Transcript

Beth Linas

Hello everyone. I'm Beth Linas. I'm from the RECOVER Administrative Coordinating Center and the moderator of today's webinar. Welcome to the RECOVER Research Review or the R3 Seminar. The goal of this webinar series is to catalyze a shared understanding of the research within the RECOVER consortium. Today's seminar is leveraging mobile health platform technologies to understand PASC. It's important to note that the seminar series is focused on scientific research and is not intended to provide any clinical guidance.

I want to start by thanking everyone who submitted questions. Please submit any questions that arise today using a 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. An FAQ Document for the seminar will be posted with the recording of the seminar on recovercovid.org. It will include the answers for questions relevant to the seminar that were submitted in advance or today. Questions about other scientific topics will be addressed in future webinars and answers to broader questions about RECOVER will be available in the FAQs at recovercovid.org.

Today's speakers will discuss what is known about mobile health platform technologies in PASC, the gaps in our knowledge and how RECOVER will contribute to filling these knowledge gaps. Today we'll hear from Dr. Vik Kheterpal, a principle with CareEvolution. CareEvolution provides secure interoperability solutions for population health management, public health reporting, digital clinical trials and consumer engagement. Their comprehensive platform enables organizations to liberate, standardize and aggregate clinical claims and consumer data into single actual standard space repository. Dr. Kheterpal received his doctorate in medicine from the University of Michigan at Ann Arbor.

Next we'll hear from Dr. Jennifer Radin, an epidemiologist at Scripps Research Translational Institute. She is the PI of the DETECT Study, an app-based research study that has enrolled over 40,000 participants and aims to use self-reported and wearable device data to better understand individual and population level changes associated with viral illnesses including COVID-19.

Next we'll hear from Dr. Arjun Venkatesh, an associate professor and section chief of Administration in the Department of Emergency Medicine at Yale University, and scientist at the Yale New Haven Hospital Center for Outcomes Research and Evaluation. Dr. Venkatesh is co-investigator and site PI for the CDC INSPIRE Registry and has been funded by several federal and foundation sources to study health outcomes, the use of digital tools for patient reported outcome measurement and large data set analyses of health system, quality and efficiency.

Next, we'll hear from Dr. Erica Spatz, a cardiologist and associate professor in the section of cardiovascular medicine at Yale School Medicine and of epidemiology at Yale School Public Health. She is the director of the Preventative Cardiovascular Health Program at Yale. Her research focuses on disease prevention,

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women's cardiovascular health and health equity. She is part of the Long COVID Recovery Team at Yale and is co-PI on the CDC grant entitled INSPIRE, designed to assess the long term outcomes of adults diagnosed with COVID.

We'll also be joined by a discussant, Dr. Andrew Weitz, an NIBIB programs director supporting a variety of Trans NIH and Trans Agency Initiatives, with a focus on health informatics, digital health and open science. Dr. Weitz leads digital health strategy for the rapid acceleration of Diagnostics RADx Tech Program and established the RADx MARS program, which is a standardizing test result reporting from over the counter diagnostics. He also has held key roles in other NIH initiatives, including RECOVER and Say Yes To COVID Test. Thank you and I will turn over to Dr. Kheterpal.

Dr. Vik Kheterpal

Good afternoon. Thank you, Beth. Pleasure to be here. I think my portion of the talk is titled Opportunity and Need for Digital Tools and Phenotyping To help understand PASC. I serve as a principle at CareEvolution as Beth mentioned. We're a sub-awardee for the Mobile Health Platform for RECOVER, as well as do some work for the All of Us Initiative and some of the work from the NIBIB, Dr. White's integration of testing and digital health that is done.

I do have an important disclosure. I come in with a very strong bias favoring the use of digital tools, smartphones, wearable sensors that enable passive collection of nearly continuous multi parameter digital data streams over a longitudal period of time. In the next 15, 20 minutes, I'm going to try to share some of our experiences over the last eight years supporting the innovators and digital and mobile health space.

So with that, I'm going on to the next slide, maybe we can focus on just this basic idea that started I think back in 2015 or maybe even earlier than that, that the traditional gold standard survey-based instruments that have been and will remain vital to help define disease progression and quality of life for patients have some inherent limitations that we are trying to always contend with. One, they tend to be infrequent and not continuous, and they tend to be a bit artificial in the sense that they do not track the lived experience of the patient at home. They require some manner of a in clinic or discontinuous measurement. This kind of work has led, I think in the next slide, the venerable Framingham Heart Study to think about how to embed a digital electronic framing cohort inside the 70 year old cohort that already is capturing tons of data.

So starting in 2015, the FHS embedded a new electronic cohort where they were handing out some manner of a wearable, a blood pressure cuff, other kinds of things to supplement the data that we already had available. Next slide.

The kinds of things that this kind of technology us to do is beginning to now show up as we develop proxies and correlates between the digital measurements we're doing on a continuous basis in the natural setting as opposed to in the zoo measurement as I like to call it, that tends to be in the clinic. This kind of longitudinal analysis becomes really important because it enables development of an individual trajectory of each individual as

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to the parameter of interest. Rather than taking something on a monthly or quarterly or even less frequent basis as an end point, we start to see what the correlates are of these kinds of measures that are continuously measured using digital devices.

Next, this kind of... Next slide please. The kinds of things that we're able to do of course are very profound because we are able to track very interesting measures such as mood, things that tend to defy being able to measure on say on a continuous basis using patient reported outcomes or survey instruments and things of that nature. And some of the work that Dr. Srijan Sen and the team is leading with the Intern Initiative is beginning to show that changes in multi parameter data such as sleep activity and other markers like heart rate or correlates like heart rate recovery, heart rate variability that might be associated with sleep and physical activity that one can discern out of that how somebody's mood or depression risk may rising or progressing over time.

On the next slide, we see other folks doing some really interesting work looking at potentially things like asthma. So the therapeutic modalities, the kinds of disease states that digital tools are able to track transcends the more traditional cardiovascular and mood to now things like asthma, pulmonary diseases. And of course this has a great relevance to PASC and COVID. This particular trial is very interesting because it's trying to focus on the idea of consumer self-efficacy and the role of digital diaries in being able to not just generate a better marker.

And if we flip to the next slide, there's an animation on this particular slide, we're able to see ecological momentary assessments that can be sent out on what is going on today that mobile technology enables us to do, and the ability to then take the data gathered from these ecological momentary assessments and co-locate that data with passively collected digital measures on a calendar view, enabling both the individual themselves and the researcher and the clinician to have access to a trendline.

The same technique has been pursued in cardiac rehab on the next slide by some of the researchers at University of Michigan, where during the pandemic we found that trying to have those who have suffered from an MI, that might be post stent placement or myocardial infarction, a CABG open heart surgery, how do we get folks to be able to exercise at home in a safe manner?

Digital tools enable us to go beyond just conducting research, but also offer tools that enable individuals to safely be able to do something like cardiac rehab while under the monitoring of a exercise physiologist, which of course is entering the world of potentially digital therapeutics. But the continuum here on the role of mobile health platforms, the point behind this sort of landscape analysis of these various initiatives that we've been involved with shows that it's far more aspirational than just observational data.

One of the things that I think we are learning on the next slide is the actual notion of what a digital phenotype is. In many cases, the kinds of attributes that define a digital phenotype is that it is continuous, it is longitudinal, it is measured in vivo in the real world, in the lived experience of the participant at home. And it gets far beyond the automated surveys or patient reported outcomes or other measures that are survey based.

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There are special sensors on these kinds of devices and many of my colleagues today are going to talk about the advanced work that comes from those special sensors, but some of that have already been developed and others that we are in the middle of trying to figure out how to develop the new digital biomarkers.

In addition to this traditional frontier technologies for digital biomarkers, there's also this notion of trying to understand something as simple as blood pressure measured in clinic versus measured at home, which is better and for what use cases. How do we get better at these kinds of things in creating an individual trajectory that better approximates the lived experience of participants at home? And of course, this entire field includes things like air quality index, weather patterns and other things that may be going on in the environment and social determinants of health that are environmental determinants of health.

Accelerometers and other kinds of tools that can be used on a smartphone give us yet another arrow in the quiver of being able to do things like tapping tests and other approaches beyond surveys in order to be able to assess the progression of disease or lack of disease and what actual quality of life an individual is having at home.

So some examples of this on the next page we start to get into this, is how to develop the next generation of digital biomarkers and how that might assist us in PASC, how the current generation of digital biomarkers like blood pressure are evolving, and moving to a world where non-traditional digital biomarkers just like ecological momentary assessments, subjective symptom diaries versus PROs that are delivered on a monthly basis, how this is impacting a variety of disease states and things that we're trying to track.

On the next page, an example of this is the classic Hauser diary in a movement disorder for Parkinson's patients. Instead of asking a patient at home to look at how they are, how their tremor or dyskinesia is progressing every half hour so we can right size their L-dopa or other medication that may be going on, we are now able to potentially give this individual a wearable on the next page where they are able to first automate the diary, if we go to the next screen. And that allows us to create a proxy to say what is the survey based answer coming off, say a wearable for the Hauser diary so it's been automated. But more importantly, using the accelerometer on the wearable, we're able to actually track the tremor and dyskinesia.

So on the next page we show that that we can have a continuous digital measure that allows for trend visualization of the tremor versus the dyskinesia. And the L on the horizontal axis represents the times when a patient is taking a medication. This kind of highly granular data that happens to be an event which is when the medication is being taken as well as digital data coming off a device allows us to be far more granular and precise in pursuit of the precision medicine ideal as to that particular individual and what else may be going on in their life.

Moving on to the next page, Jennifer is going to go through a bit of this in more detail so I'll simply leave it at the... You may have seen lots of articles that are talking about the notion of consumer grade devices like Fitbits and Apple watches and Garmins and Oura rings and the Whoop ring being able to track what is going on with the consumer and whether it's a influenza-like illness including COVID or recovery from such illnesses, the kinds of

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multi parameter data that is coming out of these devices may help inform and supplement other phenotypes that we are tracking to.

Next page. This is a study that of course Jennifer's going to go into in much greater detail that we ran with Scripps Research where we were able to enroll 40,000 individuals in the course of six to eight weeks in order to be able to gather these kinds of data. So the notion of how far and how broadly we can reach the population is also something that's very profound in mobile health platforms.

Next slide. Another kind of interesting digital biomarker is the notion of current gen markers like blood pressure only currently done usually in an ambulatory care setting to define who is even a hypertensive. We've been running certain trials that show that you can actually have home base nearly continuous certainly on a relative basis, on the next page, blood pressure measurement that allows us to understand potentially the daily diurnal variation in blood pressure and how it is associated with morning, evening, afternoon, with or without food, other things that may be going on during the lived experience of the consumer at home to see if we can have a more precise personalized evolution of how we measure and define hypertension and how we track response to hypertensive medications, anti-hypertensive medications at home to, again, in the progression of trying to get the precision medicine. Next slide.

Additional things that I think are very interesting when it comes to brain fog, things that are hard to measure with PROs, with potentially validated survey instruments, is this entire world of being able to use things that accelerometers and touchscreens on smartphones enables us to do.

Some examples of this are some of the studies going on at the National Cancer Institute right now on the next page that actually try to follow the actual, if I may use it, the fatigue, potentially the acoustic neurotoxicity and the cognitive function with the use of chemotherapy for a particular patient using simple smartphones. You don't even need a sensor because you can do tapping tests or other markers of evaluating cognition.

Next page. This entire field allows us to correlate how somebody describes in a survey instrument as to their level of fatigue or cognition or attention versus a objective measure of those very same things using the kinds of things a smartphone touch enable device such as a mobile health platform enables us to do.

On the next slide, we start to get to the final type of innovation made available in this field, which is the ability to work with other apps and innovators that are coming out, something such as the ability to track nutrition. So on the next page you'll see innovative tools that allow the tracking of nutrition not by completing a survey of how much we ate or describing the food, but rather taking a photograph of the food that you are ingesting and having a tool that says that looks like a banana. What we find is that participants and patients are far more engaged in this kind of a interaction and we end up with a better diary of something like nutrition tracking.

So if we go to the next page, we start to see how this kind of tool may be useful for post-acute sequelae of COVID. One of the things that we are learning is we're in the middle of this chicken or the egg moment when it comes to PASC. We don't really know what the symptomatology of PASC is. We have some pretty good ideas. We

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have some instruments, PROs that we have designed that describe which symptoms may be associated with PASC, but in some ways that's what RECOVER is all about, is to find out what are the precise symptomatology in the lived experience of consumers.

One of the things as a mobile health platform we're able to do is to provide participants a subjective symptom diary that they can refine and configure and personalize to their lived experience with their symptoms and which particular interventions and treatments are impacting them. This is the kind of thing that allows for greater expressiveness and granularity of symptom data that is available.

We find that participants are finding this very useful because we're able to create a trend shown on the next page as to what is going on with the symptomatology for self-efficacy. And if we go to the next page, you'll see that we're able to provide a 30-day calendar by looking at these data all managed within the mobile health platform technology that is providing value both to the participant, enhancing the granularity and richness of what they are expressing, and making it available to the researcher. Now of course this presents a challenge for the researcher to have to come up with new models by which to analyze these data because it is the individual trajectory and lived experience in keeping with precision medicine and personalized medicine that we are having to track as opposed to normative comparisons of the symptoms across a cohort.

Next page. This is the kind of thing that also enables us with the CARES Act, Cures Act, and Sync for Science. Some of my colleagues are going to provide how we can have access to real world evidence and data such as electronic health record and claims data that helps establish and create yet another phenotype more easily on a longitudinal study. It is not just the data coming from the enrollment site that is important.

On a four year basis, RECOVER participants may get care from primary care specialists, tertiary care centers. And this model on a mobile health platform enables a consumer under their control to connect to their patient portal much like they do with mint.com to their financial back ends to be able to aggregate all of that data in a single place co-located with their device data and their personal symptom trackers so that they have a single place where the data is being aggregated and shared with the researcher.

We're able to access some 80% of all US healthcare delivered by volume on an annual basis with the kinds of endpoints today that are available as part of that Sync for Science protocol that started at NIH several years ago and has been accelerated with some of the information blocking CARES and Cures Act regulations that enable each participant to have access to their EHR and claims data in an app of their choice such as the mobile health platform.

Next page. So now this idea we've talked about EMAs, but something that is really challenging to do as a survey instrument or asking folks to maintain paper-based diaries that then have to be transcribed by somebody into some sort of a canonical database. The mobile health platforms today are able to deliver these in place convenient ways to nudge somebody to say, "How are you feeling this morning, this evening?" So the granularity of the information we're able to manage is much better.

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I guess the final comment is there are things that are highly challenging to discover. So on the next page we are talking about in RECOVER it's very challenging to come up with a surveillance system potentially across 40,000 participants for new suspected COVID infections as we see more reinfections occurring. So the mobile health platform could potentially serve as a sensory system allowing and enabling convenient access by participants at home to say, "I think I might have a new COVID infection." They raise their hand within their mobile health platform and then they're able to record that data. And on the last slide we show how we can push that to the researcher, the coordinator at a center to be able to say, "Maybe we need to call this particular participant or the home to see if in fact there is an active infection so they can be in the right part of the protocol."

Thank you. I think that's all I have.

Beth Linas

Great. Thank you so much. We will toss it over to Dr. Radin.

Dr. Jennifer Radin

All right. Thank you for the great background on digital health technologies and the application for improving healthcare, Vik. I'm going to switch gears and focus a little bit more on COVID and wearable devices, specifically long COVID.

And so I'm an epidemiologist at Scripps Research Translational Institute and I'm a member of the Digital Health team. And to start out, I'll just go over what is normal and healthy. So traditionally when you go to your healthcare provider, your healthcare provider will rely on population averages to determine whether your healthy, so 60 to 100 beats per minute for your heart rate, your resting heart rate, they'll recommend seven to nine hours of sleep. You often hear the guidelines of 10,000 steps, although a little more research is needed for that particular number.

However, this was from several years ago now before COVID, I was wearing an Apple watch and looking at my own individual data and I noticed that on the left my resting heart rate was quite stable, around 60 to 63 beats per minute, which was within that population average. And then on the right I noticed when I got sick with an upper respiratory infection, my heart rate jumps rather high up to 77 beats per minute. While this is still within the population norm or average, it was outside of my own individual average, which was again about 60 to 63 beats per minute.

And so one of my colleagues also was looking at this data set that we had access to, which was 200,000 Fitbit users who wore their device for about two years. What he found was that there were times when individuals also had this little spike in their resting heart rate compared to their kind of typical average or pattern. And so he found that on average, individual's resting heart rate was quite stable. It didn't vary for more than three beats per minute from week to week. But again, when you are able to characterize your own individual normal, we can

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identify these potentially subtle changes that we would not previously pick up on if we utilized the PASC population average range of 60 to 100 beats per minute.

And so prior to COVID hitting, we also did a study that used that same data set from Fitbit of 200,000 users. We found that if you identify each person's individual average resting heart rates and sleep data, you could identify weeks where participants had values that were deviated from their average. And when you looked at the proportion of individuals each week who had this anomalous data, that it could improve predictions for real time flu-like illness surveillance. And so we looked at five different states and found that the sensor data significantly improved our ability to track infections as they were happening.

And so this was really exciting at the time because flu-like surveillance in the United States was typically delayed by one to three weeks. It just takes a long time for the data to be collected by different public health associations and sent to the CDC. It takes a long time for when people first get symptoms to when they seek care and finally get tested. And so the whole process of collecting surveillance data through this traditional clinical in-person system was really delayed, which reduced our ability to respond timely to public health outbreaks.

And so our group works a lot with sensors and digital health devices. The Pew Research Center came out with a study a few years ago that found that one in five Americans are actually wearing a smart watch or fitness tracker. And so there are some differences depending on racial background, education, whether you live in an urban or a rural area, but these numbers are continually growing. There is a recent study by the economists that now says that it's one in four. So really have great potential to pull this data from many individuals all over the country to better understand both individual and population changes associated with viral illnesses like COVID.

So when COVID hit a few years ago, our team launched the DETECT Study, which is built with MyDataHelps platform, CareEvolution's platform. This platform is great because it enabled us to collect data from any adult in the United States who was willing to join our study and share their sensor data. So we're device agnostic. We can pull in on data from Fitbits, Apple watches, Garmins, anything that connects to Google Fit or Apple Healthcare. We also have the ability to pull in electronic health records and also collect symptom data, self-reported vaccination, self-reported diagnostic test results. This allows us to examine how sensor data relates to an individual infection. And as Vik noted, we have enrolled over a 40,000 participants from all over the United States.

So I'll touch real quickly on some of the initial studies that we did. Our first one looked at whether we could utilize a sensor data to improve our ability of kind of identifying which individuals had COVID versus another viral infection. And so we found that symptom data did a decent job of identifying which individuals had COVID versus some other sort of viral infection such as flu or rhinovirus or another common colds. But when you added in that sensor data, you could significantly improve our algorithms.

This model was improved on by my colleague Dr. Quer. He found that you can even use the sensor data to passively detect who had COVID. And so this machine learning algorithm could be applied to passively collected

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data from sensors that we could then potentially notify people to get tested or collect that data to better track surveillance trends at a population level.

We have also looked at kind of the individual variation associated with vaccination. So we looked at different heart rate and step and sleep fluctuations compared to a person's baseline pre vaccination and found there were some interesting differences based on whether someone got Moderna versus Pfizer, whether they had previously been vaccinated, I mean previously infected versus not previously infected. And so this gives us some interesting insight into potentially antibody response if we could relate this data to biomarkers in the future.

And then finally, more recently we published a study that was very similar to our flu-like illness surveillance study where we use sensor data to better understand population level changes of COVID-19 in California and the United States. We used very similar models to our previous study and found that the sensor data could also be used to significantly improve our ability to track COVID-19 activity at a population level.

So again, this is really important for speeding up our ability to identify outbreaks and improve our response times. And so a lot of our sensor work has been validated by many colleagues over across us and also internationally who have found that if you better identify each person's unique baseline for these different sensor metrics, you can then identify subtle changes that may indicate they're coming down with a viral illness infection potentially even before their symptoms start.

So now I'm going to go in a little more detail on one of our long COVID studies. The great thing about using wearables is that you can continuously track people's data for weeks and months after they get an infection. This enabled us to look at people's resting heart rate step and sleep data both before and after they became infected with COVID-19.

And so on the left hand side, we compared symptomatic individuals who tested positive for COVID versus those who tested negative. And we found that the individuals on average who tested positive had this much higher resting heart rate response during the acute phase. And then there was this interesting dip in resting heart rate before it went up again and stayed elevated for on average about two to three months. Interestingly, sleep and step count went up but returned to baseline a lot faster.

And on the right, we group people based on their resting heart rate deviation during the second month post symptom onset when we found that there was a subset of individuals who had this resting heart rate that was elevated and remained elevated for much longer. It didn't even go back to baseline during our follow up period. And so we think that the sensor data can be used to better track long COVID and how people are responding to their infection, whether they're returning to baseline or whether they're still experiencing these abnormal fluctuations compared to their baseline.

So we also collected different symptom variables during the acute phase of infection and we did see that there were certain variables that during the acute phase that were associated with this longer term resting heart

rate fluctuation. And so variables such as shortness of breath during the acute phase were associated with a higher frequency of being in that resting heart rate group that was extremely elevated.

And so some of our colleagues at the Robert Koch Institute have actually replicated our findings and they have also shown that resting heart rate on average remains elevated for several months post infection. They have also looked compared vaccinated and unvaccinated individuals and found some slight differences with resting heart rate returning to baseline quicker in the vaccinated group.

And so as I mentioned early on, we are also interested in aggregating this data at a population level to better understand kind of trends in a state or a county so that these can be used to inform public health policies, resources. One part of the piece is sensor data that can be combined with many other data streams such as rapid test results, Google search data, movement of individual's vaccination and many other and wastewater surveillance. One piece is also looking at recovery from long COVID since that's a growing population of individuals across the US and globally who are now suffering from long COVID, and wearables can potentially be used to track one people who are moving into the recovery group.

I'll quickly mention that one of my colleagues is also working on a long COVID and pacing study. So we think that wearables not only can be used to better track and quantify long COVID but can also be used to potentially help manage symptoms. And so she's working on running a study that will evaluate pacing and management of symptoms.

So quickly I'll just touch on some of the possibilities and challenges of wearable sensors for long COVID. One of the great benefits is that so many individuals now wear these devices. One of the challenges is they are still quite expensive. So we're working on different ways to get around that, providing devices to individuals who might not have one or also looking at low cost solutions such as sensors in a smart watch camera that can also calculate someone's heart rate, potentially respiration rate and also activity level.

The great benefit as Vik mentioned, is this continuous data from the comfort of a person's home. So it really gives us a unique view into what their individual baseline and trends are over time. Also, it allows people to participate from any time and from anywhere, which allows us to include people from rural areas or places that might not have been included traditionally in clinical trials due to the distance to the site.

And also as these devices evolve over time, we're seeing new metrics that are more widely adopted into the commonly used fitness trackers. And so these new metrics will further improve our ability to track infectious diseases and differentiate changes associated with the viral infection versus changes associated with stress or dehydration or alcohol consumption or other causes.

One of the biggest challenges is the long term engagement. And so something that we're going back to to improve that is providing useful data back to the participant, really working on establishing trust and also always increasing diversity and representation so that these health solutions can be utilized by everybody.

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Finally, I think one of the greatest benefit potentially of these devices is they provide objective data to support some of the symptom data that many participants have experienced but if potentially been ignored or not really recognized by the medical fields. And so being able to quantify what people are experiencing through resting heart rate activity and sleep data can really give us a better idea of what each individual is experiencing.

I think in the future, the ability to predict which individuals are more likely to develop long COVID versus not is an interesting application as well as evaluating different treatments and symptom management, also looking at different subtypes. We know that some individuals go on to have this prolonged tachycardia. Some individuals experience a relative bradycardia or lower resting heart rate. So there's a lot that we still have to learn by using this sensor data.

And finally, I'll mention that none of this would be possible without our huge team at Scripps who really pivoted to work on this study during the pandemic. Oh, thank you.

Beth Linas

Thank you Dr. Radin. Next we'll hear from Dr. Venkatesh and Dr. Erica Spatz.

Dr. Arjun Venkatesh

Hi everyone. Dr. Venkatesh here from Yale along with my colleague Dr. Erica Spatz from Yale. We're sort of excited to tell you about a project that is really in some ways midway point we recently completed enrollment, but the findings and the early results are just beginning to come out. And so what we want to speak to is the aspect of our project that comes from digital health platforms within the INSPIRE Study. Go to the next slide.

This study, the INSPIRE Study, is really a data registry amongst individuals with COVID infection that's supported by the CDC. Just to sort of be clear, our presentation today is really from us as researchers at Yale and not official sort of CDC or HHS statements nor of necessarily officially from the study project itself. Next slide.

The INSPIRE Study Consortium was started really early in the pandemic. I think the CDC was thoughtful about recognizing that there would be a need to prospectively follow individuals and understand long term outcomes. There was maybe at that time very few and early anecdotal reports of things called long COVID or prolonged symptoms. And at the time, a set of eight centers as you see here on the slide, were able to pull together with Rush University serving as the administrative core for this work, the University of Washington providing the clinical core function, and ourselves as Yale as the primary analytics center for the study. And then additional sites at UT Health, UT Southwestern, UCLA, UCSF, and Jefferson supporting the enrollment of people really across the country. Next slide.

The study primary objective was to compare disease trajectories, symptoms, patient report outcomes, clinical outcomes amongst adults with COVID-19 compared to a control population. We had originally planned to enroll approximately 4,000 individuals. We were fortunate to receive CDC support, given the early success in

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enrollment, to increase that number to 6,000 participants and actually just completed that enrollment target a few months ago.

The study is designed to provide up to 18 months of follow up for all of those enrolled and collecting a variety of outcomes through a variety of data sources. What I think makes the registry unique has been an early focus and an early sort of attention to patient reported outcomes, largely using existing patient reported outcomes to understand the long term sequelae of a COVID infection. And Erica will speak to that in a little bit.

The other thing that's unique about this study is this is where the use of the digital health platform comes in, is our hope to link those patient reported outcomes to other data that may be available in real world electronic health records. The goal of this is to really determine the risk of long COVID in adults presenting with symptoms of COVID infection compared to people with a negative test.

I think one of the interesting things about our study that often gets missed is that it's not only prospective, but we're enrolling people prospectively that had symptoms at the time of enrollment at a ratio of three to one, three positives to one negative amongst those who had a positive test for COVID versus those with a negative test. Next slide.

The digital health platform really is being used in this study to link across a variety of research work functions. There is a part of the digital health platform that's essential for screening and enrollment. We have a web-based approach to recruitment where we can direct anybody to that website, really not just within the eight geographies of those enrolling centers, but across the nation.

Screening questions can be answered by anybody via that webpage. They can provide electronic consent. They can sign up for the study, they can connect to the digital health platform and they can complete the initial baseline survey necessary to be enrolled in the study. And for some who are the most electronically savvy, that can be done entirely without any additional contact. That said, we have a tremendous amount of research support and resources that we have put in to make sure that we're purposefully capturing a broader population that's more generalizable and not just those who may be the most tech savvy out there.

We can then use the digital platform to collect a variety of survey data. Some of these include socio demographics and data around employment and finances, as well as standardized measures of patient reported outcomes across a range of domains.

The same platform is then also used to connect each participant's various electronic health records to the study. The vast majority of people connect what is data from a hospital or a health system. Often, that may be the primary hospital or health system in which they receive care for COVID or testing for COVID at the time of enrollment.

That said, one thing we do notice is that particularly amongst younger populations, there may be people who don't have a primary health system, don't primarily have a lot of formal health system use and therefore may have a pharmacy portal or something else that has actually richer data available for the linkage.

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The reason this is important is that if we were to limit ourselves to studies around long COVID, people that are existing within EHRs, we'd be really prone to studying those who access care, seek care in traditional hospital or ambulatory healthcare settings and who have the ability to access care in those settings. And so our hope has been to use the digital platform here as a way to broaden access to the research study and also be able to capture populations that may otherwise be absent from prior retrospective for. Next slide.

How have we gone about recruiting and screening. One of the things that was really fascinating about doing this project is we had to flip a lot of our conventional approaches to research on their head when we kicked off the study. This was a study where the discussions with the CDC about beginning the study occurred in 2020 and the build of the actual recruitment modules and the ability to do this study were occurring by late 2020.

And so we did a lot of different things. We partnered with community leaders and health departments and several geographies to help identify individuals who tested positive or were being tested for COVID. At some sites they were able to work with their health system to get an electronic health record review of anybody who was tested, not just necessarily within the hospital, but potentially a drive up or ambulatory testing sites that are run by health systems.

We did digital advertisements via a variety of venues, both social media and non-social media. We recruited in many different settings. We found that recruiting particularly in ambulatory settings and testing sites became a higher yield way to identify individuals who are interested in the study and broaden the population. As an evolution from our very early enrollments that were largely in a hospital based setting.

We pre-invited a lot of telephone support and that text and phone based support along the way for these interactions. Some people received a very high touch approach to recruitment versus those who required less touch. And that was largely driven based on sort of not just their sort of experience with using digital health platforms, their familiarity with these types of tools, but also for them to learn about the study themselves. Our hope and ethos of this project from the beginning has been that it is a partnership with the participants in this study throughout this work. And in to do so, it was very important to us that we had an open channel of communication with anybody who was interested in this study from the beginning.

The final thing I'll note on the recruitment and screening methods for this study that are unique is in comparison to a lot of other prospective observational registries that may have in person contact, given all the limitations with recruiting individuals and participants early in the pandemic, particularly around exposures, research staff safety, we built the recruitment model for this at many sites in a virtual platform where essentially we were able to make virtual contact with patients often through something as simple as a text message early to express interest in a study and then go through the entire recruitment and enrollment process in a virtual manner without ever having the in person contact that many of our study states were used to in a pre COVID era. Next slide.

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So what did this look like? Often a participant would access a link to Hugo Health, which is the digital health platform we used via website. That could be via computer, smartphone, or tablet. Screening questions would be answered to confirm eligibility. And that would trigger a process on the participant side as well as on research staff side to identify whether or not and confirm whether an FDA approved screening test was used for COVID-19.

Once that was done, participants would link their digital health portals to the INSPIRE Study by giving permission for the research team to use their data for research purposes and then begin to receive surveys via the digital health platform, Hugo Health itself, or via emails, or they could be received text links and people would sort ask for getting the content in a way that was best suited to them. Surveys are conducted every three months from baseline up to 18 months. Intermittently, we are also able to pull digital personal health records data largely from electronic health records into the study data set as well. Next slide.

This is a quick picture of what this looks like. Click again for the animation. Amongst 5,982 that had been enrolled and were actively participating in this study, you can see that about 50%, 3,076 have an active health system portal. There are some other incremental percentage that also have a pharmacy portal that is linked to the study. But the important thing I think that's worthy of recognizing within this is that just as there is different challenges and follow up with any type of prospective observational study and outcome ascertain whether you're calling patients or you're following up with them via surveys or sending them emails, the same is true for the connectivity of patient portals and electronic health records.

So despite a lot of the improvements that came from the Cures Act at reducing data blocking, there are still many practical barriers that can make it challenging and difficult for individuals to link their own hospital health system portal to a digital platform, and more importantly, to keep it connected over time. Often there will be password changes, different sort of version changes that happen within a platform, within an app, within the actual electronic health record system used by a hospital and health system. Each of those creates a different friction point that makes sort of the sustaining of a portal connection and the sustaining of that real world data increasingly challenging. Next slide.

You can click to the next one. What kind of data do we see? When we are able to make that portal connection, when we're able to see that EHR data, what we often find is that we get a lot of diagnosis data, immunization data. Test result data particularly is probably the most prevalent of all the data types that we see. But even amongst that, what's interesting is that it's not always that there's not always a COVID data point present. We also do see a fair amount of medication data through these portals.

The challenge and the reason why I think I wanted to present this slide for everybody to understand is that in general it's very difficult to get a full fingerprint or a full picture of someone's electronic health record data. Because we receive care in such disparate and fragmented settings and from disparate and fragmented providers, what we often see is that even in a primary portal linkage where somebody has access to, in these cases often

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enterprise-wide implementations electronic health records, it's really half to two-thirds of the data that we're able to capture for many given individuals. Next slide.

Another data challenge that's presented is trying to retriangulate and understand the differences between real world electronic health record data and something such as, in our case, an RA verification of gold standard. One of the analysis we did early on was to understand the electronic health record data around COVID testing in comparison to the project study step we have in which RAs mainly verify a lab test result.

So amongst the 5,983 that had been enrolled, 3000 participants had had an EHR data portal connection, of which 1,658 had in that EHR or COVID-19 test result available at the time of their enrollment that aligned with the time that the RA verification was preserved. What we said is we said, "Let's look if plus or minus three days from when the RA verified a test result as positive negative to see if we can find the same result in the electronic health record."

What we found is in some ways very fortunate, 99% of the time if the RA said it was negative, we find a negative result in the EHR. Very low amounts of time where the NI, only one case where the RA said it was negative and the EHR had a positive test.

What's challenging here amongst all of these is the cross where the RA in 285 instances or 25% of cases identified a person as being positive for COVID even though the EHR had that as negative. That reflects the complicated nature of COVID infection. We know there are false positive and false negative results to initial tests, and that certainly is a component of this. We know that the likelihood of those test results changes with each day of illness. So you can imagine many scenarios where somebody may have a negative result on a PCR performed at a hospital, take a rapid home test the next day that comes back positive and ultimately be included in the INSPIRE registry as a positive for COVID-19 when in fact the EHR results shows something different. And so these are the sort of data considerations that we've been wrestling with as we start constructing studies/substudies within our registry. Next slide.

This is my last one. So how do you deal with this? I think from a real world perspective, when we're trying to do research with these types of data, we have to start understanding that no data is perfect, that there are a variety of data that we will get with different levels of signals and noise, and we start thinking about how we can do something smarter with that data and do research in a different way.

And so one of the things we have done within the INSPIRE Study for example is when trying to understand the relationship between vaccination and long COVID symptoms is to use both, not limit a study to only those that may have electronic health record data available or limited only the people who've responded to the surveys knowing that follow up rates vary, but rather glean what we can from both where we have 20% of participants that may have say EHR data available, but limited survey data. On the other hand, we have 50% of respondents with good survey data about vaccination status, but no EHR portal linkage. You put those two together and we get roughly 65 or 70% of the entire registry where we can start to construct a variable around who's had vaccination

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prior to their COVID infection to understand what that role of a COVID post vaccination infection is means for long term symptoms.

And so these are the ways we've sort of been dealing with some of these data. I'm going to turn it over to Erica now so she can describe some of the patient reported outcomes for this study and then describe some of the next steps of where we're going.

Dr. Erica Spatz

Thanks so much, Arjun. Next slide please.

I'm just going to take a little detour to talk about our patient reported outcome collection and discuss some of the surveys that we're using as well as some of the challenges in collecting PROs and interpreting PROs and what we anticipate to be some of the challenges that come up when we are matching with clinical data.

One of the main challenges for long COVID research is that there's no definition of long COVID. So we don't have a survey that can diagnose long COVID. Long COVID is very heterogeneous and can look very different. So one of the main questions that's asked of our study is how many people have long COVID or what is the severity of long COVID amongst people who have ongoing symptoms? There's really no good answer to that. And so we're pretty careful about not diagnosing conditions or labeling people based on symptoms or surveys that were not created for long COVID.

At the same time, we recognize that many people are experiencing symptoms and impacts on their quality of life, and we want to capture the range of these many different effects. That's important to really reflect the patient experience and to make sure that we're being comprehensive, but it also poses a challenge for analyses, right? We don't have a primary outcome. And so if we're looking for factors that are associated with long COVID, we need to kind of create composite variables that potentially describe long COVID, recognizing that we could get into a pickle of multiple analyses and what that means for understanding the factors that are associated with these outcomes.

And of course, in any longitudinal study, Arjun was mentioning the INSPIRE Study is 18 months. There's dynamic COVID positivity status. So the people that were enrolled in our study that were initially COVID negative may be exposed later on and become COVID positive. And so tracking the dynamic COVID status of patients and interpreting that in light of their PROs is another challenge that really requires good data collection, and like Arjun was saying, integration of both patient reports as well as clinical data from the EHR. Next slide.

You could go to the next slide. Great. So what are some of the PROs or other surveys that we're using in our INSPIRE Study? We are mostly looking at a pretty large range of baseline characteristics to understand the acute COVID illness, how severe it is, whether they were hospitalized. Again, as Arjun was saying, we have very few that are hospitalized since we were mostly targeting outpatient COVID testing centers will also get a baseline check

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on their symptoms from COVID, their baseline comorbidities and baseline social and lifestyle factors like their employment status and social determinants of health.

At every three months, we are doing a pretty deep dive into symptoms as well as patient reported outcomes. We are using the persons under investigation, CDC symptom checklist to understand whether symptoms have never occurred, resolved, persisted, or emerged. We are also using a CDC short symptom screener for myalgic encephalomyelitis/chronic fatigue syndrome that is used by the CDC to understand some of the more systemic symptoms.

And then for outcomes, we're using the PROMIS-29, which as many of you may know has seven dimensions including physical function, anxiety, depression, fatigue, social participation, sleep disturbance, and pain, as well as the PROMIS-8a, which assesses cognitive function. And then some more global health measures like return to work, exercise vital signs, PTSD, and global health status. Next slide.

This is the CDC short symptom screener for ME/CFS. I show it to you because the questions are really good. They delve in deeply into the things that we hear most from patients that we see clinically who are struggling with symptoms, fatigue and exhaustion, muscle aches, pain in the joints, unrefreshing sleep, forgetfulness and memory issues, difficulty thinking or concentrating, dizziness or fainting. These questions are posed to patients and they're asked, "How long have you had the symptom? Was it present before you had your COVID test?" Next slide.

And then it goes deeper into what's the frequency of these symptoms, the severity, does rest make it better, what's its impact on occupational, educational, social, or personal activities, is it worse with physical or mental exhaustion. But still the challenges is that this is a screener for ME/CFS. But as you can see, if we take a real look at what's in this survey, many of these symptoms can be present with other post-infectious syndromes that people may be presenting for as well as they can accompany chronic disease, they can accompany acute illness. So distinguishing what is long COVID from what may be another viral sequelae or other medical illness is a challenge. Next slide.

We do a good job of trying to look at our data across the different sites with quality checks. We have a few papers that are in the works around the first 1,000 patients and weekly communications around enrollment, the ratio of COVID positive to COVID negative, the survey completion rates, and the connection to EHR data. Next slide.

This is just an example of the weekly emails that we give to try to make sure that we are being as complete in our survey data collection at three months and six months. So we'll get a weekly email about how many people are up for their three month survey, how many completed it. This helps our team really rapidly pivot to engage people that are not filling out their surveys to ensure that our data are the most represented. Next slide.

I'm just kind of going to close because I know we're out of time. There's a lot of trade offs with different outcome assessments. PROs are critical to understanding long COVID, but leave a lot of data gaps. There's a lot of

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concerns that we're not measuring clinical entities like POTS, which require vital signs and lab tests and are uncertain about how much that is to characterize long COVID. And PROs may not distinguish long COVID from other post-infectious syndromes or other disease entities that cause prolonged symptoms, fatigue and other systemic disorders, but I think that they help to capture still the patient experience and help us differentiate people that are really struggling in their recovery versus those who aren't.

Thank you so much for your attention and I look forward to the Q&A session.

Beth Linas

Thank you, Dr. Spatz. Now we'll hear from the discussant, Andrew Weitz.

Dr. Andrew Weitz

Thank you. Actually, a really big thanks to our speakers. Those were some amazing state-of-the-art demonstrations about how mobile apps, wearable devices, and other electronic healthcare data can help inform the status of an individual as well as a population of individuals. There's a lot of content packed into those presentations, so I'd like to take maybe just a minute or two to review some of key points and then we can move into the question and answer session.

So first, from Dr. Kheterpal's talk, we learned about the different types of digital tools that can be used to collect health data remotely from individuals. We also learned about the advantages of using these types of tools in clinical studies. So being able to obtain continuous measurements from people in real time and in their natural setting. I guess not in the zoo like Vik called it, and to do so with minimal burden on the individual.

You can imagine how this type of remote low burden data collection could offer many benefits for studying the health of individuals with PASC with long COVID because these individuals may be dealing with excess fatigue and cognitive impairment as well as a condition that changes frequently.

So second, we heard from Dr. Radin and her talk focused on using one of those tools introduced by Vik, which was wearable devices. Dr. Radin presented several of her studies that leverage wearable device data as well as analytical or data driven algorithms to detect influenza-like illnesses, COVID, physiological responses to vaccines, long term effects of COVID, and amazingly even being able to predict COVID case counts into the future.

And then finally we heard from Dr. Venkatesh and Dr. Spatz who told us about how patient reported outcomes and electronic health records can be used to understand long COVID. But importantly, we also heard about some challenges and limitations with relying on just those data types as opposed to more traditional health assessments conducted in person at clinical sites.

So there's a lot of promise here. These technologies are quite new. They've only been commonplace for the past five or 10 years. The Apple Watch, it was invented in 2014. Smartphones have only been in our pockets for the past 15 years or so. And it's only really more recently that we've begun to use these types of technologies

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for research and healthcare. So it seems to me at least that we're only beginning to scratch the surface of what's possible. So with that, I'd like to maybe pose a few questions to some of the speakers before we take some audience questions.

So the first one I'd like to ask about is health equity. Jennifer, you touched on this briefly, but maybe we could explore it in a little more detail. So as more and more studies are leveraging wearable devices, mobile apps to capture data remotely from individuals, how can we ensure that people who don't own these devices, who don't have smartphones, computers, or wearable devices are able to participate in these studies?

Dr. Jennifer Radin

Yeah, that's a great question. I think the one thing is these devices are continuously getting cheaper and cheaper over time. As you can see, it went from one to five to now one to four Americans who now wears these devices. But I think there's great potential from almost going to less advanced devices. So your smartphone camera actually can do a great job of measuring your heart rate and your respiration rates. If you carry your phone around, you're going to get a step count. There's even apps that do sound... They listen for sound to measure sleep. So there's many different ways that we can collect this data without relying on the more traditional expensive wrist worn devices.

I think also our group has provided devices to individuals who are underrepresented to join our study, and that's another avenue although it does get quite costly. So I think, yeah, it's something to consider and something that we're continuously striving to do a better job at.

Dr. Andrew Weitz

Thanks, Jennifer. And maybe Vik, I'm not sure if you could speak to maybe how RECOVER is tackling that challenge of just people not owning these devices.

Dr. Vik Kheterpal

Yes, part of the RECOVER Initiative in order to layer in and ensure that we have diverse populations being able to participate in contributing the digital phenotype, there is approximately 10,000 devices that RECOVER will be funding and distributing with priority distribution to those that are underrepresented for whatever reason. This is the same model we have leverage in initiatives such as the All of US initiative. So that hopefully closes the gap that is obviously have great concern.

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Dr. Erica Spatz

Thank you. So next question, maybe getting into a bit more on some of the limitations or challenges that Dr. Spatz and Dr. Venkatesh discussed. We heard about how patient reported outcomes and other kind of similar measures can be less reliable than traditional assessments collected in person at the clinic. And that could speak to some potential limitations of a purely virtual approach to this type of research. So I guess the kind of in the middle approach could be some sort of hybrid approach where you have a remote option available to participants in a study, but you're also having people come into the clinic. And just curious if any of our speakers have explored that, done those types of studies. It's actually my understanding that that is the RECOVER approach. So I would open that question to really anyone.

Dr. Andrew Weitz

Thank you. And maybe I-

Dr. Arjun Venkatesh

I was going to say, I think it's also worth noting that the use of digital tools for research is by no means meant to be replacing or to eliminate or mutually exclusive with a lot of in person or more traditional research methods that have been used in the past.

I think of this often just in my clinical environment when I'm taking care of a patient, the electronic health record doesn't take care of the patient, right? It just is a tool that allows me to work in a different way, have different access to information and do that work hopefully better and take care of a patient better.

The same is true in the research world. I think often these digital tools, and you can even see this as people are presenting their projects, are enmeshing with how people conduct research. I think it allows us to conduct research at either a different scale. It allows us to potentially make research more accessible in certain ways. It allows us to potentially capture certain outcomes we otherwise couldn't have done, but all in a way that's often augmenting very human traditional research processes, very standard research designs, right? We're not totally changing the concept of how to do a research study, rather we're doing these things in a more efficient, productive way, in a way that I think is hopefully more partnered with patients and is also more accessible to people.

Dr. Jennifer Radin

Yeah. I think it depends on the research question whether you need that in person visit or not. I think there's a lot of growing potential to collect remote blood samples to, as Vik mentioned, the CARE evolution platform does connect to electronic health records so we can pull in that data. There's so many new sensors that

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can look at cough recognition that do sound recordings. So I think there really is a potential to do a truly decentralized trial as well.

Dr. Vik Kheterpal

Maybe to sort of add onto that, I do think the research techniques, the data analysis techniques for some of these digital data, whether it is due to the variation on the device itself, the wear time, there are some questions related to self-efficacy at home, I think the methodology of how we undertake analysis is a bit different. It takes a different way. It's rather than focusing on consistent data input into the statistical analysis, I do think the data science and the big data techniques to smooth out the noise much like we would do throwing out the high score and the low score, those kinds of techniques become ever more important in some of these kinds of digital health data.

And then the notion of individual trajectories tends to smooth out the day to day moment to moment. So some of the things that help out are that the end usually is massive, potentially orders of magnitude larger that we're talking about in participant pool itself. And secondly, the data itself is longitudinal. And frankly, very few initiatives have data pre four, five years out. Fundamentally, PASC is the post-acute sequelae. And so the kinds of techniques that have to be used to compare things over a three to four year basis, one has to be quite innovative about that.

Dr. Andrew Weitz

All really great answers. Thank you everyone. I think now we are going to be moving over to our audience question portion of the session.

Beth Linas

Yep, thank you. Most of the questions that came in are sort of can be thrown to anyone, so I'll just pose them and whoever feels like answering can. So the first one was, "How do you deal with hardware related variants or issues? For example, a broken hardware error can create a hole in data, whereas an improperly warm watch could change the results plus each manufacturer has other issues with the devices."

Dr. Jennifer Radin

Yeah, that's a great question. One that as Vik said, we like to compare each individual to themselves over time. So if you're always wearing your watch loosely, that will carry over time. So we won't deal with that variation of changes. I think there's definitely differences and algorithms across devices. For example, resting heart rate calculated by a Fitbit is different than an Apple watch, and these algorithms are proprietary. I think again going

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back to comparing someone to themselves over time helps to get around some of that noise that when you start comparing devices.

Beth Linas

Actually, there is a question for Dr. Radin. The question was, "Tell us more specifically what sensor data is collected that improve the machine learning algorithms. What information is collected that can improve their ability to determine that someone has COVID in particular and not just some other virus?"

Dr. Jennifer Radin

So that study was actually done by one of my colleagues. He was able to use whatever data was available. So if someone was missing their sleep data, he would use the resting heart rate and activity data. He also used self-reported symptom data for that model. But it was the basic three metrics that we've been using, resting heart rate, sleep and activity when available.

Beth Linas

Also, a general question, "What about economic biases from participants being able to afford mobile self-tracking devices? Is their work being done to engage other populations as well?"

Dr. Jennifer Radin

Yeah, I think that goes back to the initial question, is, again, going back to low tech technology, the smartphone and your camera can do a cheaper job than a wrist worn device potentially just as well. So I think looking for other solutions and providing devices when they are available.

Dr. Vik Kheterpal

And again, we are funding device distribution for the economic issue specifically.

Beth Linas

Great. Another question, very similar. There are a couple questions about understanding natural variations from true changes and as well sort of how do you know this sensor is accurate.

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Dr. Jennifer Radin

There have been a lot of validation studies for these sensors and have found that they do quite a good job at measuring, say resting heart rate when someone's truly at rest. There's a lot more noise when someone's active and moving around, but finding... They'll continually improve over time and also looking at other places people can wear these sensors. So a chest worn sensor that sticks to your chest might do a better job of say measuring temperature fluctuations than a wrist worn sensor does. So there's different places to wear them that might be more accurate as well.

Dr. Vik Kheterpal

Maybe just adding to that, certainly there's some work going on to compare and contrast the correlation between, so to speak, these multi parameter sensors that are marketed for general use or fitness use. These are not, per the FDA, medical devices, they do not require a prescription. I think part of what the reason for focusing on this, most of the kinds of data we're looking to develop in the digital phenotype is over six months, 12 months or longer as to how the lived experience of an individual is. That's really hard to achieve with medical grade devices, whether they are patches or what we tend to define traditionally in research as a gold standard device.

So I think there's a fundamental challenge of how to get high wear time, number of hours per day and more importantly over a year or two. And so there's some proxies, right? So if usually those kinds of devices are targeted towards an N of 200 or 300, here we are targeting, and in the kinds of data that have been shared, 6,000 to 8,000 in INSPIRE, 40,000 in DETECT, RECOVER is targeting 40,000 participants, maybe even a broader underlying pool. There is variation, but having that much data over a protracted period of time, one can create proxies. And a lot of the frontier work that's going on is to come up with new markers for what that means.

I'm reminded of things like consumer grade temperature probe, axillary versus oral versus rectal versus ear, and the variation in the fact that one has to come up with new models to figure out how to use those data and still find signal in it.

Beth Linas

Thank you. I think we have time for a couple more questions to the group. "As RECOVER and other initiatives begin to test new therapies for treating PASC, how can mobile apps and wearable devices be leveraged to access treatment efficacy?"

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Dr. Erica Spatz

Well, I guess I could take this question. I think there's many ways that we can check test treatment efficacy. In the case of long COVID, a lot of that is going to fall to patient reported outcomes. How well are people functioning in their daily lives?

I think that some of the key points to that are to make sure we're capturing the right outcomes. So partnering with patients to ensure that we're asking the right questions. If the therapy is targeted towards increased exercise tolerance, then the physical activity data on a smart watch can be extremely helpful for showing what their step counts are or times that they're sedentary. So it depends on what is the treatment and what are the outcomes that we're looking at, but I think that between with Jennifer and Vik are showing with wearables and sensors and combined with patient outcomes, you could really get a more full picture.

Some of the interesting things will be to use more to aggregate that data so that we can interpret it. Because you could imagine if you're just an average clinician and you have multiple data streams on these different things, we need to get a fuller picture. So maybe the algorithm creates a fuller picture and says, "How well does this match what we think is happening in your clinical recovery?" And the person says, "Yeah, that's me. I'm doing a lot more, but I'm still suffer struggling with this." So we may think about different ways that we can evaluate outcomes that are much more patient-centric.

Dr. Jennifer Radin

Yeah, I think also getting that longitudinal data, especially if someone has a device that they've worn before they got sick, that really gives us the unique baseline for what their data looks like. So what is their unique resting heart rate, activity levels, and sleep? And then figuring out when they actually return to that pre infection baseline.

Dr. Vik Kheterpal

Yeah, I think there's subjective QOL measures that constitute PROs, but there's also objective measures return to baseline of course as Jennifer mentioned. But there's things like absenteeism, days missed at school and other kinds of things interestingly that are well understood in this context for some of the more severe to moderate PASC sufferers. Those are interesting endpoints. They may not rise to ER visits or hospitalizations or diagnosis codes in EHRs, but I think that's part of the frontier of how to define in the patient's terms those kinds of objective measures beyond a survey based response.

So we think there might be three different ways of thinking about treatment efficacy. "Am I back to my normal life as defined by going to work, going to school? Am I back to normal in not having to pace myself in my activity, mobility? Is my sleep back to my normal which tends to self correct for other comorbid and other

conditions that may exist?" And third of course more traditional PROs that measure QOL.

Beth Linas

So I just want to thank our presenters very much. Thank you to our audience for attending the seminar and engaging with the Q&A. As a reminder, a recording of today's seminar will be available on recoverCOVID.org within a few weeks. I'll also be posting a Q&A document that has responses to the questions we received today, including those we did not have time to address. We have some exciting topics coming up and we hope to see you at future sessions. I believe Shane has a brief survey, a poll, sorry, that he would like you to take. Thank you and have a great day.

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/