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Negative results in long COVID clinical trials: choosing outcome measures for a heterogeneous disease

Long COVID is an umbrella term for the heterogeneous long-term consequences of SARS-CoV-2 infection. It encompasses a wide spectrum of phenotypes (sometimes overlapping), and its underlying mechanisms might vary across and within phenotypes. Trials that do not account for this heterogeneity risk false-negative results. First, endotypic heterogeneity might produce heterogeneity in treatment response, and inadequate methodologies risk eclipsing responder subgroups. Second, and the focus herein, phenotypic heterogeneity constitutes a challenge for the choice of outcome measures. Patient-reported outcome measures (PROMs) are essential elements in trial design (and key to surrogate biomarker validation), as they measure clinically relevant outcomes directly. However, long COVID's considerable phenotypic heterogeneity makes it difficult to identify PROMs that can sensitively assess dimensions of disease severity across manifestations while maintaining statistical power. Several highly anticipated long COVID clinical trials, such as PAX-LC,[1] used PROMs that might not have full validity in long COVID, potentially contributing to the negative results of these trials (table).

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	Year	Intervention	Sponsor	Efficacy	Phenotypic eligibility criteria	Primary outcome measure
STOP-PASC (NCT05576662)[2]	2024	Nirmatrelvir and ritonavir (Paxlovid)	Stanford University	Negative	At least two of the following symptoms: fatigue, brain fog, shortness of breath, body aches, gastrointestinal symptoms, or cardiovascular symptoms	Six symptoms (fatigue, brain fog, dyspnoea, body aches, gastrointestinal symptoms, and cardiovascular symptoms) assessed on a 4-point Likert scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, and 3=severe symptoms)
PAX-LC (NCT05668091)[1]	2025	Nirmatrelvir and ritonavir (Paxlovid)	Yale University	Negative	Symptoms consistent with long COVID, including but not limted to fatigue, shortness of breath, and cognitive dysfunction	PROMIS-29 Physical Health Summary Score
NCT05911009	2024	BC007	Berlin Cures	Negative	Fatigue and at least one additional symptom	FACIT-F questionnaire
NCT05592418	2024	Rintatolimod (Ampligen)	AIM ImmunoTech	Negative	Fatigue	PROMIS-F questionnaire
reCOVer (2022–001781–35)*[3]	2025	BC007	Erlangen University Hospital	Positive	Fatigue, and at least three of the following symptoms: exertional intolerance, exertional dyspnoea, concentration disorders, brain fog, exhaustion, unsteady gait, taste or smell disorders, or headache	Bell Scale for ME/CFS, Canadian Consensus Criteria for ME/CFS, Chalder Fatigue Scale, FACIT-F, Fatigue Severity Scale, Short-Form Health Survey-36, and 6-Minute Walking Test
NCT04944121	2024	RSLV-132	Resolve Therapeutics	Negative	Fatigue	PROMIS-F questionnaire
outSMART-LC (NCT05877508)	2025	AER002 (SARS-CoV-2 monoclonal antibody)	University of California San Francisco	Negative	At least two new symptoms or the symptoms have worsened since SARS-CoV-2 infection	PROMIS-29 Physical Health Summary Score

FACIT-F=Functional Assessment of Chronic Illness Therapy–Fatigue. ME/CFS=myalgic encephalomyelitis/chronic fatigue syndrome. PROMIS-F=Patient-Reported Outcomes Measurement Information System-Fatigue. *As this phase 2a trial primarily intended to evaluate the safety of BC007, the trial used a safety measure as a primary outcome measure; the outcome measures reported in this table are the trial's secondary outcome measures, chosen to evaluate the efficacy of the intervention.

Table: **Results of long COVID phase 2 clinical trials**

A 2024 meta-analysis suggested that about half of people diagnosed with long COVID meet diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[4] Trials aiming to address or include the ME/CFS presentation of long COVID should use outcome measures adequate to this phenotype. The ME/CFS phenotype is often inaccurately conflated with fatigue, and many trials such as rintatolimod (Ampligen; NCT05592418), RSLV-132 (NCT04944121), and both BC007 trials (NCT05911009 and 2022–001781–35)[3] have used fatigue scales as primary outcome measures. However, fatigue is only a small part of the disease's presentation; instead, ME/CFS is characterised by the presence of post-exertional malaise.[5] Patients with ME/CFS and expert clinicians customarily assess disease severity in terms of functional capacity deficits along the physical, cognitive, orthostatic, and sensory dimensions. Merely measuring symptoms is inadequate and can lead to false-negative results in trials. Symptom load, including fatigue, increases with exertion via post-exertional malaise, and many patients choose increased function over reduced symptoms as their disease improves, given the life-limiting nature of ME/CFS.

The FUNCAP questionnaire, a functional capacity scale designed to record the impacts of post-exertional malaise, uses benchmarks that are objective (independent of the patient's impressions and intersubjectively comparable) to evaluate changes in functionality across relevant dimensions.[6] Due to these unique features, people with ME/CFS, including those with the ME/CFS phenotype of long COVID, as well as expert clinicians, find FUNCAP particularly capable at evaluating the severity of ME/CFS compared with other commonly used PROMs. The questionnaire improves on non-disease-specific functional capacity PROMs, as functional limitations in ME/CFS usually result from constraints induced by post-exertional malaise rather than strict incapacity. Patient experts deem FUNCAP promising,[7] and early validation efforts in ME/CFS have been auspicious.[6] We urge researchers to pursue further validation efforts in diverse long COVID cohorts with the ME/CFS phenotype, to urgently identify whether FUNCAP could serve as the standard outcome measure in this population. Trialists might also wish to consider FUNCAP as an exploratory outcome measure.

Many people with long COVID do not meet the diagnostic criteria for ME/CFS. Their disease might manifest as isolated or combined cardiovascular or neurological issues, for instance. Moreover, people who do meet ME/CFS diagnostic criteria might also manifest additional phenotypes. This phenotypic heterogeneity constitutes a challenge for trials targeting pathomechanisms hypothesised to have a causal role across long COVID phenotypes, such as the STOP-PASC,[2] PAX-LC,[1] and outSMART-LC (NCT05877508) trials, which targeted viral persistence.[8] To supplement outcome measures not reported by patients, such as cognitive testing and cardiovascular event recording, a manageable set of PROMs that capture relevant changes as objectively, accurately, and comprehensively as possible across the range of long COVID phenotypes should be validated in the entire disease population to enable the formation of composite endpoints adapted to any trial's eligibility criteria and to the phenotypes thereby entailed. Existing PROMs, such as the Symptom Burden Questionnaire for Long COVID,[9] the COVID-19 Yorkshire Rehabilitation Scale,[10] the Post-COVID-19 Functional Status Scale,[11] and the Post-COVID Condition Core Outcomes set,[12] have promising elements, but none comprehensively capture central disease aspects (including functional impairments induced by post-exertional malaise, dysautonomia, food and environmental sensitivities, cardiovascular dysfunction, and neurocognitive dysfunction) with objective benchmarks. Consequently, many people with long COVID feel that these instruments cannot account for the character and severity of their illness, which potentially suggests inadequate content validity and ceiling effects that should be further investigated.

The absence of a validated PROM set considered by patients to accurately assess their disease remains a key obstacle to achieving conclusive results in long COVID trials. Sustained investment in the development and validation of a long COVID PROM set that meets this criterion, done in partnership with regulators and patient experts and involving a sustained and far-reaching dialogue with the broader community of people with long COVID, should be among the field's core priorities.

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Strengthening global preparedness and response to arboviral disease threats: a call to action

Arthropod-borne viruses (arboviruses), particularly those transmitted by *Aedes aegypti* and *Aedes albopictus*, are a growing global health threat. Approximately 70% of the world's population is at risk of infection from dengue, chikungunya, Zika, and yellow fever viruses,[1] with the burden rising sharply in recent years. This increasing risk is driven by a confluence of factors, including rapid and often unplanned urbanisation, climate change, and increasing interconnectedness through global travel and trade.

The expansion of urban environments has created ideal breeding grounds for *Aedes* mosquitoes, while climate change is extending transmission seasons, expanding vector ranges, decreasing vector extrinsic incubation periods, and increasing the frequency and magnitude of arboviral outbreaks. By 2050, it is projected that 65% of the global population will reside in urban areas, further amplifying the risk of arboviral transmission.[2] The Intergovernmental Panel on Climate Change has highlighted the profound effect of rising temperatures and altered precipitation patterns on vector ecology, with direct consequences for arboviral disease dynamics.[3]

Past epidemics are stark reminders of the explosive potential of arboviruses. The 2005–06 chikungunya virus epidemic in the Indian Ocean region resulted in millions of cases, and the introduction of chikungunya virus in the Americas in 2013–14 led to over 3·7 million cases across 45 countries and territories.[4] The Zika virus epidemic, which began in the Pacific in 2007 and subsequently swept through the Americas, caused an estimated 132 million cases, with devastating consequences, including congenital Zika syndrome in fetuses or infants and neurological complications in adults, such as Guillain-Barré syndrome.[5] The recognition of sexual transmission of Zika virus is also cause for concern. Yellow fever has also re-emerged as a substantial threat, with large outbreaks in Angola (2015–16) and Brazil (2016–18) outstripping vaccine supplies and leading to the use of fractional dosing strategies.

Despite concerted efforts to control *Ae aegypti*, 2024 saw a record 14 million dengue cases reported across 134 countries and territories, including more than 52 000 severe cases and more than 10 000 deaths.[6] Particularly concerning are the nine-fold increase of dengue virus infections in Africa since 2019,[7] and the unprecedented rise in autochthonous dengue cases within temperate regions in recent years, notably in France and Italy.[8] The global economic burden of dengue was estimated to be US$19 billion in 2022.[9]


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