August 4, 2022

The Honorable James E. Clyburn
Congress of the United States
House of Representatives
Select Subcommittee on the Coronavirus Crisis
2157 Rayburn House Office Building
Washington, DC 20515-6143

Electronic copy sent to: Yusra Abdelmeguid at Yusra.Abdelmeguid2@mail.house.gov

Dear Chairman Clyburn,

In accordance with your letter, dated July 22, 2022, relating to post-hearing points to be submitted to the official record for the Select Subcommittee on the Coronavirus Crisis regarding "Understanding and Addressing Long COVID and Its Health and Economic Consequences" held on Tuesday, July 19, 2022, please find below my responses to the questions posed.

Yours sincerely,

Hannah Davis
Co-founder, Patient-Led Research Collaborative (PLRC)

cc: The Honorable Steve Scalise, Ranking Member

1. *Please explain why performing comprehensive research into Long COVID is important.*

Multiple international institutions have now shown that between ten to thirty percent of non-hospitalized COVID survivors will get Long COVID. Vaccination does not prevent Long COVID to a substantial degree, and most Long COVID cases happen after mild acute illness. Additionally, patient groups are aware that reinfections can not only worsen Long COVID, but that Long COVID can happen in second or third infections even in those who fully recovered on their first infection. Taken together, these facts imply that the percentage of people with Long COVID will continue to increase every year until treatments are found, resulting not only in a mass disabling event as significant as any in human history, but a serious economic crisis.

From what we know from other post-viral illnesses like ME/CFS and dysautonomia – both of which appear in over half of Long COVID patients – as well as what we know from the previous SARS outbreaks, these conditions are more likely to be disabling and lifelong than they are mild or short-term. 75% of people with ME/CFS can't work, and many are housebound or even bedbound. Investing in comprehensive Long Covid research and treatment now is our only option to address this crisis.

2. *Based on your research and work with the Patient-Led Research Collaborative, what are the major research gaps as it relates to our understanding of Long COVID?*

Pathophysiology and treatments must be prioritized immediately and concurrently. There are many promising leads into the mechanisms of Long COVID, including (but not limited to):

- persisting reservoirs of SARS-CoV-2 in tissues
- immune dysregulation, with or without reactivation of underlying pathogens including herpesviruses such as Epstein-Barr virus (EBV), HHV-6, and others
- SARS-CoV-2 impacting the microbiome and virome
- autoimmunity and primed immune cells from molecular mimicry
- connective tissue damage
- microvascular blood clotting with endothelial dysfunction
- dysfunctional signaling in the brainstem
- brain inflammation and injury similar to post-concussion syndrome

Urgent research is necessary to further investigate each of these hypotheses and others. Many of these are only known from prior research into overlapping conditions like ME/CFS; all Long COVID research must build on this existing research.

Additionally, clinical trials on both repurposed and new medications identified by leading ME/CFS and post-viral clinicians and researchers should be prioritized. Clinical trials on medications need to be performed with a minimum of several hundred thousand patients, and take great care not to make the same mistakes of other post-viral research; clinical trials should not include exercise or behavioral therapy.

Much of the current funding for Long COVID is going towards incidence; this is nowhere near as important as the aforementioned areas of research. Hundreds of international studies put Long COVID incidence in the same range of ten to thirty percent; the lowest possible estimate is five percent, or 1 in 20 people, which is still a staggering number given most of the country having been infected. Our focus needs to be on mechanisms and clinical trials.

Current ME/CFS experts are substantially ahead of the curve compared to those who are new to post-viral illness, and should be funded for both research and providing education to other researchers and clinicians.

Specific researchers to highlight and fund, who have a significantly better understanding of post-viral research than most other researchers who are new to Long COVID, include: Dr. Bhupesh Prusty, Dr. Amy Proal, Dr. Maureen Hanson, Dr. Nancy Klimas, Dr. Akiko Iwasaki, Dr. David Putrino, Dr. Ron Davis, Dr. Lucinda Bateman, Dr. David Kaufman, Dr. Peter Rowe, Dr. Michael Van Elzakker, Dr. Bjorn Bragee, Dr. David Systrom, Dr. Leonard Jason, Dr. Ilene Ruhoy, Dr. Susan Levine, Dr. Resia Pretorius, and others.

The Patient-Led Research Collaborative has also released patient-driven research priorities in a National Research Action Plan: https://patientresearchcovid19.com/wp-content/uploads/2022/06/Towards-a-Patient-Driven-National-Research-Action-Plan.pdf

3. *What role do Long COVID patients have in helping to correct misinformation and fill existing knowledge gaps?*

Patients and their collective experience play an essential role in informing and steering research on Long COVID, as well as promulgating the specificities of this illness to the public. The voices of patients alone, however, are insufficient to correct misinformation when clinicians, medical professionals, researchers, and the public are not educated on the reality of this often debilitating illness, and of post-viral illnesses like ME/CFS and dysautonomia more broadly.

Because these illnesses are generally not fully taught in medical schools, a wide scale program to educate both medical students and current medical professionals is necessary and cannot be replaced by Long COVID patient advocates. Similarly, the widespread lack of public understanding about Long COVID must be addressed by the government and public health officials.

This public, provider, and researcher education must include:

- that Long COVID can and often does happen even if fully vaccinated
- that it can and often does happen after a mild or asymptomatic case
- that it is not continuing symptoms of acute COVID, but often new onset neurological, systemic, immunological, cardiovascular, and other symptoms
- that there is often a delay of weeks to months after recovery after acute COVID before Long COVID begins, even in those who initially feel recovered
- that rest and pacing are crucial to prevent more severe forms of Long COVID
- that ME/CFS and dysautonomia are common presentations
- that a wide range of blood tests are known to be abnormal and are found in ME/CFS literature
- that there are already hundreds of biomedical findings in ME/CFS and dysautonomia that should be built upon in order not to waste time

Here too, public funding for research and clinical trials on Long COVID will be extremely beneficial. Objective, peer-reviewed research findings and clinical trial results will go a very long way towards informing medical professionals on Long COVID and giving them options to treat patients.

In your written statement, you recommend expediting and funding "clinical treatment trials for anticoagulant therapy for microclotting, antivirals for both COVID and reactivations like EBV, and trials for ME/CFS and dysautonomia, including mitochondrial treatments, IVIG, and connective tissue restoration."

4. *Please briefly elaborate on why prioritizing these specific research initiatives could help Long COVID patients in the long run.*

There are currently no substantial treatment options for Long COVID, though there are several hundred medications and treatments identified by researchers and clinicians that need to be thoroughly trialed. The areas I mentioned are specifically some of the most promising initiatives with well-thought-out and historically informed hypotheses, but have not yet been developed to the point of being able to be conclusively recommended to patients nor to know which phenotypes of patients would most benefit.

On this basis, we strongly urge that clinical treatment trials including IVIG, antivirals for both COVID and reactivations like EBV and HHV-6, anticoagulants, treatments to restore connective tissue, and mitochondrial treatments be prioritized in order to investigate and substantiate these hypotheses, so that the feasibility of these treatments may be determined and Long COVID patients may have the hope of viable treatment options.

Several research directions, including connective tissue damage and craniocervical obstructions, may additionally help predict who is more likely to get Long COVID. In disability knowledge bases, connective tissue disorders like Ehlers-Danlos Syndrome (even where undiagnosed) are considered to be risk factors for developing post-viral illness; these theories must be investigated.

Therapeutic treatment will be an essential element for Long COVID patients' recovery and reintegration into the workforce, as well as their ability to reclaim the lives they led before contracting COVID-19.