

Transcript

Dr. Beth Linas:

Thanks, Cameron. Good afternoon, everyone. Welcome to the RECOVER Research Review or R3 seminar. My name is Beth Linas. I'm an infectious disease epidemiologist with the Recover Administrative Coordinating Center and the moderator of today's seminar. The goal of this seminar series is to catalyze a shared understanding of the research within the RECOVER Consortium. I want to start by thanking everyone who submitted questions in advance. Please submit any questions that arise during today's presentation using the Q&A feature in Zoom. After the presentation, we will answer as many questions as possible. A Q&A document will be posted with the recording of the seminar on recovercovid.org. It will include the answers for submitted questions relevant to today's presentation. Questions about other scientific topics will be addressed in future seminars and answers to broader questions about RECOVER will be available in the FAQs at recovercovid.org. As a reminder, we cannot answer individual questions about clinical care.

The topic of today's seminar is RECOVER-SLEEP and RECOVER-ENERGIZE: Clinical Trials for Sleep Disturbances, Exercise Intolerance and Post-Exertional Malaise Due to Long COVID. Our presenters today are Dr. Christina Barkauskas, Duke University School of Medicine; Dr. Susan Redline, Harvard Medical School in Brigham and Women's Hospital; Dr. Lucinda Bateman, Bateman-Horn Center; Dr. Janna Friedly, University of Washington; Dr. Michael Felker, Duke University; Dr. Barry Make, National Jewish Health; and Sonya Sutton, Duke University. Today's speakers will share our current understanding, the gaps in our knowledge and how RECOVER will contribute to filling these knowledge gaps, and with that, I will hand it over to Sonya Sutton.

Dr. Sonya Sutton:

Thank you, Beth. Next slide. So today we're going to focus on RECOVER-SLEEP and RECOVER-ENERGIZE, which are two clinical trials through the RECOVER Initiative that are going to focus on sleep disturbances, exercise intolerance, and post-exertional malaise. I'm the communications lead for the Duke Clinical Research Institute that manages the clinical trials. So I'm going to provide a brief overview and then we will give more details on SLEEP and ENERGIZE. Next slide please. So as I just mentioned, I'll provide an overview and an update on the three platforms that have already launched as well as... And then we'll get details from the principal investigators on both RECOVER-SLEEP and RECOVER-ENERGIZE followed by time for questions. Next slide. So an overview of the clinical trials. Next slide.

The goals of the clinical trials are to identify treatment strategies for long COVID, and so all of the clinical trials that we have initiated so far, we'll be testing different treatment strategies, some are medical and drug related and some are not, to see which ones might be able to be identified as treatment strategies for long COVID. Next slide. This is all of the groups who provided input into the clinical trial development and design process. We had critical inputs from both clinical researchers, clinicians, members of the FDA, office of the Assistant Secretary of Health, CMS, and lots of other groups as you can see here, who helped us design these trials and identified the interventions and treatments that we're going to be testing. Next slide.

Each platform protocol had a protocol working group, and so those working groups included both patient representatives, scientific experts, subject matter experts and other investigator, and these groups met regularly until the platforms were finalized to make sure that they were able to include all of those perspectives in the platforms. Next slide. These are the clinical trial portfolios. So the trials that

are fully launched are VITAL, NEURO and AUTONOMIC, and the two that are newly open for enrollment are SLEEP and ENERGIZE. Next slide.

So who can join the clinical trials? This is a question we get a lot and we will talk about in detail in future slides, but we wanted to make sure that everyone knows that these are adult trials and each trial has its own exclusion criteria and you can learn about where the sites are for each of these trials on the website that's linked here and I'll provide in the Q&A as well as on clinicaltrials.gov, and we'll have details on all of those in future slides as well. Next slide. So the three platforms that are fully launched, we wanted to give you updates on those trials. Next slide.

RECOVER-VITAL is testing viral persistence. It is currently enrolling participants. You can see the sites that are recruiting on clinicaltrials.gov under the number that's listed there in green. We are expecting to have at least 900 participants and we have 687 enrolled as of yesterday. Next slide. For RECOVER-NEURO, which studies cognitive dysfunction, that one has actually completed enrollment. So the trial is still active, but we are no longer enrolling new participants into NEURO. There are 25 sites and 328 enrolled participants in NEURO. Next slide. And RECOVER-AUTONOMIC is testing autonomic dysfunction. There are two trials through RECOVER-AUTONOMIC that are testing these two different interventions. There is a target of 50 sites and 380 planned participants. This one is newly recruiting and so we have 15 enrolled and anticipate enrolling for the next several months to reach that target. Next slide. So now I'm going to hand it over to Dr. Redline to give you more details about RECOVER-SLEEP.

Dr. Susan Redline:

Yeah, thank you very much. Next slide. And yeah, we're very delighted that the SLEEP trials are now open for enrollment. We'll be testing for interventions to our drugs that specifically target the arousal or alerting centers in the brain and are approved for treatment of daytime sleepiness and that is modafinil and solriamfetol, and two are interventions that specifically target the circadian rhythm system, which as we will discuss later, is really integral to regulating multiple physiologic systems including sleep-wake, and they include melatonin, which is a natural that regulates timing of sleep, and high dose titrated light therapy, which has been selected to specifically entrain the central circadian clock in the brain. 45 sites have been targeted and we anticipate a little more than 1000 participants across two trials. Next.

I'm very pleased today to co-represent the sleep work along with Dr. Barkauskas. I am a sleep and pulmonary specialist who has spent much of my career involved with clinical trials of looking at how sleep interventions improve heart health and brain health, and Dr. Barkauskas is a pulmonary and critical care specialist who's very actively involved in a number of inpatient COVID trials, but we're also delighted to have four principal investigators representing a myriad of backgrounds, including psychiatry, circadian and light expertise, neuroscience and pulmonary critical care and sleep medicine. For example, Dr. Buysse from the University of Pittsburgh brings exceptional expertise in insomnia treatment, Dr. Figuero from Mount Sinai is a world's leader in light and circadian therapy, Dr. Maas has special expertise in neuroscience as well as clinical expertise managing patients with sleep and COVID problems, and Dr. Parthasarathy is a pulmonary critical care and sleep specialist who has played leadership roles in multiple sleep and COVID research as well as also has extensive expertise in managing patients with sleep and COVID problems. Next slide.

So why target sleep? So just as COVID-19 impacts multiple aspects of the body, so does sleep, and in fact healthy sleep and circadian rhythms are really fundamental for brain health, including cognition and mood, overall physical health, including endocrine function, cardiovascular function, well-being, energy restoration, regeneration of tissue, and even immune function. In fact, it's now recognized that along with nutrition, physical activity and stress management, sleep is the fourth pillar of health,

and the American Heart Association in just the last year has added sleep health as a key target along with seven other fundamental aspects of cardiovascular health as a target to improve life. Next slide.

And in fact, as relevant to PASC, or long COVID, sleep regulates and integrates multiple physiologic processes. For example, as we see on the right side of the slide, during sleep, there are channels in our brain called the glymphatics that open up to help clear toxins from the brain, like amyloid, but also as seen in the bottom of the slide, sleep is a time when the electrical activity of brain cells are modulated to help improve memory, to promote plasticity of the brain cells, to even regulate hormones and immune function, and temper inflammation and modulate the autonomic nervous system. Next slide.

But not only sleep, death and sleep quality, but the regularity or the consistency of sleep is critical, and we'll be targeting that in our trials. So for example, on the right-hand side of the slide, you see those green horizontal lines that represents each line is a different day of sleep, and ideally sleep is very regular, starts and ends at the same time throughout the entire week, and on the bottom slide, those red lines show someone with a very irregular sleep schedule starting their sleep period and ending sleep period at different times, and as you can see on the right side of the sleep, that irregular sleep schedule itself can contribute to havoc in multiple organ systems, and as I starred, there are in particular and relevant to PASC, irregular sleep has adverse consequences on inflammation on the hypothalamic pituitary axis, or the stress and cortisol axis, as well as autonomic function. Next slide.

And when we think specifically about targeting sleep health in the setting of long COVID, we were targeting as you'll hear, sleepiness, insomnia and sleep irregularity, and the question is why? Well, for one, there's abundant data collected over the last few years, including a summarized here from one study of an international study that was very, very large, that showed that fatigue, insomnia, and hypersomnia, that is sleep symptoms, affect upwards of 36% of patients with long COVID. In fact, it's been suggested that sleep-related symptoms are the core of PASC-related symptoms. Next. And in fact, in developing our protocols, we actively engaged experts in ME chronic fatigue syndrome, knowing there are strong parallels with long COVID. Next slide. And what we heard was that patients with chronic fatigue syndrome who also have sleep problems often complain or report very irregular sleep-wake rhythms as I just described in the prior slide, and that very much informed our focus and our adaption of the interventions you'll hear about. Next slide.

So in the last year-plus we've worked very hard not only to select these sleep interventions, but to refine them. So as most researchers, we started with the published literature about efficacy, next, but we considered not only the effect of interventions on sleep and sleepiness, but also on other effects that those interventions may have, for example, on cognition, mood and inflammation that is potentially addressing multiple long COVID-related problems. Next. And we selected interventions in the spirit of them being pragmatic, accessible, safe and scalable. We want these interventions, should they prove effective, to be widely available. Next slide. And the process, as you heard earlier, was very iterative and it reflected feedback from not only experts, for example, from the ME/CFS community, but also from patients. Next.

We heard strongly of the interest in testing medications, next, and also we heard from, again, our CFS experts in particular the importance of targeting sleep irregularity as a core feature of sleep disturbance or of insomnia, and as you'll hear, one of our interventions does use a behavioral intervention that we specifically design to amplify the effects of other interventions we're testing, and secondly, we are using a behavioral intervention that's not psychologically-based, but physiologically-based to really improve the whole physiology of sleep and all its related processes. Next slide. Next. And as you'll hear in the next slide, we made the very explicit decision to thoughtfully treat comorbid sleep apnea in every patient screened for this study who tested positive for sleep apnea. Next.

So let me tell you just briefly about the approach for sleep apnea screening, which we've heard is at least several people contacted us to learn about. First of all, obstructive sleep apnea is common in the population, it's often undiagnosed, and in patients with long COVID, we estimate about 20 to 30% may have undiagnosed sleep apnea, and that condition we know negatively impacts multiple aspects of health, and it's very possible that patients with long COVID are especially sensitive to those adverse effects of not getting enough oxygen and working hard to breathe every night. And untreated sleep apnea moreover would decrease the efficacy of the interventions we are testing. We do know there's strong evidence-based treatments for sleep apnea, in particular PAP or positive airway pressure, and we decided rather than test PAP in these trials, we know they're evidence-based and there may actually be some ethical concerns to withholding treatment, we would rather offer this treatment, as I mentioned earlier, to every patient who was untreated but tested positive.

So our approach is in fact to screen everyone for sleep apnea by questionnaire, medical chart review, and if there was not evidence of having been recently evaluated for sleep apnea, offer them a free in-home state-of-the-art sleep study as you can see in the upper right-hand corner, and if they tested positive, we've generously got a donation from the ResMed company to offer free auto-titrating PAP machines to every participant before enrollment. Next. And the advantages of novelty of the approach is that it will expedite the diagnosis and treatment of this common condition of which often is characterized by loss of delays and pre-authorization and financial issue, thus reducing barriers, improving access, minimizing the effect of untreated sleep apnea in our study results, but most importantly, just out the front door, improving the sleep health in our patient population. Next.

So who can participate? So RECOVER-SLEEP includes adults who have had COVID and have one or more symptoms of problems falling asleep or staying asleep, poor sleep quality, or trouble staying awake or feeling very tired during the day. Next slide. We have two trials that we're launching. One of them is a trial for hypersomnia, which means excessive daytime sleepiness, and that is being targeted to people who sleep longer than usual and still feel very sleepy or tired during the day even after getting a full night's sleep, and that will be enrolling almost 500 participants. The second trial, which was actually named by our partners is called Complex Sleep... It is called Complex Sleep Disorders intervention or CPSD, and that's testing both melatonin and light, and that's targeting patients with poor sleep quality, also referred to as insomnia, patients getting problems falling asleep or staying asleep often who have very irregular sleep-wake patterns, and that's targeting 600 participants. So I'm now going to turn this over to my co-chair, Dr. Barkauskas, who will give you more details on both of those trials.

Dr. Christina Barkauskas:

Thanks, Susan. Hi, everybody. I'm going to quickly go through the two individual trials that we have within the RECOVER-SLEEP platform. Next slide please. Okay, the first trial that we have in the platform is targeting participants who have hypersomnia or excessive daytime sleepiness. Participants in this arm will be assigned by chance to take an active study drug, modafinil, versus placebo for 10 weeks. If a participant can't take modafinil because it interacts with other medications that they're already on, and typically the most common medication would be a steroid hormonal contraceptive, the participant will then be screened to see if they're eligible to receive a different active study drug called solriamfetol. If they're eligible for solriamfetol based upon drug interactions, they would then be randomized to solriamfetol versus placebo.

So to make that clear, in the hypersomnia trial we have active study drug, most participants would be eligible to receive modafinil versus placebo. If they can't take modafinil, we'll see if they can take solriamfetol based upon drug-drug interactions, and if they can take that, they'd be randomized to solriamfetol versus placebo. Participants will know if they're in the modafinil arm or the solriamfetol

arm, but they would not know if they're receiving active study drug or placebo in either arm. Both of these drugs have been used before to help people stay awake during the day and they're FDA-approved for that indication, but this is the first time that we are testing these drugs in a population of patients with long COVID. Next slide please.

So what is the rationale behind using modafinil and solriamfetol in this trial? Well, we know that both of these medications target brain neurotransmitters that increase alertness. So for patients who have hypersomnia or excessive daytime sleepiness, we need to target the part of the brain that manages alertness. As I already mentioned, these are both FDA-approved, they're generally safe, and there's really good animal and human data that supports their use, and data have shown that they have an effect on synaptic transmission, brain plasticity, and areas in the brain involved in alertness like the hippocampus. There's also some evidence for improving cognition, reducing depressive symptoms and slowing neurodegeneration, so there are sort of some beneficial side effects, if you will, from targeting the original underlying problem, which is just hypersomnia. Like I mentioned previously, modafinil will be initially considered because it has been used longer, it's been on the market longer, it's less expensive, so it makes it more generalizable for a larger population. Solriamfetol is an option for those with drug-drug interactions or other health-related contraindications. Next slide please.

We have tried to be really creative to make some adaptations for this trial to make it more user-friendly and less burdensome for the participants, and to create something that is going to be in better position to be rolled out to the larger population if we are to show benefit. So the trial was designed so that there's limited burden on participants, so we have remote data collection. One example of this is that participants are given blood pressure monitors and they could do in-home blood pressure monitoring as we titrate the drug at the beginning of the intervention period. Obviously, this is more straightforward than coming into clinic for a repeat blood pressure assessment. We've developed a protocolized titration approach for both medications so that study coordinators and hopefully future providers in the community will have a roadmap for knowing how to up-titrate drug and perhaps back off on the dose if someone is having side effects.

We've also developed a customized patient sleep diary with significant input from patients that allows us to gather more information about sleep and activity patterns in patients with long COVID. So this will help not only in understanding the effect of the interventions we're studying here, but will also give us some really valuable information about what are sleep habits like of patients with long COVID. We'll really get some detailed information about this, which will be useful to share at large and hopefully inform other studies going forward. Next slide please.

All right. The next trial I'm going to talk about is the second trial in the platform. So this is the complex sleep disturbance trial, which includes the use of melatonin and light therapy. Next slide please. So as Susan mentioned before, we call this CPSD, or complex past-related sleep disturbance trial. As Susan also mentioned, this was a title that we came upon with significant input from participants and patients who are living long COVID with sleep disturbance. They feel like this really describes what they are experiencing. So this trial targets participants who have more of an insomnia phenotype or perhaps an irregular sleep pattern, not individuals who have hypersomnia and are sleepy all the time, but sort of the opposite, right? You go to bed later than you wish, you don't sleep long enough, you wake up frequently in the middle of the night, things like that.

This trial includes an eight-week study intervention period and participants will be asked to take melatonin versus placebo, again blinded, so they don't know which they're receiving. They're also going to be asked to use a table lamp to receive light, and the light therapy that they're receiving is also blinded, so patients will be randomized to high intensity or active light, or low intensity or placebo light. Participants in the CPSD trial will also receive an individualized sleep plan, and this is really the

behavioral intervention. This individualized sleep plan includes tailored information for each individual participant for what time they should use the study interventions, when they should go to sleep, when they should get out of bed, how they should handle napping if they need to nap during the day.

So again, as Susan mentioned before, it's a way to really capitalize on the interventions that we are testing here. Together, we hope that the study interventions plus this individualized sleep plan will help participants regulate their sleep-wake patterns and improve their quality of sleep. The research team and participants will not know which group of participant is assigned to. Obviously a participant will know that they're using light, but they won't know if the light is the very bright light that can entrain the circadian rhythm or whether it's just, quote, unquote, "normal light." Next slide please.

So what is the rationale for targeting the amplifying relationships of sleep and circadian rhythm? Well, Susan touched on this before, but there's a very clear interconnection between the rhythms in your brain that tell you to go to sleep and wake up, and circadian rhythms, so things that are informed by your environment, by light exposure, dark exposure, so on and so forth. If your sleep rhythm is not normal, you're going to have side effects of this, and that can include effects on your metabolic status, reactive oxygen species, activation of some of the immune cells in your brain inflammation, and this contributes to peripheral symptoms, if you will. So it's not just sleep, poor sleep can then have manifestations in other parts of your life. We know that weak circadian rhythms may further cause sleep problems and poor sleep quality may further weaken circadian rhythms, so there's a feedback loop here. Next slide please. And one more. Perfect.

We know that long COVID can lead to complex sleep disturbances that present similarly to, but have overlapping qualities, and like I mentioned before, this can include insomnia, so sleep disturbance, you can't stay asleep, and then circadian rhythm disturbances. So your rhythm is just not normal, you go to bed at alternating times or inconsistent times, or times that are not consistent with your real world light exposure. I already mentioned the interventions that we're studying and the importance of the behavioral recommendations that underlie the therapy that we are testing. Next slide please.

So this is a little bit more about the rationale for therapies that we are using. We know that light is the primary synchronizer of circadian rhythms. We know that light therapy improves sleep, mood and behavior and individuals suffering from dementia and Parkinson's disease. So these are things that have been proven in the literature. Light therapy during the daytime improves sleep, reduces depression and fatigue, and lowers inflammatory markers in cancer patients undergoing bone marrow transplant. So again, that seems like a very specific niche, right? But I mentioned it because there is very solid evidence supporting this in the literature. We also know that light therapy improves the mood and individual suffering from depression, including seasonal depression disorder. And then likewise there's similar strong data for the use of melatonin. We know that there's strong data to show that melatonin can regulate sleep in children, particularly those with autism and can also reduce jet lag. We all either have tried or know people who use melatonin when they go on long trips because it does help to reset your circadian rhythm. Next slide please.

So what is the role of the behavioral sleep recommendations that are incorporated in this trial? There was a lot of talk about behavioral interventions and sometimes I think patients in the community feel that behavioral interventions are not necessarily helpful. We've had a lot of conversation with patients in the community and other scientists and physicians, and came upon this sort of combined approach where the behavioral sleep recommendations, which we have termed RESET PASC in this trial, they're really being used to provide a framework for the biological interventions of light and melatonin. And again, I stress that these are individual guidelines, individual framework. So Dr. Buysse and his team are going to be looking at sleep diary data of every single individual participant in this trial and crafting a very personalized sleep plan based upon their data, and we anticipate that that should really help to

anchor the hopeful benefits of the interventions that we're testing here. Again, those interventions being melatonin and light therapy. Next slide please.

What are some novel aspects of the interventions that we're testing in this CPSD trial? So again, this trial test combined approaches. So we're combining behavioral recommendations with light therapy and pharmacologic therapy in the form of melatonin. The individualized sleep plan that is created by Dr. Buysse's team has some three sort of central tenants. It's going to focus on the amount of time in bed, that's the A, irregularity of your sleep, so trying to be consistent when you go to bed, when you get out of bed, that helps to keep your sleep rhythms consistent, and timing. It's all about timing. So ART, it's the art of the individualized sleep plan and the art of this therapy. Next slide please.

What do we hope to learn? Well, we hope from this that we will understand if the study interventions are safe and improve sleep quality and daily functioning of people who have long COVID, both those who have a hypersomnia phenotype, which we're targeting in the first trial, and those who have more of an insomnia or circadian rhythm dysfunction phenotype in the second trial. The research team will use a variety of assessments, including tests to measure memory thinking, abilities, participant surveys, so on and so forth, to really understand how these interventions affect variable aspects of life, not just sleep timing and sleep quality, but other things as well, how well do they think, how well do they remember, what happens to other symptoms, like orthostatic hypotension, other things that sort of track along with long COVID and maybe tested in other RECOVER platform trials.

After the studies are complete and the data have been analyzed, we're going to share the overall study results in medical journal articles and on the RECOVER website. So we certainly plan to share this with the community at large. Next slide please. And then how can you find study sites? We encourage you to go to the RECOVER-SLEEP platform page on clinicaltrials.gov and that will point you to sites that are open and soon to be enrolling participants. And that should be the last slide. Thanks for your attention. I'm going to pass it over to our next speaker.

Dr. Michael Felker:

Great, thank you so much, Christina. I'm Mike Felker, one of the co-chairs for the RECOVER-ENERGIZE platform and I'm happy to kick off the discussion about ENERGIZE today. Next slide. So like the other trials in RECOVER, ENERGIZE is a platform protocol that includes multiple clinical trials. For ENERGIZE, we just started opening sites very recently, so we do have sites open for enrollment and additional sites are being opened. The clinicaltrials.gov identifier is here on this slide and I think people are also putting it in the Q&A. ENERGIZE will encompass two clinical trials and testing interventions in participants with different aspects of exercise intolerance. One is a personalized cardiopulmonary rehabilitation intervention that combines exercise, training, education and support, and a second trial will test a structured pacing intervention designed to help people recognize control and minimize post-exertional malaise symptoms with the assistance of a pacing coach, and that trial be specifically for patients who have PEM, which we'll talk about further. ENERGIZE will target 60 sites on a total of 660 participants. Next slide.

So this is the leadership team for ENERGIZE, and you'll hear from I think three of us today. I'm a cardiologist, I'm joined by Barry Make, who's a pulmonologist from National Jewish Health, listen to Bateman who's an internist and an expert in ME/CFS and long COVID, and Janna Friedly from the University of Washington, who's an expert in physical medicine and rehabilitation. So just like in SLEEP, we've really tried to bring together multiple different perspectives and expertises to best design these trials within ENERGIZE. Next slide.

So as I mentioned, ENERGIZE composes two clinical trials. I'm just going to provide an overview and then we'll go deeper into the details of each of these individually. So first, RECOVER-ENERGIZE for exercise intolerance. As I said, testing a personalized cardiopulmonary rehabilitation intervention for people who have exercise intolerance, but without symptoms of PEM, and that's an important point that we'll make again. So this intervention, as I said, combines exercise training, strength training, education, psychosocial support. There'll be 360 participants in that, and then a second clinical trial called RECOVER-ENERGIZE Post-Exertional Malaise, which is specifically a trial for patients with PEM, and we'll talk about what PEM is some more in later slides, and again, designed to help patients get to know, control and minimize PEM symptoms, stabilize their daily functioning and improve their quality of life, and there'll be 300 patients enrolled in this trial.

And importantly, because I know it's been a significant talking point of discussion, I want to emphasize that patients with PEM in ENERGIZE will not be included in studies that involve treatment with exercise training, because we understand and agree with the concern about the possibility of PEM being exacerbated potentially by exercise training, and of course, safety of participants in the trials is a paramount importance both in the trials, and also of course, in clinical care. Next slide.

So when we say exercise intolerance, what do we mean? What we're really talking about are symptoms that limit people during physical activity. They could be shortness of breath, muscle weakness or fatigue, extreme tiredness, things that cause you to stop doing what you're doing before you've completed a task. For example, you might have to catch your breath when chopping or climbing stairs, and we know this is one of the most common symptoms in patients with long COVID from the registry data, and of course, that makes it an important target for recovery program. Next slide.

So what is post-exertional malaise? Well, PEM is another form of exercise intolerance, but quite distinct. It involves worsening of both symptoms and function after even relatively minor physical, mental, social or emotional activity with symptoms that typically occur 12 to 48 hours after the activity is completed and may last for days or even weeks, and PEM can present with a variety of symptoms including exercise intolerance, difficulty thinking, sleep disorders, other symptoms, sore throat, headache, muscle aches and tiredness, and PEM is a common symptom in other clinical disorders potentially related to long COVID such as myalgic encephalomyelitis, chronic fatigue syndrome, or ME/CFS. Next slide. So as I said, within ENERGIZE, there's really two clinical trials. One for patients who have exercise intolerance but do not have post-exertional malaise, that will be testing cardiopulmonary rehabilitation, and a different trial testing, a pacing intervention for patients with significant PEM, and each of these will be discussed in more detail by my colleagues shortly. Next slide.

So one question is how we assess for PEM and energize. We're using a validated clinical tool, the DSQ-PEM questionnaire, which is a 10 question instrument designed to identify patients with PEM. It involves questions about frequency and questions about severity. So patients to meet the diagnostic criteria for PEM report frequency and a severity score of at least two or greater for any of these five symptoms, and if you go in the next slide, there's an additional five questions which really deal with how often these occur after physical or mental efforts and how long they last. And so this tool was designed for ME/CFS, but we're using it in ENERGIZE, especially given the potential overlap of those conditions. So this tool will be used to identify which patients are most appropriate for each trial, but also to monitor both efficacy and safety of the interventions in terms of understanding improvements in PEM or potential risks of developing PEM during the trial. And again, we'll talk about those more subsequently. Next slide.

So why study these interventions in ENERGIZE? Well, of course, we know that fatigue, exercise intolerance, post-exertional malaise, these are very common clinical symptoms in patients with long COVID or PASC, and so that obviously makes them important targets for our studies. We wanted to

target interventions that are ready to be deployed in clinical care immediately if they're proven safe and effective, and importantly, these interventions are already being used out there in clinical practice even though there's no clear data to guide either clinicians or patients. So we want to quickly understand if these are effective, and in which patients they're effective, and how to use them effectively and safely so that we can get those interventions out in the community. On the other hand, if they're not effective or safe, then we need to get that data out in the community so that the focus can turn to other interventions and not waste efforts on things that are not been proven to be useful. Next slide. And I'm going to turn it over now to my colleague Barry Make, who's going to talk in more detail about the exercise intolerance cardiopulmonary rehabilitation study.

Dr. Barry Make:

Thanks, Mike. Can I have the next slide please? So cardiopulmonary rehabilitation will be compared to control, that is we want to make sure that we know who gets the cardiopulmonary rehabilitation compared to patients who don't get it. The question is, does personalized cardiopulmonary rehabilitation, I'll define that in a minute, improve the outcomes for people with exercise intolerance and fatigue symptoms? There'll be 360 adults with exercise intolerance from long COVID in this study. The intervention will be personalized cardiopulmonary rehabilitation compared to control, and I'll define those in a minute. The duration of this study is six months. There are 12 weeks during which the cardiopulmonary rehabilitation will be implied, and 12 weeks after that a follow-up to see if the benefit, if there is any, is maintained after the intervention is performed. The health measures we'll look as outcomes are both performance-based and questionnaires that patients tell us what their symptoms are, and we'll also look at safety and tolerability. There'll be 60 sites in this study. Next slide please.

So what is cardiopulmonary rehabilitation, especially personalized? Well, cardiac rehabilitation and pulmonary rehabilitation are known interventions that are similar and are applied to people with both cardiac diseases and pulmonary diseases. In this study, we are personalizing them for patients with long COVID and we are adapting them to patients with long COVID. Rehabilitation in this sense includes progressive exercise training. I'll talk more about exercise training in a minute, but it's based on what people come to us, what their exercise capacity is at the start of the study, and we progress it based on the tolerance of the exercise training and their symptoms and their response, also includes education, nutritional counseling and psychosocial support. Next slide.

So here's the components of a rehabilitation session. First, it's aerobic exercise, and this is lower extremity aerobic exercise. What are the modes of exercise training? Well, walking, cycling, treadmill, whatever is convenient for the participant to do. We start at 10 minutes if possible. Now, some people we think may not be able to start with 10 minutes of exercise and need to start with less than that, and the amount of exercise we start with is based upon our baseline assessment of each individual patient. So by personalized we also mean individualized. We look at each participant as a unique person and we progress them and we provide exercise training based on their individual assessment and their individual response. We progress the exercise up to 30 minutes or more as the participant is able to do.

The intensity of each exercise session we determine by two ways. First, heart rate. We want to see if they have a heart rate response that's 60% or more of their predicted maximum heart rate, or their perceived exertion or perceived shortness of breath, and there's a specific scale that we give patients to tell us what their perceived exertion and perceived dyspnea are. We want that to be at a level of five to six. Next slide.

We also include education on topics like nutrition and weight management. If people are overweight, that's not good for exercise because they can exercise less. If they're underweight and a

poor muscle mass, that's not good either. So we give them counseling on nutrition and optimal weight. We talk about the fundamentals of exercise. We also want to tell them what post-exertional malaise is because we want to avoid that. We give them strategies for self-management of their energy levels of everyday life, talk about management of stress, anxiety and depression, which we know are common in long COVID as well. Some patients may need more strength training than others individualized based upon what the patient's strength is at the beginning of the study. Flexibility is important and psychosocial support of other people is important as well, not only for long COVID but for any chronic disease. Next please.

Now we're going to be very careful to make sure that patients don't develop post-exertional malaise during rehabilitation, but it is possible that some patients may. In patients that do develop post-exertional malaise after a rehabilitation session, they will not exercise until those symptoms resolve. Once the symptoms resolve, the patient can't go back to the previous level of exercise, so we need to resume exercise at a lower duration and lower intensity than the exercise that actually caused the post-exertional malaise. Patients should continue to exercise at a lower intensity and duration for some period of time for at least two sessions without developing PEM before they increase their exercise. If they're unable to resume exercise due to continued PEM symptoms after more than two weeks, participants will discontinue cardiopulmonary rehabilitation. However, if a patient stops cardiopulmonary rehabilitation for this or any reason, we want to make sure that all participants receive the follow-up assessments at the end of the study to see if they improve or not compared to control patients.

PEM symptoms will be captured and reported as an important safety endpoint. Now in terms of safety, the investigators are concerned about safety at the individual sites. We, the investigators, the principal investigators on this call are concerned, and we have something called a data safety monitoring board that all controlled trials have, and it's a group of outside people that are experts that help look at the safety throughout the study and will either stop or tell us to modify the protocol as necessary. Next.

The control group. The control group will receive general educational and exercise, but not specific training. They'll receive general educational on what post-exertional malaise is and they'll continue to receive as patients who receive cardiopulmonary rehabilitation on the regular care provided by their physicians. So we're not changing the care that your physicians who are treating you now receive. They'll continue to receive whatever care, whatever medications their treating physicians do. We're not changing any medications in this study. They'll receive weekly phone calls and follow-up visits that may be by Zoom or phone coordinated by the study staff to see how they're doing throughout the study. Next, please.

The primary outcome is whether people can exercise, and we're using a walk test, a specific walk test called an endurance shuttle walk test. We want to see if there's a change in the treatment group who received cardiopulmonary rehabilitation from the baseline before they start rehabilitation to when they end cardiopulmonary rehabilitation, or compare the change in patients who receive the cardiopulmonary rehabilitation, the patients who are in the control group, and that's our primary outcome. We have a lot of other outcomes as well. As I discussed before, we want to know how patients feel. There'll be patient-reported outcomes, questionnaires that patients can fill out that are validated questionnaires, just tell us how they feel, whatever other symptoms they may have related to long COVID. Next slide. So thank you. Next, Lucinda will talk about post-exertional malaise and structured pacing and the intervention in that part of the trial.

Dr. Lucinda Bateman:

Thank you, Barry. It's a pleasure to be part of this team and to talk to you about our structured pacing protocol. Next slide. So you saw this slide, but I think it's worth repeating. So what is post-exertional malaise, or PEM and sometimes called PEM? It's essentially a worsening of both symptoms and function after even minor physical, mental, social or emotional activity with symptoms typically occurring in a delayed fashion, 12 to 48 hours, after the activity and lasting for days or weeks. Sometimes it can occur earlier in the more severe patients. So symptoms of PEM include any symptom of illness, but predominantly exercise, trouble being active, exercise intolerance or activity intolerance, difficulty thinking, worse sleep problems, sore throat, headaches, muscle aches, dizziness or even just severe fatigue, and almost... There are many, many symptoms that may be characteristic for a given patient, and it's common in the clinical syndrome we call ME/CFS, or myalgic encephalomyelitis chronic fatigue syndrome. Next. Next slide.

So let's talk a little bit about what we mean by structured pacing. Structured pacing is a training program designed to help the participants recognize control and minimize their PEM symptoms, and this is also a very individualized intervention. The goal of structured pacing is more stable function in everyday life with less frequent and less severe PEM, fewer setbacks, less push-crash cycle. We will have trained pacing coaches who will lead each structured pacing session. Next slide.

So our study structured pacing versus controls, the question is does structured pacing improve outcomes for people with exercise intolerance and PEM from long COVID? We hope to have 300 adults who experienced post-exertional malaise from long COVID. The intervention, as we've said, includes structured pacing, but there will also be controls, and I'll be more specific about this in a minute. Similar duration, six months. That's 12 weeks of the active intervention and another 12 weeks of follow-up to look for duration of the effect, and we'll be measuring patient-reported outcomes, but patients will also have a Fitbit and we'll be able to use some of the parameters from the Fitbit to monitor physical activity, and there should be up to 60 sites involved in this trial. Next slide.

So these structured pacing sessions are personalized sessions tailored to that participant's needs and symptoms. In the beginning, the first session, they will meet with a pacing coach, hopefully in person, but it can also be done virtually to get to know each other and start to establish the plan. Then the participants will have a weekly remote session with their pacing coach to teach the participant how to recognize post-exertional malaise and especially the triggers for post-exertional malaise. They'll be undergoing a task analysis to identify and prioritize illness-impacted tasks and functions, they will develop strategies for getting must-do tasks done without causing PEM, and they'll be working on adaptations and modifications to make daily life easier and smoother for these patients. Next slide. There will be a control group, this structured pacing control group. This group of patients will receive basic education on PEM. They will continue receiving care from their treating physicians and they will also attend weekly phone or virtual follow-ups that come from the study staff, just checking in with them, making sure they're doing okay and staying enrolled and engaged. Next slide.

So our primary outcome is, we've talked about it, to see if pacing our objectives or to see if pacing as an intervention helps reduce post-exertional malaise symptoms, and especially in terms of frequency, severity, and duration versus control patients who do not get this kind of individualized structure pacing. As an outcome measure, we are going to use a modified DSQ-PEM. Now, this hasn't been used as an outcome marker, but this will be a chance to evaluate the frequency and severity and numeric scales as an outcome measure along with many other outcome measures in the study. And the endpoint is a change from baseline to end of intervention in the treatment group compared to the control group, and also including a change from baseline to end of study as well, among other numerous primary and secondary end points. Next slide.

So you've seen this, this is a reminder, how can potential participants find study sites? You can search the clinicaltrials.gov for the RECOVER-ENERGIZE Platform Protocol. You can also search RECOVER-ENERGIZE using the clinical trials identifier. Next slide. We all want to give a special thanks to all of the people with lived experience, the patient caregiver and community representatives who are part of our protocol working groups, the national community engagement group, individuals and patient advocacy organizations who shared their experiences with long COVID and with our teams. It's really made a big difference and was accepted with great respect. Next slide. And I'll now turn it over.

Dr. Beth Linas:

Thank you so much to all of the presenters. We're going to do now a panel Q&A with all the panelists and then we'll move into audience questions following the Q&A. So the first question for the group is how are studies determining a patient had COVID to be included?

Dr. Barry Make:

So the general... Go ahead, Chris.

Dr. Christina Barkauskas:

Go for it. You're good.

Dr. Barry Make:

So 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. You remember early in the pandemic people didn't get tested for COVID and they think they might have COVID, so those patients will also be included. Each study in addition has different criteria based upon that specific study. So 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. Beth Linas:

Yeah. And I think this one's specific to Dr. Felker. Last week, the NIH director publicly stated regarding RECOVER, quote, "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 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?

Dr. Michael Felker:

Yeah, thank you. So the clinical trials are monitored by a data safety monitoring board, which is independent of the investigators, which is an external group of experts, and 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. So 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, but 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.

Dr. Beth Linas:

Great, thank you. This one's for the ENERGIZE team. What are safety measures for ENERGIZE?

Dr. Michael Felker:

Maybe I'll start and other people can jump in. So 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 the trial that's right for them. So as we talked about the initial screening so that patients with 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, but 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 DSQ-EM to reassess patients after exercise testing, and also 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.

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

Dr. Beth Linas:

Great. Anyone else from the team? Okay, this one will be for the SLEEP team. Are there any opportunities to introduce craniosacral therapy into ongoing or future clinical trials?

Dr. Christina 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. I hope that answers the question.

Dr. Beth Linas:

Great, thank you so much. Dr. Friedly, this is a question for you. What steps have been taken to educate pacing coaches about PEM and RECOVER as a whole?

Dr. Janna Friedly:

Yeah, happy to answer that one. 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 and also have experience working on clinical trials and delivering these types of interventions. So they are training each of the pacing coaches. So each of the pacing coaches that are identified at the sites will undergo formal training on the intervention before they start working with participants. So 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.

And then in addition, we have fidelity monitoring. So we will be recording sessions and having the fidelity monitors, who are the pacing coach, review those sessions and provide feedback to the pacing coach to make sure that the intervention is being delivered as we are expecting it to. So there's multiple different ways that they're getting training throughout the trial.

Dr. Beth Linas:

Great, thank you. This is a question for the group, it just came in. How can individuals participate in trials or studies when we can't get our primary physician to take us seriously?

Dr. Christina Barkauskas:

Dr. Bateman, why don't you take that?

Dr. Lucinda Bateman:

Maybe we can both say something. I think once you participate... 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. Christina Barkauskas:

And 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.

Dr. Beth Linas:

Great, thank you. This one is also for the group. Sincere question, 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? Dr. Redline?

Dr. Susan Redline:

Yeah. Well, first of all, I certainly recognize that I think 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 again, 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. So 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 have 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. Beth Linas:

Dr. Felker?

Dr. Michael Felker:

Yeah, thank you. So just to first of all, I echo what Dr. Redline said, and I said earlier, 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. So one of the primary goals of RECOVER is to identify treatments that are shovel-ready, if you will, 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, and that's what therapies that can get into clinical practice as rapidly as possible, even if sometimes certainly 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.

Dr. Beth Linas:

Great. Thank you so much. This question is for the exercise team. What is the theory being addressed by exercise intervention? Is it an assumption that the non-PEM cohort is deconditioned?

Dr. Barry Make:

So the answer to that question is multiple answers. So first, yes, if you don't perform activity, you become deconditioned, so yes, that's part of the intervention, but in addition to exercise in some studies has been shown to be anti-inflammatory. In addition, 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. So we'll get an understanding of the pathophysiology of the disorder and how the intervention may change that pathophysiology.

Dr. Beth Linas:

Great. Thank you so much. This is for the sleep team, it's a little specific. I'm actually not sure if you've answered it already, but I'm going to ask. I'm being considered for the complex sleep platform. Are there any guidelines in limiting smartphone blue light exposure for the sleep diary tracking?

Dr. Susan Redline:

Yeah, I actually wrote something in the chat, but just to emphasize, 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. So we're very excited about that opportunity to improve people's circadian rhythms through light manipulation.

Dr. Beth Linas:

And there's a follow-up question to that, which is the study excluding patients already receiving light therapy?

Dr. Susan Redline:

Yeah. What would likely happen is that anyone using light in doses that we think would affect the circadian pacemaker would be asked to be washed off or withdrawn from it so that we could get a fresh look at the effect of light in the trial.

Dr. Beth Linas:

Great. And I will pivot back to the ENERGIZE team. The question is, 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?

Dr. Barry Make:

So again, in ENERGIZE we are not changing people's medications. Whatever your local physician, treating physicians give you is what we will continue. So in general, some patients with long COVID develop other cardiopulmonary symptoms and develop asthma, so we are not, again, 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.

Dr. Beth Linas:

Great. ENERGIZE again. "Is acupuncture being tested as a remedy for PEM? It was a breakthrough treatment for me," was the comment.

Dr. Lucinda Bateman:

That's very interesting. I do not know of a study that specifically looks at acupuncture and PEM.

Dr. Janna Friedly:

Yeah, and I'll mention that 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. So there is a trial that's just getting up and running at the University of Washington, looking at acupuncture and long COVID as an example.

Dr. Beth Linas:

Great. For the sleep team, what are the primary outcomes for the hypersomnia and RECOVER-SLEEP studies?

Dr. Christina Barkauskas:

I can take that one. I wrote some of this in the chat, but I think it's important to talk about in in the group at large. We are 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. So the change in PROMIS score from beginning of the study to the end of intervention is the primary outcome measure.

Dr. Beth Linas:

Great. Thank you. For the ENERGIZE team, what has your research shown regarding the use of nattokinase and NADplus to treat PEM? Apologies if I misspoke.

Dr. Barry Make:

Yeah, 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. So 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. Michael Felker:

And maybe just in follow up to that, I mean, there are many... 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, this has been said, we were really trying to focus on things that were ready to be implemented today if they work, but I do think there's certainly... The things being studied in RECOVER are not the only things that could be studied. I mean, Janna just mentioned acupuncture, which I didn't know about, but just what's being studied in this program right now.

Dr. Beth Linas:

Great. I had the question, now I can't find it. Oh. Sorry, the ENERGIZE team again. How is mitochondrial dysfunction associated with PEM?

Dr. Lucinda Bateman:

Maybe I can take a stab at that. As an expert in 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. So it's my hope that this kind of a trial will help move us that direction to really understanding what the underlying pathophysiology is.

Dr. Beth Linas:

Great. Thank you.

Dr. Barry 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.

Dr. Beth Linas:

And Christina, the question you just answered, I saw you answered in the chat, I'm trying to find it. Excuse me.

Dr. Christina Barkauskas:

Yes, about if someone is taking medication for sleep, would they be excluded from the sleep trials?

Dr. Beth Linas:

Thank you. Yes.

Dr. Christina Barkauskas:

You're welcome. The general premise is that if you are receiving a medication or therapy for sleep, you would need to hold that and allow it to wash out prior to being screened for the sleep trial, particularly if it's a similar intervention.

Dr. Beth Linas:

Great, and actually, if you can believe it, those are all the questions. You answered many of them in the chat. I know that several came in while we were speaking, so I wasn't able to parse them, but I thank all the panelists and thank you to our audience for attending the seminar and engaging with the Q&A. As a reminder, a recording of today's seminar will be available on recovercovid.org within a few weeks. We'll also be posting a Q&A document that has responses to the questions we received today, including some that we did not have time to address. There won't be any R3 seminars in July or August, but information for Fall R3 seminars will be posted on the RECOVER website. We have some exciting topics coming up and hope to see you at future sessions. And lastly, you'll see a short survey come up on your screen which asks for your feedback on the seminar. We would appreciate it if you could take a minute to fill this out. Thank you so much and have a great day.