

Responses to Participants' Questions

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

This document provides responses* to questions raised by seminar participants related to the following panel at the R3 Seminar *RECOVER Observational Studies Consortium: Where we are and where we are headed* held on January 23, 2024:

- ***The Adult Cohort***
Igho Ofotokun, MD, MSc
- ***The Pediatric Cohort***
Melissa Stockwell, MD, MPH
- ***The Autopsy Cohort***
James R. Stone, MD, PhD
- ***RECOVER Representatives***
Brittany D. Taylor, MPH
- ***Moderator***
Claire Quiner, MPH, MCP

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. How has patient representation enhanced RECOVER?

Response:

Ms. Taylor: Ensuring that there are patients as a component of representatives in RECOVER allows an opportunity for the lived experiences to be heard in real time. It sheds light on what patients and individuals experience as a result of having Long COVID and informs researchers or scientists, the leaders of RECOVER, on things that they might not have otherwise been aware of. We are informing Long COVID research with projects outside of RECOVER. Just last week there was a US Senate hearing on Long COVID where we had caregivers representing the RECOVER initiative, sharing their experiences, insight, and feedback on their experience thus far with RECOVER, but as a Long COVID patient as well.

We also contributed to the National Academies Symposium that took place last year where we shared experiences from the advocacy standpoint as a patient and also as caregivers, and that in turn is helping inform RECOVER. It also informed the process and launch of the clinical trial component of RECOVER. I think being able to inform pretty much all facets of how Long COVID affects patients and caregivers and the communities that have been disproportionately affected, it's helping to inform RECOVER as a whole.

As an example of a small impact, the National Community Engagement Group (NCEG) ensured that representatives were aware of the ADA status where you can receive disability for having Long COVID. Not all representatives were aware of that, and the NCEG made sure to send that information out and point them in that direction. In conjunction with that, we informed methods of information delivery and how it was a bit over burdensome in the beginning, with the flow of information coming from RECOVER and the need to slow that down and better categorize that. And then having patients continuously share their experiences with their providers and bringing that back to RECOVER to the researchers and the leadership, has been critical to RECOVER.

Q. How can RECOVER infrastructure be leveraged by other researchers?

Response:

Dr. Ofotokun: The data that has been collected from what is almost 15,000 people in the adult cohort, 20,000 in the pediatric cohort, the autopsy cohort, it's a huge dataset. So these are history, social demographic data from the participant samples of all types, such as blood, peripheral blood smear, swab from the nose, saliva, tons and tons and tons of specimen and data that are linked. It is, perhaps, one of the most valuable assets for understanding the mechanism of disease. All of this data is available to the public and to researchers. And so there's a mechanism, there's what we'll call an Ancillary Study team that receives a concept for a study. It's a very simple process, a concept of no more than three to five pages. It's submitted to this group and they review it for the scientific value, and this committee also includes patient representatives and the community. And then once that review is done—usually it's a very fast process that takes less than two weeks—and it's approved, then a mechanism is set in place for you to assess either the data, the specimen, or both.^{1,2}

¹ RECOVER research data from the publication "[Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection](#)" [↗](#) are available as a de-identified datafile consistent with NIH data sharing policy. Individuals who would like to access the datafile must review the Data Use/Sharing Principles and Code of Conduct for the RECOVER Data Gateway and complete the [datafile request form](#) [↗](#). Once the form is complete, requests will be reviewed and additional information to obtain the data will be provided to requestors.

² NIH is also soliciting applications to support studies that use patient data and samples of bodily fluids (biospecimens) already collected by RECOVER researchers. Research proposals are due March 22, 2024. Applicants to this research opportunity announcement (ROA) must be investigators at research sites already supported by RECOVER. See the [ROA](#) [↗](#) and application requirements at [recoverCOVID.org](#) [↗](#). Information about additional data sets and funding opportunities will be announced on [recoverCOVID.org](#) [↗](#) when available.

Q. How do observational studies form the basis of the clinical trial component of RECOVER?**Response:**

Dr. Ofotokun: Thank you for asking that question and thank you for the audience members that have asked that question. This really emphasized the value of incorporating the community and patients into RECOVER. We've heard from our community what they want, and I think the desire of the community is the true north star of the RECOVER Study. We want to find a way to diagnose the condition very accurately. We want to find a way to prevent it. We want to find a way to treat it, and the observational cohort is really the beginning of that process. Aggregating a lot of data that will help us to understand exactly what is Long COVID, how do we diagnose it, how do we understand the severity, what types of Long COVID do different people have? This information informs the type of clinical trials and treatment trials that we will be undertaking.

And the direct answer to that question is yes, clinical trials have started. There is RECOVER-VITAL, which is actually offering treatment. There will also be RECOVER-SLEEP, RECOVER-Autonomic and other clinical trials [Note: information as of time of seminar]. A lot of the information that inform the design of these clinical trials come from the knowledge that is coming out of the Observational Study. And this is what we hear from our community, from our patients, our participants, that they need treatment, and this is why we do this. We do the observational studies not because we just want to observe people, we collect this data so that we know what type of treatment to design for this condition. One of the next seminars will focus on these clinical trials that are now currently ongoing to treat patients with Long COVID.

Q. Are Long COVID patients who've met diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) being tracked?**Responses:**

Dr. Stone: We would certainly track that information within the autopsy cohort.

Dr. Ofotokun: Yes. So, remember I said in my presentation that there are different phenotypes, different subtypes of Long COVID. We are taking pains to understand all of the different phenotypes, all of the different subtypes and strains, and this is also being carefully tracked, and I think we have a paper that is nearly done to describe our findings in the adult cohort.

Dr. Stockwell: For the pediatric cohort, we have been updating our Tier 2 symptoms. We had some of the symptoms related to me ME/CFS, but are also making sure that we are adequately capturing particularly post-exertional malaise since that's something that can affect those with Long COVID, including children as well, which can be very devastating. We want to make sure that we're adequately capturing that both in our Tier 2 and then also in our Tier 3 studies as well. I did see another question just about Mast Cell Activation Syndrome (MCAS), I just want to answer that as well. We also do have some questions and are actually adding more to really make sure that we are capturing MCAS in the pediatric cohort.

Ms. Quiner: I previously served on a committee that was supporting modifications of the protocol early on, and I do note that there were additional questions and parts of the protocol that were modified to ensure that the diagnostic survey for ME/CFS was being implemented more appropriately, so that is a subgroup that's being tracked and studied in addition to what the panelists have said.

Dr. Stockwell: To add one more thing, in terms of the patient representative, parent representatives really are very much embedded into the coordinating committees and we actually get a lot of incredible information in terms of understanding how do we need to change the protocol, what our families are feeling, and really they are our eyes in the community as well as active members of the protocol changes and as we are rolling out different phases, so very much what Brittany said, very much integrated into the protocols and into the coordinating committees.

Q. Are you planning on studying small fiber nerves and skin and blood vessels? Are you planning on studying autonomic ganglia? Are there any initial observations from the study to date?

Response:

Dr. Stone: Yes. All of those are being studied as part of the autopsy cohort. There are obviously ancillary studies going on outside of RECOVER on those issues as well, but certainly within the autopsy cohort those will be studied. We don't have observations to date that we can share at this point. It's still ongoing and we're very early in the process. I know there were a lot of questions about four years of enrollment for autopsy, and the truth is fortunately most patients with PASC aren't dying quickly. So that's why it takes four years for us to get adequate numbers of the right types of patients enrolled in the autopsy study. We want to be very careful, enroll the right types of patients so that we're able to adequately answer the questions for all the different forms of PASC that are out there.

Q. On the disease trajectory slide, the chart seems to show that symptoms reduce the Quality of Life (QOL) and the QOL initially improves, but symptoms increase, and the disease burden begins to increase around 300 days post infection. Do you have any thoughts on what this means?

Response:

Dr. Ofotokun: Thank you so much for asking that question. What that paper seemed to describe, and this is what we see in real life situations, is that the disease condition waxes and wanes, so there are times when people seem to improve and then it comes back again. When we think it's gone, it's not gone and we would hope it would go away, but the experience is that it goes up and down, and the duration, the lapse, we don't quite understand yet the gap between the fluctuation of the symptoms. What we're seeing in majority of our patients is that it waxes and wanes, and a year later, a majority of people have symptoms, not symptoms alone, but symptoms that are debilitating and affect their quality of life.

Q. When will the study end? Are all the cohorts ending at the same time?

Response:

Dr. Stone: The official end date for RECOVER is May 2025. Some activities are being extended beyond this date.

Q. What is the justification for a 4-year enrollment for the autopsy cohort as opposed to the shorter enrollment periods for the other cohorts?

Response:

Dr. Stone: The vast majority of patients with PASC fortunately don't die from PASC. Thus, it takes longer to enroll patients in the autopsy cohort.

Q. What is the infection timeline for enrollment?

Response:

Dr. Stone: We are enrolling 15 days or more from infection. We don't enroll patients less than 15 days from infection.

Q. Do autopsy studies include the connective tissue/fascia?

Response:

Dr. Stone: Yes, connective tissue is being studied.

Q. Does the PASC positive cohort include any patients who were not originally hospitalized?

Response:

Dr. Stone: Yes, we have enrolled patients who were not hospitalized.

Questions about Clinical Trials

There were several audience questions about plans for RECOVER clinical trials. As plans are currently evolving, we have not provided answers to these questions. Please see [RECOVER Clinical Trials | Home \(recovercovid.org\)](https://recovercovid.org) for information and announcements about the clinical trials.

Webinar Slides

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

To Learn More

- Information about RECOVER research and to volunteer for studies: <https://recovercovid.org/research>
- Frequently Asked Questions about RECOVER and PASC: <https://recovercovid.org/faqs>

RECOVER RESEARCH REVIEW SEMINAR

RECOVER OBSERVATIONAL STUDIES CONSORTIUM: WHERE WE ARE AND
WHERE WE ARE HEADED

January 23rd, 2024
12:00 – 1:30 PM EDT

- **CDC information: Information for the general public and for healthcare providers about Post-COVID conditions:** <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/>
- **For medical/scientific terminology:** <https://medlineplus.gov/healthtopics.html>