RECOVER RESEARCH REVIEW SEMINAR

LEVERAGING MOBILE HEALTH PLATFORM TECHNOLOGIES TO
UNDERSTAND PASC

October 11th, 2022
12:00 – 1:30 PM
EDT

Responses to Participants' Questions

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

This document provides responses* to questions raised by webinar participants related to the following presentations at the R3 Seminar *Leveraging Mobile Health Platform Technologies to Understand PASC* held on October 11, 2022:

- **Presentation 1:** *The Opportunity and Need for Digital Tools and Phenotyping to Help Understand PASC*

  Vik Kheterpal, MD

- **Presentation 2:** *Using Wearable Data to Quantify Long COVID*

  Jennifer Radin, PhD, MD

- **Presentation 3:** *Digital Health Platforms for Collection of COVID-19 Outcomes Data: The INSPIRE Study*

  Arjun Venkatesh, MD, MBA, MHS
  Erica Spatz, MD, MHS

- **Discussant: Andrew Weitz, PhD**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. How can we ensure that people who don't have smartphones, computers, or wearable devices are able to participate in these studies?

Response:

Dr. Radin: That's a great question. One thing is that these devices are continuously getting cheaper over time. As noted in our presentation, the proportion went from one in five to now one in four Americans who now wears these devices. Also, there's great potential in going to less advanced devices. Your smartphone camera 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 are even apps that listen for sound to measure sleep. So, there are multiple ways that we can collect these data without relying on the more traditional, expensive wrist-worn devices.

Additionally, our group has provided devices to individuals who are underrepresented in biomedical research to join our study, which is another avenue, although it does get costly. I think it's something to consider and something that we're continuously striving to do a better job to address.

Dr. Kheterpal: Part of the RECOVER Initiative is to layer in and ensure that we have diverse populations being able to participate in contributing the digital phenotype. Consequently, RECOVER will be funding and distributing approximately 10,000 devices, with priority distribution to those that are underrepresented in biomedical research for whatever reason. This is the same model we've leveraged in other initiatives, such as the *All of Us* Research Program. Hopefully, this will help close this gap, which is obviously of great concern.

Q. How will post-exertional malaise (PEM) be captured via electronic health records (EHRs)?

Response:

Dr. Kheterpal: You're absolutely correct in raising the challenges in capturing PEM in EHRs because it often eludes a definitive "diagnosis" today. Tools designed to enable the patient to describe their complex and varying symptomatology, such as the tool we were sharing, are necessary to capture the variation across patients and within the lived experience of the patient. We've been focused in working with the PEM community to design improved tools that give the patient agency in defining and sharing their symptom; for example, Symptom Shark: https://symptomshark.org/me-cfs-long-covid.html.

Q. Following up on some of the limitations or challenges that Dr. Spatz and Dr. Venkatesh discussed. We heard about how patient-reported outcomes (PROs) and other kinds of similar measures can be less reliable than traditional assessments collected in person at the clinic, which points to some potential limitations of a purely virtual approach to this type of research. An option could be a hybrid approach that includes both virtual or remote assessments and having people come into the clinic. I'm curious if any of our speakers have explored or conducted these types of studies.

Response:

Dr. Spatz: What we need to do is to distinguish what is a study visit from what is a clinical visit with an added-on PRO. When PROs are administered to people who are not patients, we need to interpret the responses in the context in which they're answering the survey. Sometimes that context is unknown to us. So being in person is not just about how completely they're filling out the survey or having somebody to ask if they need help with a question, it also situates them in a time and a place that we may know more about.

In-person visits can complement virtual visits, but we want to think about the purpose of them and make sure that we're optimizing people's time so we can maximize what we're understanding from the patient and to think that they're necessarily the same. Somebody may says, "Yeah, no problem, I can do it virtually" or somebody who says, "No, I'd prefer doing it in person," but it's not totally clear that we're getting the same level of data because of these distinctions.

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Dr. Venkatesh: It's also worth noting that the use of digital tools for research is by no means meant to replace or eliminate a lot of in-person or more traditional research methods that have been used in the past.

I think of this often in my clinical environment when I'm taking care of a patient; the electronic health record doesn't care for the patient, right? It's just 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. Often these digital tools are enmeshed with how people conduct research. It allows us to conduct research at a different scale, to potentially make research more accessible in certain ways, and 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 and very standard research designs. We're not totally changing the concept of how to do a research study. Rather, we're doing these things in a more efficient and productive way that is hopefully more partnered with patients and more accessible to people.

Dr. Radin: It depends on the research question whether you need that in-person visit or not. For example, there's a lot of growing potential to collect remote blood samples. As Dr. Kheterpal mentioned, the CARE evolution platform connects to electronic health records, so we can pull in those data. Also, there are many new sensors that can look at cough recognition using sound recordings. There's really potential to do a truly decentralized trial.

Dr. Kheterpal: Given the research techniques and the data analysis techniques for some of these digital data, whether it's due to the variation on the device itself or the wear time (there are some questions related to self-efficacy at home), the methodology of how we undertake analysis is different. Rather than focusing on consistent data input into the statistical analysis, the data science and the big data techniques smooth out the noise much like we would do in throwing out the high score and the low score. These kinds of techniques become even more important in some of these kinds of digital health data.

The notion of individual trajectories tends to smooth out the day-to-day, moment-to-moment data. Some of the things that help are that the n usually is massive, potentially orders of magnitude larger than we're talking about in the participant pool itself. Also, the data are longitudinal. And frankly, very few initiatives have data for 4 to 5 years out. To study PASC, we need to be quite innovative about the kinds of techniques that are needed to compare things over a 3- to 4-year basis.

Q. 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.

Response:

Dr. Radin: As Dr. Kheterpal said, we like to compare each individual to themself over time. So, if you're always wearing your watch loosely, for example, that will carry over time and we won't need to deal with variation. There are definite differences and algorithms across devices. For example, resting heart rate calculated by a Fitbit is different than by an Apple watch, and these algorithms are proprietary. Going back to comparing someone to themself over time helps to get around some of the noise that occurs when you start comparing devices.

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Q. Tell us more specifically what sensor data are collected that improve the machine learning algorithms. What information is collected that can improve their ability to determine that someone has COVID specifically and not some other virus?

Response:

Dr. Radin: That study was done by one of my colleagues who was able to use whatever data were 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.

Q. 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?

Response:

Dr. Radin: Going back to low-tech technology, the smartphone, and your camera can do a cheaper job than a wrist-worn device and potentially just as well. So, I think we can look for other solutions and provide devices when they're available.

Dr. Kheterpal: We're funding device distribution to address this economic issue specifically.

Q. How can we separate variations between devices from true changes in a patient? How do we know that sensors are accurate?

Response:

Dr. Radin: A lot of validation studies for these sensors have found that they do quite a good job at measuring, for example, resting heart rate when someone is truly at rest. There's a lot more noise when someone is active and moving around. Sensors will continually improve over time. Also, there are different places people can wear these sensors to improve accuracy. A chest-worn sensor that sticks to your chest might do a better job of measuring temperature fluctuations than a wrist-worn sensor.

Dr. Kheterpal: Some work is going on to compare and contrast the correlations between these multiparameter sensors that are marketed for general use or fitness use. These are not, per the FDA, medical devices; they do not require a prescription. Part of the reason for focusing on this is that most of the kinds of data we're looking to develop in the digital phenotype is over 6 months, 12 months, or longer to understand the lived experience of an individual. That is hard to achieve with medical-grade devices, whether they're patches or what we tend to define traditionally in research as a gold-standard device.

There's a fundamental challenge of how to get high wear-time, specifically the number of hours per day and, more importantly, over a year or two. There are some proxies. If typically those kinds of devices are targeted toward 200 or 300 participants, RECOVER is targeting—and in the kinds of data that have been shared; 6,000 to 8,000 participants in the INSPIRE study; 40,000 participants in the DETECT study—40,000 participants. While there is variation, having that much data over a protracted period allows one to create proxies. And a lot of the frontier work that's going on is to come up with new markers for what that means.

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I'm reminded of things like a consumer-grade temperature probe—axillary as compared with oral as compared with rectal as compared with ear—and the variation in the fact that one needs to come up with new models to figure out how to use these data and still find a signal.

Q. 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?

Response:

Dr. Spatz: There are many ways that we can 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?

Some of the key points include making sure we're capturing the right outcomes. This entails partnering with patients to ensure that we're asking the right questions. If the therapy is targeted toward increased exercise tolerance, for example, then the physical activity data on a smartwatch can be extremely helpful for showing what their step counts are or times that they're sedentary. It depends on what the treatment is and what are the outcomes that we're looking at. But I think that what Dr. Radin and Dr. Kheterpal are showing with wearables and sensors, when combined with patient outcomes, could really provide a fuller picture.

One of the interesting things will be to aggregate these data so that we can interpret them. Because you could imagine if you're a 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 suffering and struggling with this." We may think about different ways that we can evaluate outcomes that are much more patient-centric.

Dr. Radin: 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 look like, such as what is their unique resting heart rate, activity levels, and sleep. And then we need to figure out when they return to that preinfection baseline.

Dr. Kheterpal: There are subjective quality of life measures that constitute patient-reported outcomes, but there are also objective measures of return to baseline of course, as Dr. Radin mentioned. However, there are things like absenteeism, days missed at school, and other things that are well understood in this context for some of the more severe to moderate PASC sufferers. These are interesting endpoints. They may not rise to emergency department visits or hospitalizations or diagnosis codes in EHRs, but that's part of the frontier of how to define in the patient's terms the kinds of objective measures beyond a survey-based response.

So, we think there might be three different ways of thinking about treatment efficacy: (1) Am I back to my normal life, as defined by going to work or going to school? Am I back to my normal life in not having to pace myself in my activity or mobility? (2) Is my sleep back to my normal, which tends to self-correct for other comorbid and other conditions that may exist? and (3) What more traditional patient-reported outcomes measure quality of life?

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Q. Can Dr. Radin tell us more specifically what "sensor" data are collected that improved their machine learning algorithms? What information is being collected that can improve their ability to determine that someone has COVID specifically and not some other virus?

Response:

Dr. Radin: This question is referring to a study on Passive Detection of COVID-19 with Wearable Sensors and Explainable Machine Learning Algorithms | npj Digital Medicine (nature.com) . In this study, we used any sensor data that were available to us, such as resting heart rate, activity, and sleep. In general, we've seen that symptomatic participants who tested positive for COVID-19 have much larger deviations in their sensor data compared with individuals who were symptomatic but tested negative, and likely had a different respiratory virus. This is shown in the figure in this study: Assessment of Prolonged Physiological and Behavioral Changes Associated With COVID-19 Infection | Infectious Diseases | JAMA Network Open | JAMA Network .

Q. Do clinical-grade devices show different results from commercial-grade products?

Response:

Dr. Radin: For the DETECT study, we compared each person to their baseline or average. Because we're focused on deviation or change, rather than the absolute number, it's unlikely that the data collected from commercial-grade devices would be much different. However, we didn't specially compare clinical-grade devices with commercial-grade devices for our study.

Webinar Slides

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

To Learn More

- Information about RECOVER research and to volunteer for studies: https://recovercovid.org/research

- Frequently Asked Questions about RECOVER and PASC: https://recovercovid.org/faqs

- CDC information: Information for the general public and for healthcare providers about post-Covid conditions: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/

- For medical/scientific terminology: https://medlineplus.gov/healthtopics.html