COMMENTARY

Clinical Trials: Top Priority for Long COVID

Hannah Davis

May 09, 2023

Editor's note: Find the latest COVID-19 news and guidance in Medscape's Coronavirus Resource Center.

The Centers for Disease Control and Prevention (CDC) and the US Census Bureau estimate that 6.1% of the US adult population is living with long COVID, with millions more debilitated worldwide. The demand for substantial treatment is enormous, but the urgency to fund and begin the necessary range of clinical trials has not met the severity of the problem.

While trials are slowly beginning to happen, the treatment choices and trial design require crucial nuances and understanding of viral-onset illnesses, and few research groups are creating strong trials that fully reflect the complexities of this landscape.

This article aims to share key considerations and best practices that are essential to the success of these trials. These recommendations recognize that roughly half of long COVID patients have new-onset myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and dysautonomia from COVID, which must be at the forefront of how trials are designed and conducted, and are additionally based on the current hypotheses about Long Covid's pathophysiologies.

1: Drugs Proposed by Experts in Postviral Fields Should Be Prioritized

Upward of 50 drugs for viral-onset conditions like ME/CFS, dysautonomia, AIDS, and others have been waiting for years to go to trial, but have not had the funding to do so.

Treatments proposed by experts in viral-onset illnesses (such as ME/CFS and dysautonomia) should be prioritized, as outside researchers are not familiar with these fields and their potential treatment options.

2: Drugs Targeting a Wide Range of Mechanisms Should Be Trialed

Treatments that should be trialed include anticoagulants/antiplatelets for clotting and vascular functioning, immunomodulators including JAK-STAT inhibitors, COVID-specific antivirals and antivirals against reactivated herpesviruses (Valcyte, Valacyclovir, EBV vaccine).

Other options include prescription mast cell stabilizers (ketotifen, cromolyn sodium), drugs that regulate microglial activation (low-dose naltrexone, low-dose aripiprazole), anti-CGRP medications, beta-blockers, and intravenous immunoglobulin.

Others include medications that target mitochondrial dysfunction, ivabradine, Mestinon, DRP-1 inhibitors, supplements showing success in patient communities including lactoferrin, ubiquinone, and nattokinase, therapies targeting glymphatic/lymphatic dysfunction, microbiome therapies, and therapeutic peptides.

3: Use Appropriate Long COVID Subtypes

Long COVID is an umbrella term that encompasses multiple new-onset and worsened conditions and symptoms after COVID. Roughly half of long COVID patients likely meet the criteria for ME/CFS and/or dysautonomia. Others may have new-onset diabetes, major clotting events, lung damage, neurological disorders, loss of smell or taste, and other manifestations.

Patients in different categories likely have different responses to treatments. It's critical to identify appropriate subtypes for each trial, ideally performing detailed analyses to identify the treatments that work best, and don't, for each subtype.

4: Behavioral Treatments, Especially Those That Have Harmed Similar Populations, Should Not Be Trialed

Behavioral treatments including exercise, graded exercise therapy (GET), and cognitive behavioral therapy (CBT) should not be trialed, let alone prioritized, for Long COVID.

In patients with postexertional malaise (PEM), one of the most common long COVID symptoms, exercise is actively harmful and causes dysfunctional metabolic patterns, cardiac preload failure, impaired systemic oxygen extraction, and more. GET

and CBT have failed similar populations , and exercise is explicitly contraindicated by the World Health Organization, the British National Institute for Health and Care Excellence, the CDC, and other organizations.

Resources should instead be put toward the wide range of medications that have not yet adequately undergone clinical trials.

5: PCR and Antibody Tests Should Not Be Used as Inclusion Criteria for Trial Participants

Only an estimated 1%-3% of cases in the first wave of COVID were documented, and the CDC estimates that only 25% of cases through September 2021 were documented. Similarly, antibody tests are unreliable to determine past infection, as roughly a third of patients don't seroconvert, and a similar proportion serorevert within a few months. Using PCR and antibody testing to determine who should be included in clinical trials limits who is eligible to participate in research, particularly those who have been ill for longer. Additionally, the majority of those who serorevert are women, so using antibody tests for inclusion introduces a selection bias and may miss mechanisms of immune system functioning that are part of long COVID.

PCR tests also have high false-negative rates and requiring them in research excludes people with lower viral loads with long COVID, which would confound findings.

These issues with testing also lead to COVID-infected people accidentally being included in control groups, which ruins the credibility of the research findings completely.

6: Include Comparator Groups

There are several common diagnoses that occur in people with long COVID, including ME/CFS, postural orthostatic tachycardia syndrome, small-fiber neuropathy, mast cell activation syndrome, and Ehlers-Danlos syndrome.

Identifying people with these conditions within the trial cohort improves research across all fields, benefitting all groups, and helps clarify what types of patients benefit most from certain medications.

7: Identify the Right Endpoints; Avoid the Wrong Ones

Even though our understanding of the pathophysiology of long COVID is still evolving, it's still possible to do clinical trials by identifying strong endpoints and outcome measures.

Several tools have been designed for viral-onset conditions and should be used alongside other endpoints. Postexertional malaise and autonomic symptoms, which are some of the most common symptoms of long COVID, can be measured with the validated DSQ-PEM and COMPASS-31, respectively. Tools for cognitive dysfunction trials should capture specific and common types of impairment, like processing speed.

Endpoints should be high-impact and aim for large improvements that have clinical significance over small improvements that do not have clinical significance.

Objective tests should be incorporated where possible; some to consider include natural killer cell functioning, cerebral blood flow, T-cell functioning, levels of reactivated herpesviruses, blood lactate levels, and microclots, as testing becomes available.

Mental health outcomes shouldn't be primary endpoints, except where a trial is targeting a specific mental health condition because of COVID (for example, premenstrual dysphoric disorder).

If mental health conditions are tracked secondarily, it's vital not to use questionnaires that include physical symptoms like fatigue, difficulty concentrating, difficulty sleeping, or palpitations, as these artificially increase depression and anxiety scores in chronically ill respondents. Tools that include physical symptoms (PHQ-9, Beck Anxiety Inventory, Beck Depression Inventory) can be replaced with scales like the PHQ-2, GAD-7, HADS, or PROMIS-29 subscales.

Because certain cytokines and other inflammatory markers may naturally decrease over time without corresponding improvement in the ME/CFS subtype, caution should be taken when using cytokines as endpoints.

8: Consider Enrollment and Objectives Carefully

A proportion of people with long COVID will recover in the early months after infection. Ideally, clinical trials will primarily study treatments in patients who have been ill 6 months or longer, as some natural recovery will happen before that that can bias studies.

But where resources are abundant, it is ideal for trials to additionally look at whether the treatments can help patients in the early months recover and prevent progression to the later stage.

9: Tracking Illness Duration Is Crucial

Research from ME/CFS shows that there may be an immune change in the first few years of the illness, where cytokines decrease without any corresponding change in symptom improvement.

Because of this and the possibility that other markers follow the same pattern, disease duration should be a core feature of all analyses and trial designs. Trial outcomes should be designed to answer the question of whether the medication helps patients at different durations of illness.

10: Prioritize Patient Populations Less Likely to Recover Without Intervention

Some long COVID phenotypes seem less likely to recover without intervention. Trials should take care to focus on these patient populations, which include those with neurological symptoms and those meeting ME/CFS criteria.

11: Account for the Relapsing/Remitting Nature

Outcome measures need to be assessed in a way that can distinguish a temporary remission, which is part of the natural course of the disease, from a permanent cure.

Factors that can contribute to the relapsing/remitting nature include physical and cognitive postexertional malaise, menstrual cycle changes, and seasonal changes.

12: Trial Participants Should Reflect the Diversity of the Long COVID Population

Certain demographics are more likely to be affected by acute and long COVID and need to be appropriately recruited and reflected in research, including in patient engagement.

Trials must include high numbers of Hispanic/Latinx, Black, and indigenous communities, queer and transgender populations, and women. Trial materials and design need to incorporate linguistic diversity in addition to racial/ethnic diversity.

Upward of 75% of long COVID cases happen after mild acute cases; clinical researchers should ensure that nonhospitalized patients make up the bulk of trial participants.

13: Utilize Meaningful Engagement of Patients, Especially in Treatment Selection and Study Design

Meaningful patient engagement means engaging multiple patients at every step of the trial process, from treatment selection to study design to analysis to communication of the results.

Patient experiences are extremely valuable and contain information that researchers may not be familiar with, including the nature and patterns of the illness, insights into possible treatments, and barriers to documentation and care that may also impact research. Tapping into those patient experiences will make trials stronger.

Overall, the landscape of long COVID clinical trials is ripe for discovery, and researchers choosing to go down this path will be deeply appreciated by the patient community.

Hannah Davis is a long COVID patient-researcher and cofounder of the Patient-Led Research Collaborative, an organization studying the long-term effects of COVID.

For more news, follow Medscape on Facebook, Twitter, Instagram, YouTube, and LinkedIn.

Credits:

Lead image: Robert Kneschke/Dreamstime

Cite this: Clinical Trials: Top Priority for Long COVID - *Medscape* - May 09, 2023.