Responses to Participants' Questions

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

This document provides responses* to questions raised by seminar participants related to the following presentations at the R3 Seminar *Understanding Metformin Use and Long COVID and ME/CFS [Myalgic Encephalomyelitis/Chronic Fatigue Syndrome] Following COVID-19 Infection: Insights from Two Studies,* held on May 13, 2025:

- ***Understanding Metformin Use and Long COVID***
  Carolyn Bramante, MD, MPH
  Steven G. Johnson, PhD
- ***Incidence and Prevalence of Post-COVID-19 ME/CFS***
  Suzanne D. Vernon, PhD
- **Discussant: Yu Chen, PhD, MPH**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. There seem to be different results between the 2 cohorts, PCORnet and N3C. Specifically, there's a known association in PCORnet using the computable outcome. The hazard ratio is 1.04. So, what are the potential explanations for this finding? I think you mentioned that these 2 cohorts are very different and that the computable outcomes are very different, but could you please elucidate?

Response:

Dr. Bramante: I am not a computable phenotype expert, but I will try to put these in an analogy with a clinical trial. So just looking at what was published in the paper, the unweighted frequencies are similar between the databases except for the computable phenotype. So, there's just a lot more people who met the computable phenotype definition with PCORnet's computed definition versus N3C's. And I think that PCORnet actually does have a new

definition now that might be a little bit more specific. But when you have an outcome that is so common, you can have outcome misclassification.

Let's say you hypothesize that this intervention is a professional archer. What does a professional archer do? They hit a target at a professional archer distance. Your *P*-value is the size of the target; your number of arrows is the number of analyses you do on that same pile of data. But what if you define the outcome incorrectly? You make it too easy to hit the target, you put the target too close. So basically, it's very easy to hit the target, you don't have to be a professional archer to hit the target.

And I did this in the acute outcome of the COVID-OUT [Outpatient Treatment for SARS-CoV-2 Infection] trial. We defined severe COVID as one low reading on the home oximeter, an ER [emergency room] visit, hospitalization, or death. But one low reading is not severe COVID. We know that now, but at the time we didn't know that. And so we made it too easy to hit the outcome target by just having one low oxygen reading so many people hit it. And you can see that in the results here. So, this is the same clinical trial I've shown earlier on the acute outcomes. In the first 28 days, 23% to 25% of people had the composite outcome. When you include the one low oxygen reading versus when you exclude that part of the composite outcome definition, it's 4% to 7%, 1% to 2%.

So basically, a bunch of people we think were misclassified as having the outcome, but they didn't actually have the outcome. They didn't actually have severe COVID just because they had one low reading on a home oximeter. And then when you look at the a priori sort of subgroups that look at a dose effect and the validity of the outcome, hospitalization and death, you can see how this outcome misclassification affected the results here.

And I think the same thing might be happening in the PCORnet computable phenotype where you have 25% as the incidence, so just a really high incidence. So, it might be very sensitive, but not specific. And then when you have more specific results, you get rid of people who don't actually have the outcome.

Q. Would it be justifiable to prescribe metformin even in people without diabetes or with lower BMIs [body mass indices]? Have you done any exploratory analyses to identify subgroups that may have a greater benefit from metformin?

Response:

Dr. Bramante: Yeah, so a few quick things I'll point out. So, this clinical trial, the 1,300 people, they all had a BMI greater than or equal to 25, and so they were classified as overweight or obese. And I'll come back to the second part of the question in a minute. As far as exploratory subgroups, we really haven't looked at just a BMI of 26 and below, but these subgroups were prespecified, and you can just see a little bit of a dose effect. Some started this study drug early, within less than 4 days of symptom onset, and we chose that subgroup because that was the primary analytic sample for the new antivirals being studied. But just logistically, we didn't think we could enroll an entire trial that quickly after finding people and consenting them. You can see this is for ER visit, hospitalization,

death, when you started metformin earlier, that point estimate moves to the left and that same sort of dose response was there in the Long COVID outcomes too. So earlier initiation, smaller point estimate.

So those results are there. We haven't done exploratory things, but the ACTIV-6 [Accelerating COVID-19 Therapeutic Interventions and Vaccines-6] clinical trial, that primary paper will be published soon. And that trial did not exclude people with a BMI under 25, so it included people with a BMI under 25. There were no safety events, there were no episodes of healthcare-measured hypoglycemia. And so, when that paper's published, it would probably make providers feel comfortable prescribing below a BMI of 25, but I think they could already feel comfortable and safe prescribing above a BMI of 25.

Q. ME/CFS seems to be a very important phenotype that may be related to a lot of viral infection. So, are there treatments for ME/CFS? Is there similarity between risk factors for ME/CFS and Long COVID besides the multiracial background that you mentioned?

Response:

Dr. Vernon: So, I'm not a clinician, but I work with Dr. Lucinda Bateman, who is an ME/CFS clinician and also part of RECOVER. And we spoke a little bit about metformin use in ME/CFS. Dr. Bateman has used metformin for some of her patients, and there does seem to be a particular ME/CFS phenotype that benefits more so. This is not published. And I think this is a dilemma that the whole ME/CFS field has had because again, more than around 90% of the people with ME/CFS are not diagnosed. So, there's only a handful of clinicians in the US that actually treat ME/CFS patients. There are no FDA-approved treatments. So hopefully RECOVER will help solve that. By understanding Long COVID, we will also gain a significant understanding of the pathophysiology as well as possible treatments for ME/CFS.

Q. Can you speak to what's been done to disseminate information to providers on metformin's role in reducing the risk of Long COVID?

Response:

Dr. Bramante: This could be its own lecture in and of itself, I think. The first point that I'll make is that it's very nonintuitive. It doesn't make sense at face value. So, it makes sense that even if someone saw it, it wouldn't land with them. That's one issue.

A second issue is, I was pretty inexperienced when our clinical trial results came out and I thought it was not at all my role to disseminate, just do the work and it'll shake out in the literature. But I think I have been pushed since then to do more to disseminate. And in looking at the first randomized controlled trial [RCT] of metformin versus placebo for treating acute COVID, there were a lot of mistakes and some sort of aspects of the inclusion criteria

that were not clear and that do dramatically affect the results. And we know that because the authors have been cooperative in sharing those corrections and what happens when those issues are corrected.

But when the first rounds of treatment guidelines were being developed, that was the only clinical trial available. And so, 2 treatment guidelines that I know of that mentioned metformin are sort of grounded in that clinical trial, which has an expression of concern published about it now, which means you can't use it for guidelines or decision making. But those guidelines don't necessarily take into account or even know about that update to the paper. I think the paper's going to be formally updated. And then the other guidelines just don't mention metformin. And that has been confusing to us, why it didn't reach the reviews in those guidelines.

But I do have an IND [Investigational New Drug application] for the COVID-OUT clinical trial and the FDA does review all data submitted with an IND. So, I have submitted for an EUA [Emergency Use Authorization] application as a way to help make sure we review all these data carefully and disseminate it. But that's really hard to do when you're not a manufacturer. But that process is moving forward. It will be slow, but individual clinicians don't have to wait for FDA action to prescribe something off-label.

Q. Were you able to capture or reflect any of the information for off-label use in the data you presented?

Response:

Dr. Bramante: Well, there's only one FDA indication for metformin and that's for type 2 diabetes. So, anything else is off-label. So, the prediabetes, the PCOS [polycystic ovary syndrome], it's often used for weight loss in kids and adults, so that's all off-label. And then of course the clinical trial was off-label, but we got an IND [approval] for it. And then with the new user trial and relation analysis, those were the few people who saw the early papers on metformin and who asked their clinician for a prescription when they got infected. That's who we presume, because they had no other indications for metformin, and that would also be off-label.

Q. Were there any social determinants of health associated with having ME/CFS, particularly in the racial and ethnic minority groups?

Response:

Dr. Vernon: We did not specifically look at that. But I have another question in there that asked whether or not we will dig deeper into those demographic characteristics and SDOHs [social determinants of health]. And we are. So hopefully we'll be able to answer that soon.

Q. Was post-exertional malaise the predominant symptom which contributed to the ME/CFS-like symptoms or ME/CFS-like illness among those who did not meet the full diagnostic criteria?

Response:

Dr. Vernon: I didn't look at that in particular. They could have any 1 of the 5 symptoms, but that's a good thing to look at and easy enough to do. I would suspect that post-exertional malaise is interesting because not many people know what it is. And even when they experience it, they don't know what they're experiencing. So much so that when we're studying it, we have to explain what it is in order to be able for people to say, oh geez, that's what I'm doing. Because I think there's a tendency to, when you start feeling better, to go ahead and resume normal activities, and that's actually an exertion that could then cause you to quickly relapse. It's just not something that kind of clicks in our brain.

So yes, post-exertional malaise is super serious. It is something that we all need to better understand and recognize. So, I would guess that it actually was not one of the more frequent ones, because a lot of people just don't know what it is.

Q. What was the trigger for looking more closely at metformin of all the medications and the diagnoses and everything that was happening with Long COVID? So why metformin?

Responses:

Dr. Johnson: I'll let Dr. Bramante weigh in a little bit. But the COVID-OUT study she talked about showed there was some benefit, but they asked the question, "Did the doctor say you had Long COVID or something?" It wasn't as precise as we'd like. And I would also say that, as Dr. Bramante talked about, I call them the mechanistic or simulation studies that looked at different compounds that might be effective against the molecular ways that the virus worked. I think that's what prompted some of these initial thoughts that metformin might be good to look at.

Dr. Bramante: Yeah, exactly like Dr. Johnson said, I think I went through why we did the trial and why those initial studies were done. And then as far as why we did this RECOVER EHR [electronic health records] paper, it was really to just understand the outcome from the clinical trial. And in the clinical trial, this was ongoing in real time, and we didn't know how to define it, so we said, let's just ask, "Have you been told by a medical provider that you have Long COVID? Yes or No." Because while the definition would continue to change, that was the reality that those providers had at the time, their knowledge at the time. And it was something that at least drove the patient, the participant in the trial, to go see their doctor. So, it was important to be able to look at that in the EHR, and I think the U09.9 diagnostic code is exactly the code for choosing "this patient in front of me has Long COVID."

Q. What are the next steps for related ME/CFS research?

Response:

Dr. Vernon: RECOVER has just provided an unprecedented opportunity to understand post-COVID ME/CFS. If you think back to that assessment table, included in that assessment table, all those dots across there all across time, was also the sampling framework that was used during the RECOVER observational study. And there are samples that were taken in the first tier—blood samples, fecal samples, saliva samples—that are ripe for testing and digging deeper into ME/CFS. Because now all the people that we have identified with ME/CFS in RECOVER, those samples are associated with those individuals. So that provides a crazy cool opportunity to dig deeper into biomarker discovery and pathogenesis. And then of course there are the tier 2 and the tier 3 assessments that are going on in RECOVER, which dig a little bit deeper in each tier into the various aspects of the pathophysiology.

So, my hope is that now that we've identified this particular subset of post-COVID ME/CFS within RECOVER, and the data and the samples that have been collected and the additional assessments that are being done, will just really pull back the curtain on ME/CFS and show us a lot of what's going on.

Q. Dr. Bramante and Dr. Johnson, what are the next steps for your research? Are there plans to look at children?

Responses:

Dr. Bramante: Yes, I mean that is something that I have not seen as far as a randomized trial in pediatrics, metformin versus placebo during acute infection, nor metformin versus placebo for treating Long COVID. So, I think that is something that probably should be done, unless we think results from adults do extrapolate down to children. We could look at children in EHR analyses; however, metformin prescriptions for kids are pretty rare. But you're right, we could design a study to look at a prevalent user analysis in people under age 21.

Broadly for all of us, and not just me, I have biosamples from the COVID-OUT trial, microbiome samples that I would like to analyze and do some mediation analyses. And then of course for Long COVID treatment, I think the data support—and the mechanistic support—looking at metformin as a treatment for Long COVID. And so, I know I and others collaborated on putting together a proposal to do that. There are many future directions, but the EHR analysis in kids is a good point. We could try to do that.

Dr. Johnson: Yes, I would just say that we're mostly using EHR data in the cohorts that we're looking at. It'd be difficult to do a treatment study using it, because why would people just randomly start using metformin? It's hard to see that in the observational data itself.

Dr. Bramante: And it's hard to look at Long COVID improvement in observational data. So, it's hard to understand treatments, whether it's metformin or anything, just because it's hard to quantify Long COVID resolution.

Q. From the attrition diagram for the metformin study, it looks like 15%–25% of patients using diabetes medications were under age 21. Did you look at this subgroup at all?

Response:

Dr. Johnson: We did not look at anyone under age 21.

Q. Do you have any thoughts on whether metformin could be useful as a treatment for Long COVID patients who have been sick for several years?

Response:

Dr. Johnson: We did not study the use of metformin as a treatment for Long COVID.

Q. Are there any previous or planned studies on metformin use for individuals without diabetes?

Response:

Dr. Johnson: We are working on a paper that looks at this question.

Q. Was the metformin dosing included in the first deck's Safety & Side Effects slide what patients took during acute infection?

Response:

Dr. Bramante: Yes.

Q. Did you study people using metformin off-label (which is widely done)?

Response:

Dr. Johnson: This study only looked at people with diabetes, so their metformin use is not "off-label." We will be publishing a paper that looked at people who did not have diabetes that took metformin within the first 14 days after SARS-CoV-2 infection and that showed that metformin has a benefit. That work was presented by Dr. Bramante at ID [Infectious Disease] Week in October 2024.

Q. What does RECOVER do to capture information from people with severe ME/CFS? They cannot participate in RECOVER the way it proceeds now, at least at the site I enrolled at, where the visits require travel to the site and then are lengthy and strenuous.

Response:

Dr. Vernon: Yes, this is a problem with so many studies that require in-person visits, including most of the ME/CFS studies we conduct at BHC [Bateman Horne Center]. The solution is to be able to conduct remote studies with wearable devices and assessments and at-home sampling.

Q. Would you be willing to share if this publication elicited any reaction with NIH or RECOVER leadership with this specific subgroup, from your vantage point (further resources needed for progress, more funding allocated to unravel pathogenesis, etc.)?

Response:

Dr. Vernon: I believe this study and paper has greatly raised awareness of ME/CFS. Together with other ME/CFS experts that are involved in RECOVER, I do believe that ME/CFS will be studied more intensively.

Q. Were people who had a prior diagnosis of ME/CFS and then got Long COVID studied?

Response:

Dr. Vernon: No, we excluded people with preexisting ME/CFS.

Q. Is there interest in the field to now study preventing Long COVID with the use of metformin during an acute infection? Or try to reproduce these results first?

Response:

Dr. Bramante: I have a hard time imagining the informed consent process asking someone to be willing to be in an RCT and randomized to placebo, unless we have a new variant that is totally different (inherent challenges with a changing landscape). And ACTIV-6 will publish results and includes people with prior infection but enrolled primarily during the JN.1 COVID variant period.

Q. Does anyone have (or is working on) a proposed treatment for Long COVID related ME/CFS?

Response:

Dr. Vernon: There are a number of Long COVID clinical trials under way that will likely include individuals with Long COVID related ME/CFS (because of the symptom overlap).

Q. Which ME/CFS phenotype benefited from metformin?

Response:

Dr. Vernon: Metabolic syndrome and related conditions.

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