

## 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 webinar participants related to the following presentations at the R3 Seminar *RECOVER in Action: Status of Clinical Trial Protocols* held on April 25, 2023:

- **Understanding Long COVID**  
**Eldrin Lewis, MD, MPH**  
Co-Chair of the RECOVER Clinical Trials
- **RECOVER Clinical Trials**  
**Kanecia Zimmerman, MD, MPH**  
Principal Investigator of the RECOVER Clinical Trials Data Coordinating Center
- **Patient and Community Engagement in RECOVER Clinical Trials**  
**Renee Leverty, BSN, MA**  
Engagement Lead for the RECOVER Clinical Trials
- **Other Panelists/Discussants**  
**Christine Maughan, BS**  
Patient Representative  
  
**Marta Cerda, JD**  
Patient Representative  
  
**Adrian F. Hernandez, MD, MHS**  
Executive Director of the Duke Clinical Research Institute  
  
**Christine Bevc, PhD, MA**  
RECOVER Administrative Coordinating Center  
  
**Sonya Sutton, MA**  
Duke Clinical Research Institute Communications & Engagement

\* Responses may have been edited for clarity.

## All Presenters: Questions and Responses

### Q. How will the exercise trial address the concerns of patients with post-exertional malaise?

**Response:**

**Ms. Sutton:** The exercise intolerance protocol is still under development and we're working with experts and patient representatives to take all inputs into consideration.

### Q. What drugs are you going to trial?

**Response:**

**Ms. Sutton:** Some of the protocol details, such as drugs we will test, are still being finalized. But the full protocols will be posted to <https://trials.recovercovid.org/> once they're approved.

### Q. What results do we have from the clinical trials thus far?

**Response:**

**Ms. Sutton:** The trials have just recently begun recruiting participants, so we don't have results to share yet.

### Q. What are the current clinical trials and what trials are planned in the future?

**Response:**

**Ms. Sutton:** These are the five symptom areas for the upcoming clinical trials: viral persistence, cognitive dysfunction, sleep disturbances, exercise intolerance and fatigue, and autonomic dysfunction. Each of the protocols for these areas will test at least one intervention.

### Q. How will clinical enrolling sites be selected and when will site selection begin?

**Response:**

**Dr. Zimmerman:** That information is certainly forthcoming. We've started sending out questions to sites on their capabilities to see whether sites are interested and who on their team is at the site to be able to do some of the work. So that process is happening right now. The information about the sites will be posted on <https://trials.recovercovid.org/>.

**Q. How are these clinical trials recruiting participants? How are you going to reach underserved communities and those who may not know that their symptoms could be Long COVID?**

**Responses:**

**Dr. Zimmerman:** Recruitment will primarily be site-based. We are seeking a wide range of sites over a broad range of geographic locations and making sure that the sites have certain capabilities. For example, there may be sites that we're looking for that have expertise in processing peripheral blood mononuclear cells (PBMCs). Also, there are some sites that might have the capabilities of doing things like cardiopulmonary exercise testing. Not every site can do that, but we want to make sure that if a trial calls for at least some sites to have cardiopulmonary exercise testing that we're including sites that have that capability.

But we're also really interested in being inclusive of all populations, so we're looking for sites that care for patients who may live in underserved areas and who usually aren't able to participate in clinical trials. As we've been designing the trials, we've tried to be very thoughtful about what's the lowest common denominator of the sites – the composite of capabilities. What is really needed from every single trial is to make sure that sites that have not typically conducted clinical trials but have the desire, and the population, can be included.

Concerning the second question, we need to think about how we make sure that people who don't know they have Long COVID can understand that. That's our job and the job of everyone who is part of this panel. It's the job of hopefully all the patients and patient advocates that are watching today. We've got to get the word out because it's very possible that people like, for example, Ms. Cerda, who mentioned that she didn't even know that that was one of her symptoms, and there are certainly other populations. We've done listening sessions where participants say, for example, "Oh, my gosh, I just thought I was really, really tired because I had to work so much because the economy isn't that great. I'm working two jobs now as opposed to one, and I just thought I was really tired." It's our responsibility to get information out about these types of things.

**Dr. Hernandez:** One other note along with what Dr. Zimmerman said is that I think everyone's hoping that the RECOVER Initiative is a continuous process. So as results are generated from their clinical trials and if they have an impact on an area, how can we get that information to every corner of the US and around the world as soon as possible? It seems like this community that's extremely motivated because either they've been in touch with the people who've had problems with Long COVID or are living with it and so forth are going to be the greatest channels for getting the results to the people who are suffering from Long COVID. To Dr. Zimmerman's point here, it's making sure that people are recognizing this. They may assume that they have something else and aren't seeking care.

**Ms. Cerda:** I'd like to add that when I participate in panel discussions, I'm very passionate about letting people know the symptoms that I have. I'm doing another panel next week at the state of Illinois building downstate, so

that people understand they're not alone and that other people have these issues around brain fog or stuttering or shortness of breath, all of that. I've even been interviewed here by ABC 7 Chicago. So, I get the word out about those symptoms. I do think that far too many people don't know they have Long COVID and that they could get help.

**Ms. Leverty:** I'll add that we have bilingual staff and also look for sites with bilingual staff developing community engagement toolkits. We want to partner with already trusted resources within the communities at the local and national levels. So please reach out because we know it's these already formed relationships that will help us share the messaging about the work of RECOVER.

**Q. How are you pairing PASC symptom clusters and enrollment on specific trials? Are patients within the treatment trials sub-grouped by "symptom cluster"?**

**Response:**

**Dr. Zimmerman:** I'll talk about viral persistence as an example. We know that up to 60% of patients who have Long COVID have overlapping symptoms. Some data have come from the RECOVER Long COVID cohorts and other health sources, but we've tried to be fairly deliberate about allowing people within the viral persistence protocol if they are the first arm, for example, if they not only have brain fog but also autonomic dysfunction or also post-exertional malaise, that they might potentially have an option to enroll for all three of these symptom clusters.

There are certain inclusion criteria for each of these symptom clusters. So there's not only saying, "I have brain fog," but there's also other information and other tests that need to be passed in order to be included in that particular trial. But we would be very interested in the worst symptoms if you didn't pass the other ones; for example, brain fog might be your worst symptom, but you might not have as much of an issue with the other two symptoms.

We've tried to be thoughtful about making sure that people aren't necessarily in multiple trials themselves at the same time if there are drug treatments involved, for example, because we want to understand the effect and we don't want one thing affecting another. But the details about how that will all work to make sure we're as inclusive as possible and allow people to be a part of however much they want to be as possible are still being worked out.

**Q. When reenrollment for the clinical trials open, (1) will the enrollment be posted on clinicaltrials.gov, and (2) will it be an open enrollment—that is, open for patient enrollment as compared with clinician referral?**

**Response:**

**Ms. Sutton:** Yes, the trials will be posted on clinicaltrials.gov when enrollment opens for each one. Recruitment will be based at the sites for each trial.

**Q. Can you describe how patient input is incorporated into plans? For example, how is it weighted relative to a scientific expert’s input? I have heard concerns about patient input being given, but not used.**

**Responses:**

**Ms. Cerda:** I can give you an example. I was in the gastrointestinal breakout group and speaking about what was most important to me. I did give a comment that while it’s disturbing to have vomiting and nausea, it’s not as important to me. I weighed it. It’s not as important to me as my heart racing or my lungs not functioning well. I have scarred lungs, for example, right now. So, I was able to give that discussion because it seemed that there were going to be some challenging clinical trials with that group. They did take my feedback and they said, “We hear you. We’re putting this in our notes,” and they included this in our discussion. So, it was the weighing of the importance of that study that was taken into account. I felt it was, and they told me they were moving it forward.

**Ms. Leverty:** The patient and community representatives on the protocol working training teams are full members. So as researchers come to the table with past experience learned and lived of how they see a clinical trial being developed or areas to focus on, the same works with the patient representative. It’s not a voting structure, it’s a consensus structure. It’s developing knowledge, codeveloping knowledge, and sharing knowledge and trying to lift and create a protocol that is taking in all those factors.

Now, one thing that we do is document patient and community feedback, and we follow up regarding influence. We want to do that because it helps make this protocol better to know that if something was recommended as part of a team and it wasn’t accepted, that we, I’ll put myself in the researcher camp, we as researchers know why. It helps researchers think more critically about decisions they’re making and it’s a conversation and its consensus.

So, we’re lifting systems to have the patient input as part of the working group team to be equal because we’re developing strategies for things to be created, the protocols created through consensus; but again, not like researchers, not every item that a patient representative may recommend may be in the protocol, and it’s the same for the research team on the protocol. It’s built together.

**Dr. Hernandez:** One other note to add is that it's not going to be done there just with the protocol, it's going to be through and through. So as the studies are launched, there'll be some early learnings in terms of what the experience is and/or getting others to join and then finally the results and how that's disseminated and shared with the communities. My guess is that just like the beginning of this effort has been complicated, getting the results out in a way that's understood will also be challenging. So, we need to make sure that people understand that, especially with all these overlapping issues of the different symptoms and syndromes.

**Q. How is real-world data, such as electronic health records, being integrated into these trials? How are you factoring in patients who couldn't get PCR tests earlier in the pandemic or those who have had vaccines and been boosted or not been boosted? How do the observational studies and real-world data figure into the clinical trials?**

**Response:**

**Dr. Zimmerman:** I'll start with the people who couldn't get information or couldn't get tested at the time. I'll say that this is an area where patient advocacy has been so awesome in making sure that I'm not only aware of it, but also really thinking carefully about this and thinking about this across all the protocols in RECOVER. We're opening the RECOVER trials to make sure that some people who have probable or suspected COVID could in fact still participate, especially if they had probable or suspected COVID prior to when tests were widely available so that we can make sure that we're also understanding that population.

It's not that just we understand that some of those patients have the most severe disease, we also understand that those patients didn't necessarily have access to testing because it wasn't widely available, but there's also a lot to learn from that particular group. So, our hope is to understand how duration of symptoms might even affect how you may respond or recover in these specific trials. So certainly, thanks to Dr. Bevc and Ms. Cerda for helping us to really be thoughtful and inclusive of patients who didn't have access to testing.

As for the last question on observational studies, we have meetings with the RECOVER cohort leadership—specifically, the adult cohort leadership—to make sure that we're asking very similar questions so that we can cross-compare information using things like the common data elements that have been identified. There will be both RECOVER sites and non-RECOVER sites within the clinical trials; but certainly, these RECOVER sites will allow us to capitalize on some of the information that's already been gathered within the RECOVER data.

We're going to use the electronic health record data to try to identify what we call phenotype patients so that we can more quickly identify them for the trial. I'm also excited about the wearables (e.g., Fitbits) that the cohorts are using as well, and that's a form of real-world data to be able to track heart rate and things of that nature on a consistent basis that we are also collaborating on. In fact, after this, I'm going to a meeting with the RECOVER cohort to figure out how we might be able to do that together.

## **Q. Can you clarify what cardiopulmonary rehabilitation for post-exertional malaise (PEM) looks like?**

### **Responses:**

**Dr. Zimmerman:** I'll start by saying that this is a work in progress to define not only the intervention and what exactly that looks like, but who the appropriate population is for this specific trial. I want to also say that we have certainly heard the patient feedback. Here, there have been lots of people who've given feedback, but also the people in the working group, the patients in the working group have been intimately involved in this process to tell us "Absolutely not. That's not appropriate." or "This seems to be appropriate." and that's gone back and forth with executive committees and steering committees, etc.

People are committed to getting this right and to making sure that first and foremost it's safe. So, while I can't tell you exactly what the cardiopulmonary rehab intervention looks like right now, I can tell you that safety is at the center of everything that's being done, from the inclusion criteria to the intervention itself. We are very much aware of those with PEM, those with ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) phenotype, and those who have exercise intolerance where they're having difficulty as the activity is happening. We want to make sure that we are thoughtful about all these things.

We also want to make sure that once we have the trial, once there's the appropriate population that's in that trial, that in the future we're also communicating what happens, and we're communicating it with all the nuances so that it doesn't necessarily turn into a global recommendation for everyone if that isn't the population who is in the trial. So hopefully, that's a start. I also want to emphasize there's the Data Safety and Monitoring Board. Our teams are being very thoughtful about it, as trial participant safety is number one on the list. Dr. Lewis, please take it from there.

**Dr. Lewis:** It's really challenging, and certainly we've heard a lot of the feedback. I want to say that the PASC population with exercise intolerance is in many ways different from your classic PEM population, especially the severe PEM. That being said, because they're overlapping symptoms, what we don't want would be to have people who have severe PEM as an initial component of this trial.

One of the things I'd emphasize is that many times when there's been a decade or two decades of clinical treatment and perception of understanding, it becomes very challenging to answer a question because we feel that we know the answer. For example, I used to give lectures on this in cardiovascular disease as a heart failure and transplant cardiologist. Dr. Hernandez would know this as well. For a long time, we never gave beta blockers because we said, "Why would you give a beta blocker to someone who is chronotropically or inotropically challenged?" So we basically didn't use a therapy for a long time in heart failure because of the perception that beta blockers will harm patients. In fact, I still remember when I was early in my career when someone actually shouted, "Why are you trying to kill my patient by giving beta blockers?" when the first trial came out that basically showed that beta blockers were associated with 34% improvement in survival.

Another example is hormone replacement therapy (HRT). When I was in medical school, we used to use HRT as a standard treatment for women who were perimenopausal, thinking that we were improving cardiovascular risk until we did the Women's Health Initiative trials, which was a randomized trial. When that was done, the findings showed that there was actually no benefit and in fact harm. So once again, one of the hardest things to do is to in fact test it.

What you want to do is to ensure that each participant, each of the 360 participants, will be studied in a safe way. I think it's very important that we understand this. The last example I'll give, and then I'll pass it over to Dr. Hernandez, is exercise. If you look at guidelines in years past in heart failure, they would say "Why are you going to exercise? That's dangerous. People with heart failure cannot exercise. They're going to have arrhythmias. They're going to drop dead. We should not recommend exercise. People with heart failure should sit in their chair until they die." That sounds cruel, but that's basically what we were doing, and we didn't realize until we studied, in a safe way, how exercise can make a difference. And that changed the narrative to "Okay. You know what? You should exercise. Here's a safe way to exercise." You're not going to start with the sickest people when you're going to do that protocol, people who are on life-sustaining intravenous drugs. You're going to start with the healthier population with heart failure and then do it.

There was a cardiac rehab study that looked at heart failure patients who were moderate to high risk and randomized over 800 patients in 81 centers to rehab as compared with usual care. So, it can be done, but the big thing is to make sure that it's done in a safe way and then answer the question once and for all with a randomized study.

**Dr. Hernandez:** I'll just note that I think this has to be one of the hardest areas in health and science that I've ever encountered. I think for anyone who's lived unfortunately with Long COVID or PASC, I mean, they're going along with their life and not expecting something like this, and especially early on when COVID comes out; like I said, "Oh, it's a bad flu." Well, that's the really bad flu. What are we talking about here? So, if you think about the population and essentially a new disease that has some overlap with other syndromes or other areas, it's still really challenging because you don't fully understand all the different causes and contributing factors here, which also makes it hard to understand what different types of interventions are needed.

Then when there are similarities with other areas of health that have been studied and we have some real challenges of understanding what works, then you start having other difficulties in saying "Should we just assume something on this way that it won't work or it will work or this and that?" That's defined as research, and unfortunately, that we don't know all the answers.

What we have here is a platform to get those answers, and it's going to be a continuous journey. Dr. Lewis highlighted some examples in different areas of health in which for many years we had assumed something as being so-called dogma, and it turned out when you did the larger study, the dogma was not quite right. In fact, it was the opposite answers here.



So just from the Q&A and the conversation that's in the dialogue here, it's very clear that there are no easy answers. Everyone's committed to get the best answers. I think this is going to be a continuous process with the platform for RECOVER.

Also, I want to thank everyone for reaching out and being very strong advocates in terms of the importance of PASC and Long COVID. I wish we had a consensus on everything. I think the difficulty with PASC and Long COVID is that there's not 100% consensus for most everything. I think in some cases we get to 51% and say that's consensus, but it's not a consensus for every component, and it's certainly not close to 100%. So, I think that underscores why the efforts that we have here are so important.

### **Q. What are the five PASC symptom categories?**

**Response:**

**Ms. Sutton:** The five symptom areas for the RECOVER clinical trials are:

- **Viral persistence:** When the virus that causes COVID-19 stays in the body and causes the immune system to overreact.
- **Autonomic dysfunction:** Dizziness, fast heart rate, shortness of breath, upset stomach, or other changes in body functions that happen automatically.
- **Sleep disturbances:** Changes to sleep patterns or ability to sleep.
- **Cognitive dysfunction:** Brain fog, trouble thinking clearly, memory changes, slowed attention, and other symptoms related to brain function.
- **Exercise intolerance/fatigue:** Changes in activity and/or energy level that interfere with daily life.

### **Q. There's good evidence that biochemical signals of inflammation in individuals with Long COVID are not the same in blood and in cerebrospinal fluid. Success of any trial is going to involve documenting improvements in biomarkers such as these. So, have any biomarkers been developed that can reliably be utilized?**

**Responses:**

**Dr. Zimmerman:** There's so much that we still need to learn about PASC. There's so much that we're hoping to learn from the RECOVER cohorts. There are lots of biomarkers and things that are being studied within that space. And then people outside of RECOVER, lots of things are being studied and people are trying to keep up with the literature. I think every week we get an email about something new that's come out with regard to papers that we should be reading and evaluating.

First and foremost, we're very interested in making sure that the success of the trials is defined by patient improvement; meaning how are people feeling and functioning. But you're right in that biomarkers are also going

to be an important part of this. Some of those, if we're thinking about inflammation or if we're thinking about viral persistence, some of those things we might be able to use from prior disease processes, for example; or if we're thinking about reactivation, can we measure Epstein-Barr virus at the beginning and then at the end? So, some of the things are going to be in existence from what we already know and we'll learn whether they're improved or not as we go through the course of the trials.

There are some more specific things that people are looking at, such as measuring viral persistence, for example. There's an assay that has shown some differences in the spike protein antigen between people who have PASC and people who don't have definitions of PASC, and we're hoping to incorporate some of these things within the trials themselves. But there are lots of things still to learn and lots of opportunities out there. I'm interested in people's thoughts and ideas, and I also want to make sure that those biomarkers are aligning with how people are feeling and functioning.

**Dr. Hernandez:** One of the things to note is that through the whole RECOVER Initiative, including the clinical trials, there are these tensions of so many unknowns, like trying to understand exactly what's happening or causing Long COVID with the tension of "Hey, we need answers now. We need interventions so we'll improve someone's health, their function, their quality of life." The key question is, how do we do things in parallel? Having all this available to develop some of the answers is critical because I don't think anyone in this community is really excited about serial answers that take decades. So that's why there's so much effort to do things in parallel with a multipronged strategy with different platforms for different areas of Long COVID.

**Ms. Cerda:** I can say that during the process, I did give my input and the fact that although it may be difficult for me to do an exercise intolerance exam, I would do so because of my deep desire to have a treatment or a remedy. So as Long COVID patients, I would say a majority of us are willing to go back and forth for testing so that we can get closer to a treatment or a cure. There's a willingness there that perhaps I would not have in other cases; but there is, again, a heightened sense of wanting to resolve some issues around being able to exercise a little bit more, which would be helpful to me.

Also, I have to say that most important would be some of the brain issues, given that we have challenges with memory, fog, memory loss, stuttering. I never stuttered in my life. And I forgot to mention the other important issue is anxiety. I never had an anxiety attack in my entire life and all of a sudden I've had a couple of them. They're very disconcerting and I would like to find some form of treatment. So, there was a willingness from a majority of the patient population to undergo testing and trials to get closer to some form of treatment.

### **Q. Will these trials be listed on [clinicaltrials.gov](https://clinicaltrials.gov) as well?**

**Response:**

**Ms. Sutton:** Yes, each trial will be listed on [clinicaltrials.gov](https://clinicaltrials.gov).

**Q. How many clinical trials does RECOVER plan to begin over the next 2 years?**

**Response:**

**Ms. Sutton:** The RECOVER Initiative plans to launch four platform protocols for clinical trials studying 11 interventions by the end of 2023.

**Q. How can we, the community, help in research? I belong to a large Hispanic community. Do you have clinical trials in Spanish or any other languages?**

**Response:**

**Ms. Sutton:** All clinical trial materials will be available in Spanish, and we'll work with community partners to identify diverse participants in the site communities.

**Q. Please comment on the Yale Medical School upcoming research giving Paxlovid to Long COVID patients. Are there clinical trials planned on Paxlovid as a treatment?**

**Response:**

**Ms. Sutton:** The interventions to be tested in RECOVER will be announced via a press release and study records will be on [clinicaltrials.gov](https://clinicaltrials.gov).

**Q. Has the NIH changed the current exercise and cognitive training trials due to patient advocacy and recent news coverage?**

**Response:**

**Ms. Sutton:** The exercise intolerance protocol is undergoing revisions and will take patient feedback into consideration.

**Q. Are you reviewing current ongoing clinical trials at academic medical centers to be sure you aren't doing redundant work?**

**Response:**

**Ms. Sutton:** We are staying in close touch with both the current RECOVER observational cohort study and other investigators so that our work can complement each other.

**Q. Will the recruiting for the trials draw from the patients already enrolled in RECOVER or will it be a separate effort?**

**Response:**

**Ms. Sutton:** Many sites for the clinical trials are also part of the RECOVER longitudinal cohort study. Participants at those sites who may be a good fit for the clinical trials will be contacted by their study teams.

**Q. What onsite expertise will be available at each site to ensure that individuals meeting criteria for Long COVID *and* ME/CFS are appropriately identified, in part but not solely a question of PEM. Will Long COVID subjects meeting criteria for ME/CFS be excluded from all trials?**

**Response:**

**Ms. Sutton:** Each trial will have its own set of inclusion criteria and will study symptoms that began after a patient had COVID-19.

**Q. What strategies do you plan to employ to identify individuals who have Long COVID to recruit for the clinical trials?**

**Response:**

**Ms. Sutton:** All recruitment for the clinical trials will be based at the trial sites. RECOVER will provide recruitment materials and work with community partners to identify people in the communities with Long COVID to include a diverse group of trial participants.

**Q. How is the community helping educate the general medical community on PASC? Our family continues to seek care and encounter medical providers that have no clue and are harmful to patients reaching out for care.**



**Response:**

**Ms. Sutton:** RECOVER holds regular [webinars](#) to provide updates to the scientific community about progress, and as study results are available, the study teams will publish findings in academic medical journals.

## **Webinar Slides**

To request a copy of the R3 Seminar slides, please email [RECOVER\\_ACC@rti.org](mailto:RECOVER_ACC@rti.org)

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- Frequently Asked Questions about RECOVER and PASC: <https://recovercovid.org/faqs> 
- CDC information: Information for the general public and for health care providers about Post-COVID Conditions: <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/>
- For medical/scientific terminology: <https://medlineplus.gov/healthtopics.html>