Transcript

Lisa Newman

Good afternoon. I'm Lisa Newman, contact Principal investigator for RECOVER at the Administrative Coordinating Center and the moderator for today's webinar. Welcome to the RECOVER Research Review or R3 Webinar. The goal of this webinar series is to catalyze the formation of a scientific stakeholder community within and beyond the RECOVER consortium and foster a shared understanding of the state of the science and to provide an on enduring educational resource for RECOVER investigators, the broader scientific community, clinicians, patients, and other public stakeholders.

I want to start by thanking everyone who submitted questions in advance. Please submit any questions that arise today using the Q&A feature in Zoom. After the presentation, we'll answer as many questions about today's topic and presentations as possible. Some questions may also be answered within the Q&A during the seminar. We have an impressive speaker panel today. We decided to narrow the focus of this seminar to focus on how symptoms following SARS-CoV-2 infection have been measured, the importance of understanding the scope of symptoms, and patient perception about the burden of various symptoms.

Our presenters are Dr. Sarah Hughes, Dr. Leora Horwitz, and Dr. Nedra Whitehead. Dr. Sharon Saydah will synthesize the information presented by the panelist and guide the initial discussion with them. Dr. Sarah Hughes is a research fellow at the Center for Patient Reported Outcomes Research Institute of Applied Health Research at the University of Birmingham. She has over 20 years clinical experience in the UK's National Health Service. Working across multiple conditions, her research interests focus on patient reported outcomes and their development, validation, and implementation in research and in routine health and social care. She maintains a special interest in the measurement of patient reported outcomes associated with listening and communication. Her clinical background continues to drive her research efforts to ensure the patient perspective is placed at the center of healthcare decision making and delivery of care. Dr. Hughes and her team developed and validated a symptom burden questionnaire for Long COVID. She will discuss development and validation of the questionnaire and patient reported outcomes.

Dr. Leora Horwitz is director of the Center for Healthcare Innovation and Delivery Science at NYU Langone Health, Director of the Division of Healthcare Delivery Science in the Department of Population Health at NYU School of Medicine and is a practicing internist. Her work focuses on proving the safety and quality of healthcare delivery. She is co-PI of the clinical science core for the NIH's RECOVER Program to study post-acute sequelae of SARS-CoV-2. She is responsible for the adult cohort study. She also conducts federally funded research on value and healthcare, has developed quality measures for the Centers for Medicare and Medicaid services, and co-directs the training program in population health and healthcare delivery. Dr. Horwitz will talk about methods to assess symptoms among the RECOVER adult cohort participants. And finally, Dr. Nedra Whitehead is a senior

epidemiologist and medical geneticist with more than 25 years of professional experience in genetics, epidemiology, registries and surveillance. She leads and contributes to a wide range of studies in epidemiology and genetics, including longitudinal observational studies, surveillance of genetic conditions, and evaluations of genomic and biomarker test. Dr. Whitehead served as the contact PI for the RECOVER Administrative Coordinating Center for 18 months.

As the last presenter, she will discuss development of a questionnaire by the Administrative Coordinating Center to capture incident symptoms and their bothersomeness after COVID infection. Dr. Sharon Saydah is an epidemiologist and senior scientist at the US Centers for Disease Control and Prevention and commander in the United States Public Health Service. She is currently the acting team lead for the post-COVID conditions team and leads investigations and research on the natural history of SARS-CoV-2 infection, including prospective cohort studies focused on post-COVID condition and surveillance for post-COVID conditions. Following the presentations today, Dr. Saydah, our discussant, will conclude by synthesizing the presentations, asking a few questions to just start the discussion, then we will open it up to questions from the audience. Please welcome all of our speakers. Now, I will turn it over to Dr. Hughes.

Dr. Sarah Hughes

Good morning, everyone. I'm delighted to be here. My name is Sarah Hughes, and I'm coming to you from the UK at the University of Birmingham. I'm really delighted to be able to speak to you today about work we undertook as part of the therapies for Long COVID study or the TLC study, which is one of the UK's major NIHR funded Long COVID epidemiological studies. So, I'd just like to say a sincere thanks to our patient partners and the TLC patient and public involvement group, the Long COVID support groups in the UK who are instrumental in supporting this research, our research participants, our collaborator, [inaudible 00:05:43] Limited, and of course our funders, the National Institute of Health and Care Research and UKRI.

So, this is just my funding statement and disclaimer. I think now we'll get started into the heart of the presentation and I think it's always useful to start with a definition and in this case, patient reported outcomes. So, what exactly do we mean when we talk about a PRO or a patient reported outcome? And quite frankly, it's any report of the stages of a patient's health condition that comes directly from the patient and without interpretation of their responses by anyone else. It's really the patient's own assessment of the impact of their health condition on their quality of life. And these are typically measured using patient reported outcome measures or PROs, which are self-completed questionnaires that have been rigorously developed according to specific regulatory guidance and psychometrically validated.

When we talk about patient reported outcomes in Long COVID, we're faced with some very specific challenges relating to the novelty and complexity of Long COVID. Specifically Long COVID is a new condition. We still have much to learn about Long COVID or PASC as it's often called. And the complexity means that we have a

large number of heterogeneous symptoms that are relapsing and remitting in their character and also can vary from person to person. So, when you're trying to select a measurement instrument to capture these aspects of this condition, it can be quite challenging. And I think it's also worthwhile noting that PASC is also called Long COVID. And Long COVID is a term that was developed by patients as a condition that was named by patients for patients in response to the cry for support and acknowledgement and validation of this condition that many patients were experiencing.

So, when we talk about PROs as a reflection of lived experience, we talk about Long COVID. And that's why we've called this new patient reported outcome measure the symptom burden questionnaire for Long COVID. So, the aim of the study was to develop and validate a Long COVID specific patient reported outcome to measure symptom burden. And I'll come along to the rationale and the justification for this piece of work in due course, but I think it's worthwhile sort of setting out. When we sat down to try and look at what we needed to achieve by developing a PROM, we had a very specific brief. We wanted the measure to be compliant with regulatory guidance. There's very clear guidance on the development of patient reported outcomes from the FDA, also other organizations such as the COSMIN Initiative, [inaudible 00:08:41], and ISOQOL. With such a large number of symptoms, we knew such a measure needed to be comprehensive, particularly for the TLC study, which was seeking to characterize the symptom burden Long COVID with the aim of developing some symptom clusters and phenotypes.

With such a large number of symptoms, however, we were also very cognizant that there could be significant participant burden associated with completion of such a questionnaire. So, we were very mindful that whatever decisions we took around its development that we needed to at all costs minimize participant burden. It needed to be suitable from remote data capture because the TLC study is a decentralized study in which all symptom burden, self-reported symptom burden information was being captured by a patient's own devices through the Aparito Atom5 platform, which is the picture you can see on the slide here. We also wanted a clinical alert system. In case patients or participants were reporting symptoms of clinical concern, we wanted a way to flag that through to our nurse led support service within the TLC study. And lastly, we wanted to create a measure that was flexible and that would endure. Bearing in mind with the novelty of Long COVID, it needed to be able to evolve as our understanding of Long COVID evolves.

So, in terms of the mixed method study that we undertook, this is a very quick overview. It's a multi-phase study. It started with a symptom review drawn from the literature from which we've developed a conceptual framework and constructed a draft questionnaire. We then took this forward for cognitive debriefing in which we evaluated the content validity. That is what's most important to patients or people with lived experience in terms of capturing symptom burden. And then once we've undertook that, we went through to some further field testing where we undertook an initial psychometric evaluation to describe the new PROs measurement properties in

terms of its reliability, its validity. And then the usability testing that was specific to the TLC study, we did some further testing to make sure when we deployed it within the app, that it was working to specification.

So just very quickly, in terms of that initial step, the symptom and measure review, this was work that was undertaken by my colleague Dr. [inaudible 00:11:05] here at Birmingham. And it was a rapid review of the literature to identify commonly reported symptoms in Long COVID. And we use that to develop a conceptual framework of the various symptom domains that we felt would be necessary to include in a measure. But we also used it to understand whether a new measure would actually be needed. PRO development is timely and resource intensive work. And so, we wanted to know whether there would be possibly an existing PROM that we could use within the TLC study.

So, we identified a range of measures, some of these were disease specific measures that were used in Long COVID clinics and the NHS, the National Health Service in the UK, and also surveys that had been developed specifically for some of the other Long COVID NIHR funded studies in the US, as well as disease specific measures of symptom version for other conditions. So, this would be cancer and flu. And what we found was when we mapped the items from these measures across to our conceptual framework, then on average only about 35% of the symptoms were covered off by these measures, a range of between 27 to 64%. So, we felt that provided the justification we needed to take the step to develop rapidly a new patient reported outcome measure for deployment in the TLC study.

So, we started with an item pool of 97 items and used that to construct the questionnaire and then we took that forward for content validation. So, this was a qualitative element to the study that included two parts. First of all, a clinician survey that included clinicians from a range of specialties including general practice, public health, respiratory, and also experts in Long COVID and clinicians working in Long COVID clinics. They provided information on terms of providing clarity to the items, suggesting additional items, but no items were removed on the basis of this survey because we felt that this is really a call that needs to come from the patients themselves.

So, we also undertook cognitive debriefing interviews with 13 patients or persons with lived experience. And in that, we asked them about the relevance of the questions to their experience, the comprehensiveness. We're recapturing everything that was important to them about their lived experience of Long COVID, was it acceptable, Were the questions phrased in such a way that they weren't overly sensitive, were they clear, and was the app itself user-friendly? And what we were expecting with 97 items, we were quite concerned, we thought, "Oh, we're going to take some items out." But actually, it was exactly the opposite that happened that we ended up with an expanded item pool of 166 items grouped into 14 domains. And our participants were very clear in telling us that they didn't mind the length of the questionnaire, they didn't mind the length of the SBQ because they felt that it really helped them to articulate their experience and to validate their experience. And there's a couple of participant quotes here on this slide.

So, once we had a draft version that had been refined through the content validation process, we sent that forward for psychometric evaluation and further refinement. And we did this through field test. We recruited via social media and Long COVID support groups and participants downloaded the Atom5 app to their phone or their device, logged in, provided informed consent, and then were asked to complete remotely the SBQ in its form, the EQ-5D as a measure of health status, and also a demographic survey. We had 906 hits to the URL of which 330 went on to provide informed consent. And of those 330, we had a completion rate with complete data set for 83% of respondents which were 274.

In terms of the demographics, we had a predominantly female population sample. We had self-reported Long COVID, but all had to confirm that they'd had SARS-CoV-2 if they'd had a test. We also recognized that some of our participants had COVID before testing was widely available in the UK. So, we weren't able to supply a test, but the majority were. They were of older age range. The mean age was 45 and very much kind of represented some of the demographics that we've seen reported in some of the other epidemiological studies. We used Rasch analysis, which is a particular psychometric technique based on modern measurement theory to first refine the rating scales to make sure they were working, they were measuring severity, frequency, or interference in a way that met the model criteria, and we also used it to construct the scales to group them into symptom domains that were clinically sensible. And then lastly, we did a full psychometric analysis using Rasch to report the measurement properties for the final version.

Now, I'd love to take the time to go into the Rasch analysis in more detail, but that's just beyond the scope of this presentation. So, I would invite anyone who is interested in learning more to find our paper in the British Medical Journal that was published in April. So, what does the Symptom Burden Questionnaire look like? First of all, it's a multi-domain item bank. And an item bank is simply a pool, a repository of validated questions that have been psychometrically evaluated. You could also describe it as a modular PRO instrument. So, it has 17 standalone scales, so that means each scale could be delivered on its own without any of the other scales. But equally, if you wanted to measure comprehensively symptom burden in Long COVID, you could administer all of them. The recall period following from discussions with our patient partners was set at the last seven days. And the response scales after Rasch refinement were either yes, no to denote symptom presence or a four-point scale that reported either the symptom severity, symptom frequency, or symptom interference or so impact on an individual's daily activities.

In terms of administering the SBQ, it can be delivered as either a paper-based PRO or as an electronic PRO. So, as we are through TLC doing that through action five, but it can be migrated onto to any ePRO platform. Currently it's available in UK English with translations plan. And in fact, we have started doing some translation work and we've recently partnered with the Mapi Research Trust who will be coordinating all of the translation and ePRO migration work on our behalf. In terms of administering the SBQ as a PRO, our preference is self-completed, but we also recognize that not everyone is able to self-complete a questionnaire. And so, in these

cases, we would recommend that it be delivered as an interviewer administered scale or set of scales. It's not been designed as a proxy measure where a carer or a family member reports on behalf of another. It needs to be self-reported.

The completion time really depends on the mode of delivery and the number of scales that are administered. Within the Atom5 app in TLC, we're able to deliver the complete questionnaire at about eight minutes, but this will vary from person to person. In terms of scoring, each scale returns a sum draw score. So, there's not a global score yet, but the item bank certainly would allow us to do that in future if that was what was of interest to people and researchers. So, we score each scale as a sum draw score, which then gets converted to a zero to a 100 score, and that allows us to compare symptom burden across domains. In terms of interpretation, the higher the score is indicative of greater symptom burden. And we're currently doing another round of data collection within the TLC study with a representative cohort in which we'll be doing some further psychometric evaluation. And in that, it will include determining meaningful change for the SBQ scores. We also undertook a consensus-based workshop to identify clinical alerts.

So, we worked with a panel of experts, these are Long COVID experts and also clinicians and academics, to identify symptoms of clinical concern to rank these symptoms that we would consider to require a clinical alert, agreed on a final list and then we agreed the alert trigger thresholds, which in the case of the TLC study, this was the presence of any of the symptoms included in the blue box. And within TLC, a trigger alert would go through to the dashboard and be picked up by the nurse-led support for follow up. In terms of application, of course, within TLC, this is being used for remote data capture of symptom data to allow us to do further analysis to characterize the symptom clusters associated with Long COVID and do phenotyping. Equally, this approach could also be used and implemented in clinical trials and other treatment evaluations. The SBQ is also available for use by clinicians who require either a comprehensive or a targeted measure of Long COVID symptom burden. And as delivered as an ePRO, this really supports remote monitoring so that we can capture relapsing and remitting symptoms if their people are reporting weekly or using it to report on ad hoc basis. And lastly, with the electronic alert capability, that can be also configured to specific need based on a specific trial or need within routine care.

The Symptom Burden Questionnaire was launched when we published the initial validation paper in the BMJ last April. And since that time, we're delighted to say that it's been picked up by researchers and clinicians in 51 countries. We've now downloaded nearly 400 review copies and we've issued 124 licenses, and that's split roughly 60-40 between clinical. So, for research studies, about 60% and about 40% for clinical use. For anyone who's interested in learning a little bit more about the Symptom Burden Questionnaire, there is a website. You can use the QR code on the screen to go to that website to download a review copy, access for information, or to request a license.

So, just to wrap up and to summarize and perhaps leave you with a few key messages, I think it's really important to stress the important role that PRO measures can play in terms of providing evidence of the risks and

benefits of therapies for Long COVID from the patient perspective. We know there's a real need to find new treatments and new therapies for Long COVID. And in finding and evaluating these from the perspective of what is most important to the person with lived experience, this is a role that PRO can play, whether that be early phase trials, or later phase trials, or within more interventional studies. We also need PRO measures that facilitate cross comparison and aggregation of data sets and to do this on a global basis. And we hope that the SBQ will start to offer a tool to research to allow this particularly as we partner with Mapi Trust to develop the translations and make those accessible to clinicians and researchers.

It is a condition-specific measure of symptom burden. There are very few measures currently available and it has been recommended for use within the post-COVID core outcome set that was announced this month and is endorsed by the World Health Organization. And lastly, we are planning for further work to develop a further measure based on the adult version to offer a measure of symptom burden for adolescents. And we're partnering with another of the NIHR funded studies to undertake this work. And lastly, we hope that because we've tried to plan for the future in designing an item bank, that the SBQ will evolve and provide a robust tool for measuring symptom burden as our understanding of Long COVID evolves. Thank you very much for listening and I look forward to the discussion later. Thank you.

Dr. Leora Horwitz

It's a pleasure to be here today. So, I'm here to talk about the development of the RECOVER Adult Survey Instruments, very similar to the work that Sarah just described. This is for the NIH's RECOVER program. So the overall goal of RECOVER, just to situate everybody for our conversation, is first to understand how many people are getting Long COVID or PASC as a more technically is referred to, why some people get Long COVID or PASC and others do not, what symptoms people feel when they get Long COVID or PASC, how long do people feel sick when they get Long COVID, and what causes Long COVID or PASC to happen? So fundamentally, these are the goals of the RECOVER observational studies. I'm going to talk specifically today about our study of adults to line up with the other work that you're hearing about today. Our adult study is intended to include about 17,680 participants who are adults. The majority of those are people who have had COVID, which means in our case, people who have had a positive test or just had symptoms that are consistent with COVID. Just as Sarah mentioned, many people have not been able to have tests, so they're included as well. We also include people who have never had COVID.

And importantly, for the purpose of today's conversation, every participant in RECOVER gets a set of surveys that they answer every three months for the duration of the study, which will be three to four years. So, what we're going to talk about today is how we think about what questions should be on those surveys. So general principles. First, we define PASC or Long COVID based on what symptoms people have. There is no blood tests for Long COVID. There is no x-ray for Long COVID. This is a patient reported syndrome or set of conditions. And so, our symptoms survey, which we ask every three months, is foundational to defining what PASC is and who has it.

We also have obligations though. One of our aims, as you know, is to define the risk for PASC. And so if we want to define the risks for PASC, we also have to ask about a lot of other things. We need to understand what their original COVID infection was like. We need to understand their vaccination status. We need to understand something about the demographics or the characteristics of the people in the study. What sex they are, gender they are, race or ethnicity they identify with. We want to know about their other diseases, about their habits and behaviors, about their education, about their neighborhoods. We want to encompass both socioeconomic sorts of risks as well as clinical or biological risks. So, we have to capture all of this in our survey set.

So right now, this is what our survey set looks like. We ask people when they come into the study, so at enrollment. We give them a whole slew of different surveys. There's a survey about their demographics, survey about their symptoms, survey about their vaccine status, social determinants, disability status, use of alcohol or tobacco, what sorts of experiences they had during pregnancy, comorbidities, other diseases that they have, the way in which they were treated for their original COVID infection, and whether they're in any trials. And everybody gets at least 152 to 155 questions just on the core set of questions in those instruments. But many of those questions have additional questions that get asked depending on how they answer. It's very similar to the survey that Sarah just described. So, if they say, "Yes, I have X." We might say, "Oh, tell me more about that." Or, "Tell me how severe it is or how frequent."

So, if somebody says yes to everything, they could answer as many as 380 questions. And just as Sarah described, a foundational part of our development of all of these surveys collectively was to make sure we were minimizing these participant burden. We know that people who have Long COVID get easily fatigued, we know that it is hard to concentrate, we know that participating in a research study is already a big commitment. And on top of that, we don't want to make people worse by spending hours and hours on questions. We want to make sure that they're willing to come back again, and again, and again, and again because we want to ask these questions for years. So, we have to be extremely attentive to the overall burden of the surveys on top of the burden of the rest of the study, which involves coming in person, giving blood, having tests on its own. So that's how we sort think about the questions in total.

On follow up, we also ask almost all the same sorts of questions, slightly fewer. We don't have to ask some of the demographic questions again, but we ask all the same PASC symptoms and all the same sort of habit questions. So again, think at about 100 questions at a minimum follow up and as many as 300 something if they have symptoms. So, by way of example, I'll just walk you through one of these, the PASC symptom survey again to be consistent with other topics for today, but this is of course only one of many of the surveys that we use in RECOVER.

Just as Sarah described, we similarly had an intensive development process. In our case, it's very tightly compressed into four weeks last June of 2021. As we were urgently developing this protocol so we could start recruitment as quickly as possible in order to develop the surveys, we had a whole slew of work groups each

focused on a particular topic area including specific organ systems or sort of parts of the body as well as other things like social determinants and habits and so on. Every one of those groups involved a patient representative or an advocate from the community so that we can make sure to hear the patient voice. But then we did some pilot work, we enrolled our first 30 patients, we got extensive feedback from them on how the surveys went and we revised them further.

This is how we were thinking about what to put in the symptom survey back in June of 2021. Back then especially and even today, Long COVID or PASC wasn't formally defined. We didn't have a definition for it yet. And so, since that's our first aim, our first aim of RECOVER is to define PASC and we weren't sure exactly what it was. Our first priority we felt was to capture as many symptoms as we could because we understood already even then from the patient community that Long COVID is not just one thing, not just two things, that people were having all kinds of different symptoms. And so, we wanted to make sure fundamentally that our instrument captured as many of those experiences as we could. So that was our primary goal. And of course, we believe the only way to know what symptoms are important to capture is to ask the people experiencing them. So that's what we drew these symptoms from.

We looked first at the report from the patient led research collaborative, which is an organization led by patients that has focused on Long COVID and put out a survey very early on into the pandemic asking about 257 different symptoms and extensive questions about each one. So, we took that list to start with. We looked as well at the list that had been created by the World Health Organization. Here's a screenshot of some of them. They also had listed a bunch of symptoms. So, we started with that whole long list and we asked our work groups to narrow them and to focus on them and organize them. We also very quickly realized, of course, just because you have symptom doesn't mean it's because of PASC. People have symptoms for all sorts of reasons.

One thing that was apparent to us as we were designing our study in which people come in after having had infection, that we had to capture the timing of the symptoms so that we could figure out what symptoms were already present pre infection and we could figure out the trajectory of symptoms as they wax and lean over time. And since our aim is to define the trajectory or the evolution of the disease over time, we wanted to capture timing for that purpose too. But besides having a symptom or not and knowing when people have had it, there's lots of other things you might want to know about a symptom. You might want to know more about the symptom itself. So, if we ask, "Do you have problems with sleep?" And someone says yes, we might want to know more about that. "Well, what do you mean problems with sleep? Do you have trouble falling asleep? Do you have trouble staying asleep? Do you have trouble waking up too early in the morning? Do you have trouble where you sleep, but you don't feel refreshed? Are you snoring?"

There are many sorts of things you can imagine for any kind of symptom that we might ask that we want to know more about. We might want to know the severity of the problem. So, if the problem that they're having is trouble falling asleep, we might want to know how hard is it to fall asleep? Really hard or only sort of hard? We

might want to know the frequency of the problem. How many days a week is it difficult to fall asleep? We might want to know the burden of the problem. How much does trouble falling asleep affect your quality of life? These are all different sorts of things you might want to know about any of these 250 something symptoms that people may be experiencing. Collectively, these add up to a lot of questions very quickly.

As we are thinking about these issues, we were also thinking, we really want to be able to compare what's going on in Long COVID to the existing literature we have about what's going on with these same sorts of symptoms and other diseases. So, we could try to get an understanding of the similarities and the differences to the ways in which people were experiencing symptoms because of COVID and the way they're experiencing symptoms because of some other biologic process. That helps us get insight into what's actually causing the problems with Long COVID. We also want to be able to characterize the symptoms that people are having in ways that are generally agreed upon so we can compare to other literature and other [inaudible 00:34:55]. So that meant that wherever possible if we were going to be asking additional questions, we wanted to try to use some standardized and validated instruments. Even though those haven't been developed specifically for PASC, they give us that option to compare to literature or to characterize their symptoms.

Finally, because in the way that we design our protocol, we're not just asking questions, we're also doing other tests, we use some of those symptom questions to determine who should have additional testing. So, if you say, "I have shortness of breath." Maybe we want to take a look at your lungs. We might want to, especially to have more information about those sorts of symptoms so we can best identify who's most important to go on and do further testing. So, these big principles were all of the things we were thinking about in our crammed four-week interval in June of 2021 when we were developing the PASC symptoms survey. So, we decided our highest priority is capturing as many symptoms as we can, capturing the correct set of symptoms, and the timing of them so we could really understand what was new and what was not new. And we used those to define to create the definition of PASC. Then we also, we don't want to ignore this question of understanding the severity, the frequency of the burden for these symptoms. We didn't feel like we could ask all of that for every single symptom. So, we prioritize as had standardized instruments, those that were seeming to be most common, those that were prompting for their testing, those that were most problematic to patients. Those are the ones we wanted more information about.

But in many cases, it's sufficient just to have an understanding of yes or no. Do you have hair loss? Yes or no? That actually is really important to know even on its own, even if we don't ask something about frequency, which doesn't make sense or that kind of a symptom. So, I'll just give you one example. If somebody tells us they have headache, then they go on and get this thing called the headache inventory test, which is six more questions. This instrument we like a lot because it actually captures all of these things. It captures severity, captures frequency, and it captures the burden. So, for example, the first question is about how severe it is, how often it's severe. Second, fourth, and fifth questions here are about how much your activities are limited, how burdensome

is it and does it influence your quality of life? And then of course the responses are about frequency. So, we're able to kind of capture all those concepts with this one instrument.

I get a lot of questions all the time about very specific questions. Which question exactly are you using for this and that? Which instrument are you using? So, I just thought I would show you some of how that works. This is pretty technical. For most of you, it's not that important, but I wanted to have it available for those of you who are going to come back and look at this step later. So, what do we ask about? We ask the PROMIS-10. PROMIS is a measurement set that was developed by the US government to create as part of a set of standardized instruments. And it's organized where they know what the average is in the US population as a whole and they've scored and they know and they score it so that the range of it is known. So, we know what proportion of people have different scores. So, we use that as an overall quality of life score.

It has 10 questions that asks about the overall health, asks about the overall quality of life, asks about people's estimation of their physical health, their mental health, their satisfaction with social activities and relationships, their ability to carry out social activities, carry out physical activities, ask about anxiety and depression, ask about fatigue, ask about pain. It's actually a lovely instrument for Long COVID because it captures a lot of these different domains that are important to people. If people answer certain things yes, they may go on to get additional questions. Neuro-QOL, neurologic quality of life, a similar set of instruments is also created by the US government to ask some standardized questions. So, in some cases they'll go on to get additional questions about their ability to think about their exact kinds of physical function things that they can do, their exact fine motor things they can do, and where their pain is. We ask everybody a screen about depression, about suicidality, about anxiety, about trauma not because we think Long COVID is not real, not because we think it's all in their head, but because we understand that Long COVID can influence people's quality of life to such a degree that they may experience some of these other challenges. We want to know that so that we understand quality of life.

In many cases, these will go on if you say yes to additional more formal screening instruments that are all abbreviated on the side are not important to talk about here. We ask about loss in breathing and then we have our core set of about 30 symptoms. Specific sentences are related we think aLong COVID, and we ask about use of hospitalization. Sos our set of 30 symptoms includes fatigue, it includes question about post-exertional malaise, includes questions about weakness, flue-like symptoms, loss of or change in smell or taste pain, which goes on to a set of questions about where the pain is, shortness of breath, cough, palpitations or heart problems, swelling of the legs, gastrointestinal symptoms, which goes on to many more questions. Bladder problems, same thing. Many more questions. Nerve problems, same. Many more questions. Problems with anxiety or depression, problems thinking, problems with sleep. This is a question feeling faint, dizzy, or goofy. That comes word for word from an [inaudible 00:40:47] instrument. Color changes, dry mouth, excessive thirst, and so on and so forth. Vision problems, problems with hearing, problems with hair loss, problems with your teeth, and then some questions

about sexual function and reproductive function. So, this is the sort of core set of the questions that we ask for RECOVER.

I'm happy to say that we have designed this sufficiently with attention to burden that those who are starting the symptoms survey are completed almost universally. So, they are answering 98% of all of our core questions, which is really important for us because what we worry about is missing data where we're not sure is it missing because they have all those symptoms and they're so tired. They can't even fill it out or is it missing because they don't. We don't have to worry about that because 98% of the questions are being completed. So, I'm going to stop there. And later, very happy to take questions.

Dr. Nedra Whitehead

Thank you. I think Shane is bringing up my slides. So, I'm going to talk today about a survey that we also developed quickly, but to look at the bothersomeness of symptoms that people had developed after they had COVID. Next slide, Shane. So, the purpose of this was to gather information, as I said, on how much symptoms bother people. It is a slightly different concept than severity or burden or impact on quality of life, but although related to those clearly. And part of the reason for doing this, developing this survey and doing the pilot was to inform which symptoms should be targeted for clinical trials. Thank you. Next slide. And you've seen this list of considerations already for the other, but we were concerned about trying to both get a comprehensive as possible symptom list while minimizing the complexity and the time to complete the survey. And we also plan to do this through an online self-administrative survey. So, the design had to be appropriate for that. Thank you. Next one.

So, we build on all the work that had already been done, used the World Health Organization outcomes that both Sarah and Leora referred to build on Sarah's work with symptom burden survey and Leora's with the RECOVER survey instruments as well as a couple of other surveys to come up with a consolidated list of symptoms. And then for the bothersome scale, we used the scale from the University of College London survey on Long COVID for their most debilitating symptoms questions. Next slide. And this schematic shows you briefly how all these different questionnaires came together to give you the list of symptoms that we considered for the Bothersomeness survey.

Thank you. Next slide. Once we had a draft survey, we asked for patient and community input. We invited feedback from 54 patient and community representatives that we identified from the RECOVER National Community Engagement group or from Community Advisory Boards at the RECOVER cohort study sites. We received input from 31 of those. 11 provided written feedback, 11 participated in a live discussion group, and nine provided feedback through both mechanisms. Thank you. Next slide. Okay. And these representatives were patients, they were caregivers of patients, members of advocates of groups focused on Long COVID, or scientists and researchers who were working in the area of Long COVID. Next slide. And they span a range of ages, racial and ethnic groups, and education levels, although we tended towards more educated ... having people with more

education. Thank you. Next line. This in the next slide shows some of the concerns that were raised and list the specific modification we made. In general, we added questions, symptoms. We revised some symptoms. We reorganized the questionnaire to group symptoms into body systems so that it was easier to understand and flow through the question. We added language to the introduction, advising patients that reading some of these may trigger a reaction and encourage them to take a break if they needed. And we built the questionnaire so that they could stop, come back to it, monitor how much progress they'd made.

The next slide. There were a few things that we were not able to incorporate. They got comments that it'd be good to ask about medical care experiences and how negative experiences cause or [inaudible 00:45:56] symptoms. Sorry about that. We could not incorporate that just because of the length of the existing questionnaire. And there was also too the waxing and waning of symptoms and the fact that the timeline for developing symptoms might differ. We found no good way to incorporate that in an online survey. We'll continue to look at that. Thank you. And I will note that we started out with the seven-day timeframe, but it didn't seem to make sense to the patients that respond provided input onto our survey. So, we adjusted it. Thank you. Next slide. In total, we ended up with 99 symptoms that were organized into 12 categories, and we asked them in the order that they're listed here. Next slide. And so now that we had our content, we developed the survey instrument.

Go to the next slide, Shane. Okay. Thank you. This was developed by experienced survey methodologist at RTI to make ... increase the likelihood that it would work well on the first try. The design considerations that we built into this was the symptom descriptions had to be easy to understand to the people who would be completing the survey. And we wanted to minimize the respondent burden and fatigue. We tested it internally with 14 testers, three of which had not been involved in the rate development. And it was tested by the research firm that was administering the survey prior to the launch of the pilot. Next slide. There were three questions for each set of symptoms. We ask about the experience people had with the symptom, whether they'd had it, whether they had it before COVID, they had COVID, after COVID, or both. We ask about what happened with the symptom after they recovered from COVID, and we ask how much the symptom bothered them. We ask about the change in the botherness questions only if they had responded that they experienced at least one symptom in that given set.

Thank you. Next slide. And this is an example of the question on the presence of the symptom where we ask if they had it, they only had it before COVID, they had it before and after COVID, or they only had it after COVID. Next slide. And then we ask what happened after they recovered from COVID, if they didn't have it any longer. If they didn't have the problem now but it lingered for some time after they recovered from COVID, if they still have the problem and it remained the same, or if they still had the problem and it got worse. Next slide. And then we used a five-point scale to ask people to rate how much the symptom bothered them, with the option to respond, don't know, if they couldn't rate it.

Thank you. Next slide. And so, then we piloted the survey and did some evaluation on it. We're still in the process of evaluating the survey and looking at a few more things, but these are our additional results. We go to

the next slide. We piloted this in June of 2022 using a national research panel recruited and maintained by a commercial research firm. The advantages of using such a panel are that the panel is already consented so you can get it in the field quickly and that you know they're able to respond to web based surveys and it also provides you a very large and diverse sampling frame. Thank you. Next slide. So, we had a target sample size of 1000 people. We wanted them distributed across the US. We had specific education and race ethnicity targets to ensure that we had a diverse sample. People were eligible if they had had a previous COVID infection. They did not have to be self-diagnosed or diagnosed ... clinically diagnosed with PASC. In total, just about 2,500 people responded to our screening questionnaire. Of those, about half were eligible and we got 1003 completed surveys, but we stopped once we reached 1,000. We actually got respondents from every state that's at Montana, including the District of Columbia.

Next slide. And this slide in the next slide shows how the members of the panel, those that completed the screener or those that were eligible, and the respondents compared to the US population. [Inaudible 00:50:55] we have some small differences, but in general all the groups are pretty comparable. And that's true of the demographic comparison characteristics showed here. And Shane, if you'll go to the next slide. It's also pretty huge, true of the socioeconomic characteristics. Okay. And you see we have only income on data, on income from the US and from the online panel that we drew from and only data on respondents from our insurance, from our respondents. Next slide. And we got people who responded from across the spectrum of the time period at which people have had COVID infections. And while not precisely exact the same, they follow the same pattern as the number of cases in the US.

Next slide. Turning now to the findings from the evaluation and the performance of the survey. Leora, we got very good data completeness. These little flags at the bottom of the poll shows you the minimum completeness for any given survey questionnaire or any given symptom. The top shows you the maximum and the little gold flag is the average. And so, we had more than 90% completeness across the board for all of our symptoms. Looking at some of the other evaluation measures, we had very few don't know responses looking at the bothersome questions. So, people were able to answer that question. And one of the things we wanted to look at is we ask about other specified category so that we allowed people to write in a symptom if we didn't have it. Ideally, those fall under 10% of your responses. We were over that for movement and cognitive, which were the first two sets of questions we asked. But when we dug into that a little more, many of the symptoms that were written in there actually showed up later in the questionnaire.

Next slide. This slide lists the additional symptoms that were written in, and this slide lists the ones that showed up more than once. Note, it's depression, non-specific depression. We ask about depression related to medical care, but a generalized depression was the most common written in symptom. We ask about several types of pain, but non-specified pain was also commonly written in. And the other symptoms that were common were sort of a general malaise feeling off, not like themselves. So next slide. So based on this, we concluded that the

questions performed well overall. The symptom list captured almost all of the common symptoms. There were some revisions in additions to consider. I'd look at the mental health conditions and revise some of the items there. The vision symptoms showed up and we did not capture those. Incontinence, particularly urinary incontinence, was mentioned fairly frequently. And then we need some questions on systemic, but less specific question symptoms. The next step is to continue the data analysis. So, the next time we can actually give you data on what people are reporting and possibly do some focus groups to understand more about what makes a symptom or a condition bothersome and what that concept means to the people responding. And is it in fact the concept we're trying to capture? That's it. Thank you.

Dr. Sharon Saydah

Thank you. I actually don't have any slides to show, but I just going to discuss what's been presented. Good afternoon, everyone. I really want to thank the RECOVER seminar organizers for inviting me to discuss this important topic, and also, I really want to thank each of our speakers for their excellent presentations. And these presentations really highlight a lot of the challenges we have in measuring the frequency and burden of symptoms following SARS-CoV-2 infection, and also the importance of patient and community input as we develop these measures. These discussions each highlighted the multiple steps involved in the development of these surveys and questions from cognitive debriefing and field testing and usability testing.

So as the speakers mentioned, Long COVID is really broad. At CDC, we define Long COVID or post-COVID conditions as a wide range of new recurring or ongoing health problems that people might experience after being infected with SARS-CoV-2 and having COVID-19. Most people who have COVID-19 do get better within a few weeks or days after infection. But for for CDC, we consider at least four weeks after infections started when we're looking for post-COVID conditions. Each presenter also discussed the wide range of symptoms and the core questions that were included, and this really reflects it. Long COVID refers to a wide range of physical mental health consequences. Some of these might be from severe illness and hospitalization or post intensive care syndrome, but many may be more specific to the infection itself, such as systems specific effects including new or newly diagnosed neurological conditions, kidney damage or failure, diabetes, cardiovascular damage, skin conditions. And as was also highlighted, many of these symptoms may have an unclear pathology. It might be similar to [inaudible 00:57:17] or many other post-infectious syndromes.

So, this wide range of reported symptoms is also part of why we have a wide range in reported estimates. In measuring the frequency and burden for long, it does seem to depend on the definitions that are being used, the populations, the research methods and timeframes and the source of enrollment into studies, whether or not people have preexisting conditions and different social determinants of health. So, using these survey instruments is one way for us to tackle these different challenges in our research. For example, at CDC, we've been using multiple approaches to try and estimate how many people might have or experience post-COVID condition. And

each approach really is providing a different piece of the puzzle that'll give us a better picture on estimating that frequency and burden. So, for example, we used electronic healthcare data and we estimated that among adults who are COVID 19 survivors, one in five between ages of 18 and 64 and one in four between ages over 65 years had experienced a condition that might be related to their COVID-19. But using electronic health records really does not fully capture the patient experience or even assess the full impact of these symptoms on person's day-to-day activities.

Another survey that CDC has done is the household pulse survey, and this has been conducted by the US Census Bureau and CDC's National Center for Health Statistics. And this is a very simple question that just asks respondents if they've had symptoms lasting for three months or longer if they had prior ... that they did not have prior to having COVID-19. And 7% US adults report currently experiencing long and 15% of adults who had 19 are current currently experiencing Long COVID symptoms. The most recent cycle of the survey also included a question on whether these long-term symptoms impacted respondent's ability to carry out day-to-day activities. And among adults who currently have Long COVID, approximately 25% are reporting that there are significant activity limitations due to this.

So as mentioned, all three of these presentations really discuss the complexity Long COVID, the importance of including patients lived experience, and also, the work to minimize participant burden in the completion of the survey. I thought Dr. Hughes's presentation was very interesting in that it discussed the importance of including the patient's lived experience. And one of the feedback that they received was that patients were open to including more conditions and symptoms as opposed to fewer to really capture that true lived experience. The survey they developed also can be used for multiple purposes from measuring the prevalence to outcomes in clinical trials and ultimately possibly to ongoing patient care. So, this really would allow us to translate research findings across from community surveys to clinical trials and benefit patient care. And she also really did highlight the importance of flexibility in being able to modify this over time as we go.

Dr. Horwitz's presentation reviewed a lot of the core questions and really did leverage a lot of existing instruments in developing the survey instrument. And this I think is really valuable in that it'll allow us to compare the prevalence of these symptoms and reports to what we have from pre-pandemic times using those PROMIS outcomes. And then the inclusion of what I guess you call trigger questions that go into deeper dives in these core areas will provide really rich information on the impact of the symptoms on patients' health and much of this information would not be available if we were only relying on health records or even healthcare provider reports. And then Dr. Whitehead's presentation discussed the work that they did to develop a core set of questions to pull in across different initiatives, and also incorporating patient feedback. So, the feedback I thought was really valuable is being able to start and stop a survey, especially given the long wide range of symptoms and the long list, especially for patients who might be experiencing fatigue is an important thing to try and to measure in terms of or to include as we develop surveys. And the survey instrument also aimed to capture symptoms whether or not

they were present prior to COVID-19, whether there was a change in how bothersome they were, and impact on their daily activities.

So together, each of these speakers have really discussed the complexity of measuring the burden and the frequency of the symptoms of Long COVID and all the initiatives taken to really try and incorporate patients' lived experience. One other thing I noted was that it's clearly a challenge to capture everything and to fully measure the frequency and burden of all of these symptoms and balance this with not making it too time consuming for respondents. So, design. There's also the need for design considerations in terms of the survey platform and understandability of these instruments. So, I'd like to start with a few general discussion questions for our presenters. And also, just note that these are all for the adult population. As Dr. Horwitz noted, there's a separate RECOVER initiative that's also focusing on the pediatric population. So, the first is, given the large impressive amount of work that's been done to develop these instruments, are they available to other researchers? If they're not available to other researchers, would you recommend that this process, a similar process be followed for new research studies or that people try and adapt what's been developed for their work? Who wants to take that question or just start?

Dr. Leora Horwitz

I'll take it quickly. On the behalf of RECOVER, I actually put this in the chat as well or in the answer section as well. All of the instruments for RECOVER are posted publicly on the RECOVER COVID website and we also working with a variety of other agencies to post the more technical versions of them for researchers who just want to download and use is the instruments. Those of you who are going to go look at them, I want to just add that they're a little ugly to look at because the way we post them is to show every possible question, but obviously many of those are only relevant if you say yes somewhere earlier in the queue. So, I do just want to caution you that they look a little intimidating because they include all those 300 something questions you might get, but that's the way that we have to post it on paper.

Dr. Sarah Hughes

Yeah. So, I'll add to that. So, the SBQ is available. We do ask that anyone who wishes to use the SBQ take out a license for non-commercial research academic use clinical use that's free of charge. There's no cost. And if you're looking to do translations, we are really aware that in many lower middle-income countries there's a need for measures which will need to be translated into local languages, and that's why we've partnered with Mapi who will facilitate that again without cost, not at any cost to the researcher. So that can be accessed via our website on the University of Birmingham.

Dr. Nedra Whitehead

I think we'd be perfectly happy to share the bothersome questionnaire. Before I post it publicly, I'd like to do one more set of revisions.

Dr. Sharon Saydah

Great. Thanks. And I have one more question and then we can also open it up for the Q&A. So, I noted that in each of the surveys you've developed, it talks about that these are for post-COVID conditions or PASC or Long COVID. I know we recently implemented a survey where we made a point of not saying that the symptoms we were asking about were related to COVID to just try and get people to report their symptoms, not necessarily attributing it to COVID and wanting to know what your thoughts were on that approach. And if you think it impacts, do you think, how people are, whether or not they're likely to respond to all of the symptom questions, whether or not they think they have Long COVID.

Dr. Sarah Hughes

I'm happy to start with that one. Yeah. It's a really, really excellent question. So, thank you to the attendee who posted that. In terms of the argument around disease specific versus generic instruments, I think we touched on that. You touched on it just now in terms of will participants actually complete the survey or the questionnaire if those questions are perhaps as related, but not necessarily wholly relevant to their condition. So yes, I think that certainly in the case of the SBQ, we are looking at it in terms of whether it is appropriate for other conditions because fatigue is fatigue is fatigue. A symptom is not necessarily wholly associated with Long COVID. And I guess one of the challenges going forward for researchers is to actually tease out what is Long COVID. But certainly, these from the SBQ perspective, although it's been developed for Long COVID, which means in terms of its validity, it's really has strong content validity for that condition. And you always validate and measure in the condition and not the measure itself. So, it is possible to use it in other measures. But if you wanted to have psychiatric evidence, you would need to look at that in that condition.

Dr. Leora Horwitz

I think as the common misperception about RECOVER, that we're only enrolling people with COVID or even only enrolling people with Long COVID, that's not the case. In fact, it's very important to us to enroll people who've never had COVID at all and people who have had COVID and have recovered just fine. So, our questionnaires are designed to apply to people whether they have had Long COVID or not. We don't ask them to tell us whether the symptom is because of COVID. We don't know that, probably they don't know that either. And

so, we just ask presence or absence and that helps us later. As Sarah mentioned, it will help us to disentangle things that are common across the board, things that are more common in this group versus that group.

Lisa Newman

Thank you.

Dr. Nedra Whitehead

[inaudible 01:09:32] went down to the middle on that and I think that there are both pluses and minuses to tying it to COVID, one of which is it helps people with the timeframe and gives them a time anchor. But it does perhaps create some of a recall bias of them recalling symptoms that they might not have otherwise.

Lisa Newman

Thank you Dr. Saydah. Are we ready to move on the Q&A?

Dr. Sharon Saydah

Yes.

Lisa Newman

Okay. And as been mentioned previously, we've gotten some questions in advance and we also have the Q&A live today and we'll be posting responses on the website following the seminar. So, Leora, I think this is for you. Some symptoms and tests seem to be different depending on the phase of the disease. For example, acute, intermediate, autoimmune, and chronic. As symptom profiles are developed to characterize this disease, will we take into consideration the phase of the illness?

Dr. Leora Horwitz

This is really important and really true. And certainly people have very different symptoms in the acute moment of infection than they do perhaps six months or a year later. So, we prioritize timing in our questions. Our questions when you show up for enrollment, if you had the infection in the past or a negative test in the past, we try to distinguish at what time periods you have had various symptoms. I want to be clear; we actually also are 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, but that way we can capture what symptoms are people having right away when they're having COVID and how does that compare to the sort of symptoms they get later on. It

also allows us to collect biospecimens, and blood tests, and urine, and saliva, and other things from people in the moment of infection, which is very important to helping us predict what kinds of things happening in that initial infection are related to later stage.

So, I'm just going to take this moment to do a public service announcement to say we are still looking for those sorts of enrollees. We're actually done on the enrollment for people who had infection in the past we had tremendous interest. We filled those slots very quickly. But we do still have space in our study for people who had infection within the last 30 days, even if it's a repeat infection. And we still have some slots for people who've never had COVID at all. So, if you want to sign up, I'll put the website in the A&A.

Lisa Newman

Thank you. Okay. Are there any specific research papers that neurologists and psychiatrists should read to make sure they keep up with the latest literature on Long COVID neuropsychiatric symptoms? Dr. Horwitz, maybe that's for you as well.

Dr. Leora Horwitz

Well, I will say that the literature on Long COVID is voluminous. I myself have trouble keeping up with it. We actually have a whole dedicated librarian with RECOVER whose whole job is to tell us all about great new papers. So, I would hesitate to speak to only one or another. But we are hoping to provide those sorts of summaries of research that has caught our eye to the public and not just within our consortium. So, I look forward to being able to do that hopefully in the future.

Lisa Newman

Thank you. And Dr. Hughes, I think you can start the discussion about this one. Please discuss how US information compares to what other countries have learned such as from surveys conducted in the UK.

Dr. Sarah Hughes

Yeah. Thank you for that question. So as Sharon, Dr. Saydah 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 does looks at self-reported Long COVID with symptoms persisting beyond four weeks. And I believe with the US survey it was around about 7%, whereas in the UK the estimates are about 3.5% of the population are still experiencing symptoms of Long COVID beyond four weeks, which roughly equates to about 2.3 million people.

Lisa Newman

Thank you. 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 versus the full self-report surveys?

Dr. Sarah Hughes

Okay. [inaudible 01:14:26].

Lisa Newman

Dr. Hughes, yeah. Go ahead.

Dr. Sarah Hughes

Okay. I think this is an interesting question. I'm hoping I've understood it correctly in terms of the role of the clinician within self-report. So, PROs, by their definition, are reports from the patient without interpretation by anybody else, but that does not mean they're not relevant within the clinical care from a communication perspective, from a treatment decision making perspective. And we also know that they also can play a role in terms of how you triage patients. So, in terms of managing, we know that Long COVID clinics are under immense pressure. There's too few of them. We need more, we have a large patient population. So, PROs can play a role for supporting clinicians in triaging patients. And there's lots of evidence out there and other specialties where EPRs are being used to support those sorts of decisions. In terms of the validation, clinicians can ... There are immense support. If there's studies going on to look at validation, it can sort of encourage patients to take part. And certainly in terms of their development, having clinicians involved early in the early on in the development phase, in that sort of qualitative phase in terms of ensuring that the items are relevant to their clinical experience and what they enter, the measures will have good utility once they translate into the clinic. Yeah, there's certainly a role for clinicians there. I hope that's answered your question.

Lisa Newman

Any other panelists who want to comment on that? Okay. If researchers or applied epidemiologists are developing their own instruments, is there core guidance that should be followed with respect to case definitions, symptom domains, et cetera? Dr. Whitehead, any guidance there?

Dr. Nedra Whitehead

I think that the field will get to the point where there's a consensus set of questions. I do think that in the moment it's important to look and see as you're developing a questionnaire, is yours actually adding anything new or is there an existing questionnaire that will meet it? I don't think many of us develop ... did the work in developing one for the fun of it. And there are more fun things to do at epidemiology, but I don't know that we're confident yet that we know everything we want to ask. And so, each questionnaire adds a little more. Eventually, we'll be at the point I think where we've got a firm set of questions like we do for many other conditions.

Dr. Sarah Hughes

Yeah. I'll just add to that. So, I mentioned the post-COVID core outcome set in my presentation. Now that was a consensus exercise, a delphi exercise that was undertaken through 2022 where they first worked out the domains, what's important to measure in post-COVID from a multiple stakeholder perspective and then the second part of that delphi exercise was to work out how to measure that. So that's just been published in the last week or so or at least it's on their website and due to be published shortly. It might be in pre-print already, but as a starter for 10, I think as Nedra says, this will evolve as our understanding of Long COVID evolves and the measures are likely to evolve as well. But as a starter, there are some core recommendations that have just been released.

Lisa Newman

Thank you, Dr. Hughes. Okay. Are you seeing progression of symptoms, especially for those who caught the virus in the first wave in 2020? Anything we can say about that? Dr. Horwitz?

Dr. Leora Horwitz

We are still in the midst of recruiting. We're trying to be good citizens, not peak at our data constantly. So I can't speak to the differences that we're seeing yet among people who had infection early on in those later, but there is a lot of literature on that and it does seem as though some of the newer variants like Omicron plus minus vaccination maybe lead to less frequent incidents of Long COVID, which isn't to say it doesn't exist with them and there's certainly plenty of people who have Long COVID who have had newer variants or who have had vaccinations on. But it seems like there are probably differences across time probably as a combination of the variant and the treatments and vaccination status and so on so forth.

Lisa Newman

Thank you. And this question is also for you. As you know, the current study protocol doesn't collect severity and frequency proposed exertional malaise. What tools or instruments are you considering to sufficiently capture these data in order to identify these important aspects of PEM?

Dr. Leora Horwitz

Oh, that's a good question. So right now, we use post-exertional malaise just do you have it at all as a really important trigger for ongoing ... for further testing. It doesn't even matter to us how severe it is. We just feel like that's so specific to ME/CFS that we really just want to explore more with those participants. However, that said, we are doing a big kind of re-look at our survey instrument now that we are about 10,000 people in and really trying to understand clearly which questions are missing as we have new data coming out about new symptoms and which questions maybe are not that informative that we could swap for something else. Just like Sarah said, are protocol is very adaptive just as hers. So, one of the questionnaires that we're looking at is the DePaul [inaudible 01:20:51] form, which is six items looking at ME/CFS. And it has two questions about post-exertional malaise. One is the one that we have already in our instrument and the second one is slightly different, muscle soreness after exertion. And both of those come with a severity and frequencies score. So, it's possible that we will be able to add those items in with their severity and frequency. That's something we're looking at because it's well validated and also short and burden is important to us.

Lisa Newman

I think we have time for one last question. Again, Dr. Horwitz, for you, what are the most common neurological symptoms reported by individuals with PASC? And do we have any evidence regarding specific etiology of those symptoms?

Dr. Leora Horwitz

That's also a good question. So, if you consider smell and taste and neurologic symptom, which we do, that is the one with the most difference between people who have had infection with COVID and those who have not. The increase in risk versus people with Long COVID is very substantial, very clearly related to COVID, but it's not the most common symptom that people report. So, the most common neurologic symptom that people report is trouble thinking. Sometimes they call it brain fog, sometimes they call it trouble concentrating. And so, as a consequence in RECOVER, we actually have a whole battery of instruments that we are using for people when they report trouble thinking. We ask a core set of additional questions that comes from the Neuro-QOL that we talked about, but then we also do formal cognitive testing on these folk because it's really important for us to try to

disentangle what kind of trouble thinking are people having. There's all kinds of different processing and that helps us try to localize where in the brain are things happening? And that will help us answer your last part of the question, which is why is that? We don't know yet, but because we're doing all these really very specific additional tests as well as things like brain MRIs and even lumbar puncture, we should be able to answer questions like that in the future.

Lisa Newman

Very much. What a great set of informative presentations. Thank you to all of our panelists and thanks to the audience for joining us today. An FAQ document for this webinar will be posted along with the recording of the webinar on recovercovid.org. It will include the answers for all questions relevant to the seminar that were submitted in advance so that we're asked during today's Q&A. Questions about other scientific topics will be addressed in future seminars and answers to broader questions about RECOVER will be available in the FAQs also at recovercovid.org. So, Shane, if you'll share the slide of upcoming webinars. There are two more for 2022 and the 2023 webinar schedule will be forthcoming. And right now, all of you should be seeing a short poll of three questions that is launching on your screen. And we'd really like for you to answer these questions. These responses will be very important for future webinar planning. So, thanks very much in advance. And thanks to all of you, thanks again to our panelists. It was great discussion today.

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/