Preparing to Face the Next Global Challenge: Studying Post-Acute COVID-19 Syndrome

Post-acute COVID-19 syndrome (PACS) could affect up to 30% of patients who contract COVID-19. Symptoms are wide-ranging and can be debilitating, but the full clinical picture is still being revealed. The challenges to conducting clinical trials for this as yet undefined disease are myriad. PPD is well-positioned to help sponsors overcome these challenges and bring needed therapeutics to patients.

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Post-Acute COVID-19 Syndrome: An Evolving Understanding

The initial response to the COVID-19 pandemic focused on the development of treatments for acute infection and, in parallel, preventative vaccines. The first clinical studies investigating therapeutic treatments focused on assessment in severe hospitalized patients, and most studies limited recruitment to patients requiring ventilatory support, many of whom were more than 10–14 days post-infection or onset of symptoms. The focus for data collection was acute outcomes. Patients were typically evaluated at days 14 and 28 and had either succumbed to the virus, remained in the hospital while recovering, or returned home.

As the pandemic progressed, therapeutic development expanded, with a shift toward the development of treatments

that could be administered earlier in the outpatient setting to prevent the worsening of the disease and its potential long-term effects.

The indications of a more drawn-out disease process or syndrome associated with COVID-19 infection were first seen in patients who were not able to resume normal life functions after recovering from the initial infection. Eventually, as some of these patients recovered, the profusion of those "long-haul" patients drew the attention of clinicians.

The term *post-acute COVID-19 syndrome* (later abbreviated as *post-COVID syndrome*) was adopted to describe the broad constellation of symptoms, including exercise intolerance, dyspnea, chest pain, palpitations, chemosensory impairment, lymphadenopathy, appetite loss, fatigue, poor concentration, and pulmonary or cardiac complications in patients who have recovered from the acute infection.[1-5]

As time has progressed, more sponsors are including an extended post-treatment observation period for trial participants at three-, six-, and 12-month timepoints or longer. Simple questionnaires, which are relatively inexpensive to develop and execute, can provide a great deal of information about effects on long-term outcomes, while also helping build our understanding of post-COVID syndrome.

We are encouraged by our early discussions with sponsors who are pursuing experimental treatments for these complex and perplexing sequelae. We are committed to applying the full range of knowledge and expertise that PPD offers — clinical therapeutic experience, data analysis capabilities, and real-world evidence solutions — to advance therapeutic options for these patients.

As biopharma companies work to address the unmet medical needs of patients with post-COVID syndrome, they will require clinical research organization (CRO) partners with broad experience and innovative solutions. We are encouraged by our early discussions with sponsors who are pursuing experimental treatments for these complex and perplexing sequelae. We are committed to applying the full range of knowledge and expertise that PPD offers — clinical therapeutic experience, data analysis capabilities, and real-world evidence solutions — to advance therapeutic options for these patients.

Uncertainty About Long-Term Effects

An early study found that 87.4% of patients who had recovered from COVID-19 reported persistence of at least one symptom — particularly dyspnea and fatigue — at a mean evaluation time of 60.3 days after onset of the first COVID-19 symptoms, with 44.1% reporting a worsened quality of life.[6] A later study found that 30% of recovered COVID-19 patients reported persistence of at least one symptom (most commonly fatigue, loss of the sense of smell or taste, or "brain fog") as long as nine months after the acute disease phase.[7]

Many post-COVID syndrome patients meet the clinical criteria for myalgic encephalomyelitis, commonly referred to as chronic fatigue syndrome (CFS).[8] Based on data available to date, it appears that somewhere between 10% and 30% of people who have had COVID-19 — whether mild or severe and whether they tested positive or not — will develop these long-term symptoms.[7] A U.K. study published in March 2021 found that 71% of COVID-19 patients discharged from hospitals had not fully recovered five months later, with 20% exhibiting persistent symptoms that met the threshold for a new disability and 19% experiencing a health-related change of occupation.[9]

It is still too early to know how long these symptoms will persist, what percentage of patients will have symptoms at one year, two years, and longer, and whether some patients who appear to have recovered from a post-COVID syndrome might subsequently relapse. It is also unclear how patients who have experienced complications, such as cerebrovascular accidents, or show evidence of myositis or lung fibrosis will progress compared with patients with these conditions from traditional etiologies.

In addition to the physical damage caused by the virus, patients with COVID-19 also may experience psychological complications and even post-traumatic stress disorder (PTSD). The March U.K. study reported that over 25% of discharged COVID-19 patients had clinically significant symptoms of anxiety and depression, with 12% exhibiting symptoms of PTSD at five-month follow-up.[9] While this may be most evident for patients who have been hospitalized and experienced traumatic healthcare interventions, the anxiety associated with an unpredictable disease course or the fear of infecting others means that even patients with mild disease may be left with a degree of trauma disproportionate to the acute illness they experienced.

Bringing Experience to Address a Myriad of Challenges

CROs involved in post-COVID syndrome studies will need to have considerable experience supporting COVID-19 therapeutic clinical trials, bringing the necessary understanding of who the potential participants are and how to locate them. As one of the first CROs to support COVID-19 trials, PPD is optimally positioned to support post-COVID syndrome studies.

Our COVID-19–specific experience, which spans treatment to prophylaxis, began early in 2020. We gained valuable experience encompassing a broad

Establishing a Case Definition

To establish a case definition, a large quantity of patient data is needed, particularly in light of the multiplicity of post-COVID syndrome manifestations. In an early attempt to describe post-COVID syndrome, distinct subgroups of patients have been identified, including:

- Chronic fatigue syndrome patients with brain fog;
- Post-ventilator syndrome patients, whose symptoms may include physical weakness, cognitive dysfunction, and posttraumatic stress syndrome;
- Patients with true neurologic symptoms, such as rigidity and tremors, that likely reflect effects of the virus on the brain; and
- Respiratory patients with lung damage and compromised lung function.

While this is a preliminary grouping, we expect this listing to evolve, perhaps with the addition of other subgroups or new combinations of symptoms. Cluster analysis of large data sets may eventually identify phenotypes within post-COVID syndrome sufferers or even predict which patients are at greater risk of developing a particular pattern of symptoms.

Medical claims and patient charts can be used to determine new diagnoses that follow a COVID-19 diagnosis. However, as many of the symptoms of post-COVID syndrome can only be identified and reported by patients themselves (fatigue, pain/discomfort, dyspnea), additional research that directly engages patients, either through qualitative (e.g., focus groups) or quantitative (e.g., web-based surveys) methods, will be required to fully understand the patient experience of post-COVID syndrome.

range of patient populations, inpatient and outpatient settings, study phases, trial designs, global geographical locations, and types of drugs and drug formulations. PPD has demonstrated the ability to rapidly respond to changes in direction dictated by the evolving epidemiology of the pandemic and has been recognized by clients for its agility and speed.

Lack of a Standardized Definition

We may easily identify who has had COVID-19, but we still do not know how to definitively identify people suffering from post-COVID syndrome. This is due in part to the lack or a formal case definition, though the medical community and academic researchers are actively progressing this issue. However, any proposed definitions likely will undergo numerous revisions before a universally accepted case definition is adopted.

A significant number of patients describe disruptive neurologic symptoms, such as emotional detachment and cognitive disorders, tremors, extreme fatigue, phantom smells, dizziness, and bouts of profound confusion — generally termed “brain fog.” Patients may experience one or more of these symptoms but may lack an identifiable physical cause. This is not unprecedented; the connection between chronic neurologic conditions and infectious viruses has been known for almost a century. It may be helpful to differentiate these patients with less well-understood symptoms, for whom conventional imaging and testing modalities appear normal, from patients with lung fibrosis or evidence of cardiac damage and hence a more obvious cause for their fatigue and breathlessness.

Extended ICU stays are independently associated with prolonged or incomplete recovery and may be associated with autonomic function disturbances (e.g., fatigue, lung and nerve damage) that also are recognized in patients with post-COVID syndrome. For patients who have had extended hospitalization or who required prolonged intubation

and ventilation, it may be difficult or even impossible to distinguish the impacts of COVID-19 from those of the interventions themselves.

PPD has worked with many different viral infections and infectious diseases, as well as indications related to other viral and post-viral symptoms, including complications of HIV and post-HIV development of AIDS, as well as CFS. In addition, we have extensive experience in neurology, psychology, immunology, and respiratory and cardiovascular diseases, all of which may have relevant application to post-COVID syndrome clinical development programs.

PPD has extensive experience working with patients under these conditions to enable understanding of their histories, current symptoms, and the range of impacts on their lives.

Lack of Disease-Specific Validated Outcomes Assessment

Given the diversity of patients and symptoms associated with post-COVID syndrome, a wide range of operational and medical scientific experts will need to be involved in clinical trials. Multiple endpoints will be needed within each patient subcategory based on the predominant symptoms. Initially, we expect that established and accepted endpoints, including patient-reported outcomes (PROs), will be adopted from other conditions where we see clinical similarities.

Our extensive experience identifying the nuanced information important to various groups and then developing evidence-generation strategies to support tailored value messages strongly positions PPD in accelerating this area.

New Test for Past COVID Infections Can Potentially Increase the Prospective Patient Pool

For a significant part of the pandemic, testing availability was limited and rationed. Many patients were unable to obtain testing, and others may have chosen not to be tested. This, coupled with a relatively high percentage of suspected false-negative tests, could reduce the pool of patients with confirmed post-COVID syndrome eligible for clinical trials.

The FDA's recent granting of emergency authorization for a new T cell test could change this. The first-of-its-kind test uses T cells to detect whether someone was previously infected with SARS-CoV-2, bringing clarity to these patients with suspected but not confirmed infection.

PROs or other clinical outcome assessments (COAs) likely will be required as primary efficacy endpoints in some clinical trials evaluating treatments for post-COVID syndrome, particularly when the syndrome manifests in symptoms that only patients themselves can report (e.g., fatigue, dyspnea, loss of appetite). Evidence of validity and reliability, as well as clinically important differences of these tools in post-COVID syndrome, will need to be established in order to enable their use as registrational endpoints for acceptance by regulatory authorities (FDA 2009).

The complexity of trial designs and implementation of post-COVID syndrome studies will require the services of CROs like PPD with extensive operational and scientific expertise across multiple therapeutic areas involved in treating these patients. A broad array of resources will be needed for data analysis, including both epidemiological experts and data scientists. These trials will also require experience in the determination of practical and patient-focused endpoints/outcomes that provide reliable and valuable results.

For both orphan diseases and COVID-19 itself, PPD has often had to select and validate existing tools and rating scales/scoring methods for one sequela and apply it and make it more relevant to the bigger picture. For instance, we have engaged with sponsors to adapt our FLUPRO patient-reported outcomes instrument for evaluating the severity of flu symptoms. This tool was developed in collaboration with the National Institutes of Health for use in COVID-19 treatment and vaccine trials to evaluate treatment benefit in terms of reduction in disease severity.

Defining Need and Value

Sponsors may recognize post-COVID syndrome as a legitimate disease with a strong unmet medical need. However, work is still needed to understand the value associated with improved outcomes: this value proposition may be different for payers, regulators, clinicians treating patients with post-COVID syndrome, and the patients themselves. Mapping and understanding the often-conflicting priorities of various stakeholders is an important part of how development in this space

proceeds. Our extensive experience identifying the nuanced information important to various groups and then developing evidence-generation strategies to support tailored value messages strongly positions PPD in accelerating this area.

Through advisory panels with payers across all key markets, our market access consultants gather clear insight into what payers consider when assessing products for reimbursement. Our researchers focused on patient involvement use a myriad of methods to elicit patient preferences and priorities to help guide both development and uptake once on the market. By understanding what is important to each stakeholder, the right evidence can be generated for the right audience to optimize product approval, access, and adoption.

Both regulators and payers will expect that PROs used as important efficacy endpoints will be reliable, valid, and responsive in post-COVID syndrome populations and to evaluate treatment benefits that are meaningful to patients. Existing PROs and other outcome measures will be adapted for use in post-COVID syndrome, but evidence still will need to be obtained to ensure that PROs included in clinical trials are relevant, comprehensive, reliable, valid, and individualized to the symptom complex associated with the disease.

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In addition to symptom or function endpoints of interest to regulators, payers will look for measures that reflect quality of life and economic impacts, including utility measurements, work productivity, and activity impairment determinations. Some payer bodies, such as the U.K.'s National Institute of Clinical Excellence (NICE), are interested in ascertaining patient input on protocol designs and clinical trial operationalization to ensure that clinical trials are patient centered, meaning they maximize benefits and minimize burden for patients.

Finding Sites to Support Post-COVID Syndrome Trials

Selection of clinical personnel to treat patients in a post-COVID syndrome trial will present a new challenge. Patients presenting with COVID-19 symptoms may have had minimal healthcare interaction at the time of initial infection, and diagnosis may have been via a walk-in test center not associated with delivery of care. For patients requiring hospital care, this may have been supported by an acute care team, pulmonologist, or infectious disease specialist. Patients with unresolved symptoms or who have not returned to their baseline level of functioning are most likely to present to primary care providers. Any referral to secondary care will depend on the symptoms the patient has and whether dedicated post-COVID syndrome clinics are available. Dedicated post-COVID clinics with access to a range of specialists may become the optimal structure to evaluate and manage these patients, given the potential for a broad range of clinical complications. Such dedicated post-COVID syndrome clinics are being established in many countries, but this is not universal. Many of these clinics are in their infancy, and, owing to the lack of standardization of assessments for these patients, the range of specialists and services may vary from center to center.

Sponsors may not always have the luxury of being able to recruit from dedicated post-COVID clinics. As a large CRO, PPD can supplement sites from our extensive network of investigators across therapeutic areas, including specialists in neurology, rheumatology, and respiratory diseases, who may be investigating and managing patients with post-COVID syndrome.

Finding and Recruiting Patients with Post-COVID Syndrome

While patients with post-COVID syndrome may be highly motivated, they may have difficulty remaining engaged with a clinical trial due to the debilitating nature of their symptoms (e.g., brain fog, severe fatigue, or perhaps even grief and depression.) Patients may not want to or be able to make regular visits to clinical trial sites. A CRO with strong experience and infrastructure to support decentralized trials and drive patient-centric solutions can provide relevant strategies that will benefit study design and make participation more feasible for patients and their caregivers.

With PPD's experience in the development of increasingly patient-centric trials and running virtual and direct-to-patient studies, we are ideally positioned to support and encourage ongoing patient participation in post-COVID syndrome trials. We know how to bring studies to patients using e-Consent, home-health nurses, video visits, and electronic PROs, all within decentralized trial designs. Our experience with long-term follow-up of gene therapy patients is also directly applicable to post-COVID syndrome patients. We keep the patient experience in mind and identify solutions that optimize efficiency and effectiveness with the goal of maintaining the necessary level of connection with the patient, the site, and the treating physician, while minimizing the burden across all of them.

Other questions sponsors will need to consider include:

- How do we know when patients are suitable for a trial?
- At what point do you assign patients having reached a baseline

level for the study?
- If that point cannot be determined, how should the inclusion/exclusion criteria be established?
- It is also important to identify not only the symptoms, but whether there is active disease that is potentially amenable to an intervention.

Conclusions

With our enterprise-wide approach, PPD is able to develop bespoke solutions for each client and trial that will allow optimum connectivity with the patient and continuous data collection to meet regulatory and payer needs, both within and outside of standard care. Our insights, together with our proven and agile strategies, enable us to bring all of the necessary components and functions together to offer a comprehensive solution that can be personalized depending on the needs of each sponsor, regulators, and payers. We also bring a strong focus on prioritizing the needs of post-COVID syndrome patients as we work together to help them find resolution of their long-term sequalae and restoration of health. ■

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