PATIENT-LED RESEARCH COLLABORATIVE

Patient-Focused Drug Development for Long COVID
Public Comment

We are Patient-Led Research Collaborative, a group of people with Long COVID and associated conditions who conduct, fund, and advocate for research on Long COVID. We conducted the first research on Long COVID in May 2020, were the first to document the over 200 symptoms of Long COVID, and co-authored a review in *Nature Reviews Microbiology* on Long COVID research to date.

We write to urge the Food and Drug Administration (FDA) to consider Long COVID a top priority in drug development and clinical trials. Nearly 6% of all American adults are experiencing Long COVID, and for roughly one-quarter of those people, their symptoms severely limit their daily activities. Patients with Long COVID have been found to have functional impairment worse than stroke and on par with Parkinson's, a lower quality of life than patients with metastatic cancers, and worse fatigue than patients with stroke, bowel disease, and end stage renal disease. As of August 2022, a conservative estimate of 4 million Americans were unable to work because of Long COVID, potentially accounting for $170 billion in lost wages and 15% of the labour shortage. The substantial toll of Long COVID on patients' health and quality of life demands an urgent response. Particularly given that our numbers are only growing as COVID spreads and reinfections increase the risk of Long COVID, it is imperative that FDA not be the agency that stalls progress, but instead actively leads the way by guiding trial sponsors and industry toward successful trials.

When regulating clinical trials for Long COVID, please ensure:

1. **Positive PCR/antibody tests are not required:** There is documented evidence that only 1-3% of cases in the early days of the pandemic were detected, and only 25% of cases were reported as of September 2021. Requiring a positive COVID test, whether PCR or antibody, has equity implications for who is included in clinical trials. People of color, poor people, and other minority groups such as LGBTQ people and rural communities are less likely to have healthcare access, more likely to not have a PCR test on record and/or not get tested at the right time. PCR tests have high false negatives particularly among women and people under 40 years old, and women and people with mild infections are more likely to not seroconvert and/or serorevert. It is critical for clinical trials to at minimum have an arm that allows for clinical diagnoses of COVID, which aligns with the World Health Organization definition of Post COVID-19 Condition.
2. **Endpoints include quality of life and functional ability endpoints.** A main reason for this is that there are over 200 symptoms of Long COVID, with people having differing symptoms that most impact their lives. One symptom improving may not have a meaningful difference on their ability to work, socialize, and do what's important to them.
3. **For drugs that target a specific symptom, ensure endpoints include measures of other Long COVID symptoms.** If trials are targeting individual symptoms, ensure that other symptoms, particularly ones more common in Long COVID, systemic symptoms, symptoms that impair quality of life, and additional symptoms in a

specific phenotype, are also measured. This is critical given the wide range of symptoms experienced by people with Long COVID, that the likely mechanisms behind Long COVID cause a variety of symptoms, and in order to see if a specific therapeutic can help multiple subtypes of patients.

4. **The right validated tools are used.** Validated tools of the common and most impactful symptoms should be used as endpoints - for example, the DePaul Symptom Questionnaire for post-exertional malaise and the COMPASS-31 for autonomic dysfunction. Tools to screen for depression and/or anxiety should not have overlapping questions on fatigue, palpitations, or other classic Long COVID symptoms; common scales like the PHQ-9 and Beck Anxiety Inventory should be substituted for validated tools without somatic symptom questions, like the PHQ-2 and GAD-7.
5. **Endpoints include existing biomarkers**, particularly based on the existing literature in ME/CFS and dysautonomia and reviews of the Long COVID literature. Examples of these include cerebral blood flow, cerebral glucose consumption, markers of neuroinflammation, natural killer cell function, T cell functioning, levels of reactivated virus (including EBV and HHV-6), elevated lactate in the blood or CSF, and four-point salivary cortisol tests.
6. **Options like expanded access, fast track designation and breakthrough therapy designation are considered**, given the severity and impact of many people's symptoms.
7. **Clinical trials that are of importance to the patient community are prioritized.** These include antivirals, antihistamines, anticoagulants, JAK-STAT inhibitors, and immunomodulators.
8. **Clinical trials that are decentralized or fully remote are encouraged.** Trials with multiple, long in-clinic visits that require a lot of travel may unintentionally exclude people who have more severe forms of Long COVID and/or result in drop off of these patients due to the participation in the trials resulting in crashes and lowering of baseline.
9. **The nature of the condition is understood by researchers and accounted for in trial design.** Symptoms can change by the hour, day, week, or month. Certain triggers, like menstrual cycles and seasons, are important to account for in a clinical trial. Trial sponsors should recognize that the majority of people with Long COVID experience post-exertional malaise. As one of the most disabling symptoms, post-exertional malaise should be measured before and after interventions, and trials should plan to accommodate participants who suffer from post-exertional malaise. Additionally, trial analysis plans should incorporate an analysis of endpoints from those who experience post-exertional malaise compared to those who do not.
10. **Encourage crossover trials and/or option to receive the drug at end of trial.** When suitable, crossover trial design should be applied, and when accounting for the washout period between interventions, the fluctuating nature of Long COVID symptoms should be taken into consideration. Crossover trials where all patient participants have a chance to receive the intervention are more equitable, and thus are more appealing to patients, which facilitates participant recruitment process.
11. **Proper safety monitoring for this population.** There must be an adequate process and length of monitoring for adverse events, coupled with healthcare support for

participants who experience adverse events. Clinical trials must be prepared to support participants experiencing adverse events such as post-exertional malaise and crashes being triggered days following last data collection and lasting weeks to several months.

12. **Representative recruitment based on populations impacted by COVID and Long COVID.** It is critical for clinical trials of Long COVID to oversample populations who are disproportionately impacted by COVID and Long COVID, particularly trangender people and racially marginalized people. Additionally, it is important to require use of the "Recommended Approach to Data Collection: The Two-Step Method" when asking questions regarding gender identity to ensure accurate data collection.
13. **The incorporation of new imaging and testing techniques as they become available.** Techniques such as XE MRI for respiratory issues, ImmunoPET-CT for visualizing viral reservoirs, imaging of the glymphatic system, and microclot testing should be integrated as they become more widely available.

Additionally, in any clinical trial of COVID therapeutics, there must be a Long COVID endpoint and a subgroup of people with Long COVID, since evidence is building that some acute COVID therapeutics can reduce the likelihood of Long COVID and can lessen symptoms.

We also attach our co-lead Hannah Davis' recent article in Medscape on clinical trials for Long COVID for additional critical considerations.

Thank you for the opportunity to submit a public comment on what is important to consider in drug development for Long COVID. We urge you to consider Long COVID one of your top priorities and to implement the recommendations in this comment.