Executive Roundtable

Uncovering Long-Term COVID in Drug Development

How can clinical trials be designed to best study therapies for treating long COVID?

Brand Insights - Thought Leadership from Marketers I Paid Program

As progress is made in addressing the COVID-19 pandemic with vaccines and treatment pathways, reports about the long-term effects of the infection are building. Post-acute Sequelae of SARS-CoV-2 (PASC) (i.e., long COVID, long-term COVID, long-haul COVID) is an umbrella term used to describe long-lasting physical and mental health symptoms in patients, weeks to months after the onset of the initial COVID-19 symptoms. Long-haul symptoms are diverse and include shortness of breath, cognitive dysfunction (i.e., brain fog), fatigue, anxiety, chest pain, depression and more. Some people who had severe COVID-19 illness experience multiorgan effects, and even asymptomatic individuals that test positive for COVID-19 might suffer from long COVID.

This condition is far from well-understood, spurring Congress in December 2020 to earmark $1.15 billion in funding over four years for the National Institutes of Health (NIH) to support research into the prolonged health consequences of COVID-19 infection. The industry, however, still needs much more discussion and clarity on how best to study this complex condition in an effort to bring new therapeutics to market for treating it.

To start such conversations, *Pharmaceutical Executive* (in collaboration with Parexel) organized a roundtable of experts from various stakeholder groups to discuss the current research into long-haul COVID; the challenges of diagnosing and researching this condition; and potential clinical trial models for PASC treatment development.

Participants in the roundtable were:
Clare Grace, PhD, (Host/Moderator), Chief Patient Officer, Parexel
Lisa Henderson (Facilitator), Editorial Director, *Pharmaceutical Executive*
Patricia (Trish) Bradley, US Chief Commercial Officer, Huma
Richa S. Chandra, MD, MBA, Clinical Development Head, Communicable Diseases, Global Health, Novartis
Michael Chen, PhD, Head of Innovation, PureTech Health
Alecia (Slade) Clary, PhD, M.S.W., Associate Director of Research, Reagan-Udall Foundation for the FDA
Rany Condos, MD, Director of the Post-COVID-19 Clinic, NYU Langone Health
Mark DiNubile, MD, CMO, BioAegis Therapeutics
Michelle Hoiseth, Chief Data Officer, Parexel
Seth Lederman, MD, CEO, Tonix Pharmaceuticals
Richard Marsden, CEO, Synairgen
Mari Mitrani, MD, PhD, CSO, Organicell Regenerative Medicine
Christopher Recknor, MD, COO, CytoDyn
Frances Oko, Senior Solutions Consultant Director, Parexel
Nathalie Sohier, MD, MPH, Senior Vice President, Global Head for Infectious Diseases and Vaccines Franchise, Parexel
Sylvia Taylor, PhD, MPH, MBA, Director Epidemiology, Medical Evidence Strategy Lead, Vaccines & Infectious Diseases, AstraZeneca

CURRENT STUDIES AND DEFINITIONS

Nathalie Sohier, MD, MPH, Senior Vice President and Global Head for Infectious Diseases and Vaccines Franchise with Parexel, began the discussion with a review of what is known about long COVID. According to Nathalie, one of the challenges around studying this condition is the diversity of symptoms and definitions.

For starters, the Centers for Disease Control and Prevention lists more than 20 potential post-COVID symptoms that are a "wide range of new, returning, or ongoing health problems" that occur "four or more weeks after first being infected with the virus that causes COVID-19."

Meanwhile, the UK's National Institute for Health and Care Excellence notes in its guidelines that ongoing symptomatic COVID-19 may occur four to 12 weeks from the initial illness and that post COVID-19

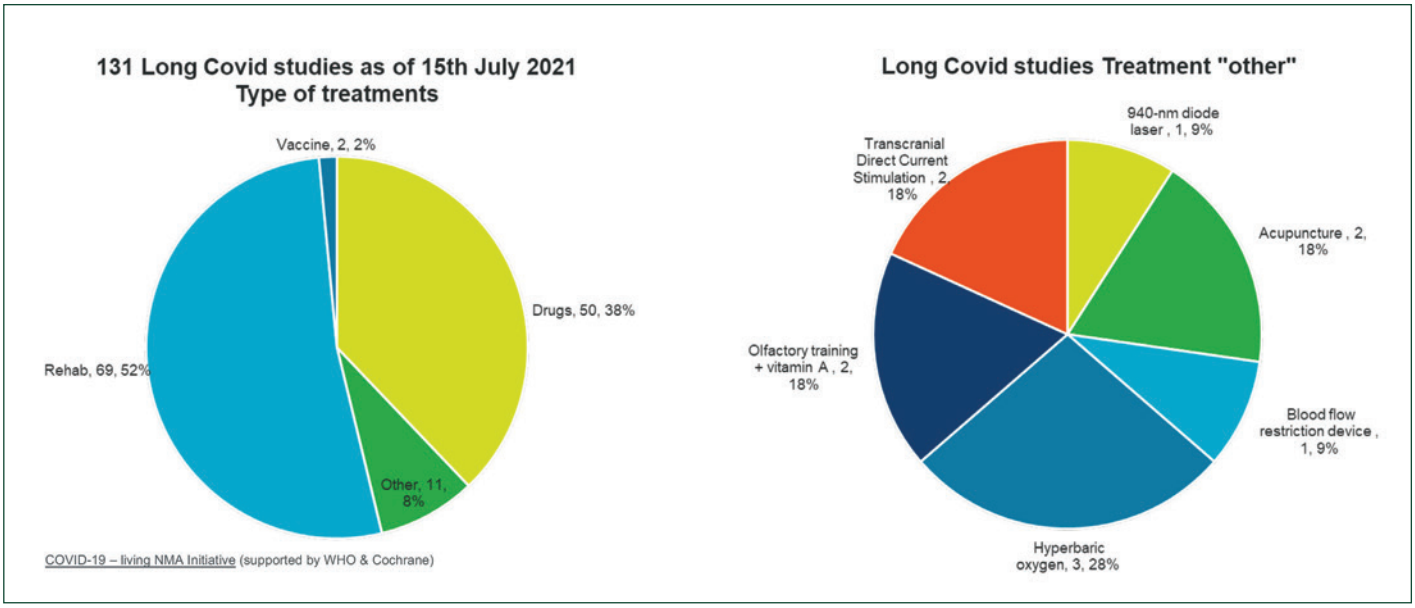

Figure 1. Treatment types used in post-COVID-19 Syndrome studies (as of July 15, 2021)

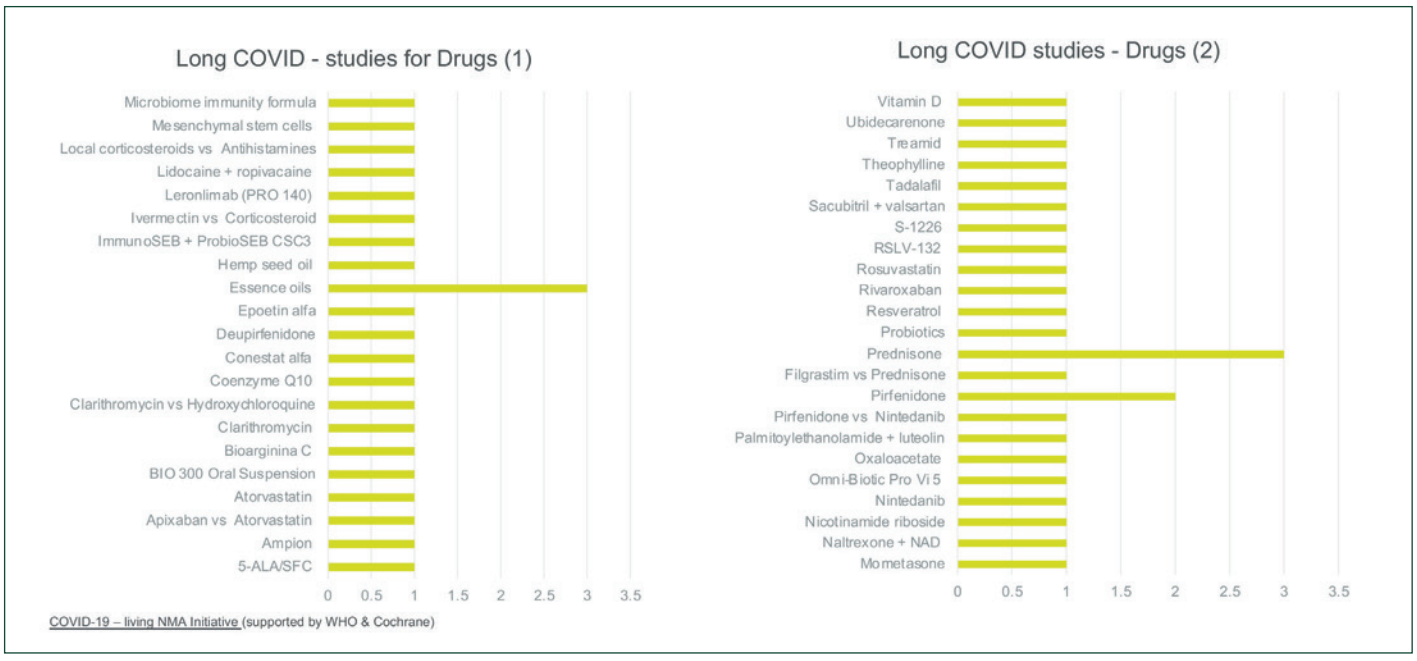

Figure 2. Specific drugs and treatments studied in Post-COVID-19-Syndrome research (as of July 15, 2021)

syndrome is defined as symptoms that occurred during COVID-19 infection and continue for more than 12 weeks.

While the definitions differ, researchers agree that the condition is complex and warrants significantly more research. "Many mysteries persist about the disease," Nathalie stated.

Among them, she pointed out that no one understands just yet why some people get so much sicker than others, or why lung damage appears to worsen well after the body has seemingly cleared the virus. And of course, another puzzle is what is behind the extended multi-organ illness that lasts for months in some patients.

"One of the reasons probably involves autoantibodies," she stated, noting that more than 5% of hospitalized COVID-19 patients have large numbers of autoantibodies in their blood, which block antiviral defenses, wipe out helpful immune cells like B-cells and T-cells, and target organs, brain and the immune system itself, resulting in long-term damage.

"The more autoantibodies that COVID-19 patients had in their blood, the worst the disease," she explained. "These patients had more autoantibodies than people with lupus, for example." Autoantibodies may therefore be a factor in helping diagnose long COVID in patients.

Nathalie also presented the combined results of 131 studies on post-COVID symptoms as of July 15, 2021 (77 were recruiting more than 7,700 patients, 46 were not recruiting, and 8 were completed of which 1 was published). The pie chart on the left side of **Figure 1** shows the breakdown of treatments used in these studies like vaccines and drugs. The chart on the right shows the use of other less traditional treatments such as acupuncture, hyperbaric oxygen and olfactory training. **Figure 2** illustrates the diversity of treatments being explored to help address this condition. These include immune modulators, fibromyalgia treatments, anti-inflammatory drugs and vitamins.

With much of the current research being conducted in academia, with great utilization of electronic health records and other real-world data sets, how can the industry take advantage of collaborations for future drug development?

LUMPERS VERSUS SPLITTERS

Parexel's Chief Patient Officer, Clare Grace, PhD, led the group in a discussion about how best to study long COVID and the role of collaboration in the post-acute COVID arena.

Grace: Clearly, a lot of work is underway to better understand this space, but let's hear from our participants about the current state of long COVID research. What are you seeing?

> ***The most frustrating group are those that had COVID, severe or not severe, have persistent complaints and yet none of our conventional testing is showing abnormality. That's also the most interesting group because we need to think outside of the box to determine what's triggering these symptoms.***

Michelle Hoiseth (Parexel): One thing that leaps out to me is how many treatments are just being looked at in a single study. How is that data emerging toward a standard of care, and what off-label treatments are being tried?

Frances Oko (Parexel): I've seen many academic centers opening post-COVID syndrome or COVID recovery clinics. I find that their treatment plans are very holistic—incorporating physical, psychological, and mental support—using a range of drugs, some off-label.

Rany Condos, MD (NYU Langone Health): I run the Post-COVID Clinic here at NYU, and we've been open for over a year. We've seen more than 500 post-COVID patients in that time. What strikes me looking at the charts is the difficulty in nailing down the extent of long COVID and its symptoms. A patient usually has two or more symptoms—plus others that are not COVID-related.

We are aware of the dissemination of information over social media about alternative treatments and hear anecdotally of drugs being prescribed off-label by physicians. It's great to be proactive in terms of therapy but I still don't think we have a very good idea of what the disease is and what we should be targeting with therapies.

Hoiseth: So, should we be looking for drugs with common mechanisms to address multiple body symptoms or should we take a body system by body system approach?

Condos: This can be tricky; it depends on the symptoms. If the patient is short of breath, we target the lung. Meanwhile, the complaint of fatigue, which is very common with long COVID, can involve multiple organ systems.

Mark DiNubile, MD (BioAegis Therapeutics): I think the biggest problem is definition. Should we be "lumpers" (i.e., studying all long COVID patients as one group) or "splitters" (i.e., looking at patients based on smaller groupings of symptoms)?

Long COVID involves a variety of symptoms and mechanisms, some of which are not unexpected. In addition, we see an unusual constellation of symptoms that we feel go together with mechanisms. Research shows that this isn't a persistent infection, so there is a high likelihood that it's an immunologic response. The precise definition continues to confound us, however.

It's clear, though, that long COVID is not a unitary concept or syndrome. If we study the disease as a lump sum, we may miss the boat because various disease presentations may respond differently. It would help if we had an objective test for some of the syndromes such as an antibody test.

> ***One of the challenges with using some of our large data sources and thinking about how we may use a synthetic control arm is that we don't yet understand how the data on these patients are being collected across the healthcare system.***

But I think we should be doing studies that separate groups by constellations of symptoms.

Michael Chen, PhD (PureTech Health): To Mark's point, it's interesting that 15, 20 years ago, data-driven tools weren't available to help split a group into clusters of symptoms that naturally aggregate. Today, tools allow us to match biology to the data. Hopefully, such data will let us get to the cautious splitting point, which I think is a really great way to develop new therapies in this space.

Richard Marsden (Synairgen): If I had a drug that I thought would be helpful for long-term lower respiratory tract complications, I'd want to zoom in on lung-related trial endpoints and test them in patients with breathing difficulties. Otherwise, the drug could be doing something good for the lungs, but the overall effect would be lost amongst the many other general endpoints such as nasal symptoms and anosmia. So, I'm a pro-splitter.

Chen: I'm also a cautious splitter. To Richard's point, we'd want to select a patient population that has respiratory complications for a respiratory-oriented drug. If we select a broad long COVID population for a clinical trial, just based on the immense variety that Nathalie showed in terms of the symptoms encountered by long COVID patients, it would really dilute any potential therapeutic effect that's specific to the system being studied with an intervention.

Others who are looking at data in a different way might have the luxury of being able to lump a little bit and get a better understanding of long COVID as a whole.

Condos: When I think about the patients that I see, I separate them into three groups, so I'm a splitter. One is a group of patients who were critically ill, have evidence of end organ damage, and yet their symptoms are improving. The second group are those that were not critically ill, yet are coming in with specific complaints and have evidence on testing of specific end organ damage. That's a big group. It's an easier group because you have a symptom and a complaint, and you have an organ system that's being affected that you can actually do a measurement on.

The most frustrating group are those that had COVID, severe or not severe, have persistent complaints and yet none of our conventional testing is showing abnormality. That's also the most interesting group because we need to think outside of the box to determine what's triggering these symptoms. Perhaps there is a mental status exam that we should be thinking about incorporating.

Christopher Recknor, MD (CytoDyn): We look at it in that way, too. Some patients have obvious symptoms, and we're looking in detail at cellular biomarkers. Then, there's the group that the biomarkers get better and the symptoms get better. The concerning group is the one whereby their symptoms improve, but biomarkers are ongoing. So, we're able to look at this with each of the patients, and then we're getting close to tagging this genetically to how our medication works. We look at it from an immunomodulation standpoint, so it's not one particular organ system; it's all organ systems.

Mari Mitrani, MD, PhD (Organicell Regenerative Medicine): I am a lumper as well in terms of the autoimmunity component we are seeing. I find it very important to track all those biomarkers as we are seeing systemic multi-organ inflammation. We are starting to collaborate with a physician who has tracked around 7,000 COVID-19 long-haul patients and have identified a spike in an uncommon monocyte in all the patients.

Sylvia Taylor, PhD (AstraZeneca): There's a real opportunity here to develop machine learning that helps us to define these groups. But, we need more clinical guidance to avoid machine learning being a completely exploratory activity.

THE ROLE OF DATA COLLECTION AND TECHNOLOGY IN STUDYING LONG COVID

Grace: There are so many complaints with long COVID and it's challenging to parse apart the individual symptoms. Is there a way we can take advantage of synthetic control arms in how we run these studies? How can we achieve efficiencies that will drive solutions faster?

Alecia (Slade) Clary, PhD (Reagan-Udall Foundation for the FDA): One of the challenges with using some of our large data sources and thinking about how we may use a synthetic control arm is that we don't yet

understand how the data on these patients are being collected across the healthcare system. And then, you have challenges with the interoperability of the data. If the definition of long COVID relies on the patient having a confirmed COVID diagnosis, how are the data being connected if the patient is diagnosed with COVID outside of the primary care provider who may diagnose their long COVID? So, we're trying to think through how we may better connect all of the data sources to facilitate the identification of these patients and their inclusion in trials.

We also must consider that the way the healthcare system has been built and historically accessed will affect our ability to identify patients with long COVID. Under-diagnosis of patients with long COVID will be a concern in the future because you may not be able to accurately identify those that have long COVID due to poor access to the healthcare system and changes in healthcare seeking behavior.

Moreover, the way we are collecting data on symptoms may be relevant to our ability to develop a synthetic control arm for a clinical trial. Providers may not be using symptom questionnaires at regular intervals that will help you identify when patients have symptoms, when they are resolving, or when they're getting worse.

These are some of the many challenges of using large data sets for understanding long COVID at this time.

Patricia Bradley (Huma): We have collected millions of data points from patients across countries and can monitor them from early symptoms to long COVID. We've found that symptom trackers are critical on this front. Like others have mentioned, patients have a long list of symptoms and they vary from person to person. So, it's important to look at data banks for comparison. What's the difference between this post-viral syndrome versus other post-viral syndromes? Can you find differentiators that might create new ways to treat or study the disease?

In some places, technology has allowed us to study patients holistically and pull in their entire medical records to get a 360-degree view of what's going on. If patients went to an urgent care center and they see a different clinician from who's studying them, that information can still get tied together if the systems are connected. For instance, in the UK, we noticed that people who had urinary tract infections or kidney infections had a bad outcome with COVID-19.

This can be harder in the US where data is much more fragmented. To improve outcomes long term and reduce the burden of costs, we need a connected system here in the US.

Taylor: Absolutely. On that front, an issue that is preventing us from moving COVID-19 research very far forward in the US is that vaccination data is not linked to the status of patients. That information is being kept at the state register level and is very hard to link to. Likewise, testing data is very hard to link to. It would be helpful if some of the focus in the US were on setting up those systems because it would help us in the future with real world evidence.

> ***"I think it's clear that four pillars of long COVID have emerged: widespread pain, fatigue, sleep problems and brain fog. Yet the challenge gets more difficult when you have 31 endpoints."***

Hoiseth: I agree. To study this area appropriately, the data sets will need to be broad and deep. To do the pattern detection required for the cautious splitting of patient groups and to understand context, we will need to collaborate as an industry. I see it as a public–private partnership at its base, where the data are coming in with technology companies equal with the clinical development companies to solve for the data interoperability and the completeness and depth of the data sets. It's going to be a collaboration.

Grace: There's no way we can do without global collaboration. The UK has data sets that can be utilized and projected from for other countries even. Sharing that information effectively across boundaries will be critical.

NEW APPROACHES TO RWE AND COLLABORATION

Hoiseth: Our traditional way of developing therapies is to tightly control the patient population, make it as modular a test as possible. So, the only variable we're looking at is the treatment impact. Then, when we understand safety and efficacy, we look at it out in the messy, real world.

With all the confounding variables—the constant evolution of the symptom profile, the lack of clarity on the adequacy or regulatory accessibility of endpoints, the lack of clarity about what other treatments might be going on for patients and how they're accessing treatment—we might need to do the opposite of a traditional design. Rather, we take a real-world evidence-based approach to start and confirm what we see in those broad studies in a randomized clinical trial.

Bradley: I agree. When you have the ability to pull in the patient records, it changes your view dramatically and may give us some ideas for how to treat or how to get into proactive, predictive care that really could change outcomes for people for the long haul.

What you proposed—designing clinical trials in a different manner—is something we, as a collective group, should think about together.

Clary: We are seeing the dawn of a new era with opportunities for many different organizations and disciplines to come together to solve problems that are affecting each of our disciplines in a unique way. Stakeholders are open to helping us define patients and outcomes, incorporating patient perspectives, and finding and/or developing validated tools to assess different endpoints.

WORKING ON PRIORITIES

Grace: Are there certain symptoms that are moving faster than others? Are there areas that we should tackle first?

Seth Lederman, MD (Tonix Pharmaceuticals): A key challenge is determining validated endpoints, and there will be work to do with the FDA. I think some of the early developers of drugs are going to have to collect a lot of data and begin to inform FDA about what are reasonable endpoints.

I think it's clear that four pillars of long COVID have emerged: widespread pain, fatigue, sleep problems and brain fog. Yet the challenge gets more difficult when you have 31 endpoints like in the "PROMIS 29 plus 2 Profile," which is now called PROPr.

Condos: I've seen the situation evolve over the last year. Initially, this was a respiratory illness. Brain fog was not on my list of questions I'd ask patients. So, we started adding things and have become more adept at identifying the range of symptoms associated with this condition but perhaps we are less adept at deciding what are the endpoints and what we should be monitoring. We need to be advised by older studies used to study the same complaints to determine what the endpoints should be. The range of symptoms is a moving target and we're going to have to adjust as we get more information.

Richa S. Chandra, MD (Novartis): We have all this data collection ongoing right now. We are trying to identify causative factors and where to intervene in the whole spectrum of disease presentations, but maybe it's time to step back and simply ask: What are the target product profiles we are trying to address here? Which populations of patients and at what stage? Is it preventive? Is it therapeutic? For which constellation of symptoms? And then, what endpoints do we want to really evaluate for each of those? If you treat with an antiviral, could you prevent long COVID? Could vaccination help?

Clary: There are many outstanding questions about which symptoms lead to a diagnosis of long COVID. It appears from the data Nathalie shared that the more symptoms the patient reports, the more likely they are to develop long COVID. But we don't know what effect vaccines have on a patient's likelihood of having long COVID.

Chandra: It would be good to have a focused workshop on how to develop a drug for long COVID, starting with the target product profiles. Perhaps the FDA could organize this.

Mitrani: Another priority should be establishing definitions. We have an approved FDA trial for long haulers that focuses on fatigue and mental fog. Agreeing on definitions and populations was challenging. The approved IND defines long COVID as six weeks past symptoms, which is a different timeline than used elsewhere like Nathalie mentioned.

Oko: I am concerned about the under-diagnosis of long COVID and the ability to capture all of this information. I think we need to expand medical awareness to get more clinicians looking for this.

Grace: There are so many areas where we need to collaborate. What are some of the ways in which we can do that? Do we need to coordinate on the definitions of subpopulations?

Mitrani: There's a real opportunity to bring together epidemiologists, tech people, pharma, clinics and others to help us contextualize our findings.

Marsden: Collaborative work is essential, particularly while trying to get to grips with a new challenge such as COVID-19 and to generate hypotheses, then we need to collaborate further to confirm the hypothesis.

Grace: Yes, and it's also important to get awareness out to the general population so people can identify symptoms and seek treatment.

SUMMARY

There is much work to be done in identifying and treating long COVID. The condition presents with a variety of symptoms and diagnosis is difficult. This roundtable brought together experts from around the field to discuss ways to collaborate and address the big data challenges of looking at a disease that can have 31 symptoms. The industry must be prepared to address clinical trial design, patient registries and other challenging areas in the development of therapeutics for post-acute COVID.

The ideas and opinions expressed in this article are solely those of the participants and should under no circumstances or in any way be considered to reflect those of their employers or any organizations of which they may be members.