Transcript

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Quinn Barnette:

Welcome, everyone, to the RECOVER Research Review (or R3) seminar. My name is Quinn Barnette. I'm an epidemiologist for the RECOVER Administrative Coordinating Center and I'll be your moderator for today's session. The goal of this seminar series is to catalyze a shared understanding of the research within the RECOVER consortium.

I want to start by thanking everyone who submitted questions in advance and remind everyone that you can submit any questions during today's presentation using the Q&A feature in your Zoom menu. After today's panel, our speakers will answer as many questions as possible.

The Q&A document will also be posted with the recording of the seminar on recoverCOVID.org. The document will include the answers to the submitted questions relevant to today's presentations. Questions about other scientific topics will be addressed in future seminars, and answers to broader questions about RECOVER will be available in the FAQs found at recoverCOVID.org. As a reminder, we cannot answer questions about individual clinical care.

I'm pleased to share that our panelists today are Dr. Fei Wang, Dr. Rainu Kaushal, Sandy Preiss, and Abhishek Bhatia; and our discussant will be Hannah Mandel. Dr. Wang is a professor of Population Health Sciences in the Division of Health Informatics and founding director of the Institute of AI for Digital Health at Weill Cornell Medicine. His research interests are machine learning and artificial intelligence and biomedicine. And he's an elected fellow of the American Medical Informatics Association, American College of Medical Informatics, and the International Academy of Health Sciences and Informatics, and also a distinguished member of the Association for Computing Machinery.

Joining Dr. Wang for today's Q&A is Dr. Rainu Kaushal, Senior Associate Dean for Clinical Research, Chair of the Department of Population Health Sciences; and Nanette Laitman, Distinguished Professor at Weill Cornell Medicine. Dr. Kaushal is a national leader in pediatric patient safety, health IT, and value-based care. And she currently directs a major NIH-funded PCORnet study as part of the RECOVER Initiative. Dr. Kaushal is an elected member of the National Academy of Medicine and the Association of American Physicians.

Sandy Preiss is a data science manager in the Center for Data Science and AI at RTI International, where he applies machine learning methods to a variety of public health and social science domains. For RECOVER, Sandy co-led two target trial emulations and contributed to several others, and he also contributed to a machine-learning-based computable phenotype for Long COVID as a part of the RECOVER Initiative.

Abhi Bhatia is a PhD candidate in health informatics at the University of North Carolina at Chapel Hill. Abhi's research focuses on combining disparate data sources to estimate the effects of various spatiotemporal exposures on individual health. To do this, he applies computational methods and

spatial analysis, machine learning, and causal inference to large-scale clinical demographic and geospatial data. In his role as a researcher within the RECOVER Initiative, he conducts target trial emulations with real-world data to assess the comparative effectiveness of clinical interventions.

Finally, Hannah Mandel is a senior research scientist with a RECOVER clinical science corps at NYU Langone. Her work focuses on leveraging electronic health record data to support population health and clinical quality improvement and has spanned a range of institutions, including departments of health and community health centers.

The topic of today's seminar is Effectiveness of Paxlovid in Protecting Against Long COVID: EHR Insights. Today's speakers will present findings from two studies examining whether Paxlovid treatment in the acute phase of COVID-19 helps to prevent Long COVID.

The study teams used electronic health records from the National COVID Cohort Collaborative (or N3C) and the National Patient-Centered Clinical Research Network (or PCORnet) RECOVER Repository. Please welcome all of our speakers. And with that, I will turn it over to our first speaker, Hannah.

Hannah Mandel:

Great. Thanks, Quinn. And I'm really pleased to introduce these two analyses. So, first I'm going to orient you to some of the context about what the EHR cohort is and then provide some background about how we use EHR data to define Long COVID.

And then I don't want to get too technical, but one of the reasons these papers are unique is that both of them use an approach we call target trial emulation. So, I'll also introduce what that means before handing things off to our presenters, who will go into greater detail. Next slide.

So, the EHR cohort has presented during prior R3 seminars, but I did want to give some very brief context. The cohort actually consists of three participating clinical data research networks. And today, we'll be focusing on preprints from two of them. So, as Quinn mentioned, [these are] N3C and PCORnet. And these networks collect patient health record data from sites across the country and align that data to enable analysis across them. This allows for analysis on large numbers of patients using information such as demographics, labs, medications, diagnoses, and other types of data produced from their interactions with the healthcare system.

I also wanted to mention that EHR data is particularly helpful at offering insights rapidly as the data is available without having to wait for a clinical trial to be conducted. And that's especially relevant for today's presentations. I think we can go to the next slide. Great.

I also wanted to give some brief context about how we define Long COVID based on EHR data, because these networks do approach it in different ways. There is a diagnosis code for Long COVID, which is the ICD-10 code U09.9, but this was introduced after the start of the pandemic—actually, in fall of 2021—and it relies on patients having a clinician document a diagnosis. So, it has more limited use for identifying Long COVID patients within EHR-based analyses.

So, instead, both of our networks have developed algorithms, which we also call computable phenotypes, to identify patients beyond those with just a coded diagnosis. These algorithms have been iteratively modified and improved to better reflect and identify patients with probable Long COVID as the pandemic has progressed. And they also vary in terms of their sensitivity and specificity, which since definitions are often disputed as being too sensitive or too specific, we do find value in seeing patterns across this range of definitions.

So, on the left, you can see that N3C is a bit more on the restrictive side. It's trained to predict Long COVID using records from adults who were diagnosed with Long COVID or visited a Long COVID clinic at least twice. And on the right, PCORnet's model is a bit broader. It's a rules-based algorithm, meaning it looks for a prespecified set of criteria to be met. And more specifically, this is based on looking for patients that have new diagnoses belonging to around 24 categories of conditions after their acute COVID infection. Both of these computable phenotypes are looking at the same time frame, so looking for Long COVID within 180 days of the patient's acute COVID infection. Next slide. Great.

So, the randomized control trial (or RCT) is the gold standard for medication effectiveness research, but there are some potential problems with it. For example, it's not always ethical to look at what you want to look at. It can be costly, and it can take time. But on the other hand, observational data is more prone to bias and confounding.

So, both of the talks you'll hear today are about something called a target trial emulation. And in essence, this is emulating an RCT but using observational data. So, this has a few benefits. It reduces confounding and biases that are often present in observational studies. It's a faster and less expensive way to gauge medication efficacy, and it also reflects real-world use of medications. So, it can be more generalizable.

And it starts with designing an ideal RCT and then specifying its hypothetical protocol. So, for example, defining components such as eligibility criteria, treatment strategies, and assignment, among others. And then finally, adapting the protocol to be implementable with the observational data on hand. So, yeah, you'll hear more about these methods from the presenters today. I think we can go to the next slide. Great.

And the two target trial emulations you're about to hear about do have methods and definitions of Long COVID, but they're aligned in a lot of ways. They both are investigating Paxlovid's role in Long COVID prevention, leveraging large EHR-based data sets, evaluating probable or Long COVID as an outcome, using computable phenotypes, and then also analyzing the impact of Paxlovid on selected Long COVID symptoms. So, yeah, that was my overview. And then with that, I'll hand it off to the presenters to describe these analyses in more detail. Thanks.

Fei Wang:

Thank you. So, I appreciate the opportunity of sharing our work. So, next slide. So, this is what I'm going to talk about. First, some introduction on the background of PCORnet. Next slide. So, this is like Hannah mentioned. So, this is like the governance structure of RECOVER Consortium and the observational cohort under that. And we are part of the EHR cohort and there are three members, PCORnet adult, PCORnet pediatric, and then N3C. Next slide.

So, PCORnet is PCORI (Patient-Centered Outcome Research Institute) founded clinical research network. It includes 65 members or networks across the United States and we are including 37 of them in our research and study. And as you can see on the blue box on the right, so it has a huge amount of data, including more than 15 billion roles. Next slide.

So, this is our work; as Hannah said, this is a preprint and we are studying the effectiveness of Paxlovid for outpatient [inaudible 00:10:44] patients. Next slide. So, this is some of the background. So, before our study, so there are some prior knowledge, like Paxlovid is prescribed for COVID patients with high risk of severe acute COVID illness. I'm going to explain in the next slide what do we mean by high risk.

And we know that Paxlovid is effective for reducing the risk of severe acute COVID outcomes, specifically hospitalization or death. And there is limited research on the efficacy of Paxlovid on Long COVID prevention. Next slide.

And this is what I'm talking about. By high risk, we really mean the patient with presence of some existing conditions like older age, smoking status, and some underlying chronic comorbidities, [such as] cardiovascular, diabetes, obesity, cancer, and others. And low risk means that the patient are without any of these prior conditions. Next slide.

So, these are more details on the literature review before our study. So, there are several groups all over the world that have done some similar studies, like the first JAMA Internal Medicine paper looking at older population, 65 plus, and showed that Paxlovid was associated with a small reduction in the incidence of Long COVID.

And the second one, the researchers looking at vaccinated, nonhospitalized individuals, they didn't observe a significant effect on Paxlovid for preventing Long COVID symptoms. And the third one is focusing on veterans, VA population, with the dominant population being white males. And they showed Paxlovid use was associated with a significant reduction of Long COVID.

But nonetheless, so there are limited studies showing like for the general citizen population, what is the effect of Paxlovid for preventing Long COVID? So, that's also the motivation of why we're doing this study. So, the next slide.

So, Hannah already mentioned, but just briefly. So, target trial emulation aims to emulate a clinical trial, or what we call a target trial, using observational data. So, we have to have a target trial to emulate. So, this is the target trial from clinicaltrials.gov that we are trying to emulate. So, essentially, we are replicating their eligibility criteria outcomes in whatever those different elements, defining the trial using the observational data, and applying causal inference type approaches to estimate the treatment effect. So, next slide.

So, this is our design. So, we leverage the patient records within the period of March 1st, 2022, until February 1st, 2023. We start from that time is because that was a time when Paxlovid was becoming popular. And I'm going to show you a more detailed inclusion in cascade, but we identified around half a million COVID patients from 29 EHR repositories and we define three outcomes. One is the rule-based Long COVID definition, one is hospitalization in the post-acute period, and the deaths in the post-acute period. The post-acute period is 30 to 180 days after COVID confirmation.

And we also require Paxlovid treatment of these patients to be within 5 days of COVID confirmation. And the comparator groups are the patients who didn't receive Paxlovid in that time period. So, next slide.

Hannah also mentioned the different definitions of Long COVID between us and N3C, which you will hear later. So, for us it is really based on one of our prior studies from the data, like how can we derive a set of symptoms and signs that could be associated with Long COVID. And then we derive rules on top of that and have our clinician groups working together with collective intelligence. So, we build this rule-based system to leverage the diagnosis code to identify Long COVID symptoms and signs. And it includes, in total, 24 condition clusters. Next slide.

[Here are] some more details about the statistical method. We do the TTE (or the target trial emulation). We use a framework called inverse probability of treatment waiting because observational

data are not randomized, so there are lots of confounding. So, we need to appropriately balance those confounders to make sure the comparison is fair. So, IPTW is one of the frameworks to achieve this.

And then to estimate the outcomes, we look at two outcomes. I mean, two ways of quantifying the outcomes. One is hazard ratio, one is cumulative incidence. So, we use Cox regression because this is a time-to-event type of analysis. So, we use Cox regression to estimate hazard ratio, and Aalen-Johansen estimate to estimate the cumulative incidence. And we also want to estimate the statistics of not just the point estimate of those outcomes. So, we use bootstrapping to estimate the 95% confidence interval. Next slide.

So, this is, I'm sorry for a little bit busy slide, but the left panel is the inclusion/exclusion cascade I'm talking about. So, we started with over 1.7 million patients who had records within the time period we were investigating. And then we looked at COVID confirmation and then we did some exclusion if the patients already had a Long COVID diagnosis or they had severe baseline conditions or they had some other COVID treatment in the time period, and so on and so forth.

And then we got about half a million eligible patients for analysis. And then we looked at if they received Paxlovid within 5 days after COVID confirmation or no. And we also excluded the patients who received continuous Paxlovid treatment even after the 5 days. And then so we got two groups, and based on our definition of high risk, those baseline conditions, we further dichotomized each of the groups into high risk and low risk groups to facilitate our comparative analysis.

And the right panel is just a table showing you the summary statistics of the demographics and also some of the baseline conditions of the treated group and the comparative group. And next slide.

And this is our result. And the results are shown in these figures. The vertical axes are the cumulative incidence of Long COVID. And how you read this figure is, you look at until 180 days after COVID confirmation, the cumulative incidence of the treated group and the comparative group. And this is a high-risk group. So, for figure A in the top left corner. So, what this figure shows is essentially until 180 days, the cumulative incidence of any Long COVID conditions for the treated group has on average, per 100 persons, three less compared to the controlled group. So, that means that with the Paxlovid treatment in 5 days after COVID confirmation, it can reduce the incidence of Long COVID symptoms and signs.

And Figure B, it shows it's not Long COVID, but in terms of the post-acute hospitalization. So, until 180 days, we still see that for the treated group, you observe 2.37 per 100 patients less compared to the control group. And same thing for the death, we also see a slight difference with less death event, post-acute death events for the treated group compared to the control group.

So, all of these results demonstrate that with the Paxlovid treatment in the acute period can effectively reduce Long COVID or hospitalization or death to some extent during the post-acute period. And all of these results showed statistical significance according to the *P* value. So, the next slide.

And because as I said, our definition of Long COVID is pretty broad, it includes 24 different condition clusters. So, we further separate them into different condition groups and see if there is any difference. If we look at a particular type of Long COVID conditions, I mean, if there is any difference in terms of the treated group and the control group.

So, as you can see here, we organize those different Long COVID conditions according to the organ systems, like neurologics, skin, pulmonary, circulatory blood, metabolic, digestive musculoskeletal, and general. In the first two columns, CIF is a cumulative incidence. So, you can see

with every 100 patients, so the cumulative incidence of these events compared to the second column is the cumulative incidence of these events in the control group.

And so, more intuitively, you can see in the middle figure, which is the hazard ratio, and if you see a dot that falls on the left of that vertical dashed line, which has a ratio of one, it means no effect at all. So, you see a lot of these dots fall on the left part, which means that in the treated group, there is less risk of these events compared to the control group.

And there are some exceptions, like you see hair loss, you don't see that. And across all these conditions, although you see there are some differences in the scale of these different hazard ratios, like you see dementia, you see lower hazard ratio, which suggests a stronger effect; and you also see pulmonary embolism.

But if you look at the cumulative incidence for these conditions, the cumulative incidence is really small. As you can see for dementia, it's just 0.26 for the treated group and 0.34 for the control group. So, because the hazard ratio is a ratio, so by calculating the ratio, you see some difference on the scales. But because of the limited cumulative incidence of these events, I wouldn't overinterpret these results. But you do see a relatively homogeneous reduction of all of the different kinds of conditions in the post-acute period for the treated group compared to the control group. So, next slide. The previous slide. Yeah.

So, this is another investigation we have done. So, the previous slide shows we separate the conditions into different condition groups. We stratify the patients into different groups according to these patients that have a risk factor. And we compare the cumulative incidence for the treated and the control group and also according to the infection period, which may correlate with the waves of the COVID and also the different socioeconomic or geographical area, according to rural-urban commuting, and so on and so forth.

But you do see, from these analyses, you do see a fairly general reduction trend because of the lower than one hazard ratio value, as you can see from the middle figure. And one thing I do want to point out here is as you can see in the green box, the low-risk patients, you don't really see an effect there. So, the hazard ratio is really around one: it's 1.03. So, that means that for low-risk patients, we don't really observe statistically significant benefits for Paxlovid treatment within 5 days in the acute period in terms of reducing Long COVID symptoms in size. Next slide.

So, overall, for high-risk outpatients, we do see general benefits of treatment with Paxlovid within 5 days after COVID confirmation in terms of preventing Long COVID symptoms and signs in the post-acute period. And we see an absolute reduction according to cumulative incidence as about three events per 100 persons and a hazard ratio of about 0.88, but we don't really observe statistically significant results for low-risk patients. Next slide.

So, this is a final slide. Certainly, our study is not without limitations, like this is observational analysis. So, although we have done lots of techniques to reduce the potential confounding, but there could still be residual confounding and we only examined incident conditions; we didn't look at exacerbated or prolonged conditions and we only used the structured fields of the EHR to conduct this study. But lots of information could be buried in the clinical notes. And because this is a general EHR population, it is challenging to determine the adherence to Paxlovid treatment after the prescription.

The conclusion would be this study is one of the largest observational studies for acute Paxlovid treatment for Long COVID prevention. And we do cover a diverse patient population in terms of their demographic and geographical compositions. And that's all from mine. Thank you.

Sandy Preiss:

I think I can jump in. We can go to the next slide. Thank you. Hey, everyone. I'm Sandy Preiss and I'll be presenting the first half of the N3C side of today's seminar and then we'll hand it over to my colleague Abhi Bhatia about halfway through. So, the paper that we're talking about today is very similar in motivation and methods to the one that Dr. Wang just presented. So, we're looking at assessing the effect of Paxlovid treatment during acute COVID-19 on Long COVID onset. Next slide.

Bottom-line findings before I start getting into the weeds: We found similarly that Paxlovid reduced Long COVID incidents by about 6%. So, a small but significant relative risk reduction when Paxlovid is given during acute COVID-19 on the likelihood of developing Long COVID afterward.

And to put that into absolute terms, we like to use this metric of [inaudible 00:27:48]. So, to prevent one case of Long COVID, 366 people would need to be treated with Paxlovid, according to the findings of our study. So, this is where our findings differ a little bit from the findings from the PCORnet paper and we'll get into that a little bit more later on. Next slide.

So, I'll give a brief introduction to N3C or the National COVID Cohort Collaborative. This is an NIH program to put together a very large and nationally sampled dataset of COVID patient data—electronic health records. So, it is the largest publicly available free centralized EHR dataset in US history, not just in COVID history. So, a really, really exciting development that came out of the pandemic was the impetus to put together this size and scope of national EHR dataset.

So, it includes patients from all 50 states, very similar in a demographic mix to the US population. And all of these records from EHR all over the country are harmonized into a single data model, which makes analyses like these much, much easier, faster, more feasible to pull off in a reasonable amount of time and do on this really big representative data set rather than in just a single health system at a time, as most EHR research had to happen in the past.

The impact of N3C has been really impressive. So, the work that we are presenting here is one teeny tiny little slice of all of the team science that has come out of N3C, and even just the Long COVID-related work from RECOVER is a small piece of all of the research that has been done with this data resource that NIH pulled together. Next slide.

Okay. I'm going to give the third definition of target trial emulation for the day. I won't belabor the point since we've talked about this a lot already, but my favorite way to think about target trial emulation is it's not really a method in and of itself. It doesn't entail doing things a whole lot differently than people were doing causal inference studies with observational data before this TTE framework came about.

But it's a really nice way to think about doing that kind of work because this thought experiment of—how would I design a clinical trial to assess this topic, and then how can I emulate each element of that protocol using observational data—really helps with good study design. It helps the researchers identify some "gotchas" or things that they might not have otherwise considered and it helps people understand the work. So, I think of target trial emulation like that. It's a really helpful framing for this constellation of causal inference methods that we are pulling together to do this kind of work.

And really the big difference is the assignment mechanism. With observational data, we don't have a randomized treatment assignment. So, the real bulk of the statistical work to pull off this causal inference with observational data comes in emulating that randomization. And the rest of aligning our study with the trial protocol is often quite similar because we can do things like establishing inclusion

and exclusion criteria and defining follow-up periods and things like that, very similarly with electronic health records or with other observational data as we can with clinical trials. So, that's my two cents on target trial emulation. I'm sure we'll get into this more in the discussion. And we can go to the next slide.

I also want to make a quick plug, while we're taking a step back here, for this concept of real-world evidence in general. So, both of these studies and really the observational EHR cohort of recovery in general are focused on this idea of real-world evidence in that clinical trials are super important. They're the gold standard. They're the bedrock of our understanding of how medications work, but they're also really well-complemented with research that uses real-world data sources and considers similar study questions in a real-world setting.

So, in our case, we're hitting the left side of this timeline here of doing these real-world studies of Paxlovid and its effect on Long COVID while the wheels are still getting spun up to do the clinical trials that assess this kind of thing. So, real-world evidence can be very helpful in that sort of pre-trial period of beginning to understand the mechanisms of some dynamic of interest in the real world. And they can be really helpful in helping to design those clinical trials and set the clinical trials off in the right direction with a hypothesis of what kind of effect size they might be seeing, what strata they might want to consider, and that sort of thing.

And then of course, they also come into play later on downstream. So, after clinical trials and approval, real-world evidence is very important for pharmacovigilance and understanding how the effects that we're observing in the trials play out downstream. Okay. Next slide.

All right. So, we're done with our high-level stuff, getting into the content, getting into the weeds here. So, I'll begin by talking through our outcome measures, which as Hannah and Dr. Wang have already mentioned is one of the major differences between these two studies. So, we identified patients with Long COVID in two different ways. The primary measure that we used was this computable phenotype, which fundamentally is a machine learning model that's trained to identify people who have Long COVID.

So, in the universe of the N3C cohort, all these people with electronic health records in N3C, there's a very small number of people who actually got the Long COVID diagnosis. There are a lot more people who have Long COVID that has not been officially diagnosed, and then there's an even larger group of people who have conditions similar to Long COVID, but they might not say themselves, "I have Long COVID," or their physician might not say that.

So, what we were trying to do is use the information that we have on what conditions are associated with folks who get those 09.9 Long COVID diagnoses, use that to train a model to identify that middle group, and try to parse them apart from the people who have similar conditions but not actually Long COVID.

Our secondary outcome, we also looked at some symptom clusters to try to get at this disaggregation of Long COVID. We know that Long COVID is a very complex constellation of symptoms and conditions. It's not just one thing; there are lots of different manifestations of it, and it affects everyone differently. So, it is very important to study Long COVID in the way that PCORnet has. And the way that we're getting at it here is breaking it apart into different subphenotypes or different components.

So, we did simpler version where we just had three different clusters. These were identified in a study from the global burden of disease group, sort of the three principal clusters of Long COVID symptoms of cognitive fatigue and respiratory symptoms. And these were identified in a rule-based way

similar to the PCORnet Long COVID definition. Can we go to the next slide. Oh, I'm sorry. Can we go back one? One more. Can we go back one more slide? There we go. Okay. Sorry. A little out of order here but works just as well. I think this is just describing the cohort and timeline of the study in a little bit more detail.

It's quite similar to the way that Dr. Wang already described PCORnet approaching this. So, I won't go into a lot of detail here, but we used a very similar timeline where the key index date for each patient in the cohort was the date of their documented COVID-infection. Then we look back at historical data to establish the exclusion and inclusion criteria. We look forward to give them that grace period of getting Paxlovid treatment within 5 days. And then in our follow-up period, we observe Long COVID from days 29 to 180. Okay. I think we can go forward too. And then I'm going to hand it over to Abhi.

Abhishek Bhatia:

Great. And this is good timing because I am seeing a lot of conversation in the chat around this relationship between RCTs and target trials. And a big benefit of an RCT is that randomization, where you think about someone being assigned to a treatment or someone receiving a treatment not being associated with any of their individual characteristics. And if you do that enough, then over time and with numbers, the folks that are receiving the treatment and the folks that are receiving the control on average look the same.

And while that's not possible with observational data, we are able to use all the information in the patient EHR, as closely as possible, to think about what are those factors that would influence your treatment uptake or your access to care or your health encounter and, retroactively, recover the benefits of that randomization. And so, we start there. We start with thinking through a list of factors that typically would confound the relationship between a person receiving Paxlovid or not or a person having the outcome of PASC or not.

And on the left we've isolated those effects to a list of a few variables. They are operationalized demographic variables, variables associated with preexisting comorbidities or burdens, both in terms of what the CDC defined as high-risk comorbidities that would place someone at a high risk of severe COVID-19; or operationalized as the Charlson comorbidity index.

We also had variables on how frequently someone has accessed healthcare in the past, acknowledging that there is some amount of truncation and for a lot of people, there might be less of a patient history than others. We also have data on different sites, where these care sites are, and what sort of care they provide on average, along with measures for time and measures for place in terms of how someone's place in neighborhood and spatial surroundings affects their health. Next slide.

And so, with that, we are then able to think about what are those present biases and how do you control them? [There are] two specific biases that we thought about for this study. The first being patients will differ on those baseline characteristics. And one of these established ways to recover the benefits of randomization is to weigh patient groups, weigh patients such that on average the two groups look similar.

And so, the first set of weights is an inverse probability of treatment weights. And what this corresponds to is we're able to think through factors that would disproportionately be associated with increased probability of receiving Paxlovid. And we accordingly weigh patients such that some of those factors that are associated with a lower probability of Paxlovid uptake are well represented along with those that are associated with a high uptake rate.

The second set that we needed to think about was that this is a time-to-event study and there is a relationship between receiving a treatment and some amount of attrition. So, folks dropping out of the study, healthier folks not coming back, people dying in the follow-up time.

And so, this contributes to something called informative censoring, where there is a difference in terms of how the two groups behave and our ability to follow them over time. And so, we add a second set of weights called censoring weights. And together these two sets of weights, one applied to individuals across both groups, allow us to on average establish that the two treatment and control groups have similar distributions of all of the covariates in panel one. And then next slide.

Once we've established that these two groups are similar, we're then able to use some of these methods to estimate the effects of a treatment on the outcome. And because we've established that these groups are similar, we're able to isolate the effects or the differences across the groups in terms of how they respond to the treatment or not to the treatment to the drug itself.

So, specifically here, like the first study, we map out a few different measures, both epidemiologically relevant and also clinically relevant. So, we have measures of cumulative incidence and how risk accumulates over time, relative risk for difference between the two groups, and an absolute risk difference and the number needed to treat, both of which have more clinical and practical applications. Next slide.

And on average, overall our main set of findings – I won't dive into the numbers heavily; our paper will be linked in the chat if you'd like to go deeper into that – was that treatment was associated with a modest reduction in overall PASC risk. And I say modest here because while the relative risk is significant, it is higher than in some of the other studies, and we go into some of those details later.

We also saw protective effects against symptom clusters, specifically the cognitive symptom cluster and the fatigue/malaise didn't see a positive association with or protective effect of Paxlovid in the respiratory symptom cluster.

And we do have a sister paper that's been published while we examined the association between Paxlovid and hospitalization and death over a 28-day span. And they looked at different time windows just given that one paper was done earlier than the other. We were able to corroborate the effect being consistent in this study as well that the effectiveness of Paxlovid as a protective drug against hospitalization and mortality was in line with what we had found earlier. Next slide.

And thank you to Fei for speaking about some of the other established studies. There were some very robust and statistically sound studies that were out there. And just given the fact that this is a continuously evolving disease, and at the point in time when the VA paper was out was still mid-pandemic, we wanted to think about how close we could get to the methods that they had used and whether we would be able to either validate what they had found or support it or just encourage conversation in that way.

So, part of our paper hinged on replicating as closely as possible a patient population that mirrored the patient population at the VA, which is what this *JAMA Internal Medicine* paper looked at. And what we found was similar in direction but not similar in magnitude. We saw a stronger protective effect against the primary outcome.

Similarly, there was some variation in the symptom clusters. Notably, we found no protective effect across any symptom cluster within a VA-like population. We also did a few checks across tightening some of our inclusion criteria. So, we started to think through how effects differ in cohorts

that we have reliable vaccination information on, which is coming from a smaller set of study sites where there's high fidelity and reliability of that vaccination data. And we saw that within this population, there was a marginally stronger benefit from treatment as well. Next slide.

We were also aware of the fact that there are many different ways to look at the outcome. And so, we tried to establish a window of how we're measuring our outcomes starting with just using the diagnostic code, for which we saw nonsignificant effects.

So, receiving Paxlovid was not associated with bearing the U09.9 code at a differential rate in a 180-day time period. We also started tinkering with some of the parameters for our computable phenotype, just to check whether our treatment effects were truly a function of the drug and not a function of how we had tuned or decided some of the parameters in terms of our threshold sensitivity for prediction and the follow-up period for our computable phenotype. And varying any of those parameters didn't significantly alter our main effect.

There are a few other tests of robustness in terms of how we handle timed inclusion of patients and others that would contribute to some of these biases and you'll be able to see that in more detail in our paper. Next slide please.

And in general, when we started thinking and comparing our results to what was already well established out there, and some of the work that Fei's team is also doing, I think that there was good consensus between the two papers in terms of the fact that directionally, Paxlovid does have a protective effect on PASC.

Both in terms of how we measured our main outcome and also in terms of how we thought through symptom-based outcomes, there were some absolute effect differences. Notably ours was a lower effect than the estimate that PCORnet had found. And we hypothesized that this is a very hard thing to measure. And so, I don't want the takeaway for this to be that the results are all over the place. I'd like for the takeaway of this to be that together, the results are very complementary and the N3C phenotype is a little bit stricter and narrower, and likely more specific; and PCORnet captures a likely more sensitive set of outcomes. And I think that that establishes good bounds in an evolving condition where we're likely learning more with time. Next slide.

I think I'll leave with a few recommendations based on what we found. I think there are some recommendations here for research purposes, for clinical purposes, and also for further trials. Starting with the fact that I think we've seen evidence for potential heterogeneity and treatment effects across a few different PASC symptom clusters, and I think that that gives us a little bit more scope for us to extend this target trial-like framework to look at how treatment heterogeneity varies across the symptom clusters. This also lends itself to more subphenotype stratification, which we didn't get the chance to do in our work. And we're hopeful that the next set of research picks up on that.

Clinically, this evidence of symptom heterogeneity may hopefully guide future research, but more importantly guide some clinical assessment when it comes to assessing treatment efficacy for PASC within patient populations. I think as clinical trials continue and start feeding into this feedback loop of how target trials with real-world data influence clinical trials, this gives us an opportunity to start thinking through designs that would affect and effectively address symptomology to PASC. And exploring these symptom-specific mechanisms from a pathway lens may help us think through treatment responses in a more precise manner than we're able to do with current observational data. Next slide.

With that, thank you. This was a large team of folks; I just wanted to acknowledge some of the other folks on the paper as well, and the patient representatives and clinicians that supported this work. That's all.

Quinn Barnette:

All right. Thank you, Abhi. I think now, we will turn to Hannah to lead the discussion section.

Hannah Mandel:

Great. Thanks, Quinn. But yeah, before we get to the Q&A—and I see a lot of questions coming in, so that's great—I'll briefly highlight some of the main takeaways here. And I know Abhi just did a great job doing that.

One major finding is that across both preprints' primary analyses, high-risk patients who took Paxlovid saw a significant preventive effect for Long COVID. It was weaker than in some other studies, but this really reinforces a lot of prior findings, and in addition to benefits for acute COVID infection could be another benefit of taking Paxlovid if you are a high-risk patient.

We also saw that this effect was greater for certain symptoms such as fatigue. And given that Paxlovid reduces viral load, this suggests that symptoms or symptom clusters that demonstrated lower risk after Paxlovid may be tied to the persistence of SARS-CoV-2, which is one hypothesized cause of Long COVID.

And finally, only PCORnet looked at low-risk patients. But findings here were consistent with prior research indicating no benefit for PASC prevention. I did see a question in the Q&A about the risk and benefits of Paxlovid for Long COVID prevention in low-risk patients. So, I think that's the answer there.

And then finally, these findings were fairly consistent across the different TTE methods and Long COVID definitions and I think N3C's presentation just did a great job at putting some of the other findings, like the difference in the absolute effect differences, in context of some of these methodological differences. So, next slide.

What's next? Yeah. So, we still need to find ways to prevent or treat Long COVID, and within the EHR cohort, there are a few things we're working on that I wanted to highlight. One is we are planning on and executing more target trial emulations. So, for instance, we're currently looking at low-dose naltrexone and central nervous system stimulants, but we are planning to do more this year.

We also plan to use the electronic health record data to provide more information on how medications of interest are being used with the goal of informing which may be better clinical trial candidates. We do hope to work with RECOVER-TLC on this, but yeah, using the EHR data as a screener to see what candidates may be more appropriate to study.

And this is in addition to work outside of the EHR cohort, which I can't speak to as well, but there are other efforts across RECOVER focusing on identifying successful interventions via clinical trials. And so, there's work across RECOVER and RECOVER-TLC, which you can read about more on the website.

And with that, I thought I would start us off with a question or two. I do see there's a lot that are open right now. So, we can start off with this one maybe, but I know we just alluded to this a bit in the presentations: How do target trial emulations or pragmatic clinical trials using electronic health record

data complement traditional clinical trials like those being conducted across RECOVER or other clinical trials?

Fei Wang:

So, maybe I can start. So, I think, Hannah, you already elucidated this. So, essentially, traditional RCTs, they take time and also lots of efforts to see the results, but we already have these practiced evidence from the EHRs. So, by doing this TTE analysis before the trials, we can have sort of like, real-world database signals to 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 as 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.

Sandy Preiss:

I can pick that one as well and 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 and understanding 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, so 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, okay, 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, really helpful on both ends of the timeline, before and after.

Rainu Kaushal:

I think I agree with both of you and I think I would add that I think about clinical trial emulations as 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.

I think the second is that it can assist 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 I think that it's also very helpful on the analysis side by expanding your pool of nonintervention patients in order to achieve greater power and to have more conclusive results as well as at times to deal with bias within a study, and so a method of reducing potential bias.

Hannah Mandel:

Great. Yeah. Thanks for those answers. I think we're at 1:00 and I see that there are more questions in the Q&A, so it might make sense to turn it over to the questions from those in the audience.

Quinn Barnette:

Sure. Thanks, Hannah. Well, thanks everyone for that rich discussion. We're going to open it up to our audience with some questions in the Q&A chat and this will include a few questions that we

received in advance. And just a reminder to the audience that we will post a Q&A document on recovercovid.org for any relevant questions that we can't get to today.

So, my first question I think I'll direct to Dr. Wang and Dr. Kaushal. How many days was Paxlovid used in your study, and are you able to assess for rebound COVID after Paxlovid has discontinued? And maybe this is a question for everyone, but I'll start with Dr. Wang and Dr. Kaushal.

Fei Wang:

Maybe I can first comment about the study setting. So, essentially, as I mentioned in one of the limitations, because these are general EHR data, so it is hard to justify or to extract the drug adherence information. So, we only look at the prescription of Paxlovid within 5 days after COVID confirmation. Whether the Paxlovid was persistent or no, it is hard to extract that information from an EHR. So, that could be one of the area that in the future we can leverage other patient-reported data to study a question that we can study.

Rainu Kaushal:

And I would just add that what we are doing in the observational set of 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.

Quinn Barnette:

Right. Thank you. Our next question asks, in addition to the evidence about protecting or not protecting against the development of Long COVID, is there any evidence of Paxlovid affecting how Long COVID manifests in the body, for example, specific symptom clusters? And I know Abhi and Sandy, your presentation spoke to this a little bit. There was a bit of interest specifically about the cognitive symptoms group. So, I wonder if you could just expand on your findings and any limitations.

Sandy Preiss:

Abhi, you want to take this one or shall I?

Abhishek Bhatia:

Start and I will jump in. I'm processing.

Sandy Preiss:

Okay. Cool. Yeah, so just to reiterate, the finding that is being alluded to here is when we studied the three symptom clusters, cognitive 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.

So, this allowed us to generate an additional hypothesis—which is what we've talked about already here—that 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. So, 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.

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

Abhishek Bhatia:

And 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 who is represented well in these data and how we've been able to attribute symptom cluster-based codes to potentially Long COVID adjacent and not.

There is a set of papers and I will link them in the chat for the audience that started thinking about some of these subphenotypes and how they are represented across different demographic groups. And I think that part of this is also how PASC manifests differentially and how these subphenotypes show up differentially across different demographic strata, and its relationships to health encounters and how folks are accessing care, because they aren't necessarily independent.

And so, there is somewhat of a disproportionate set of patients across symptom clusters, but they're not necessarily equal. And so, hopefully once these subphenotypes are better established in clinical literature and we have a better understanding of treatment heterogeneity, we'd 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.

Quinn Barnette:

All right. Thank you. Our next question speaks a little bit to some of the limitations that folks have already spoken to, but it asks, to what extent can the persistent symptoms observed in Long COVID patients be associated with recurrent asymptomatic reinfections? And they point out that a large portion of the population experienced asymptomatic viral phases and some of the most severe cases occurred predominantly during an inflammatory phase that had negative biomarkers. I think anyone could comment on this, but maybe I'll start with Dr. Wang. Is this something that you were able to assess for in your analysis?

Fei Wang:

Yeah. I think first I would comment. So, as you said, one of the limitations is for asymptomatic patients if you don't interact with the health system. So, there's no way this information can be reflected in our data. But there are other studies, especially in the UK, where they really 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.

And another thing is you mentioned about the assessment of the persistent symptoms and as I said, so again, one of the limitations is that we only look at incidents for now, but we do have a plan for looking at persistent and exacerbated symptoms and signs in the post-acute period which needs more work on. Let's say we currently have efforts on expanding the data sources from structured to the unstructured nodes 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 are currently doing.

Quinn Barnette:

All right. Thank you. We received a couple of questions related to how Paxlovid compares to or might be combined with other treatments such as metformin, and we also heard some interest in ongoing recovered clinical trials and what the timeline might look like for doctors to begin prescribing if Paxlovid is determined to be an effective treatment. So, I wonder if Dr. Kaushal, you could just speak to some of these points, particularly if the trials are approaching any of these comparisons and what some potential timelines for clinical use might be.

Rainu Kaushal:

I'm going to take on the latter question first, which is when could Paxlovid be utilized for treatment of Long COVID? Given that Paxlovid is an 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.

In terms of the clinical trials, they are active. Metformin is an early agent that we're looking at in the clinical trial side. And 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.

I think 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 to really try to understand underlying mechanisms of the disease. Because if we had a keener understanding of underlying mechanism of disease, that would facilitate putative drug identification, therapeutic identification, and facilitate the optimized trial interventions.

Quinn Barnette:

Great. Thank you. Our next question, I will open it up to the panel. It's a general question of if individuals who are pregnant were included in these analyses, or if not, if those are included or expected for future analyses?

Fei Wang:

I think I can answer that first. So, for our study, because we are evaluating the actual Paxlovid trial, so where the pregnant patients were excluded, we excluded them as well for our study. But we do have a dedicated study similar to the TTE analysis on a pregnant cohort. So, that's certainly on our agenda and just to stay tuned for more results from our analysis.

Quinn Barnette:

All right. Thank you. Our next question is, we know the frequency of repeat COVID infections increases the risk of developing Long COVID. Were you able to assess this? And the question would be whether benefits of Paxlovid would increase for people experiencing a third infection versus their first COVID infection? I know you've spoken a little bit to some of the limitations, but maybe I'll throw this one to Abhi and Sandy to comment on.

Sandy Preiss:

Yeah. We thought about this and ended up not doing it for a few reasons, principally because this was starting to take place in the phase of the pandemic where it was really difficult to assess from the EHR whether an infection was their first infection or a reinfection. So, the first documented infection by the time you were in 2022 was often not the initial, the person's first bout with COVID.

So, that misclassification made us a little bit hesitant to do that, and I think that's just an EHR limitation or at least with this particular condition and study period. But I do think it's a very interesting research question. We did do some other work just assessing the relationship of reinfections and Long COVID in general that I'm happy to drop in the chat, not Paxlovid related.

Quinn Barnette:

All right. Our next question asks about the many with Long COVID who have no temporary improvement in symptoms when they take Paxlovid for an acute infection. Are there potential studies that are planned for longer term treatment of Long COVID with the use of Paxlovid? And I know that we've already spoken a little bit about clinical trials, but I wonder if folks would like to comment on this and I'll open this up to the panel.

Fei Wang:

I think certainly we can study this. That's actually another advantage working with observational data. So, you can essentially capture the patients who got treated within 5 days. Again, this is replicating the real-world trials and also there could be patients who got a prolonged prescription of Paxlovid, and we look at the difference. We do that in this study, but we can certainly do that in future studies.

Abhishek Bhatia:

And I just want to also flag that something that we are unable to measure that we need to just assume is adherence. And so, 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 and when your course started, 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 dose.

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 say in terms of some of these prolonged dosage-based treatment plans. But I think that acknowledging those limitations, there's scope for us to use some of these EHR data to make those inferences.

Quinn Barnette:

I think we have time for maybe one more question. And I've received a couple questions about variant-specific analysis. Were either of the studies able to do this, for example, looking at the Omicron variant specifically, is this something that you're able to assess? Maybe I'll start with Dr. Wang.

Fei Wang:

Yeah. 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 we started from March of 2022. That's really when the Paxlovid prescription became prevalent.

So, before that, because Paxlovid was not prescribed in a prevalent way, so we cannot really assess that. But after March 2022, it was the Omicron-dominant time period within that year. But we still stratify that. So, certainly, I mean going into the future, I mean currently our study is until February of 2023, but we can certainly, because the data were continuously coming in, so we can investigate what is being suggested here of doing variant-specific analysis. So, currently it is Omicron dominant.

Abhishek Bhatia:

I'll echo that for our case. I think just, in the Paxlovid era, most of our work was somewhat also intentionally restricted to the Omicron dominant and post-Omicron phase. And I also just want to acknowledge the fact that there is the 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 is a good amount of papers that have started looking at that relationship. In our prior paper that we had linked in the chat, we looked at the relationship between Paxlovid and acute hospitalization. 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, where for the most part in our research, we're just doing that by 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.

Quinn Barnette:

All right. Well, thank you all. I think that will conclude our Q&A session for today. So, I want to say thank you so much to all of our presenters. Thank you to our audience for attending this 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. And we'll also be posting a Q&A document that has responses to the questions that we received today, including some that we did not have time to address.

But before we conclude, a reminder that researchers both in and beyond the RECOVER Initiative can now apply to use RECOVER data for ancillary studies. So, this includes data from three RECOVER cohort studies, adults, including pregnant adults, pediatric data, and autopsy and biospecimens collected from cohort study participants.

Interested researchers must submit an ancillary study proposal and receive approval, and researchers must also have independent funding to support the conduct of the proposed study. And to learn more about that, you can visit recovercovid.org/ancillary.

And with that, we do hope you'll join us again. Please keep an eye on recovercovid.org updates and for a list of future seminar topics. Additionally, you'll see a short survey come up on your screen, which will ask for your feedback on this seminar. And we do appreciate if you take a few minutes to fill out this brief survey. Thank you and have a great day.