Responses to Participants' Questions

The overarching goal of the R3 Seminars is to catalyze a shared understanding of the research being conducted by the scientific stakeholder community within the RECOVER Consortium. The R3 Seminars and the Q&As typically feature highly scientific material intended for researchers and clinicians. For other audiences interested in these topics, a link to the National Library of Medicine's MedlinePlus medical dictionary is provided at the end of the Q&As as a resource to help in understanding the scientific terminology.

This document provides responses* to questions raised by seminar participants for the following panelists at the R3 Seminar ***RECOVER-SLEEP and RECOVER-ENERGIZE: Clinical Trials for Sleep Disturbances, Exercise Intolerance and Post-Exertional Malaise Due to Long COVID*** held on June 25, 2024:

- **Christina Barkauskas, MD**
- **Lucinda Bateman, MD**
- **G. Michael Felker, MD, MHS**
- **Sonya Sutton, MA**
- **Susan Redline, MD, MPH**
- **Janna Friedly, MD, MPH**
- **Barry Make, MD**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. How are studies determining a patient had COVID to be included?

Responses:

Dr. Make: Generally, there is a recognition that Long COVID is related to people who have had COVID and there are specific definitions for who has Long COVID. Early in the pandemic people didn't get tested for COVID and they think they might have COVID, so those patients will be included. In addition, each study has different criteria based upon that specific study. For the ENERGIZE protocol, people need to have Long COVID in the past plus for 12 weeks or more after Long COVID have exercise intolerance or post-exertional malaise. So those specific additional criteria about the details of Long COVID what each patient has are different for each study. They're different for SLEEP, they're different for NEURO, they're different for VITAL, they're different for ENERGIZE.

Dr. Barkauskas: For RECOVER-SLEEP, we are asking participants questions about their COVID diagnosis (home test, PCR, etc.). Did they contact with an individual or individuals with known COVID? Did they have symptoms of fever, respiratory tract infection, etc.? Were they hospitalized?

Q. The NIH director publicly stated regarding RECOVER that "interventions not showing promise can be quickly terminated and the trials can quickly pivot to test new interventions as needed." Is this understanding also known to the principal investigators (PIs) that are monitoring these trials, like SLEEP and ENERGIZE? In the event these trials aren't showing positive results, should we expect that this will be informed to leadership?

Response:

Dr. Felker: The clinical trials are monitored by a data safety monitoring board (DSMB), which is independent of the investigators, which is an external group of experts. We have one data safety monitoring board for all the RECOVER trials, and they monitor the study conduct and also very importantly, safety. If there's safety signals or anything concerning about participant safety, the DSMB is empowered to stop a trial, switch aspects of a trial. That monitoring is critical. Typically, the investigators are not monitoring efficacy (that is, does the treatment work during the conduct of the trial), especially for these relatively small and relatively short-term clinical trials. One of the nice aspects of the sort of platform protocol approach, which is being used throughout RECOVER, is the ability not to test interventions one at a time, but multiple potential interventions simultaneously.

Q. What are safety measures for ENERGIZE?

Response:

Dr. Felker: We spent a lot of time discussing both amongst our working group and also with feedback from patients and caregivers about how to optimize safety within ENERGIZE. Part of it is getting the patients into the trial that's right for them. So, as we talked about, there’s the initial screening so that patients with post exertional malaise (PEM) have a trial focused on PEM that doesn't involve exercise training, patients who don't have PEM symptoms are more appropriate for the cardiopulmonary rehabilitation trial. Even then there's ongoing monitoring about the patients who develop PEM, because we recognize some patients may have the syndrome but not have thought of it quite in that way. So, we're using the Post Exertional Malaise Short Form (DSQ-PEM) to reassess patients after exercise testing, if they develop signs or symptoms of PEM, and also as an endpoint because we need to understand the balance of benefits but also risks, and that's true of both the pacing trial and the cardiopulmonary rehabilitation trial.

We went to a lot of effort to try to build in participant safety and even though we've taken all these precautions, what happens if people do develop PEM during exercise? Barry went through that in his presentation. If PEM develops, exercise is halted and then restarted at a lower dose, if you will, and potentially could be stopped altogether if patients have persistent symptoms.

Q. Are there any opportunities to introduce craniosacral therapy into ongoing or future clinical trials?

Response:

Dr. Barkauskas: That's definitely an interesting idea and certainly there are some folks out there who are using that type of therapy. I think we designed this as a platform trial so that the infrastructure, the base is there and other interventions can be put into the platform trial as we see fit. I think as far as if and when that would occur, that's sort of up to the powers that are not me. It sort of comes down to funding and things like that, but certainly we designed this so that we can include other interventions down the line if the data suggests that that would be valuable.

Q. What steps have been taken to educate pacing coaches about PEM and RECOVER as a whole?

Response:

Dr. Friedly: We have a team of pacing coach trainers who have experience working with patients with Long COVID and have incorporated pacing into their clinical work with patients. They also have experience working on clinical trials and delivering these types of interventions. They're training each of the pacing coaches. Each of the pacing coaches that are identified at the sites will undergo formal training on the intervention before they start working with participants. This is a formal training that's about four hours in length, and they have a standardized coaching manual as well as a participant manual for the pacing intervention—and then once they've been trained, they will have ongoing sessions with the pacing coach trainers on a monthly basis to review any questions that come up, make sure that they have a good understanding of the pacing intervention, and do some troubleshooting.
In addition, we have fidelity monitoring. We'll be recording sessions and having the fidelity monitors—who are the pacing coach trainers—review those sessions and provide feedback to the pacing coach trainee to make sure that the intervention is being delivered as we are expecting it to. So, there are multiple different ways that they're getting training throughout the trial.

Q. How can individuals participate in trials or studies when we can't get our primary physician to take us seriously?

Responses:

Dr. Bateman: If you qualify and participate in a trial, that really validates your diagnosis and should help your primary care providers understand more about this illness. Getting all primary care providers up to speed on Long COVID is an effort we all are making and that we all need to work on.

Dr. Barkauskas: I'll echo that. I think talking about these trials, letting primary care doctors be aware of the fact that they exist and are enrolling patients is certainly step one. It just lends credence to the fact that it's important and these are real problems, and they're real criteria and real interventions.

Q. Why is RECOVER proceeding with these costly soft therapy trials when many patients already have tried these interventions and the science has moved forward to suggest pharmaceutical interventions?

Responses:

Dr. Redline: First of all, I certainly recognize that we would all love some silver bullets that directly targeted one or more of the basic mechanisms for Long COVID. At this point, as I indicated, we're using the best evidence we know, and with principles like effectiveness, safety, scalability, and pragmatism, but I'd like to push back and say that the interventions being designed have been adapted and protocolized to really not be off-the-shelf and generic types of interventions. For example, even the sleep-wake programs are really, really tailored very specifically. It's never been enrolled in just like this way to maximize circadian amplitude and strength, again focusing on physiologic factors. I think it's very important that folks know that although a lot of the words we use sound familiar, the way we're operationalizing things has been done very thoughtfully to try to get at the physiology of the underlying problems we've identified as likely to be the culprit problem.

Dr. Felker: I echo what Dr. Redline said, people are using some of these approaches or approaches like them, but without clear evidence about how best to do them or how to do them effectively, or how to do them safely. One of the primary goals of RECOVER is to identify treatments that are "shovel-ready" that can be deployed in the most effective way, but also to show that they work or that they don't work. Both are equally important, because as everybody on this call knows, there's a huge burden of suffering out there that we have a mandate to try to address and alleviate. That is why we're testing therapies that can get into clinical practice as rapidly as possible, even if we recognize that it would be great, as Susan said, to have specific drugs for specific mechanisms, but the science for that often takes longer to catch up, and these are mostly interventions that can be deployed rapidly.

Q. What is the theory being addressed by exercise intervention? Is it an assumption that the non-PEM cohort is deconditioned?

Response:

Dr. Make: The answer to that question is multi-faceted. First, yes, if you don't perform activity, you become deconditioned, so yes, that's part of the intervention. But in addition, exercise in some studies has been shown to be anti-inflammatory. And all studies in RECOVER will be examining biomarkers, withdrawing blood and obtaining urine to see if there are markers of inflammation or other things that will be changed after the therapy. We will get an understanding of the pathophysiology of the disorder and how the intervention may change that pathophysiology.

Q. Are there any guidelines in limiting smartphone blue light exposure for sleep diary tracking?

Response:

Dr. Redline: Everyone in that particular platform is going to get an individualized sleep plan, and in the individualized sleep plan, we're specifically addressing the aspects of optimal sleep-wake habits, including light exposure. So, everyone will have a guidance of when is a good time of the day to be exposed to light and when it's time to actually withdraw from light, including blue light. We're very excited about that opportunity to improve people's circadian rhythms through light manipulation.

Q. Are you finding that the cardiopulmonary patients require an inhaler of some sort, either daily steroid inhaler or an emergency inhaler? Is there a comparison between patients requiring an inhaler versus patients that do not require one?

Response:

Dr. Make: In ENERGIZE, we aren’t changing people's medications. Whatever your local physician, treating physicians give you is what we will continue. In general, some patients with Long COVID develop other cardiopulmonary symptoms and develop asthma, so we aren’t changing that or looking at that in this protocol, but your individual physician should look at whether an inhaler might be helpful for you as an individual.

Q. Is acupuncture being tested as a remedy for PEM?

Response:

Dr. Friedly: There are some ongoing and upcoming trials of acupuncture for a variety of symptoms for Long COVID, but not as part of what we're studying here. There is a trial that's just getting up and running at the University of Washington, looking at acupuncture and Long COVID, for example.

Q. What are the primary outcomes for the hypersomnia and RECOVER-SLEEP studies?

Response:

Dr. Barkauskas: I think it's important to talk about it in the group at large. We're using assessments called the PROMIS Sleep-Related Impairment and Sleep Disturbance assessments, and we use these to determine the severity of an individual's symptoms to, number one, determine eligibility for the trial, and then number two, we use a change in those PROMIS scores to assess response to the interventions we're testing in these trials. The change in PROMIS score from beginning of the study to the end of intervention is the primary outcome measure.

Q. What has the ENERGIZE study's research shown regarding the use of nattokinase and NAD+ to treat PEM?

Response:

Dr. Make: Those interventions were considered but are not going forward as part of the trials. I need to emphasize that all these trials have had a number of outside experts. It's not just the people on the call and the PIs in the trial that are participating and have participated to determine their trials. We've had expert panels that have looked at all these other things and decided that there's insufficient evidence to move them forward at the current time.
Dr. Felker: To follow up to that, we're obviously working in an area where the science is evolving rapidly and people are understanding new things constantly and there's new data about pathophysiology and those may lead to more specific treatments, but in launching the trials, we were really trying to focus on things that were ready to be implemented today if they work, but the things being studied in REOCVER are not the only things that could be studied. Dr. Friedly just mentioned acupuncture, which I didn't know about, but just what's being studied in this program right now.

Q. How is mitochondrial dysfunction associated with PEM?

Responses:

Dr. Bateman: As an expert in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), we've been studying PEM for a very long time, and while we recognize that it occurs and how to prevent it, we don't really understand everything about it. The science is suggestive that there's mitochondrial dysfunction among other issues such as perfusion of the bloodstream and the delivery of oxygen to tissues, but it's really a matter of intense study, and I think raising awareness about PEM is the first step for all of us to start to understand how to adapt both exercise and pacing. It's my hope that this kind of a trial will help move us that direction to really understand the underlying pathophysiology.

Dr. Make: In terms of exercise intolerance, it has also been suggested the mitochondrial dysfunction that plays a role and rehabilitation may improve that. As part of the cardiopulmonary exercise testing, we'll be assessing that in a subgroup of patients, and we think that's a potential mechanism for exercise intolerance as well.

Q. Do we have an agreed upon definition of Long COVID? If so, does that include those who are vaccinated and/or boosted?

Response:

Dr. Barkauskas: We characterize a participant's prior COVID diagnosis through certain criteria (suspected vs. probable vs. confirmed), and then Long COVID symptoms should be present for at least 12 weeks since that infection. For RECOVER trials, we are collecting information about vaccination status, but this is not part of the official definition of Long COVID (at least as it stands currently).

Q. What percentage of the people in the observational study have sleep disturbance/ insomnia as a Long COVID symptom?

Response:

Dr. Redline: More than 20% have sleep apnea; a large portion also report combinations of symptoms of insomnia and sleepiness.

Q. Does the trial use sleep studies to diagnose sleep apnea?

Response:

Dr. Barkauskas: Yes, the trial will use home sleep apnea testing (HSAT) to evaluate for sleep related breathing disorders (including obstructive sleep apnea [OSA]). HSAT will be done for participants with no prior sleep studies,

for participants with remote sleep studies, or for participants with questionable adherence to therapy for previously diagnosed OSA. This screening for sleep related breathing disorders will be done during study screening.

Q. What about central sleep apnea. How common is this? And what are some possible causal mechanisms in Long COVID?

Response:

Dr. Redline: Central sleep apnea is much less common than obstructive sleep apnea, but is more prevalent in patients with heart failure or who have had a stroke and have autonomic dysfunction. In the RECOVER cohort, our initial data however suggests that central sleep apnea is uncommon.

Q. Where can I find the clinical trials numbers?

Response:

Ms. Sutton: All the numbers are listed here: https://trials.recovercovid.org/design

Q. Is RECOVER-VITAL fully enrolled?

Response:

Ms. Sutton: No, RECOVER-VITAL is actively recruiting participants. Only NEURO is fully enrolled.

Q. A patient is found in a sleep study to have episodes of apnea, but no OSA. The patient simply stops breathing. Oxygen levels can reach 85% within 30 seconds even while wearing a CPAP. What direction would you go with this?

Response:

Dr. Barkauskas: Good question. Participants with central sleep apnea of a certain severity or greater would not be eligible to participate. Central sleep apnea can potentially be the result of some other underlying conditions which should be evaluated.

Q. I have heard of cases of what seems to be true narcolepsy, which may have an autoimmune mechanism. Would the treatments used in these trials be expected to help that at all, or would other interventions be necessary?

Response:

Dr. Redline: As mentioned, sleep and circadian processes affect many physiological processes, including immune function. We will learn from these trials how these treatments work. We will study to see if there are certain people who respond best/less well and reasons for this.

Q. Are people who tested positive with sleep apnea excluded from the trial?

Response:

Dr. Barkauskas: People with moderate to severe OSA will need to be receiving appropriate treatment. Once we know that they're adherent to this therapy, they're eligible to participate in the study.

Q. Is the sleep diary an electronic Clinical Outcome Assessment (COA)?

Response:

Dr. Barkauskas: Yes. The sleep diary is an electronic COA, but there is a paper option for individuals who aren't able to manage the electronic platform.

Q. When can the community expect the first results from NEURO? Will RECOVER release these as soon as they have them, or will RECOVER hold them until publication?

Response:

Ms. Sutton: We anticipate results being ready to share in 2025; it is a 6-month intervention, so those who just enrolled won't be finished until December.

Q. So what are the primary outcomes for the hypersomnia and RECOVER-SLEEP studies?

Response:

Dr. Barkauskas: Good question! Both the Hypersomnia and Complex Sleep Disturbances trials have the same primary outcome. We are screening for eligibility based upon scores on two assessments: PROMIS Sleep Related Impairment (SRI) and PROMIS Sleep Disturbance (SD). Participants with severe enough symptoms based upon

these assessments would be eligible for enrollment. We look for change in the PROMIS SD and/or SRI assessments as the primary outcome.

Q. How much melatonin will be administered in the RECOVER-SLEEP study?

Response:

Dr. Barkauskas: The dose is 3 mg immediate release capsule.

Q. Will the CSD study exclude patients already receiving light therapy?

Response:

Dr. Barkauskas: Good question! I think we would need to know more about the type of light therapy you are receiving. Typically, if a participant is receiving a therapy that could affect sleep, we ask that the therapy be held prior to screening for trial, allowing for any "washout" of that therapy's effect.

Q. How would I determine if I am eligible for the study?

Response:

Dr. Barkauskas: In order to determine eligibility for the individual trials (Hypersomnia and CPSD), we assess responses to the PROMIS Sleep Related Impairment and PROMIS Sleep Disturbance assessments.

Q. Do participants have to be in a particular state?

Response:

Dr. Barkauskas: A participant would need to be able to come for two in-person assessments for the trial. One at the baseline visit and one at the end of intervention visit. So, if the participant is willing and able to travel for this, it's ok for them to live somewhere else.

Q. I have heard many stories of people with Long COVID having restless-legs-like symptoms, sleep-related involuntary movements, disrupted breathing regulation, and internal tremors that could affect sleep. Are you collecting any data to see whether these types of symptoms are present and whether the presence of these symptoms is associated with poor response to your interventions?

Response:

Dr. Redline: Yes! All participants will be asked questions on symptoms of restless legs. We will use this information to inform future research and trials.

Q. I read a study showing lack of muscle atonia during REM, which seemed to result in excessive movements and disrupted sleep with reduced REM sleep. Would the interventions you are using address this at all?

Response:

Dr. Redline: The Complex Sleep Disturbances trial intervention is designed to improve sleep quality, which may have effects on sleep depth (REM sleep). Treatment of sleep apnea also often increases REM sleep.

Q. Clinicaltrials.gov does not show that the ENERGIZE trials are recruiting. Where can I find information on applying to be part of the trial?

Response:

Ms. Sutton: RECOVER-ENERGIZE is activating sites, and more will be listed on clinicaltrials.gov very soon.

Q. Will some SLEEP/ENERGIZE studies be remote?

Response:

Ms. Sutton: The studies are not remote, but many of the assessments and treatments will be done at home. You can see all the clinicaltrials.gov study records linked here: https://trials.recovercovid.org/design

Q. Dr. Make, are you accepting candidates who took the mRNA vaccine? Are you examining for myocarditis?

Response:

Dr. Make: Individuals who have received SARS-CoV-2 vaccination and those who have not been vaccinated are candidates for the trial. Those with acute myocarditis are not candidates for ENERGIZE Exercise Intolerance.

Q. I wonder if you might miss detecting central sleep apnea and sleep-related movement disorders if using home sleep studies. Is there any plan to test a subset with standard full polysomnogram in a sleep lab?

Response:

Dr. Redline: The home sleep apnea test has state-of-the-art respiratory bands that are highly accurate for distinguishing central from obstructive apneas. Patients found to have an elevated number of central apneas will be referred for treatment for this disorder.

Q. What dose (or range) is proposed for solriamfetol and modafinil? I see melatonin is 3 mg. Will that be titrated up or down?

Response:

Dr. Redline: Those drugs each will be titrated to address symptomatic improvement without excess side effects. We have a protocol for both up and down titrating over a 3-week period. Modafinil starts at 100 mg and solriamfetol starts at 75 mg.

Q. What steps have been taken to educate pacing coaches about PEM and RECOVER as a whole?

Response:

Dr. Friedly: We have a team of pacing coaches who are training all of the pacing coaches before they start the trial. In addition to the initial training, they will be meeting with the pacing coaches on an ongoing basis to continue training, making sure that they are delivering the intervention in the best possible way. We also have a fidelity monitoring plan to ensure that the pacing coaches are delivering the intervention as they are supposed to be doing. They have a standardized approach to delivering the pacing intervention with coaching manuals and participant manuals, but these interventions are individualized for each participant based on their own experience with PEM.

Q. Are children eligible for any of these studies?

Response:

Ms. Sutton: All of these studies are for adults, but we do hope to have pediatric studies in the future.

Q. For ENERGIZE, what are the considerations being given to prior levels of athleticism, such as endurance athletes, rather than the general population?

Response:

Dr. Make: Exercise training is based on current level of exercise and prior level of exercise and activity.

Q. Will there be additional updates on RECOVER NEURO in the same manner as these for ENERGIZE and SLEEP?

Response:

Ms. Sutton: Yes, we will give more updates on NEURO, VITAL and AUTONOMIC at future webinars and will give a presentation focused on NEURO results when they are ready.

Q. Light therapy seems a benign intervention. Can PASC suffers with sleep disturbances try it at home, even if they cannot be in the clinical trials? if so, when and how long each day?

Response:

Dr. Barkauskas: If possible, the best intervention is exposure to sunshine—early in the day! The circadian rhythm is best entrained with light exposure early in the day, within a few hours of waking up.

Q. What is the best way to apply to become a participant in these studies?

Response:

Ms. Sutton: Each trial has different locations, so you'll need to test each clinicaltrials.gov study record to find the sites. You can find all the links here: https://trials.recovercovid.org/design

Q. In the sleep trials, will you be looking at improvements to quality of sleep stages and sleep consolidation?

Response:

Dr. Barkauskas: Yes, we will be able to gather some of this information. Our participants will be given activity trackers (Fitbits) which should allow for collection of discrete data which can be interpreted along with sleep diary data.

Q. For the PEM study, will the amount of social or cognitive exertion be measured or controlled for?

Response:

Dr. Friedly: As part of the pacing intervention, the pacing coaches are trained to identify not just physical exertion, but also cognitive, emotional, and social exertion triggers for PEM, as we recognize these are all important triggers

of PEM. The participants are asked as part of the pacing intervention to recognize and identify these triggers, and the pacing coaches will work through how to manage these with participants.

Q. Are patients already taking a higher dose of extended release and combination melatonin products still eligible for the insomnia trial?

Response:

Dr. Barkauskas: Patients who are taking a higher dose of extended release/combination melatonin products would be eligible if they are willing to stop the therapy and allow a washout period prior to study screening.

Q. Are there any plans to conduct research for teen (13–17 years old) Long COVID patients with the same sleep/energize symptoms?

Response:

Ms. Sutton: We don't currently have a teen study planned, but we hope to use the results of these trials to expand to other groups in the future.

Q. What was the name of the home sleep study device being used in the SLEEP study?

Response:

Dr. Redline: NOX T3

Q. For the exercise team, will you evaluate for abnormal lactic acid accumulation?

Response:

Dr. Make: Blood and urine for biomarkers like lactic acid are being collected at the start and end of the RECOVER trials. A subset of participants in ENERGIZE Exercise Intolerance will undergo cardiopulmonary testing that will also evaluate lactic acid levels.

Q. Does the team consider the data collected with the Fitbit to be accurate? I know that some sleep specialists don't consider the sleep stages data on trackers to be accurate.

Response:

Dr. Redline: The Fitbit trackers will provide information on how patients' total sleep and wake patterns vary—this information is considered to be reliable. Those trackers also report light, deep, and REM sleep; while not as accurate as in-lab EEG-based test, they do provide good estimates of sleep stages.

Q. Can I participate in a RECOVER study if I am taking prednisone for inflammation?

Response:

Dr. Barkauskas: Prednisone use is not an exclusion for the RECOVER SLEEP studies.

Q. Thanks for this. As you know, many people have been suffering for years. What's the timeline for treatment?

Ms. Sutton: Our goal is to return results as soon as possible, but all of these trials will take at least 1 year to return data and analyze the results. When results are available, we will share them widely in academic publications and on the recovercovid.org website.

Q. How would an individual know if they have EI or PEM? Does the questionnaire define the category?

Ms. Sutton: Yes, the screening process will help to determine which study is the best fit for each participant.

Q: Is it possible to get information on pacing protocols or coaches for people who won't be able to join the study?

Ms. Sutton: The pacing manuals will not be available during the study period, but the full protocol is available at this link.

Q. Are the 60 sites for RECOVER-ENERGIZE chosen?

Ms. Sutton: Most of the sites have been selected, and you can see the full list at this link.

Q. How often will the inflammation markers be checked in the exercise cohort?

Ms. Sutton: Participants will receive a phone call or online survey to monitor any signs of PEM 2–3 days after an in-person visit with physical activities. The study team will also check participants' well-being during the study visit to monitor for any safety concerns.

Q. Will the study accept all levels of PEM severity (mild, moderate, and severe) or only severe?

Ms. Sutton: The screening questionnaire will help to determine the best fit for a participant, but different levels of PEM will be included.

Webinar Slides

To request a copy of the R3 Seminar slides, please email RECOVER_ACC@rti.org.

To Learn More

- Information about RECOVER research and to volunteer for studies: https://recovercovid.org/research
- Frequently Asked Questions about RECOVER and PASC: https://recovercovid.org/faqs
- CDC information: Information for the general public and for healthcare providers about Post-COVID Conditions: https://www.cdc.gov/covid/long-term-effects/
- For medical/scientific terminology: https://medlineplus.gov/healthtopics.html