Responses to Participants' Questions

The overarching goal of the RECOVER Research Review (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 (edited for clarity) to questions raised by seminar participants related to the following presentations at the R3 Seminar ***Effectiveness of Paxlovid in Protecting Against Long COVID: Electronic Health Record (EHR) Insights*** held on April 8, 2025 (videos for this and previous seminars are available from https://recovercovid.org/r3-seminar-series):

- ***Real-World Effectiveness of Nirmatrelvir in Protecting Long COVID for Outpatient Adult Patients – A Large-Scale Observational Cohort Study from the RECOVER Initiative***
  Fei Wang, PhD
  Rainu Kaushal, MD
- ***Effect of Paxlovid Treatment During Acute COVID-19 on Long COVID Onset: An EHR-Based Target Trial Emulation (TTE) from the N3C and RECOVER Consortia***
  Sandy Preiss, MS
  Abhishek Bhatia, MS
- **Discussant: Hannah Mandel, MS**

All Presenters: Questions and Responses

Q: How do TTEs or pragmatic clinical trials using EHR data complement traditional clinical trials like those being conducted across RECOVER or other clinical trials?

Responses:

Dr. Wang: Essentially, traditional randomized controlled trials (RCTs) take time and also lots of effort to see the results, but we already have evidence from the EHRs. By doing this TTE analysis before the trials, we can have real-world database signals that help us understand some of the hypotheses we may have and also that can inform the real-world RCTs to be conducted in more effective and efficient ways.

And not only by replicating a trial but also through this analysis, we can potentially generate other hypotheses by looking at other potential treatments, see their signals, and maybe inform new trials. So, the benefits are multiple.

Mr. Preiss: I couldn't agree more with everything that Dr. Wang just said. I'll just add that, in addition to this time point before clinical trials are completed, as we've talked about with these two studies, there's also a lot of value at the time point after clinical trials are completed to understand how a dynamic might differ in the real world from what was seen in the clinical trials.

So, for example, the work here on assessing the effect of Paxlovid on hospitalization and death, that is an on-label treatment; that's exactly what Pfizer's clinical trials assessed as their main outcomes. And here we're able to study, for example, we saw X amount of risk reduction on these outcomes in the clinical trials. Now how much do we see in the real world? So, it is really helpful on both ends of the timeline, before and after.

Dr. Kaushal: I agree with both of you, and I would add that I consider clinical trial emulations exceedingly helpful in three or four unique areas. The first is identifying putative drug targets that are already commonly used in the market. It's an opportunity to rapidly assess a lot of different medications.

The second is assisting in developing rigorous inclusion and exclusion criteria, which can then power studies more accurately, so they're not too big and too expensive, or too small and not reaching conclusions.
And then clinical trial emulations are also very helpful on the analysis side by expanding your pool of nonintervention patients to achieve greater power and to have more conclusive results as well as at times to deal with bias within a study. That is a method of reducing potential bias.

Q. How many days was Paxlovid used in your study, and are you able to assess for rebound COVID after Paxlovid has discontinued?

Responses:

Dr. Wang: I can first comment about the study setting. Essentially, as I mentioned in one of the limitations, because these are general EHR data, it is hard to justify or to extract the drug adherence information. We only look at the prescription of Paxlovid within 5 days after COVID confirmation. Whether the Paxlovid was persistent or not, it is hard to extract that information from an EHR. So, that could be one area that in the future we can leverage other patient-reported data to select a question that we can study.

Dr. Kaushal: I would add that what we are doing in the observational portion of this work with the EHR cohorts is taking already available data and assessing outcomes. So, we are not able to prescriptively say that we'd like to study patients who are exposed to 10 days of Paxlovid rather than the typical 5.

Q. In addition to the evidence about protecting or not protecting patients in the development of Long COVID, is there any evidence of Paxlovid affecting how Long COVID manifests in the body, for example, with specific symptom clusters?

Responses:

Mr. Preiss: So just to reiterate, the finding that is being alluded to here is when we studied the 3 symptom clusters—cognitive effects, fatigue, and respiratory symptoms—we found that Paxlovid had a stronger protective effect against cognitive symptoms in particular. Fatigue was in the middle and we found no significant effect on respiratory symptoms.

This allowed us to generate an additional hypothesis. This is another nice aspect of TTEs. So, we know that there are lots of different etiologies of Long COVID symptoms. We're not sure exactly how Long COVID manifests, but we know that it manifests in different ways and that there are probably different underlying causes of all those different manifestations.

So, there's this theory of autoimmune response. That is, the virus triggers an aberrant autoimmune response. There's this inflammatory cascade idea that there's persistent inflammation. And finally, this idea that there could be a persistent increased viral load.

Because Paxlovid has an effect on viral load and not these other two hypothesized etiologies of Long COVID, that allowed us to generate a hypothesis: maybe these cognitive symptoms are more associated with persistent viral load rather than these other etiologies. Again, that's just a hypothesis for now, and obviously, something that would need a lot more research.

Mr. Bhatia: I also want to add the fact that there are two parts to how these symptom clusters manifest in our data. One is the true biological pathway and the second is the actual data generation process, including who is represented well in these data and how we've been able to attribute symptom-cluster–based codes as potentially Long COVID–adjacent and not.

There is a set of papers that started thinking about some of these subphenotypes and how they are represented across different demographic groups.[1] Part of this is also how post-acute sequelae of SARS-CoV-2 (PASC; i.e., Long COVID) manifests differentially—that is, how these subphenotypes show up differentially across different

[1] (1) Pfaff ER, Madlock-Brown C, Baratta JM, et al.; RECOVER Consortium. Coding long COVID: characterizing a new disease through an ICD-10 lens. *BMC Med.* 2023 Feb 16;21(1):58. doi: 10.1186/s12916-023-02737-6. PMID: 36793086; PMCID: PMC9931566.
(2) Reese JT, Blau H, Casiraghi E, et al.; N3C Consortium; RECOVER Consortium. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes. *EBioMedicine.* 2023 Jan;87:104413. doi: 10.1016/j.ebiom.2022.104413. Epub 2022 Dec 21. PMID: 36563487; PMCID: PMC9769411.

demographic strata, what the relationships to health encounters are, and how folks are accessing care, because they aren't necessarily independent.

There is somewhat of a disproportionate set of patients across symptom clusters, but they're not necessarily equal. Hopefully, once these subphenotypes are better established in clinical literature and we have a better understanding of treatment heterogeneity, we'll be able to tease out what is a product of biases prevalent in these data and what's a product of true biological pathways. In the absence of that, I think we have to just make a broad set of assumptions.

Q. To what extent can the persistent symptoms observed in Long COVID patients be associated with recurrent asymptomatic reinfections?

Response:

Dr. Wang: One of the limitations is for asymptomatic patients if they don't interact with the health system. There's no way this information can be reflected in our data. But there are other studies, especially in the United Kingdom, where they send phone apps to the patients and they collect patient-reported symptoms and signs. So, these other data sources can complement what we have found in these clinical data.

Another thing you mentioned is assessment of the persistent symptoms. Again, one of the limitations is that we only look at incidence for now, but we do have a plan for looking at persistent and exacerbated symptoms and signs in the post-acute period. We currently have efforts underway on expanding the data sources from structured to the unstructured notes so that we can have more comprehensive capture on the mentioning of those symptoms and signs, because you need that if you want to look at these persistency-related outcomes. But that's definitely the plan that we currently have.

Q. Can you speak to Paxlovid compared to metformin? What are the timelines for clinical use based on the status of the clinical trials?

Response:

Dr. Kaushal: I'm going to take on the latter question first, which is essentially, when could Paxlovid be utilized for treatment of Long COVID? Given that Paxlovid is a U.S. Food and Drug Administration (FDA)–approved medication, it could be utilized in an off-label capacity at any time. There just needs to be sufficient evidence for physicians to feel comfortable prescribing it for their patients.

Clinical trials are active. Metformin is an early agent that we're looking at in the clinical trial side. There are discussions under way about Paxlovid and it feels like it's going to be important to talk about Paxlovid, Paxlovid plus metformin, metformin alone, and many other combinations.

One thing I would say about the RECOVER Initiative is that it was wisely set up as a combination of EHR-based studies like these. The clinical trials are so critically important, and then the pathobiology elements are needed to really try to understand underlying mechanisms of the disease. If we had a keener understanding of the underlying mechanism of disease of Long COVID, that would facilitate putative drug identification, therapeutic identification, and facilitation of the optimized trial interventions.

Q. Were individuals who were pregnant included in these analyses, or if not, will they be included or expected for future analyses?

Response:

Dr. Wang: For our study, we are evaluating the actual Paxlovid trial, where pregnant patients were excluded, so we excluded them as well for our study. But we do have a dedicated study similar to the TTE analysis but on a pregnant cohort. So, that's certainly on our agenda. Stay tuned for more results from our analysis.

Q. We know the frequency of repeat COVID infections increases the risk of developing Long COVID. Were you able to assess this? And would the benefits of Paxlovid increase for people experiencing a, say, third infection versus their first COVID infection?

Response:

Mr. Preiss: We thought about this and ended up not doing it for a few reasons, principally because the study was starting in the phase of the pandemic where it was really difficult to assess from the EHR whether an infection was someone's first infection or a reinfection. So, by 2022, the first documented infection was often not the person's first bout with COVID.

So, that potential for misclassification made us a little bit hesitant to do that, and I think that's just a limitation with EHRs or at least with this particular condition and study period. But I do think it's a very interesting research question. We did some other work just assessing the relationship of reinfections and Long COVID in general.[2]

Q. Are there potential studies that are planned for longer term treatment of Long COVID with the use of Paxlovid?

Responses:

Dr. Wang: I think certainly we can study this. That's actually another advantage of working with observational data: you can essentially capture the patients who got treated within 5 days. Again, this is replicating the real-

[2] Hadley E, Yoo YJ, Patel S, et al. Insights from an N3C RECOVER EHR-based cohort study characterizing SARS-CoV-2 reinfections and Long COVID. *Commun Med*. 2004 Jul;4(129). doi: 10.1038/s43856-024-00539-2.

world trials and also there could be patients who got a prolonged prescription of Paxlovid, and we look at the difference. We did not do that in this study, but we can certainly do that in future studies.

Mr. Bhatia: I want to also flag something we are unable to measure, that we need to just assume, is adherence. Especially for a shorter course—for acute sickness for 5 days—we're able to statistically account for a little bit of that uncertainty in terms of when you were prescribed Paxlovid, when your course started, and when your COVID infection was. For a 15-day course, we are unable to do all of this; we're unable to measure whether someone who was prescribed Paxlovid truly took Paxlovid per the dosing regimen.

And so, that protocol effect is not something that we can estimate. And I think that there might be some amount of uncertainty in terms of what we're able to truly measure with some of these prolonged dosage-based treatment plans. But I think that, while acknowledging those limitations, there's scope for us to use some of these EHR data to make those inferences.

Q. Were either of the studies able to conduct variant-specific analyses?

Responses:

Dr. Wang: In the table I show in the second results page, the stratification analysis, we did have a sensitivity analysis stratified by time period. But one point I want to raise here is that we started in March of 2022. That's really when the Paxlovid prescription became prevalent.

So, before that, because Paxlovid was not prescribed in a prevalent way, we cannot really assess that. But after March 2022 came the Omicron-dominant time period within that year. But we still stratify on strain. Our study went through February of 2023, but because the data were continuously coming in, we can investigate this suggestion of doing variant-specific analysis. So, currently it is Omicron-dominant.

Mr. Bhatia: I'll echo that for our case. In the Paxlovid era, most of our work was somewhat also intentionally restricted to the Omicron-dominant and post–Omicron-dominance phase. And I also just want to acknowledge the fact that there is the Veterans Administration (VA) paper and some of the other papers that Dr. Wang spoke about, which together serve as some amount of stratified analyses that capture different eras of the pandemic.

So, while we were unable to look at the effectiveness individually in ours in the Delta era, there are a good number of papers that have started looking at that relationship. In our prior paper, we looked at the relationship between Paxlovid and acute hospitalization.[3] Some of that comparison was done and some of the absolute risk differences in the differences in the papers were attributable to differences in strains. In the PASC era, for the most part in our

[3] Preiss A, Bhatia A, Aragon LV, et al. Effect of Paxlovid Treatment During Acute COVID-19 on Long COVID Onset: An EHR-Based Target Trial Emulation from the N3C and RECOVER Consortia. *medRxiv* [Preprint]. 2024 Jul 31:2024.01.20.24301525. doi: 10.1101/2024.01.20.24301525.

research, we're comparing and contrasting the effect estimates across papers and not necessarily stratifying patient populations within our own data. And I think that that's still a valid approach.

Q. Are the researchers able to adequately control for healthy user bias, whereby users with healthier lifestyles are more likely to seek out medical care and medication during acute illness?

Response:

Mr. Bhatia: Yes! While we're limited by the data that are collected within a patient's health record, we're able to identify patients who interact with the health system more frequently than others, as well as patients with a baseline of a lower or higher set of comorbidities and risk factors for severe disease prior to acute illness. A core part of the analytical approach in a TTE is to try to account for biases that would differentiate patients who have received a therapy vs. those who did not (including healthy user bias), and account for it when we're trying to estimate the effectiveness of that therapy.

Q. Does anyone have a reference on how TTE works method-wise?

Response:

Mr. Preiss: This paper is the best starting point: Hernán & Robins (2026).[4] Many other later papers from Miguel Hernán and collaborators get into the nuances if you'd like to dig deeper.

Q. Are women more prone to getting Long COVID, whether they are low- or high-risk patients?

Response:

Dr. Mandel: Research does suggest this; here is a recent R3 seminar that covered this topic if you're interested: RECOVER researchers shared study findings that suggest women are at a higher risk than men of developing Long COVID.

[4] Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *American Journal of Epidemiology.* 2016 Mar:183(8):758-764. doi: 10.1093/aje/kwv254.

Q. Why is being female not listed as a risk factor?

Response:

Mr. Preiss: We based the high-risk definition on Paxlovid's treatment indication (i.e., at risk for severe acute COVID-19). Being female was not among those. But we do control for it as a potential confounder, since we know Long COVID incidence is higher among females.

Q. Is there any comparison between risk reduction from monoclonal antibody treatments vs. antivirals like Paxlovid?

Response:

Mr. Preiss: I know of at least one ongoing trial of monoclonal antibodies for treating Long COVID, but I am not aware of any work assessing their potential for preventing Long COVID.

Q. How is "high risk" defined?

Response:

Mr. Bhatia: I believe both papers quantified "high risk" similarly, with the guiding set of criteria being defined by the U.S. Centers for Disease Control and Prevention (CDC) and highlighted by FDA when it approved the use of Paxlovid. We operationalized this based on the patient data that were collected—some of those criteria evolved with time, however; see more at the CDC web page on who qualifies for COVID-19 treatment clinical care for outpatients.

Q. Can you talk a little more about the finding that Paxlovid seemed to have more of a protective effect with the cognitive symptoms group? Is there a hypothesis that you have that might explain that finding?

Response:

Dr. Wang: I would not overinterpret the results there because the cognitive symptoms in the post-acute period are less common than other symptoms such as cough. In order to say the observed protective effect is real, we need biological mechanistic studies or actual clinical trials.

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