidence intervals] between the treatment groups. Continuous endpoints will be analyzed using ANCOVA linear regression models.

10.4.4 ANALYSIS OF THE EXPLORATORY ENDPOINT(S)

Exploratory analysis will include analysis of sleep disturbance rebound, (as measured by PROMIS 8a SRI and PROMIS 8b SD), rebound sleep-wake patterns (as measured by the activity tracker), symptom burden, HRQOL, autonomic dysfunction, post-exertional malaise, viral and immune biomarkers, and healthcare utilization. Symptom burden analysis will be presented with consideration to subgroups by baseline symptoms, racial and ethnic subgroup, gender, acute COVID-19 severity, and timing after acute infection. Forest plots will be utilized for subgroup analyses on the primary endpoint. For participants who received study-issued PAP devices, PAP device adherence data will be analyzed in relationship to baseline symptoms, racial and ethnic subgroup, gender, and acute COVID-19 severity; adherence will be explored as a potential intervention effect modifier in this group. Refer to the SAP for details.

10.4.5 PLANNED INTERIM ANALYSES

Interim evaluation of clinical and key safety endpoints will be performed approximately quarterly, with additional meetings or conference calls scheduled as needed. An independent, NIH-appointed, DSMB will monitor participant safety and review the performance of the trial.

The primary goal of these interim analyses is to ensure the safety of the participants enrolled in the trial and evaluate the accumulating endpoints data by treatment group in order to make assessments of futility. As a general guideline, statistical boundaries (stopping rules) for futility will be generated using Lan and DeMets beta-spending functions.[51] The actual boundaries (and frequency of looks) will be calculated at the precise information time (percent of enrolled participants with 10-week follow-up) when the DSMB convenes for a meeting. These statistical boundaries will need to be considered by the DSMB in light of the totality of clinical risk/benefit. The first futility analysis will be planned to occur when the study enrolls at least 50% of the targeted sample size. If the statistical futility boundary has been crossed, then the unblinded statistical team needs to provide the DSMB with the conditional probability (CP) under 2 scenarios: (1) CP under the current observed trend and (2) CP under the “best”

alternative, ie, under the sample size assumed effect-size. Typically, these CPs range between 0.10 and 0.20, indicating a futile study when CP <0.10 under scenario 1 and CP <0.20 under scenario 2.

Additionally, interim monitoring may involve a review of participant recruitment, compliance with the study protocol, status of data collection and completion, as well as other factors that reflect the overall progress and integrity of the study and may inform changes in eligibility criteria.

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

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 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 study intervention/control, study procedures, and risks and benefits will be given to participants, and documentation of informed consent is required before starting study procedures. Informed consent is a process that is initiated before an individual agrees to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved. Participants will be allowed to carefully read and review the consent form and ask questions prior to signing. Participants will be provided with the study team's contact information. This will allow them to communicate with the site investigators (or their delegate), receive further explanations of the research study, and ask questions that may arise.

Participants should be given time to think about the study and discuss the study with the study team and their family members prior to agreeing to participate. Participants will sign the informed consent document before any procedures are done specifically for the study. Participants may withdraw consent at any time during the study. A copy of the informed consent document will be provided to the participants for their records. The rights and welfare of the 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 study intervention and the desire to withdraw consent for study follow-up (per Section 7).

11.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

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

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

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 the 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 the 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 the 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 will be independent of the study conduct and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The DSMB will meet at least quarterly 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 risk-based approach to monitoring with routine and periodic review of site-submitted data to review the informed consent process, select eligibility criteria, review 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. Follow-up from the sites is expected to keep participants engaged.

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:

- Training: Before the start of enrollment, the clinician investigators and key study personnel at each site will be trained on 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.

- 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.

- 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.

- 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 pragmatically conducting the trial will facilitate trial completion despite strained clinical and research resources. Data may be collected by electronic methods, supplemented by telephone or videophone follow-up, and from the electronic health record.

Data will be collected directly from participants using Medidata's Rave EDC through text messaging or email with a survey link, or by phone call as a backup; paper will be used, as needed. 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. Copies of the eCRF will be provided and maintained for recording data for each participant enrolled in the study.

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 study 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 site staff.

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

Failing to wear the activity tracker during the entire intervention is not a deviation; only the 7 days at the beginning and end of the intervention are required.

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. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

11.1.11 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 will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with 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
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CMP	Complete Metabolic Panel
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease of 2019
CPSD	Complex PASC-Related Sleep Disturbances
CRF	Case Report Form
CSA	Central Sleep Apnea
CT-DCC	Clinical Trial Data Coordinating Center
DCRI	Duke Clinical Research Institute
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EOI	End of Intervention
ESI	Events of Special Interest
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equations
HIPAA	Health Insurance Portability and Accountability Act
HRQOL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IL-6	Interleukin-6
IND	Investigational New Drug Application
IRB	Institutional Review Board
LFT	Liver Function Test
MAOI	Monoamine Oxidase Inhibitor
mITT	Modified Intention-To-Treat
MOP	Manual of Procedures
NIH	National Institutes of Health
OSA	Obstructive Sleep Apnea

PAP	Positive Airway Pressure
PASC	Post-acute Sequelae of SARS-CoV-2 Infection
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PRO	Patient Reported Outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT/INR	Prothrombin Time/International Normalized Ratio
RECOVER	Researching COVID to Enhance Recovery
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SASS-Y	Split Week Self-Assessment of Sleep Survey
SD	Sleep Disturbance
SRBD	Sleep-Related Breathing Disorder
SRI	Sleep-Related Impairment
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States

11.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change
1.0	25SEP2023	None, original protocol
2.0	11DEC2023	• Added the potential benefit that participants who screen positive for OSA may receive a Positive Airway Pressure (PAP) device (Section 2.3.2) • Changed the exclusion of percentage estimated sleep time at an oxyhemoglobin saturation <90% (T90) to <88% (T88) (Section 5.2) • Removed the PROMIS-29+2 and COMPASS 31 from the list of PROs administered (Sections 3 and 8) • Added a fifth exploratory objective (Section 3) • Clarified language around SRBD screening (Section 8.2.2) • Added that participants who have their OSA treated with a therapy other than a PAP therapy, such as an oral appliance, hypoglossal stimulation, bariatric surgery, or other conservative treatment, will be referred to HSAT (Section 8.2.2) • Updated SRBD screening duration from 14 days to 6 weeks or more (Section 8.2.2) • Added that PAP treatment adherence definitions are in the MOP (Section 8.2.2.3) • Added that participants can self-report height, but they must be weighed on a scale (Section 8.3) • Removed sleep history questionnaire form EOI (Section 8.5) • Added that the Healthcare Encounter survey will be administered at every patient contact during the intervention and at EOI (Sections 8.4.2, 8.5, 13.1.2, 14.1.2) • Removed blood collection for clinical labs at EOI (Sections 8.5) • Removed blood collection for coagulation panel and CMP at EOI visit (Appendix A, Section 13.1.2)

		• Added alternative therapies to be reviewed with concomitant medications at baseline (Section 8.3) • Removed sleep history tied to medical history (Section 8.2.2, 13.1.2, 14.1.2) • Added the Sleep Phenotype questionnaire at baseline (Section 8.3, 13.1.2, 14.1.2) • Added the Neurocognitive Battery, with corresponding changes throughout (Section 8.8.2.2) • Removed the screening labs hs-CRP, CBC (Appendix A, Section 13.1.2) • Removed the screening labs hs-CRP, CBC, and coag panel (Appendix B, Section 14.1.2) • Added analysis text on PAP device adherence (Section 10.4.4) • Added measuring blood pressure and pulse at the pre-randomization visit (Appendix A, Section 13.1.2) • Added that regular use of prescribed hypnotics for sleep (≥3 times per week) is an exclusion (Appendix A, Section 13.2) • Clarified titrations for modafinil and solriamfetol (Sections 13.4.4 and 13.5.4) • Changed information on the RESET-PASC behavioral therapy to be more focused on education (Section 14) • Added that expected AEs are those listed in the protocol appendix (Section 14.5.1) • Administrative changes such as punctuation and grammar throughout
3.0	25JAN2024	• PGIS added as an exploratory outcome (Sections 3, 8, 14) • PGIC added as a questionnaire (Sections 8, 14) • PCR test added as an option for SARS-CoV-2 testing (Section 8) • Added a footnote to medical history that at every clinic visit after screening visit, changes in medical history including SARS-CoV-2 infection since last visit will be collected (Sections 13, 14)

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13 APPENDIX A: MODAFINIL AND SOLRIAMFETOL FOR HYPERSOMNIA

13.1 STUDY DESIGN AND RATIONALE

The Hypersomnia Appendix A is a double-blind, phase 2, randomized, placebo-controlled, interventional trial of a wake-promoting drug (modafinil or solriamfetol) to treat hypersomnia, defined by elevated scores (>60) on the PROMIS 8a SRI scale, in participants with symptoms of hypersomnia that first occurred or worsened after a COVID-19 infection. Participants in Appendix A will be randomized to study drug or control. Participants who meet the eligibility criteria for modafinil will receive either active modafinil or the modafinil-matched control. If modafinil is contraindicated for any reason, participants will be assessed for their ability to take solriamfetol. If participants are eligible for solriamfetol, they will receive either active solriamfetol or the solriamfetol-matched control. If solriamfetol is contraindicated, participants will be excluded from Appendix A. Modafinil and solriamfetol will be analyzed as a single wake-promoting drug condition versus control. The intervention duration will be 10 weeks.

Hypersomnia is a disabling symptom in patients with narcolepsy, sleep apnea, and shift work disorder. For these patients, the FDA has approved modafinil (for all three conditions) and solriamfetol (for narcolepsy and sleep apnea). Modafinil has been shown effective in treating hypersomnia and fatigue in large randomized clinical trials,[52-55] and has been used off-label for other conditions with related fatigue. Solriamfetol is associated with improved functional status, work productivity, and quality of life.[56] However, to date, no existing studies have investigated these drugs in patients with PASC.[57]

13.1.1 PRIMARY OUTCOME MEASURES AND ENDPOINTS

Primary: PROMIS 8a SRI to assess sleep-related impairment

Secondary outcome to the Primary Objective: PROMIS 8b SD

13.1.2 SCHEDULE OF ADDITIONAL PROCEDURES

The full schedule of procedures from Table 2 is shown for operational ease starting on the next page.

Table 2 abbreviations: EOI – End of Intervention; PASC – Post-acute sequelae of SARS-CoV-2 infection; PROMIS – Patient-Reported Outcomes Measurement Information System; PT/INR – prothrombin time/international normalized ratio; CMP – complete metabolic panel; LFT – liver function tests

Table 2. Schedule of Procedures for Appendix A - Modafinil and Solriamfetol for Hypersomnia

Procedures	Pre-randomization Visits	Baseline Visit	Pre-intervention	Intervention		End of Study
Study weeks	Wk -6 to -1	Day 0	Wk 1	Wk 2-10	EOI Clinic Visit[2] Wk 11	EOI + 30 days
Informed consent, platform	X					
PROMIS 8a SRI and 8b SD	X	X[3]			X	X
Sleep-screening questions	X					
Demographics	X					
Concomitant medications	X	X[3]			X	
Medical history	X[4]					
Pregnancy test	X	X[3]				
Nasal swab	X	X[3]				
SRBD screening/HSAT[5]	X					
Appendix-level eligibility criteria	X					
Blood for coagulation panel[6]	X					
Blood for CMP w/ LFT	X					
Informed consent, appendix level	X					
RANDOMIZATION		X				
Height (H) and weight (W)		H/W			W	
Sleep Phenotype questionnaire		X				
PROMIS 10a Fatigue		X			X	
ECog2		X			X	
Neurocognitive Battery		X			X	
PASC Symptom Questionnaire		X			X	

[2] An Early Termination Clinic Visit will be request for participants who prematurely discontinue the intervention. It will mirror the EOI Clinic Visit. Refer to Section 8.6.
[3] If necessary; see Baseline visit, Section 8.3
[4] At every clinic visit after screening visit, changes in medical history including SARS-CoV-2 infection since last visit will be collected.
[5] Not necessary if participant has had a sleep apnea screening and documented adherence within 6 months of Screening
[6] Coagulation panel inclusive of prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (APTT)

Procedures	Pre-randomization Visits	Baseline Visit	Pre-intervention	Intervention		End of Study
Study weeks	Wk -6 to -1	Day 0	Wk 1	Wk 2-10	EOI Clinic Visit[2] Wk 11	EOI + 30 days
ISI		X			X	
OHQ		X			X	
DSQ-PEM		X			X	
PGIS		X			X	
PGIC				X	X	X
Sleep diary		Distribute	Complete[7]		Complete[7]	
Activity tracker		Distribute	Wear[7]	Wear (optional)	Wear[7]	Wear[7]
Blood for Biorepository		X			X	
Stool for Biorepository		X			X	
Distribute blood pressure monitor		X				
Blood pressure and pulse	X[8]	X[8]		X[8,9]	X[8]	
Blinded investigational product		Distribute		X	Return[10]	
Dosing titration calls[11]				X[12]		
Safety assessment		X		X[13,14]	X	X[13]
Healthcare Encounter survey				X[14]	X	
Pill count/adherence				X[15]	X	

[7] Data to be collected for 7 days. Refer to the MOP for specific timing and duration of data collection.
[8] For blood pressure, take 3 readings sequentially after 5 minutes of seated rest.
[9] May be collected multiple times during the intervention. Will be collected at home.
[10] Investigational product should be taken until the EOI Clinic Visit.
[11] Specified in the MOP as occurring approximately every 5 days by phone call for about 20 days after initiation of drug intervention
[12] See the dosing and administration for each investigational product for titration details
[13] Phone call only
[14] At 42 ±7 days. Other phone calls can occur as necessary; assessed at every patient contact.
[15] By phone call; can be combined with the safety assessment.

13.1.3 BLINDING

The participant, treating clinicians, and study personnel will know which appendix the participant is in and which study drug/placebo group they are in (modafinil or solriamfetol). The participant, treating clinicians, and study personnel will remain blinded to study drug versus placebo assignment. However, a study pharmacist will be unblinded to control study drug and placebo disbursement. Blinded personnel will remain blinded until after the database is locked and blinded analysis is completed. Only the biostatistical team that is preparing closed interim reports will be unblinded. Specifically, study drug/control will be dispensed with packaging and labeling that would blind treatment assignment. Unblinding will occur only if required for participant safety or treatment, at the request of the treating clinician. Refer to the MOP for further details.

13.2 ADDITIONAL APPENDIX-LEVEL EXCLUSION CRITERIA

1. Self-reported sleep duration <6 hours per night
2. Poorly controlled hypertension (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg)
3. Moderate to severe hepatic impairment (ie, Child-Pugh class B or C)*
4. Known estimated glomerular filtration rate <30 mL/min/1.73 m^2 and/or chronic dialysis*
5. Recent myocardial infarction (<1 year), unstable angina, serious cardiac arrhythmias, or other serious heart problems, at the discretion of the investigator; refer to the MOP for details.
6. Current use of stimulant or wake-promoting medications, unless a washout is permitted; refer to the MOP.
7. Regular use of prescribed hypnotics for sleep (≥3 times per week); washout period is permitted. Refer to the MOP for a list of hypnotics.

*characterized by the screening labs: coagulation panel and CMP w/LFTs

13.2.1 MODAFINIL EXCLUSION CRITERIA

1. Modafinil can affect drug metabolism given its effect on enzymes such as CYP3A4 and CYP2C19. To assess for drug interactions, investigators should use the Lexicomp Drug Interactions System that is available at most institutions.
    - If the search yields "D" – Consider Modifying Therapy or "X" – Avoid Combination, then the ACTION is to exclude the potential participant.
        - An important example of this is **steroid hormonal contraceptives**.
    - If the search yields "C" – Monitor Therapy, then discuss with site PIs on a case-by-case basis.
    - If the search yields "A" – No Known Interaction or "B" – No Action Needed, then proceed to screen/include the potential participant.
    - See the MOP for examples of common drugs that fall into these categories.

2. Known severe left ventricular hypertrophy, mitral valve prolapse; see the MOP for definitions.

13.2.2 SOLRIAMFETOL EXCLUSION CRITERIA

1. Concurrent treatment with a monoamine oxidase inhibitor (MAOI) or use of an MAOI within the preceding 14 days
2. Current use of dopaminergic drugs

13.3 HALTING RULES

Study drug dosing and enrollment will be temporarily suspended pending review of the DSMB if 3 or more participants on the same study drug within Appendix A experience an SAE of the same type that is determined to be related to the study drug. The DSMB recommendations will be considered by the NIH and the study Principal Investigator prior to making any decisions regarding study continuation or discontinuation.

13.4 MODAFINIL INFORMATION

13.4.1 RISK ASSESSMENT

Modafinil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, and shift work disorder. Participants taking modafinil have reported serious rash requiring hospitalization and discontinuation of treatment. The most commonly observed AEs (≥5%) associated with the use of modafinil in primary disorders of sleep and wakefulness were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia.[58]

13.4.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Modafinil is a small molecule with the chemical name of 2-[(diphenylmethyl)sulfinyl]acetamide. Modafinil will be an oblong, blue tablet.

The placebo will be tooled to look similar to the modafinil tablet, but it will not contain the active ingredient.

Modafinil and the placebo will be packaged in high-density polyethylene bottles with a child-resistant screw cap. All packaging will be labeled to indicate that the products are for investigational use.

13.4.3 DRUG DISPENSING, STORAGE, AND STABILITY

Unblinded study personnel will manage modafinil and placebo disbursement to maintain blinding among participants and blinded study personnel, including site investigators.

Modafinil and the placebo should be stored at 20 °C to 25 °C (68 °F to 77 °F) with excursions permitted between 15 °C to 30 °C (59 °F to 89 °F).[58]

13.4.4 DOSING AND ADMINISTRATION

Modafinil administration will total 10 weeks. Over the first 3 weeks, modafinil will be titrated starting at 100 mg daily in the morning. Specifically, every 5 days (±2 days) the study team will call participants to discuss titration according to the following schedule:

1. 100 mg daily in the morning˚
2. 200 mg daily in the morning˚
3. 200 mg daily in the morning˚ and 100 mg in the early afternoon•
4. 200 mg daily in the morning˚ and 200 mg in the early afternoon•

˚morning is 11:59 am or earlier

•early afternoon is at least 4 hours after morning dose and at least 8 hours before scheduled bedtime.

Example: A participant with a scheduled bedtime of 11:30 pm would take the early afternoon dose no later than 3:30 pm, which would require taking the morning dose no later than 11:30 am

Following the titration (the last 7 weeks), the minimum dose will be 100 mg in the morning up to a maximum dose of 200 mg in the morning plus 200 mg at noon (total daily dose of 400 mg), depending on the participant's tolerance as assessed by regular phone calls and symptom reports. Placebo dosing will follow the same titration scheme.

13.4.5 RATIONALE FOR SELECTION OF DOSE

Modafinil is used off-label based on supporting published evidence in major depressive disorder (antidepressant augmentation), multiple sclerosis-related fatigue, Parkinson disease–related excessive daytime sleepiness, and severe cancer-related fatigue (in patients receiving active treatment). Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg dose.[58]

13.5 SOLRIAMFETOL INFORMATION

13.5.1 RISK ASSESSMENT

Potential safety risks associated with the use of solriamfetol include serious psychiatric events, increases in blood pressure and heart rate, and potential for abuse. Psychiatric events occur more commonly in the narcolepsy population; participants with narcolepsy and severe psychiatric disorders will be excluded from this study per the Platform Protocol exclusion criteria (Section 5.2). Participants at risk for cardiovascular events are excluded from Appendix A. Nonclinical and clinical data that show the potential for abuse with solriamfetol are low.

Clinical trials in patients with narcolepsy and OSA indicate that the following AEs occur at a higher percentage in those who receive 75 or 150 mg of solriamfetol versus placebo: headache (1% to 9%), nausea (0% to 4%), decreased appetite (6% to 7%), anxiety (2% to 6%), and insomnia (0% to 1%).[59]

13.5.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Solriamfetol is a small molecule with the chemical name of (*R*)-2-amino-3-phenylpropylcarbamate hydrochloride. It will be a blue tablet.

The placebo tablet will be tooled to look similar to the solriamfetol tablet, but it will not contain the active ingredient.

Solriamfetol and the placebo will be packaged in high-density polyethylene bottles with a child-resistant screw cap. All packaging will be labeled to indicate that the products are for investigational use.[60]

13.5.3 DRUG DISPENSING, STORAGE, AND STABILITY

Unblinded study personnel will manage solriamfetol and placebo disbursement to maintain blinding among participants and blinded study personnel, including site investigators.

Solriamfetol and the placebo should be stored at 20 °C to 25 °C (68 °F to 77 °F) with excursions permitted between 15 °C to 30 °C (59 °F to 89 °F). Do not freeze the product. Both active solriamfetol and the placebo are stable at these temperatures for 60 months.[60]

13.5.4 DOSING AND ADMINISTRATION

Solriamfetol dosing will total 10 weeks, including 3 weeks for titration and 7 weeks of maintenance.

Over the first 3 weeks, solriamfetol will be titrated starting at 75 mg (1 tablet) daily in the morning. Every 5 days (±2 days), the study team will call participants according to the following schedule.

- Day 5: participants will be contacted to discuss symptoms but no titration will occur.
- Day 10: participants may increase to 150 mg (2 tablets) daily in the morning according to the titration guidance in the MOP. The goal of titration is for participants to take the highest dose permitted by symptoms.
- Day 15: participants may titrate or maintain their dose depending on their symptoms and tolerance to solriamfetol.
- Day 20: participants may titrate or maintain their dose depending on their symptoms and tolerance to solriamfetol. The dose selected or maintained at this day will be the dose for the following 7 weeks of maintenance.

Placebo dosing will follow the solriamfetol dosing scheme and goal.

Dosing will follow this schedule in the absence of adverse reactions deemed likely attributable to treatment by a study physician, with special attention to headache, nausea, decreased appetite, insomnia, anxiety, or BP exceeding the threshold described in the study exclusion criteria. See the MOP for detailed guidance. In the case of adverse reactions, the dose may be reduced to the most recent prior dose at weekly intervals until adverse symptoms are alleviated or the medication is discontinued.

13.5.5 RATIONALE FOR SELECTION OF DOSE

The proposed doses and the schedule of dose escalation are consistent with currently approved FDA labeling for solriamfetol for other disorders of excessive daytime sleepiness.[60]

13.6 EVENTS OF SPECIAL INTEREST

The following ESIs will be collected for Appendix A:

- Hypertension
- Headache
- Diarrhea
- Nausea/vomiting
- Back pain
- Rhinitis
- Pharyngitis
- Rash
- Psychiatric event

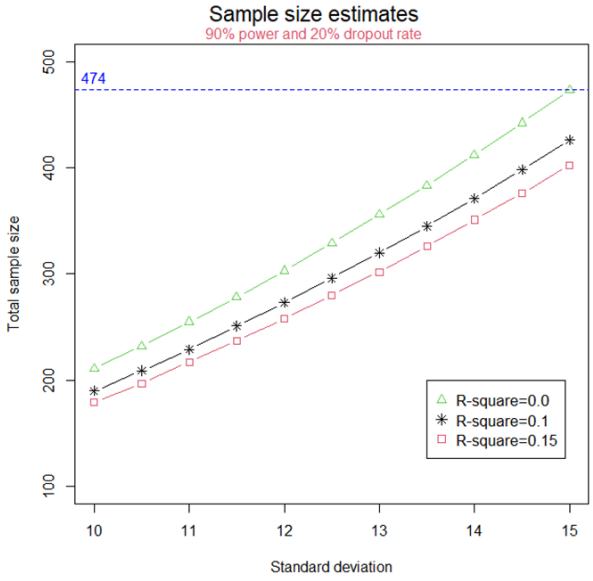
13.7 STATISTICAL CONSIDERATIONS (APPENDIX LEVEL)

13.7.1 SAMPLE SIZE DETERMINATION

An Analysis of Covariance (ANCOVA) linear regression model will be used to compare PROMIS-8a T-scores for the investigational intervention versus control at post-treatment measurement with an

adjustment for the baseline PROMIS-8a measurement. The key determinants of power include the number of participants (ie, sample size), the hypothesized difference in mean T-scores at follow-up for investigational intervention versus control among participants with similar baseline T-scores (ie, the treatment effect), and the standard error of the regression coefficient representing the mean difference in the ANCOVA model. A clinically meaningful treatment effect is assumed to be 5 T-score. The amount of statistical information about treatment effect (β_{trt}) can be quantified as $\mathrm{I} = \left[Var\left(\hat{\beta}_{\text{trt}}\right)\right]^{-1}$ which is the reciprocal of the estimated treatment effect variance in the primary analysis ANCOVA model. In order to detect a treatment effect of ($\beta_{\text{trt}} = 5$) with power $1-\beta$ and two-sided type-I error α, the required amount of statistical information is given by $\mathrm{I} = \left\{\left(z_{\alpha/2} + z_{\beta}\right)/5\right\}^2$ where $z_{\alpha/2}$and $z_{\beta}$are the $(1-\alpha/2)$ and $(1-\beta)$ quantiles of the standard normal distribution. The sample size estimation is based on the rough approximation of $V\left(\hat{\beta}_{\text{trt}}\right) \approx \frac{4\sigma^2\left(1-R^2\right)}{n} \cong \frac{4\sigma^2}{n}, when\ R^2 \approx 0$, here σ^2 is the variance of PROMIS-8a T-scores within each treatment group, R^2 is the ANCOVA model's coefficient of determination, and n is the total sample size for active intervention plus control. If the estimated treatment effect is assumed to be 5 units, $\hat{\sigma} = 15$ units (ie, an effect size of .33), two-sided type I error of .05, thus the required total sample size for 90% power to detect a treatment effect of 5 T-score units is 379 participants. Accounting for a 20% attrition rate will lead to a total sample size of 474 participants, which is 237 participants per group (Figure 4).

Figure 4. Sample Size Estimates Using the ANCOVA Model

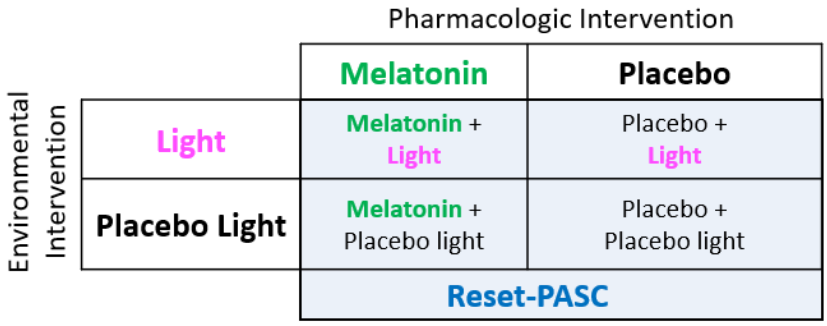


14 APPENDIX B: COMPLEX PASC-RELATED SLEEP DISTURBANCES (CPSD)

14.1 STUDY DESIGN AND RATIONALE

The Complex PASC-Related Sleep Disturbances (CPSD) Appendix B combines brief education and a tailored sleep timing prescription for CPSD (referred to as RESET-PASC) with therapies that modify circadian timing for participants who report poor sleep quality or daytime sleep-related impairment. The intervention therapies involve tailored lighting (TL) and melatonin. Participants will be randomly assigned to one of four groups: (a) active TL + oral melatonin, (b) active TL + placebo melatonin, (c) placebo TL + oral melatonin, and (d) placebo TL + placebo melatonin. All groups will receive RESET-PASC. The 2x2 factorial design schema is shown in Figure 5. The intervention duration will be 9 weeks.

Figure 5. Appendix B 2x2 Factorial Design



PASC can lead to complex sleep disturbances that present similarly to but have overlapping qualities of known types of disturbed sleep, such as insomnia and circadian rhythm/sleep-wake disorders. Both types of sleep disturbances affect one's ability to sleep at night, and many patients with PASC present with symptoms of both insomnia and sleep-wake rhythm disturbances, suggesting common underlying mechanisms. Intervention strategies for the two conditions often overlap. Thus, the interventions in this study target common underlying mechanisms and represent the typical, real-world approaches for treating patients with complex sleep disturbances.

Light-dark patterns are the major synchronizers of circadian rhythms to the local light-dark cycle, which influence sleep timing and quality. Insufficient exposure to morning light or exposure to high light levels in the evening or night can lead to circadian disruption, resulting in sleep-wake irregularity, poor sleep quality, poor cognitive performance, higher depressive symptoms, higher stress, and increased fatigue. Light in the built environment, especially at home, can be too low to entrain the circadian system during the day. Lack of entrainment or circadian misalignment may reduce the strength of circadian rhythms, and can also negatively impact immune function and inflammation. Melatonin is a hormone produced during darkness at night. It prompts appropriate nighttime behaviors and physiological functions including, in humans, sleep. Circadian misalignment may dysregulate melatonin production at night. Poor sleep and other symptoms may be improved by optimizing the alignment of a participant's circadian rhythms with environmental time cues, a process known as entrainment to a robust light-dark pattern. Circadian rhythms strengthening and alignment can be accomplished with the administration of appropriately-timed light in the morning and oral melatonin 2 hours before the scheduled bedtime.

1) The RESET-PASC educational component will be delivered by video (and/or paper brochures) and electronic reminders and will include content on optimal sleep habits, the role and use of melatonin and light for sleep, and recommendations on bedtimes (based on information on the sleep diary and the Split Week Sleep Assessment of Sleep (SASS-Y)).

Sleep onset variability, assessed from an activity tracker used for 7 days at Baseline and EOI, is an endpoint for only this appendix. Night to night sleep onset variability is an objective measurement that, when combined with the subjective PROMIS 8b SD, will help characterize the intervention's effect on CPSD. Further, sleep onset variability is a clinically interpretable and meaningful measure as it correlates strongly with overall sleep-wake variability (eg, sleep midpoint variability).

14.1.1 PRIMARY OUTCOME MEASURES AND ENDPOINTS

Primary: PROMIS 8b SD to assess sleep disturbance *and* activity tracker to assess sleep onset variability

Secondary outcome to the Primary Objective: PROMIS 8a SRI

14.1.2 SCHEDULE OF ADDITIONAL PROCEDURES

The full schedule of procedures from Table 3 is shown for operational ease starting on the next page.
Table 3 abbreviations: EOI – End of Intervention; PASC – Post-acute sequelae of SARS-CoV-2 infection; PROMIS – Patient-Reported Outcomes Measurement Information System

Table 3. Schedule of Procedures for Appendix B - Complex PASC-Related Sleep Disturbance

Procedures	Pre-randomization Visits	Baseline Visit	Pre-intervention	Intervention		End of Study
Study weeks	Wk -6 to -1	Day 0	Wk 1	Wk 2-8	EOI Clinic Visit[16] Wk 9	EOI + 30 days
Informed consent, platform	X					
PROMIS 8a SRI and 8b SD	X	X[17]			X	X
Sleep-screening questions	X					
Demographics	X					
Concomitant medications	X	X[17]			X	
Medical history	X[18]					
Pregnancy test	X	X[17]				
Nasal swab	X	X[17]				
SRBD screening/HSAT[19]	X					
Appendix-level eligibility criteria	X					
Informed consent, appendix level	X					
RANDOMIZATION		X				
Height (H) and weight (W)		H/W			W	
Sleep Phenotype questionnaire		X				
PROMIS 10a Fatigue		X			X	
ECog2		X			X	
Neurocognitive Battery		X			X	
PASC Symptom Questionnaire		X			X	
ISI		X			X	
OHQ		X			X	
DSQ-PEM		X			X	

[16] An Early Termination Clinic Visit will be request for participants who prematurely discontinue the study intervention. This visit will mirror the EOI Clinic Visit and obtain as much data as the participants allow. Refer to Section 8.6.
[17] If necessary; see Baseline visit, Section 8.3
[18] At every clinic visit after screening visit, changes in medical history including SARS-CoV-2 infection since last visit will be collected.
[19] Not necessary if participant has had a sleep apnea screening and documented adherence within 6 months of Screening

Procedures	Pre-randomization Visits	Baseline Visit	Pre-intervention	Intervention		End of Study
Study weeks	Wk -6 to -1	Day 0	Wk 1	Wk 2-8	EOI Clinic Visit [16] Wk 9	EOI + 30 days
PGIS		X			X	
PGIC				X	X	X
Blood for Biorepository		X			X	
Stool for Biorepository		X			X	
Sleep diary		Distribute	Complete[20]		Complete[20]	
Activity tracker		Distribute	Wear[20]	Wear (optional)	Wear[20]	Wear[20]
RESET-PASC		Session 1		Sessions 2-5		
SASS-Y + light use		X		X		
Blinded melatonin		Distribute		X	Return	
Blinded tailored light		Distribute	Installation[21]	X[22]	X	
Blue Iris light sensor		Distribute	Wear[20]	Wear (optional)	Wear[20]	
Safety assessment		X		X[23,24]	X	X[23]
Healthcare Encounter survey				X[24]	X	
Pill count/light adherence				X[25]	X	

[20] Data to be collected for 7 days. Refer to the MOP for specific timing and duration of data collection.
[21] Tailored lighting team members will call as needed to assist participants with light sensor use.
[22] Tailored lighting team members will call as needed to assist participants with timer set-up.
[23] Phone call only
[24] At 30 ±7 days. Other phone calls can occur as necessary; assessed at every patient contact.
[25] By phone call; can be combined with the safety assessment.

14.1.3 BLINDING

Participants, treating clinicians, and study personnel will be blinded to the assigned intervention group for each participant until after the database is locked and the blinded analysis is completed. Only the biostatistical team that is preparing closed interim reports will be unblinded. Specifically, TL will be delivered similarly to both active and placebo groups, but the circadian stimulus (the amount of light) will be different, albeit practically unidentifiable to participants; the light bulbs used to deliver the different light will be masked. Moreover, melatonin and its placebo control will be dispensed with packaging and labeling that will blind assignment. Unblinding will occur only if required for participant safety or treatment, at the request of the treating clinician. Refer to the MOP for further details.

14.2 ADDITIONAL APPENDIX-LEVEL EXCLUSION CRITERIA

The following additional exclusion criteria are to be considered together for determining eligibility. They are separated here by TL and melatonin only for presentation. RESET-PASC presents no additional exclusions.

14.2.1 TAILORED LIGHTING EXCLUSION CRITERIA

1. Severe visual impairments affecting sensitivity or ability to respond to light
2. Severe photosensitivity dermatitis
3. Severe progressive retinal disease, eg, macular degeneration
4. Permanently dilated pupil, eg, following certain cataract surgeries
5. Unwilling to remove or not wear blue-light-blocking glasses during TL dosing

14.2.2 MELATONIN EXCLUSION CRITERIA

1. Sleep medication, if not willing to washout for 4 weeks. Please see the MOP for a detailed list of prohibited medications.

14.3 HALTING RULES

Study drug dosing and enrollment will be temporarily suspended pending review of the DSMB if three or more participants receiving either active intervention experience an SAE of the same type that is determined to be related to the intervention. The DSMB recommendations will be considered by the NIH and the study principal investigator prior to making any decisions regarding study continuation or discontinuation.

14.4 TAILORED LIGHT INFORMATION

14.4.1 RISK ASSESSMENT

Tailored Light (TL) is considered non-significant risk. Side effects of TL have not been extensively reported. A rare side effect is headache. Further, participants may be withdrawn at the investigators' discretion.

14.4.2 LIGHT DELIVERY METHOD

The modified table/floor lamp will deliver polychromatic white light from up to 12-16 inches from the open eye for at least 1 hour in the morning (within 2 hours of waking, but no later than noon). The table/floor lamp is a controlled plug-in fixture that will be placed on a timer. The timer will be set to turn the light table on at desired wake times and turn it off 4 hours before desired bedtimes.

Participants will also wear a light sensor (Blue Iris Labs Mobile Sensor) to measure existing surrounding lighting during the intervention. The Blue Iris is a personal light meter calibrated to measure circadian-effective light. It can store 60 days of light measurements at 1-min intervals. It will characterize the light exposure of each participant. This light sensor will help verify compliance with the light exposure protocol. Importantly, the Blue Iris is noninvasive, not a medical device, and produces no harmful emissions. Similar to wearing a badge, participants will be asked to wear the device for the duration of the study, but at a minimum for 7 days after TL installation and 7 days before EOI. If they choose not to wear the Blue Iris device for the duration of the study, they will be asked to keep a daily log with the start and end times they were exposed to the intervention.

14.4.3 DOSING

The table/floor lamp will provide a circadian stimulus equal to 0.3 at the cornea,[61] and will be delivered for 8 weeks.

Placebo delivery will be through the same lamp method; however, it will be programmed to deliver a circadian stimulus less than 0.1, which is below the threshold for activating the circadian system. This will be accomplished by utilizing a low brightness bulb.

Light from the table/floor lamp must be delivered within 2 hours of waking for at least 1 hour. Lamp use greater than 1 hour during the daytime hours (between desired wake times and 4 hours before desired bedtime) will be encouraged.

The table/floor lamp will be programmed to be turned off 4 hours before desired bedtimes.

Participants will be encouraged to minimize exposure to all ambient and device-related light, including from electronic devices and daylight, 1 hour before their scheduled bedtime.

Interventionists will call participants throughout the intervention to encourage light adherence.

14.4.4 RATIONALE FOR SELECTION OF DOSE

Tailored lighting in the morning will produce light levels (circadian stimulus = 0.3) at least 5 to 10 times higher than typical household evening light, thereby ensuring a high circadian light-entrainment contrast between day and night. This amount of circadian stimulation is effective at entraining the circadian system and improving sleep when delivered during the daytime.[62,63] Morning doses of light are associated with strengthening circadian rhythms and improving sleep. Additionally, individuals with bright compared to dim indoor lighting report fewer sleep disturbances, which is similar to individuals who spent at least 1 hour outdoors compared to those spending 15 minutes or less.[62] Tailored lighting options delivering a circadian stimulus of 0.3 will deliver at least 300 to 400 lux at the eye at the suggested times in the morning. This dose delivered for 1 hour is equivalent to a nocturnal melatonin

suppression by 30%, suggesting that this dose can affect the biological clock.[64] Greater amounts of daytime light have been shown to increase melatonin production during the nighttime.[65]

14.5 MELATONIN INFORMATION

14.5.1 RISK ASSESSMENT

Melatonin AEs are rare. The only one occurring at a frequency greater than 1% is daytime sleepiness at 1.66%.[66] Adverse events occurring less than 1% include, but are not limited to, headache and dizziness. The presence of at least one of the above-mentioned mild symptoms was about 6% more common in people who took melatonin than those who took the placebo. Melatonin presents no significant safety risks in adults. Further, participants may be withdrawn at the investigators' discretion.

Expected AEs are those listed in the protocol appendix.

14.5.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Melatonin is a small molecule hormone with the chemical name of N-[2-(5-methoxy-1H-indol-3-yl)ethyl] and whose preparation is well characterized. It will be a capsule.

The placebo will be encapsulated to look similar to the melatonin capsule, but it will not contain the active ingredient.

Melatonin and the placebo capsules will be packaged in high-density polyethylene bottles with a child-resistant screw cap. All packaging will be labeled to indicate that the product is for investigational use.[60]

14.5.3 DRUG DISPENSING, STORAGE, AND STABILITY

Unblinded study personnel will manage melatonin and placebo disbursement to maintain blinding among participants and blinded study personnel, including site investigators.

Melatonin and the placebo should be stored at 20 °C to 25 °C (68 °F to 77 °F) with excursions permitted between 15 °C to 30 °C (59 °F to 89 °F) and away from heat, moisture, and light. Neither product should be frozen.

14.5.4 DOSING AND ADMINISTRATION

Melatonin will be administered for 8 weeks. Melatonin dosing will be one capsule of 3 mg immediate release daily consumed 2 hours before the participant's scheduled bedtime, which is defined as the time at which the participant tries to fall asleep.

Placebo dosing will be one placebo capsule once daily consumed 2 hours before the participant's scheduled bedtime.

14.5.5 RATIONALE FOR SELECTION OF DOSE

The proposed dose has previously been shown to phase shift the biological clock[67,68] and promote daily entrainment in blind individuals who cannot perceive light.[69] Other studies have shown that oral melatonin can help minimize jet lag symptoms.[70,71]

14.6 RESET-PASC INFORMATION

RESET-PASC will involve providing participants with education on healthy sleep behaviors through short videos (and/or paper brochures); a tailored prescription for timing of bedtime, light and melatonin/ placebo use; and electronic messages to reinforce sleep timing. Educational videos will be accessed by the participant at the beginning of the intervention period. A central investigator will review each participant's survey data remotely and will develop an initial prescription for when the participant should be exposed to the tailored light/sham light, when he/she should take melatonin/placebo, and when the participant should go to bed. This prescription will be communicated to the participant during a telephone call by a central investigator. After the initial "sleep prescription," the participant will be contacted by telephone or text message approximately every 2 weeks for 6 weeks to reinforce (or troubleshoot) light and drug/placebo adherence and bedtime routines. To inform recommendations, a central team will review responses from periodic electronically distributed questionnaires (SASS-Y, PGIC). The central team assessing the surveys will be blinded to the participant's intervention allocation.

14.7 EVENTS OF SPECIAL INTEREST

None

14.8 STATISTICAL CONSIDERATIONS (APPENDIX LEVEL)

14.8.1 RATIONALE FOR SELECTION OF DOSE

Complex PASC-related Sleep Disturbances is a 2X2 factorial design. There will be two independent primary endpoints, namely (1) PROMIS 8b SD and (2) variability in sleep onset. Thus, each endpoint will be tested at .025 type I error rate to maintain the overall error rate at .05. Similar assumptions as in Appendix A (Section 13.7.1) will be used to calculate the statistical power for PROMIS 8b SD endpoint, except using type I error rate at .025 level. A total of 560 participants is needed to detect a 5-unit difference between groups with at least 90% power. For the variability in sleep onset with type I error rate of .025, a total sample size of 600 participants is needed. The study will have at least 90% power to detect an effect size between .35 and .45, assuming variability in sleep onset of SD = 70 minutes in the control group and roughly SD = 45 minutes in the intervention group. Thus, this study will require a total of 600 participants to maintain at least 90% power for both primary endpoints.