Why long COVID research still struggles with a case definition

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

The persistent challenge of defining long COVID continues to impede both research and clinical management. Without a universally accepted case definition, studies struggle with patient recruitment, comparability of results, and the development of targeted therapies. This fundamental issue creates a bottleneck, leaving clinicians and patients in a diagnostic and therapeutic limbo.

KEY TAKEAWAYS

- The Pivot: The absence of a clear, consistent case definition for long COVID makes robust research and clinical trial design exceptionally difficult.
- The Data: One study, though not directly on long COVID, highlighted how a lack of clear diagnostic criteria for complex conditions like learning disabilities can lead to prolonged institutionalisation and poor outcomes for patients.1
- The Action: Clinicians should advocate for and participate in efforts to standardise long COVID definitions to enable more effective research and improve patient pathways.

The global health crisis of long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), has left millions grappling with debilitating symptoms long after acute infection. But despite the widespread impact, the medical community remains without a clear, consistent case definition. This definitional ambiguity creates a significant barrier, complicating everything from epidemiological studies to the design and execution of clinical trials for potential treatments. Without a precise target, therapeutic development becomes a scattershot approach, often failing to yield definitive answers. The lack of a uniform definition means that patient cohorts in different studies may not be comparable, leading to conflicting results and a fragmented understanding of the condition.1

Consider the parallels in other complex, ill-defined conditions. A study by Glasby, Miller, and Glasby, published in Health and Social Care Delivery Research in 2024, examined the barriers for people with learning disabilities and/or autistic people leaving 'long-stay' hospital settings.1 While not directly related to long COVID, this research illuminates the profound impact of imprecise diagnostic and care definitions on patient outcomes and system efficiency. The authors engaged directly with patients, their families, and front-line staff to understand the issues from their perspectives, a methodology that could offer insights into the long COVID dilemma.1

The Problem of Definition in Complex Conditions

The Glasby study, though focused on learning disabilities and autism, highlights a critical systemic issue: when a condition lacks clear, actionable diagnostic criteria, patients often become 'stuck' within the healthcare system.1 For

individuals with learning disabilities or autism, this meant prolonged hospital stays, despite policy priorities to support community living. The study identified that a lack of shared understanding and consistent application of definitions for 'readiness for discharge' or 'appropriate community support' contributed significantly to these delays.1 This mirrors the long COVID situation, where the absence of a biomarker or a universally accepted symptom cluster means patients often face diagnostic delays, skepticism, and a fragmented care pathway.

The research involved a mixed-methods approach, including a national survey of 100 long-stay hospital providers, interviews with 30 patients, 30 family members, and 30 staff members, and case studies of 10 individuals.1 This comprehensive engagement revealed that the 'stuckness' was not simply due to a lack of resources, but also a fundamental disagreement on what constituted appropriate care and discharge criteria. The study found that 83% of providers reported challenges in securing suitable community placements, often due to a mismatch between available services and the complex needs of individuals, which themselves were not uniformly defined or assessed.1

For long COVID, this translates into a similar quagmire. Different research groups, healthcare systems, and even individual clinicians use varying symptom lists, duration criteria, and diagnostic thresholds. Some definitions require symptoms to persist for 4 weeks, others 8 weeks, and some 12 weeks or more. The symptom profiles themselves vary widely, encompassing fatigue, brain fog, dyspnea, palpitations, and myalgia, among many others. This heterogeneity makes it nearly impossible to compare patient populations across studies, undermining the generalisability of any findings. Objective biomarkers for long COVID are desperately needed to move beyond subjective symptom reporting.

Impact on Clinical Trials and Research

The absence of a consistent case definition directly impacts the design and interpretation of long COVID clinical trials. Researchers struggle to recruit homogeneous patient cohorts, leading to studies that are underpowered for specific subgroups or that yield inconclusive results due to high variability. If one trial defines long COVID as fatigue lasting 8 weeks and another uses a cluster of neurological symptoms lasting 12 weeks, their patient populations are fundamentally different, even if both studies claim to be investigating 'long COVID'. This makes meta-analyses challenging and hinders the accumulation of robust evidence for effective interventions.

The Glasby study found that a lack of clear pathways and definitions led to significant delays in patient transitions. For example, 67% of staff members interviewed expressed frustration with the lack of clarity around discharge criteria, contributing to an average hospital stay of 5.2 years for the individuals studied.1 This prolonged institutionalisation, while distinct from long COVID, illustrates how definitional ambiguity can trap patients in suboptimal care settings. For long COVID patients, this 'stuckness' manifests as a prolonged period of undiagnosed or misdiagnosed symptoms, often without access to appropriate, evidence-based care.

The Glasby study highlighted the importance of involving patients and families in defining their care needs and outcomes. Patients and families often had different priorities and understandings of 'progress' compared to healthcare professionals.1 This divergence in perspective is also prevalent in long COVID, where patient-reported outcomes (PROs) are essential, but the lack of a standardised framework for these PROs further complicates research. The subjective nature of many long COVID symptoms, combined with the absence of objective markers, makes it difficult to distinguish true treatment effects from placebo responses or natural fluctuations in symptom severity.

The Need for Standardisation

International efforts have attempted to establish a consensus definition for long COVID. The World Health Organization (WHO) developed a clinical case definition in 2021, describing post-COVID-19 condition as symptoms present for at least 3 months after the onset of acute COVID-19, lasting for at least 2 months, and not explained by an alternative diagnosis. But even this definition, while a step forward, remains broad and relies heavily on patient self-report, lacking the specificity needed for rigorous clinical trial enrolment or biomarker identification. Universal definitions for conditions like heart failure have significantly advanced research and care; long COVID needs a similar breakthrough.
The Glasby study's findings show that even with policy directives to improve care, without clear, operational definitions, implementation falters. The 'Transforming Care' agenda in the UK aimed to move individuals with learning disabilities and autism out of hospitals, but progress was slow because the practicalities of 'transforming care' were not uniformly defined or measured.1 This suggests that for long COVID, simply stating a definition is insufficient; it requires widespread adoption, clear diagnostic algorithms, and perhaps most critically, objective biological markers that can validate the clinical presentation.
The study also pointed to the significant emotional and financial burden on families when care pathways are unclear and protracted. Families of individuals with learning disabilities and autism reported high levels of stress and a constant battle to secure appropriate support.1 Long COVID patients and their families report similar struggles, navigating a healthcare system often ill-equipped to diagnose or manage a condition that remains poorly understood. This can lead to a cycle of referrals, missed diagnoses, and a profound impact on quality of life and economic productivity.

Where Long COVID Research Falls Short

The current state of long COVID research, while extensive, is hampered by this foundational issue. Many studies are observational, describing cohorts of patients with varying symptom profiles, making it difficult to identify common pathophysiological mechanisms or effective treatments. Interventional trials often struggle with recruitment, as patients who meet one research definition may not meet another, leading to small, heterogeneous samples that cannot provide definitive answers. This is a critical limitation, as the field desperately needs large, well-powered trials to identify effective therapies.
The Glasby study's insights into the barriers to discharge for patients with learning disabilities and autism, such as a lack of suitable housing, insufficient community support, and communication breakdowns between services, offer a cautionary tale.1 These are systemic issues that resonate with the challenges in long COVID care. If the 'system' cannot agree on who has the condition or what their needs are, it cannot effectively provide the necessary support or develop targeted interventions. The relationship between COVID and other conditions, like pediatric type 1 diabetes, also requires clear definitions to avoid confounding.
Until a more precise and widely accepted case definition emerges, long COVID research will continue to operate in a fragmented research environment. This requires a concerted, international effort involving clinicians, researchers, patients, and policymakers to establish clear diagnostic criteria, identify reliable biomarkers, and develop standardised outcome measures. Only then can the field move beyond descriptive epidemiology to truly understand the underlying pathology and develop effective treatments for this debilitating condition. The Oxford Handbook of Clinical Medicine (11th ed), a concise bedside reference, highlights the importance of clear diagnostic criteria across internal medicine, a principle that long COVID urgently needs to adopt.

CLINICAL IMPLICATIONS

The ongoing struggle to define long COVID is not merely an academic exercise; it has direct, detrimental consequences for patient care and resource allocation. Clinicians are left to manage a complex, multi-system illness with no clear diagnostic pathway, often relying on symptom clusters that vary widely between individuals. This ambiguity leads to diagnostic delays, patient frustration, and a lack of consistent treatment approaches, perpetuating a cycle of uncertainty.

For the pharmaceutical industry, the absence of a standardised case definition presents a significant hurdle for drug development. Designing clinical trials without clear inclusion and exclusion criteria for long COVID patients is akin to shooting in the dark. This uncertainty deters investment and slows the progress of much-needed therapies, leaving millions without effective treatment options.

Patients, meanwhile, bear the brunt of this definitional vacuum. They face skepticism from healthcare providers, struggle to access appropriate specialist care, and often feel dismissed when their symptoms do not fit neatly into existing diagnostic boxes. This can lead to prolonged suffering, reduced quality of life, and significant economic burden due to inability to work.

The lesson from the Glasby study, though in a different context, is clear: without a shared understanding and operational definition of a complex condition, patients get stuck. For long COVID, this means a continued reliance on symptomatic management and a delayed path to definitive, evidence-based interventions. The medical community must prioritise the development of a robust, biomarker-supported case definition to unlock progress in research and clinical care.

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1. 1. Glasby J, Miller R, Glasby AM. 'Why are we stuck in hospital?' Barriers to people with learning disabilities/autistic people leaving 'long-stay' hospital: a mixed methods study. Health Soc Care Deliv Res 2024;12(5).

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