

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 *Measuring the Frequency and Burden of Symptoms Following SARS-CoV-2 Infection* held on October 25, 2022:

- **Presentation 1: *The Symptom Burden Questionnaire™ for Long COVID: A New Patient-Reported Outcome Measure***
Sarah Hughes, PhD
- **Presentation 2: *Development of the RECOVER Adult Cohort Survey Instrument***
Leora Horwitz, MD
- **Presentation 3: *Bothersomeness of Incident Symptoms After COVID Questionnaire***
Nedra Whitehead, MS, PhD
- **Discussant: Sharon Sayad, PhD, MHS**

All Presenters: Questions and Responses

Q. I'm wondering if you have explored use of the Symptom Burden Questionnaire™ for Long COVID (SBQ™-LC) with people who don't already identify as having Long COVID. Is this a tool that could be integrated into monitoring of people who have had COVID-19 to assess for new onset of Long COVID?

Response:

Dr. Hughes: As part of the UK government-funded Therapies for Long COVID Study, we'll be undertaking further validation in a clinically confirmed cohort of individuals with Long COVID and matched controls. This work will allow us to establish thresholds for minimal important changes to the SBQ™-LC and will support the monitoring of individuals for new onset Long COVID.

Q. I assume there are similar surveys for chronic fatigue syndrome. How do they compare?

Response:

Dr. Whitehead: We haven't compared the Bothersomeness of Symptoms Questionnaire to surveys on chronic fatigue syndrome.

Dr. Hughes: We haven't compared the SBQ™-LC with patient-reported outcome measures developed for chronic fatigue.

Q. For the RECOVER adult population, I see that the requirement for enrolling is that the person has had COVID. Is there an expectation for the share of the enrollees who have Long COVID?

Response:

Dr. Horwitz: Actually, there isn't even a requirement to have had COVID, as we also need people who have not had COVID to participate. To answer your question, though, no we don't have a preset number of people with Long COVID we're trying to enroll. Because the first aim for RECOVER is to determine how many people have Long COVID, we can't prespecify a number.

Q. Outside of the RECOVER Initiative, there are many researchers and applied epidemiologists who are coming up with their own survey and surveillance instruments, resulting in a high amount of variation in methodological approaches. Are any of the surveys or instruments discussed today available for other researchers who don't want to reinvent the wheel? If not, are there plans to make them available in the near future?

Response:

RECOVER administrative team: Yes, you can find the whole set of RECOVER instruments at <https://recovercovid.org/protocols>. We're also working with other agencies to publicly post the technical specifications.

The Bothersomeness of Symptoms Questionnaire is available by emailing RECOVER_ACC@rti.org.

Dr. Hughes: The SBQ™-LC is freely available to academic researchers and publicly funded clinicians and at a cost for commercial entities. The SBQ™-LC can be obtained at <https://licensing.micragateway.org/product/the-symptom-burden-questionnaire-for-long-covid-sbq-lc>. You'll need to complete a license agreement. Also, the Mapi Research Trust is supporting the development and distribution of translations of the SBQ™-LC and migration to electronic platforms for digital delivery. More information on translation and e-versions is available at <https://eprovide.mapi-trust.org/instruments/symptom-burden-questionnaire-for-long-covid>.

Q. Some symptoms and tests seem to be different depending on the phase of the disease; for example, the acute, intermediate, autoimmune, and chronic phases. As symptom profiles are developed to characterize this disease, will we take into consideration the phase of the illness?

Response:

Dr. Horwitz: This is a really important point and very true. People certainly have very different symptoms in the acute moment of infection than they do perhaps 6 months or a year later. Consequently, we prioritize timing in our questions. When a participant shows up for enrollment, if they've had the infection in the past or a negative test in the past, we try to distinguish at what time periods they've had various symptoms. We're also reserving half the slots in our study for people that we enroll within 30 days of infection. This doesn't have to be the first infection. It could be a repeat infection. This way we can capture what symptoms people are having right away when they're having COVID and how these symptoms compare with the type of symptoms they get later on. It also allows us to collect biospecimens—such as blood tests, urine, and saliva—and other things from people in the moment of infection, which is very important in helping predict what kinds of things happening in that initial infection are related to later stage.

I'm going to take this moment to do a public service announcement to say that we're still looking for these types of enrollees; that is, people who had infection within the past 30 days. In fact, we've completed enrollment for people who had infection in the past. We had tremendous interest. We filled those slots very quickly. But we still have space in our study for people who had infection within the past 30 days, even if it's a repeat infection. And we still have some slots for people who've never had COVID.

Q. Please discuss how the US information compares with what other countries have learned, such as from surveys conducted in the UK.

Response:

Dr. Hughes: As Dr. Sayad spoke about in terms of the CDC survey and the household survey, we recently had the latest release from the Office of National Statistics in the UK, which looks at self-reported Long COVID with symptoms persisting beyond 4 weeks. I believe that with the US survey it was around 7% of the population that are still experiencing symptoms beyond 4 weeks, whereas in the UK the estimate is that about 3.5% of the population are still experiencing symptoms of Long COVID beyond 4 weeks, which equates to about 2.3 million people.

Q. What do the speakers feel the role of the point-of-care clinician is or should be relative to completion and validation of the surveys as compared with the full self-report surveys?

Response:

Dr. Hughes: This is an interesting question. I'm hoping I've understood it correctly in terms of the role of the clinician within self-report. Patient-reported outcomes (PROs), by definition, are reports from the patient without interpretation by anybody else. While the patient perspective is key to establishing content validity—does the instrument reflect what is most important about the target construct (in this case, Long COVID) from the patient perspective—it's also important that clinician views are captured to ensure the instrument has good clinical utility. That is, is it providing useful information that can support clinical care from a patient-clinician communication perspective and from a treatment decision-making perspective. We also know that PROs can play a role in terms of supporting clinicians with triaging patients. There is evidence from other specialties where electronic delivery of PRO measures is being used to support patient management. In terms of the validation, if there are studies going on to look at validation, clinicians can encourage patients to take part. Certainly, in terms of the development of survey instruments, there's a role for clinicians early in the development phase; for example, in the qualitative phase in terms of ensuring that the items are relevant to their clinical experience and will have good utility once they translate into the clinic.

Q. If researchers or applied epidemiologists are developing their own instruments, is there core guidance that should be followed with respect to case definitions and symptom domains, for example?

Response:

Dr. Whitehead: The field will get to the point where there's a consensus set of questions. In the moment as you're developing a questionnaire, it's important to look and see if you're actually adding anything new or is there an existing questionnaire that will meet the need. I don't think we're confident yet that we know everything we want to ask. Consequently, each questionnaire adds a little more. As Dr. Hughes mentioned, the World Health Organization has developed a consensus list of outcomes that are important to measure, but not the questions per se. Eventually, we'll be at the point where we have a firm set of questions for Long COVID, which is similar to the types of questions we have for many other conditions.

Dr. Hughes: I mentioned the post-COVID core outcome set in my presentation, which was a consensus exercise. This was a Delphi exercise undertaken through 2022 where they first worked out the domains; that is, what is important to measure in the post-COVID condition from a multiple stakeholder perspective. The second part of that Delphi exercise involved working out how to measure these domains. This guidance has been published recently on the Post-COVID Condition Core Outcomes website at <https://www.pc-cos.org>. As Dr. Whitehead noted, this will likely evolve as our understanding of Long COVID evolves and the measures are also likely to evolve. But as a starter, these are core recommendations that have just been released, with the aim of reducing study heterogeneity in the future.

Q. Are you seeing progression of symptoms, especially for those who caught the virus in the first wave in 2020?

Response:

Dr. Horwitz: We're still in the recruitment phase. We're trying to be good citizens and not peek at our data constantly. So, I can't speak to the differences that we're seeing yet among people who had infection early on and those who had infection later. However, there's a lot of literature on that and it seems as though some of the newer variants, like Omicron, plus vaccination may lead to less frequent incidents of Long COVID. This isn't to say it doesn't exist with them, and there's certainly plenty of people who have Long COVID who've had newer variants or who've had vaccinations. But it seems that there are probably differences across time, likely as a combination of the variant and the treatments and vaccination status and so forth.

Q. The current study protocol doesn't collect severity and frequency of post-exertional malaise (PEM) data. What tools or instruments are you considering to sufficiently capture these data to identify these important aspects of PEM?

Response:

Dr. Horwitz: That's a good question. Currently, we use post-exertional malaise—for example, does someone have it at all—as an important trigger for further testing. It doesn't matter to us how severe it is. We just feel like that's so specific to ME/CFS that we just want to explore more with those participants. However, we are doing a big review of our survey instrument now that we have about 10,000 participants and trying to understand clearly which questions are missing, as we have new data coming out about new symptoms, and which questions may not be that informative that we could swap for something else. As Dr. Hughes noted, our protocol is very adaptive, as

is her protocol. One of the questionnaires we're looking at is the DePaul Symptom Questionnaire Short Form (DSQ-SF), which is six items looking at ME/CFS. It also has two questions about PEM. One question we already have in our instrument. The other question is slightly different and is about muscle soreness after exertion. Both these questions include a severity and frequency score. It's possible that we'll be able to add these items in with their severity and frequency. We're looking at the DSQ-SF because it's well validated and short, and burden is an important consideration.

Q. What are the most common neurological symptoms reported by individuals with PASC? Do we have any evidence regarding specific etiology of those symptoms?

Response:

Dr. Horwitz: If you consider smell and taste to be neurologic symptoms, which we do, that's the one with the most difference between people who've had infection with COVID and those who haven't. The increase in risk as compared with people with Long COVID is very substantial and clearly related to COVID, but it's not the most common symptom that people report. The most common neurologic symptom that people report is trouble thinking. Sometimes they call it brain fog or trouble concentrating. Consequently, in RECOVER we have a whole battery of instruments we're using for people when they report trouble thinking. We ask a core set of additional questions that comes from the Neuro-QOL (quality of life) that we talked about, but we also do formal cognitive testing because it's important for us to disentangle what kind of trouble thinking that people are having. There are different kinds of processing and that helps us try to localize where in the brain things are happening. This will help us answer the last part of your question, which is why is that? We don't know yet, but because we're doing all these very specific additional tests and things like brain MRIs and even lumbar puncture, we should be able to answer these types of questions in the future.

Webinar Slides

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

To Learn More

- Information about RECOVER research and to volunteer for studies: <https://recovercovid.org/research>
- Frequently Asked Questions about RECOVER and PASC: <https://recovercovid.org/faqs>
- CDC information: Information for the general public and for healthcare providers about post-Covid conditions: <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/>
- For medical/scientific terminology: <https://medlineplus.gov/healthtopics.html>