NIH to Open Long COVID Clinical Trials to Study Sleep Disturbances, Exercise Intolerance and Post-Exertional Malaise

Part of the NIH RECOVER Initiative, the trials will test four treatments in approximately 1,660 patients.

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The National Institutes of Health (NIH) will launch clinical trials to investigate potential treatments for long-term symptoms after COVID-19 infection, including sleep disturbances, exercise intolerance and the worsening of symptoms following physical or mental exertion known as post-exertional malaise (PEM).

The mid-stage trials, part of NIH's Researching COVID to Enhance Recovery (RECOVER) Initiative, will join six other RECOVER studies currently enrolling participants across the United States testing treatments to address viral persistence, neurological symptoms, including cognitive dysfunction (like brain fog) and autonomic nervous system dysfunction.

The new trials will enroll approximately 1,660 people across 50 study sites to investigate potential treatments for some of the most frequent and burdensome symptoms reported by people suffering from long COVID.

"The group of symptoms these trials will try to alleviate are truly disruptive and devastating for so many people struggling with long COVID," said Walter J. Koroshetz, MD, director of NIH's National Institute of Neurological Disorders and Stroke, and co-lead of the RECOVER Initiative. "When people can't get reliable sleep, can't exert themselves and feel sick following tasks that used to be simple, the physical and mental anguish can lead to feelings of utter helplessness. We urgently need to come up with answers to help those struggling with long COVID feel whole again."

RECOVER-SLEEP clinical trials will soon begin enrolling participants and include:

- A trial to test two drugs (modafinil and solriamfetol) approved by the Food and Drug Administration to treat people who have problems staying awake during the day, known as hypersomnia. These medications are well-known but have not been studied widely in people

with long COVID. Participants will be randomly assigned to receive either the active study drug or a placebo control for eight to 10 weeks, depending on the assigned study drug.

- A trial to test potential treatments for complex sleep disturbances due to long COVID, including melatonin, an over-the-counter supplement commonly used to treat people with sleep disorders and general insomnia; and light therapy, which is used to help people reset their sleep cycles. Participants will be randomly assigned to receive either melatonin or a placebo control, and either high-intensity (active) light therapy or low-intensity (placebo) light therapy for eight weeks.

RECOVER-ENERGIZE clinical trials will soon begin enrolling participants and include:

- A trial to test a program that combines exercise training, strength and flexibility training, education, and social support, collectively known as personalized cardiopulmonary rehabilitation. The program is designed to help people who experience exercise intolerance with symptoms such as shortness of breath and fatigue during exercise after having COVID-19. All participants in RECOVER-ENERGIZE trials will be screened for PEM. Participants who are identified as having PEM, via a validated PEM questionnaire, will not be included in this trial. Participants will be randomly assigned to receive either personalized cardiopulmonary rehabilitation or basic exercise education for three months.
- A trial to test a program known as structured pacing, which is designed to help participants with PEM identify, control, and minimize symptoms that developed after having COVID-19 by regulating or pacing their daily activities. Currently, structured pacing is the only intervention used to treat PEM. The trial will not include any exercise training or physical movement to protect participants from developing worsened symptoms of PEM. Participants will be randomly assigned to receive either structured pacing with a trained coach or basic PEM education for three months.

All four trials were developed using comprehensive feedback from the community and in close partnership with patient representatives, whose insights were especially important for the PEM trial. The PEM trial was developed to address concerns expressed by patient advocacy groups about patient safety, and to better understand how this study program may help improve PEM symptoms.

“Structured pacing is currently the only intervention used to prevent post-exertional malaise, so we hope to test its effectiveness and determine how to best guide patients regarding activity management,” said Lucinda Bateman, MD, an expert in PEM and founder of the Bateman Horne Center, Salt Lake City, a facility specializing in treating people with ME/CFS, long COVID and fibromyalgia.

Diversity among trial participants is a high priority for the RECOVER Initiative. To support diverse and inclusive representation, study sites are chosen based on geographic location, their connection to communities, and track record for enrolling diverse research participants. Teams at the selected study sites will recruit participants from their health systems and surrounding communities.

Sites currently activated for each trial can be found on ClinicalTrials.gov (RECOVER-SLEEP NCT06404086, NCT06404099, NCT06404112 and RECOVER-ENERGIZE NCT06404047, NCT06404060, NCT06404073). New sites will be added to clinicaltrials.gov as they begin enrolling participants.

With the launch of these four studies, RECOVER is currently testing 13 treatments across eight clinical trials and continues to enroll participants. Those interested in learning more about RECOVER clinical trials should visit trials.recovercovid.org.

About RECOVER: The National Institutes of Health Researching COVID to Enhance Recovery (NIH RECOVER) Initiative brings together clinicians, scientists, caregivers, patients, and community members to understand, diagnose, and treat long COVID. RECOVER has created one of the largest and most diverse groups of long COVID study participants in the world. In addition, RECOVER clinical trials are testing potential interventions across five symptom focus areas. For more information, please visit recovercovid.org.

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