

# The current landscape of long COVID clinical trials: NIH's RECOVER to Stanford Medicine's STOP-PASC initiative

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The US National Institutes of Health (NIH) officially announced intent to evaluate therapeutics against long COVID on July 31, 2023. The trial will be conducted through the RECOVER (Researching COVID to Enhance Recovery) initiative to evaluate the safety and efficacy of therapies against long COVID. They will evaluate four potential treatments for long COVID through clinical trials. They will also explore seven additional treatments for long COVID in the future. Recently, Kozlov reported in *Nature News* about the NIH's RECOVER initiative. Kozlov also indicated that the clinical trial would be the world's largest trial and would assess the possible therapies against different conditions of sleep disruption, brain fog, and several other conditions of long COVID.<sup>1</sup> It is an excellent initiative of NIH in terms of long COVID. There are substantial numbers of individuals who are experiencing long COVID. It has been noted that over 65 million patients are affected by long COVID. Therefore, all were waiting for fruitful clinical trials for long COVID. In his direction, an editorial in *The Lancet Infectious Diseases* has raised the question: where are the long COVID trials?<sup>2</sup> Therefore, this clinical trial initiative is very timely and one of the efficient strategies that will help. Millions of individuals are suffering from long COVID around the world.

Like NIH's RECOVER initiative, STOP-PASC is an initiative for a clinical trial of long COVID by Stanford Medicine of Stanford University, CA, USA, which was incited on November 8, 2022. The unexplained symptoms of long COVID, post-COVID conditions are also called PASC (post-acute sequelae of SARS-CoV-2 infection), as the un-

explained and heterogeneous clinical symptoms of long COVID. The clinical trial was initiated to evaluate treating clinical symptoms of long COVID. The study has been named STOP-PASC because it is a Selective Trial Of Paxlovid (STOP) for PASC. STOP-PASC is one of the few clinical trial initiatives evaluating pharmacological interference in long COVID.<sup>2,3</sup> In this trial, researchers evaluate the efficacy of two antiviral molecular combination drugs, Paxlovid, a combination of Ritonavir and Nirmatrelvir, for long COVID patients. In this placebo-controlled trial, participants will take the placebo or drug for the first 15 days. They also require five planned visits to the clinic where the study is conducted over 15 weeks. Stanford University has sponsored the study, and Pfizer is the collaborator of the STOP-PASC ([clinicaltrials.gov](https://clinicaltrials.gov); NCT05576662).

Long COVID is a multisystemic clinical condition that extends beyond the acute SARS-CoV-2 infection and can last for months. In long COVID, over 200 symptoms have been observed with impacts on multiple organ systems. Over 65 million individuals are projected to have long COVID worldwide.<sup>4</sup> It has been noted that roughly 1 in 10 people have experienced long COVID after infection. Several organizations have defined long COVID. According to WHO and NICE (the UK National Institute for Health and Care Excellence), symptoms should persist 2–3 months or more than 3 months after the primary infection.<sup>5–7</sup> However, according to US Centers for Disease Control and Prevention, long COVID symptoms should continue more than 28 days after the initial infection of the

SARS-CoV-2 virus.<sup>8</sup> However, in the case of different symptoms, the onset may vary across individuals. It has been noted that neurological symptoms have a belated onset of weeks to months. The onset of cognitive symptoms has been reported after 1 month of COVID-19 infection. Pain in muscle, bones, joints, back, neck, etc., was experienced by people after 1 month, and it persisted for up to 1 year. Aesthesia, hair loss, and blurry vision were experienced after 2 months of infection. The onset of parosmia has been reported on an average of 3 months after the SARS-CoV-2 infection.<sup>4</sup>

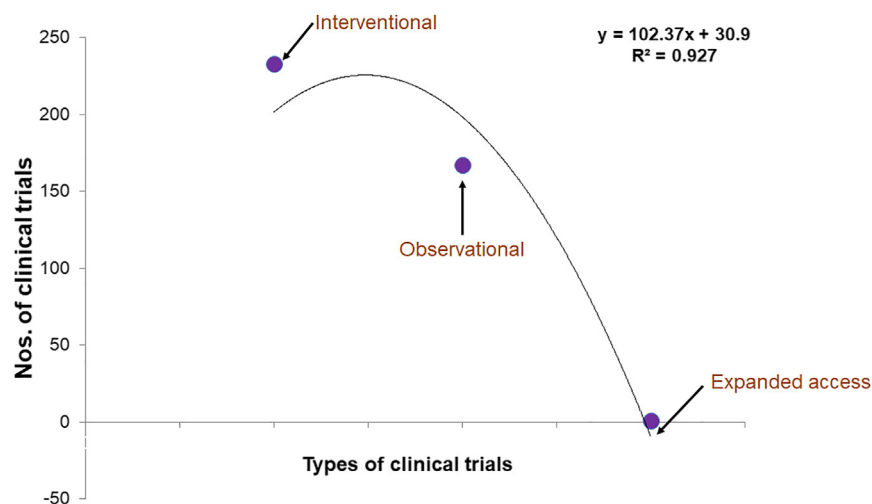
Under the search term “Long COVID,” currently [ClinicalTrials.gov](https://ClinicalTrials.gov) lists about 401 clinical trials for long COVID. Among those clinical trials, three types of clinical trials have been found: interventional, observational, and expanded access. 233 clinical trials are interventional, 167 clinical trials are observational, and 1 clinical trial type is expanded access (Figure 1). Among all these clinical trials, it has been noted that 13 clinical trials are NIH funded; 12 clinical trials have been funded by other US federal agencies, and 60 clinical trials are industry funded. However, some significant clinical trials have been listed. Among these clinical trials, it has been noted that Montelukast helps improve respiratory PASC symptoms ([clinicaltrials.gov](https://clinicaltrials.gov); NCT04695704). Similarly, the S-1226 molecule also helps improve respiratory PASC symptoms ([clinicaltrials.gov](https://clinicaltrials.gov); NCT04949386). At the same time, some clinical trials have been conducted for long COVID using Paxlovid. Here, these studies have tried to evaluate the efficacy of the drug molecule for virus clearance and a decrease in inflammatory response ([clinicaltrials.gov](https://clinicaltrials.gov); NCT05595369 and NCT05576662). Similarly, it has been noted that lithium, an antimanic agent, has been used to treat brain fog and improve

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**Figure 1. A statistical model shows the different types of clinical trials for long COVID**

The model listed three clinical trial types: interventional, observational, and expanded access.

fatigue, which was evaluated through a clinical trial ([clinicaltrials.gov](https://clinicaltrials.gov); NCT05618587) (Table 1). There is a prolonged list of potential thera-

peutics for treatments for long COVID, including antivirals with protease inhibitors, antivirals with RdRp inhibitors, anticoagu-

lants or platelet inhibitors, immunomodulators, and modulators of metabolism or neurological function, and modulators of organ-specific functions.

There was significant heterogeneity in symptoms to define long COVID; therefore, the assessment of treatment outcomes will be very different. At the same time, it has been noted that diagnostic and treatment options are presently inadequate; consequently, clinical trials are urgently needed for better diagnostic procedures and therapeutics. However, artificial intelligence-based diagnostic procedures might help in this direction. At this juncture, improving our understanding of the mechanisms of long COVID and the pathophysiological conditions is necessary. A better understanding of the mechanisms of long COVID might help in the search for more therapeutics for this disease. Presently, there is a despairing and urgent

**Table 1. The table lists some important clinical trials for long COVID**

Sl. no	Clinical trials number	Drug	Drug class	Treatment purpose of clinical trials for post-acute sequelae of SARS-CoV-2 (PASC)
1.	NCT05618587	Lithium	antimanic agent	reduces brain fog and fatigue
2.	NCT05472090	TNX-102 (cyclobenzaprine)	muscle relaxant	pain
3.	NCT05096884	Metoprolol succinate	beta-1 antagonist	enhances cardiac function
4.	NCT05152849	AXA1125	endogenous metabolic modulator	improves muscle functioning
5.	NCT04652518	LYT-100 (deupirfenidone)	antifibrotic	antifibrotic as well as anti-inflammatory agent
6.	NCT03554265	Somatropin	growth hormone	address the disorder related to hormone secretion
7.	NCT05047952	Vortioxetine	selective serotonin reuptake inhibitor (SSRI)	improves cognitive functioning
8.	NCT05216614	Fluvoxamine	selective serotonin reuptake inhibitor (SSRI)	improves parosmia
9.	NCT05481177	Ivabradine	hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker	manage postural orthostatic tachycardia syndrome
10.	NCT05595369 NCT05576662	Nirmatrelvir/ Ritonavir	protease inhibitor	clears the virus and decreases in inflammatory response
11.	NCT05513560	Pentoxifylline	xanthine derivative	regulates immune response and acts as a vasodilator
12.	NCT04695704	Montelukast	leukotriene receptor antagonists	reduces the symptoms related to respiratory PASC
13.	NCT03554265	RSLV-132	RNase-Fc fusion protein	reduces fatigue
14.	NCT04448119	Favipiravir	SARS-CoV-2 RNA-dependent RNA polymerase inhibitor	clears the virus and decreases in inflammatory response
15.	NCT05507372	Pimozide	dopamine receptor antagonist	treat tinnitus
16.	NCT05220280	Imatinib	kinase inhibitor	antiinflammatory agent
17.	NCT05690503	CI-581a, CI-581b	glutamate modulator	analgesic and anesthetic agent
18.	NCT05911009	BC 007	DNA-based oligonucleotide (aptamer)	neutralization of pathogenic autoantibodies
19.	NCT04949386	S-1226	synthetic bronchodilator	lubricant properties to remove mucus

All these trials are also listed in [ClinicalTrials.gov](https://ClinicalTrials.gov).

need for long COVID treatments. Many clinical trials associated with long COVID are mostly inadequate. Therefore, we urge researchers, funders, physicians, countries' policymakers, and institutions to get involved and search for potential treatments against the symptoms of long COVID. It is time for the world to adopt more clinical trials like the RECOVER initiative to fight against the symptoms of long COVID.

#### DATA AND CODE AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

#### DECLARATION OF INTERESTS

The authors declare no competing interests.

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