

A Long COVID Definition

**A Chronic, Systemic Disease State
with Profound Consequences**

Report Briefing Presentation



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Study Sponsors

Administration for Strategic Preparedness and Response
(ASPR) and Office of the Assistant Secretary for Health
(OASH)

Report Background: Statement of Task and Committee



Need for a Clear Definition

- Since the onset of the COVID-19 pandemic, millions of individuals across the globe have experienced ongoing symptoms following infection with SARS-CoV-2. The long-term health effects of COVID-19, known as Long COVID, are profound.
- Despite Long COVID's relatively recent emergence, numerous definitions and descriptions of Long COVID have already been published. However, no common definition for Long COVID has yet been agreed upon.
- There exists a high heterogeneity in existing definitions; this heterogeneity limits opportunities to compare interventions and accumulate evidence on Long COVID.
- The lack of a generally accepted and consistent definition for Long COVID presents challenges for clinical management and treatment, research, surveillance, and support services.

Committee Charge

- Recognizing the desirability of broad input and careful consideration of an improved definition, the National Academies was asked by the **Office of the Assistant Secretary for Health (OASH)** and the **Administration for Strategic Preparedness and Response (ASPR)** to take up the issue of defining Long COVID and:
 - Review additional evidence for definitions of Long COVID;
 - Consider efforts that have already been completed on this topic area;
 - Recommend new definitions for Long COVID and related technical terms, with descriptions of the circumstances under which these new definitions and terminology should be adopted.

Committee on Examining the Working Definition for Long COVID

- **HARVEY V. FINEBERG, (CHAIR)**, President, Gordon and Betty Moore Foundation
- **KEVIN M. ALEXANDER**, Assistant Professor of Medicine, Stanford University
- **DONALD BERWICK**, President Emeritus and Senior Fellow, Institute for Healthcare Improvement
- **KARYN BISHOF**, Long COVID Patient Advocate, President and Founder, COVID-19 Longhailer Advocacy Project (C19LAP)
- **LILY CHU**, Vice President, International Association for Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis (IACFS/ME)
- **BETTY DIAMOND**, Director of the Institute of Molecular Medicine, The Feinstein Institutes for Medical Research
- **ABIGAIL DUMES**, Assistant Professor of Women's and Gender Studies, University of Michigan
- **E. WESLEY ELY**, Professor of Medicine, Vanderbilt University Medical Center
- **DENNIS LARRY KOLSON**, Professor of Neurology, University of Pennsylvania
- **JERRY KRISHNAN**, Professor of Medicine and Public Health, University of Illinois Chicago
- **PETER PALESE**, Professor of Microbiology and Chair Icahn School of Medicine at Mount Sinai
- **CAITLIN PEDATI**, Public Health District Director, Virginia Beach Department of Public Health
- **LINDA SPRAGUE MARTINEZ**, Professor of Medicine and Public Health Sciences, Director of Health Disparities Institute, UConn Health
- **MARK SMOLINSKI**, President, Ending Pandemics
- **ANDREA B. TROXEL**, Director of the Division of Biostatistics, Professor of Population Health, NYU Grossman School of Medicine
- **MONICA VERDUZCO-GUTIERREZ**, Professor and Distinguished Chair, Department of Rehabilitation Medicine, University of Texas Health Science Center at San Antonio

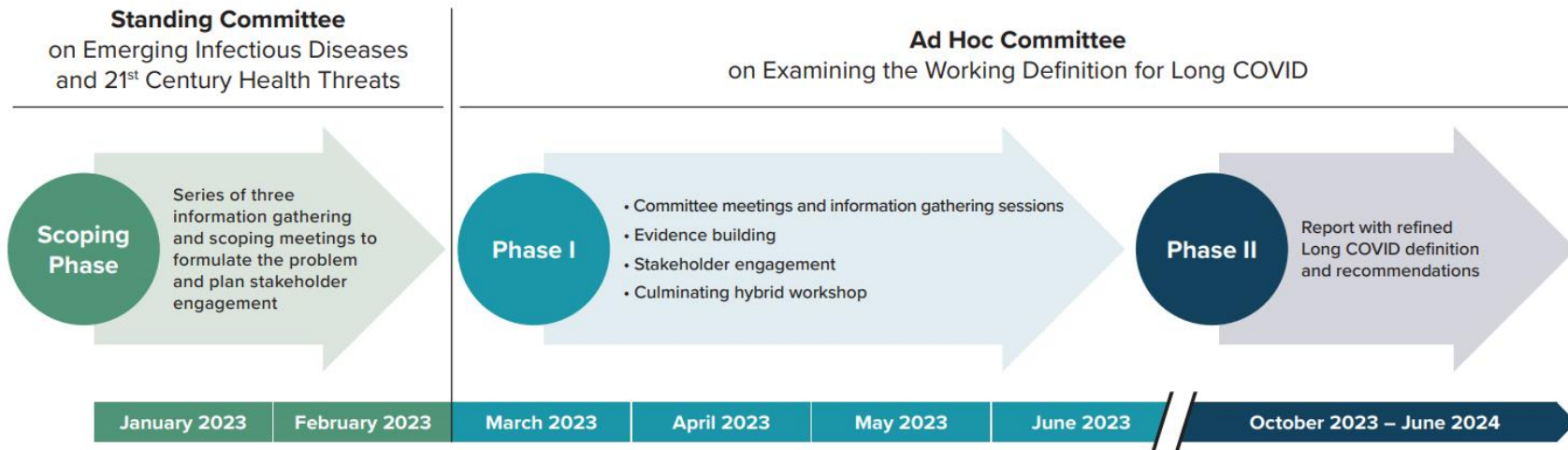
Report Overview and Methodology



Report Structure

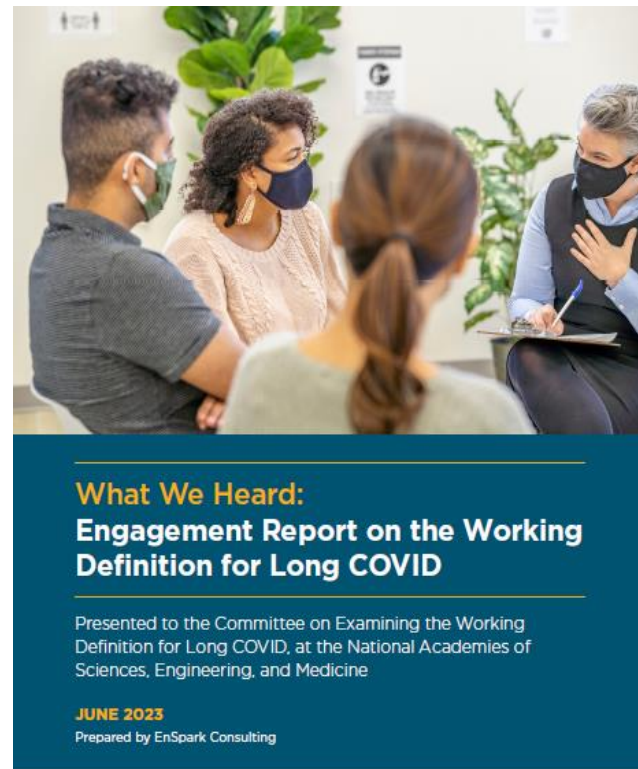
- The report contains seven sections:
 - **(1)** Introduces and discusses the background for the study.
 - **(2)** Presents the 2024 NASEM Long COVID Definition, in written text and in figure format.
 - **(3)** Summarizes evidence supporting key elements and features of the definition.
 - **(4)** Outlines frameworks for applying the definition for multiple purposes, specifically clinical care, research, and public health surveillance applications.
 - **(5)** Discusses the need and parameters for updating the definition as evidence accumulates and understanding evolves, and also identifies priority areas for future research to improve the definition.
 - **(6)** Articulates the key limitations, prominently including limitations imposed by the available knowledge about and understanding of Long COVID.
 - **(7)** Includes the committee's concluding remarks and three recommendations.

Multi-Phase Process



Download the Engagement Report

- Download the engagement report on the project webpage:



Throughout the engagement activities, participants shared how Long COVID is having a tremendous impact on people living with the disease.

One participant said: *“Patients need to be able to understand it and see themselves in the definition, because they may need to advocate for themselves or their loved ones for initial care (or continued care or recognition).”*

What Constitutes a Definition for a Disease?

- No published, standardized guidelines for the development of disease definitions.
- The committee articulated several possible key elements of a disease definition.

Element	Description
Attribution	Source responsible for causing the disease
Time	Onset of disease
Clinical Features	Symptoms, symptom course and duration, and symptom severity of the disease to be defined
Equity	Identify persons affected and consider equity implications
Functional Impairment	Effect of the disease on daily activities
Exclusions/Alternative Diagnoses	Consideration of alternative diagnoses
Biomarkers and Laboratory Criteria	Objective tests (e.g., blood tests, neuroimaging, cognitive batteries) that help identify the disease
Risk Factors	Characteristics associated with a higher probability of disease or adverse outcome

Terminology

- **Using consistent terminology is as important as using a consistent definition.**
- **Long COVID** – Patient-developed term and its simplicity and familiarity can facilitate communication within and between the scientific community and public.
- **Infection-associated chronic condition (IACC)** – Applies to a variety of chronic conditions that can be triggered by viruses, bacteria, fungi, or parasites. Use of this term highlights the ongoing nature of Long COVID and its association with a triggering infection without conveying any unwarranted conclusions about pathobiological mechanisms.
- **Disease state** – To stress the systemic reality of Long COVID.

2024 NASEM Long COVID Definition



2024 NASEM Long COVID Definition

Long COVID (LC) is an infection-associated chronic condition (IACC) that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.

2024 NASEM Long COVID Definition

LC manifests in multiple ways. A complete enumeration of possible signs, symptoms, and diagnosable conditions of LC would have hundreds of entries. Any organ system can be involved, and LC patients can present with

- **single or multiple symptoms, such as:** shortness of breath, cough, persistent fatigue, post-exertional malaise, difficulty concentrating, memory changes, recurring headache, lightheadedness, fast heart rate, sleep disturbance, problems with taste or smell, bloating, constipation, and diarrhea.
- **single or multiple diagnosable conditions, such as:** interstitial lung disease and hypoxemia, cardiovascular disease and arrhythmias, cognitive impairment, mood disorders, anxiety, migraine, stroke, blood clots, chronic kidney disease, postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), mast cell activation syndrome (MCAS), fibromyalgia, connective tissue diseases, hyperlipidemia, diabetes, and autoimmune disorders such as lupus, rheumatoid arthritis, and Sjogren's syndrome.

2024 NASEM Long COVID Definition

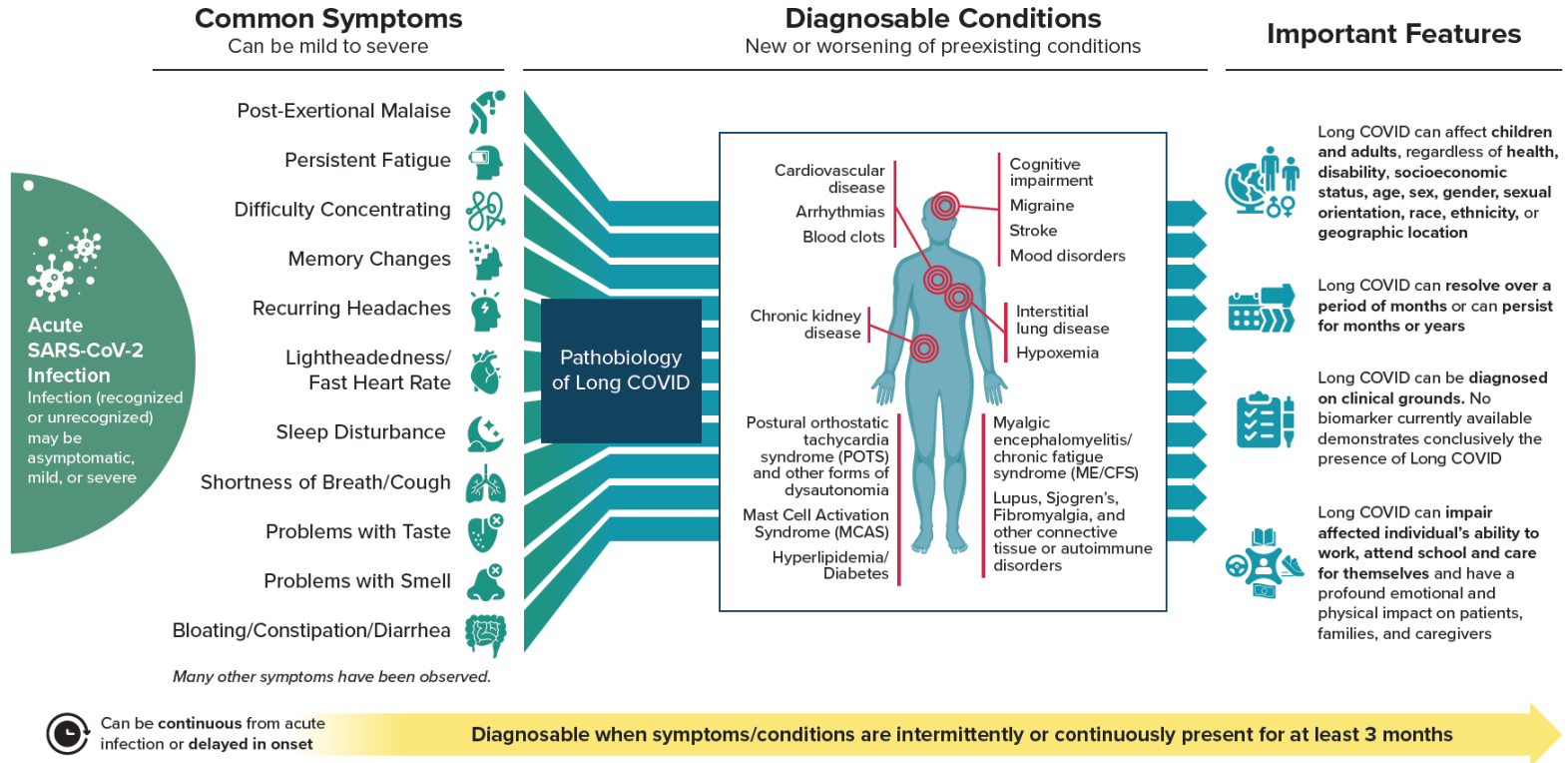
Important Features of LC:

- LC can follow asymptomatic, mild, or severe SARS-CoV-2 infection. Previous infections may have been recognized or unrecognized.
- LC can be continuous from the time of acute SARS-CoV-2 infection or can be delayed in onset for weeks or months following what had appeared to be full recovery from acute infection.
- LC can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, gender, sexual orientation, race, ethnicity, or geographic location.
- LC can exacerbate pre-existing health conditions or present as new conditions.
- LC can range from mild to severe. It can resolve over a period of months or can persist for months or years.
- LC can be diagnosed on clinical grounds. No biomarker currently available demonstrates conclusively the presence of LC.
- LC can impair individuals' ability to work, attend school, take care of family, and care for themselves. It can have a profound emotional and physical impact on patients and their families and caregivers.

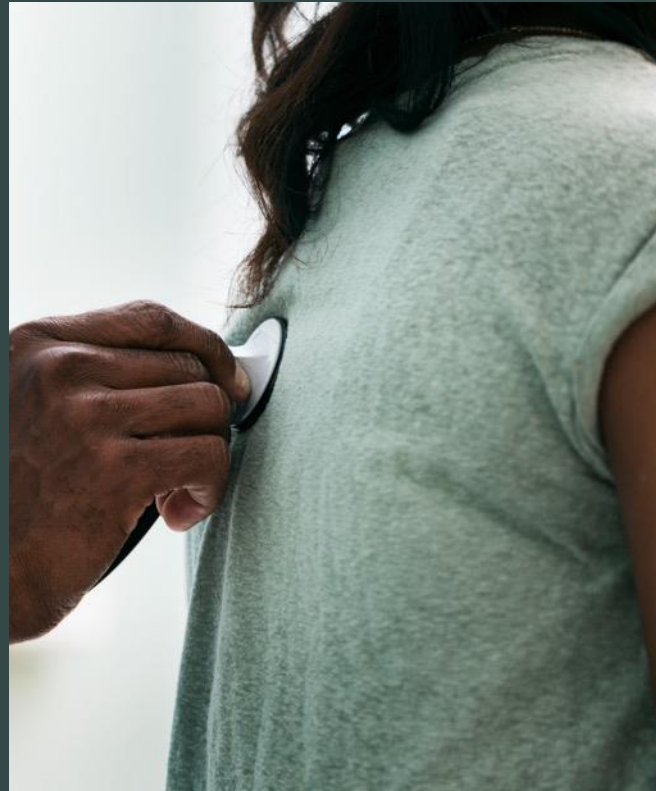
Definition Figure

The Disease State of Long COVID

An Infection-Associated Chronic Condition (IACC)



Key Considerations



Foundational Criteria

- In developing the definition, the committee considered the following criteria: **precision, feasibility, acceptability, accessibility, balancing benefits and harms, potential impact on health equity, and unintended consequences.**
- The committee grappled with:
 - Ensuring that patients who experience Long COVID will be included in the definition, and
 - Avoiding wrongly including patients whose condition is not related to prior SARS-CoV-2 infection.
- This is a familiar dilemma in any diagnostic challenge. The definition is intentionally inclusive, to satisfy the first objective; however, the committee acknowledges the potential for false positives.
- The committee believes the patient's treating clinician is best poised to strike the right balance between avoiding a false positive and a false negative classification.

How is this Definition Different?

- The **2024 NASEM Long COVID Definition** uses intentional terminology (Long COVID, IACC, and disease state) and introduces a few *new features* that existing definitions lack:
 - **(1)** Provides explicit examples of common symptoms and conditions characteristic of Long COVID.
 - **(2)** Requires symptoms or conditions to be present for a duration of 3 months or longer, but it is not necessary for symptoms to be experienced continuously from the time of the acute infection.
 - **(3)** Includes an explicit statement on equity.
- Other *notable features* include **(1)** No requirement for laboratory confirmation, positive test, or other proof of initial SARS-CoV-2 infection; **(2)** Indicates course of Long COVID and what we know now (can resolve or persist for months to years); **(3)** Acknowledges lack of biomarker, but indicates diagnosis on clinical grounds; and **(4)** Firm acknowledgement of the impact of Long COVID on function.

Definition Elements and Implementation Considerations



Attribution to Infection

- The definition **does not require laboratory confirmation or other proof** of initial SARS-CoV-2 infection.
- Long COVID can follow asymptomatic, mild, or severe SARS-CoV-2 infection.
- The initial infection may or may not have been recognized, in part due to the lack of availability of and limited access to tests early in the pandemic, limited sensitivity of some SARS-CoV-2 tests and the potential for false negatives, and an overall decline in testing rates later in the pandemic.

Onset and Duration

- The definition **requires symptoms or conditions to be present for a duration of 3 months or longer, although the timing of those 3 months is unspecified.**
- It is not necessary for symptoms to be experienced continuously from the time of the acute infection.
- Although the definition specifies a minimum duration of 3 months to qualify as Long COVID, a clinician should recognize, acknowledge, and monitor concerning symptoms before the 3-month mark. These symptoms should be assessed and treated appropriately, and the ICD-10 code U09.9 (post COVID-19 condition, unspecified) may be used even before establishing a Long COVID diagnosis.
- Because there is still ambiguity regarding the relationship between the timing of SARS-CoV-2 infection relative to Long COVID onset, the definition does not include a maximum latency period.

Symptoms

- The definition **offers examples of how Long COVID could manifest**, including some symptoms and conditions, and how Long COVID could present as a new condition or an exacerbation of pre-existing conditions.
- This list is not meant to be exhaustive or to dismiss the significance of other symptoms or conditions.
- The definition does not list any symptoms or conditions as being required and does not list any symptoms or conditions as being exclusionary.
- Another notable feature of Long COVID is the **variable temporal pattern and duration of symptoms**.
- The definition also recognizes that the **severity of Long COVID symptoms can range from mild to severe**.

Equity

- Engagement participants emphasized the need to address equity in the definition, with one participant saying, ***“It could be helpful to include a specific statement around health equity in a Long COVID definition. That would maybe be a little unusual to include in a definition, but it is important, if not in the definition, somewhere else.”***
- Considering this, one of the definition’s important features is “Long COVID can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, gender, sexual orientation, race, ethnicity, or geographic location.”

Functional Impairment

- The 2024 NASEM Long COVID Definition emphasizes that **some** individuals with Long COVID **are severely affected and can have a variety of activity limitations** and may affect functionality in different domains like daily home functioning, employment, and/or education.
 - This can profoundly affect patients' and caregivers' lives and is an important feature of Long COVID.
-
- Engagement participants noted, “***What we need to be able to do with the definition, or a subset of it, is determine a degree of impairment because so many people are disabled.***” and “***When I think about Long COVID, it's about the symptoms that are causing functional impairment that you do not see.***”

Other Definition Elements

- **Alternative Diagnoses**

- The committee elected not to include a statement regarding exclusions or alternative diagnoses in the 2024 NASEM Long COVID Definition. First, there is no scientific evidence that any medical condition prevents or cannot exist alongside Long COVID.

- **Biomarkers**

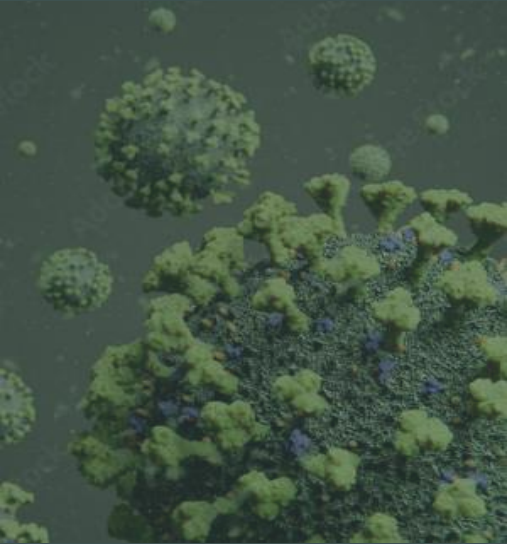
- Long COVID can be diagnosed on clinical grounds. No biomarker currently available demonstrates conclusively the presence of Long COVID.
- Long COVID is a physical health condition.
- Further discoveries may enable biomarkers to be incorporated in a revised, future definition.

- **Risk Factors**

- Various risk factors, such as underlying comorbid conditions, may influence the risk and presentation of COVID-19 and Long COVID in a particular individual and may be useful in assessing individual patients or populations at risk.
- However, as risk factors do not in themselves define a disease, the committee chose not to include risk factors in the 2024 NASEM Long COVID Definition.

Implementation

2024 NASEM Long COVID Definition is intended to be applied to many purposes.



- The committee describes ways in which the 2024 NASEM Long COVID Definition may be applied for different purposes (clinical care, research, and public health surveillance) and provides considerations as well as illustrative examples, tables, and resources.
- The committee recognizes the need to adopt the definition for policy and service uses and refers the reader to the National Academies report, *Long-Term Health Effects Stemming from COVID-19 and Implications for Social Security Administration* for key considerations and resources.
- All stakeholders involved in social safety net programs need to be aware of Long COVID to properly support patients, and their families and caregivers in need.

Recommendations and Concluding Remarks



Working Definition and Research Agenda

- The committee confronted many difficulties in its efforts to define Long COVID.
- The committee sought to define Long COVID while simultaneously recognizing that there is more to learn and understand about it, and this means acknowledging inherent limitations and anticipating that changes will be made as the science advances.
- A research agenda to improve the definition could focus on the key definition elements and should lead to a more complete understanding of the natural history, etiology, therapy, and clinical management of Long COVID.
- *The 2024 NASEM Long COVID Definition will evolve as new evidence emerges and our understanding of Long COVID continues to mature.*

Recommendations

- **Adopt**

- The federal government, state, tribal, local, and territorial health authorities, clinical societies and associations, public health practitioners, clinicians, payers, researchers, drug industry, employers, educators, international organizations, and patients should **adopt the 2024 NASEM Long COVID Definition and should use the term Long COVID.**

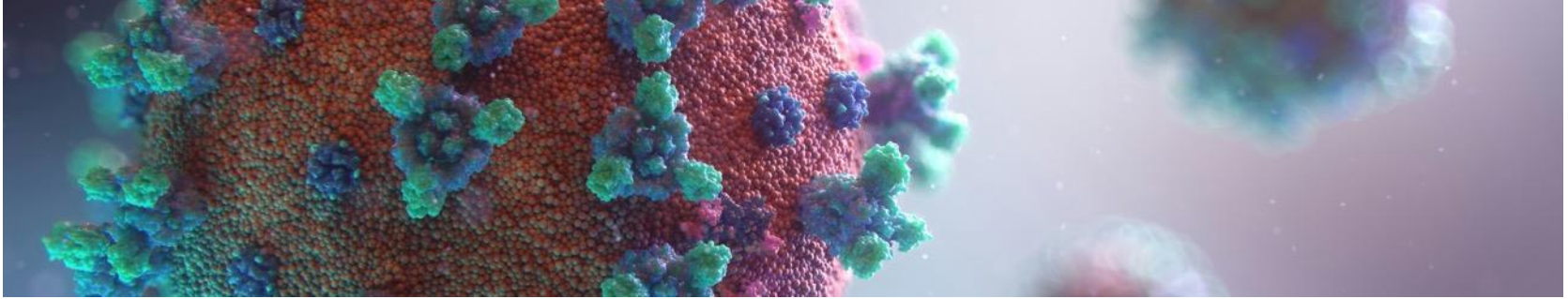
- **Implement and Monitor**

- The Office of the Assistant Secretary for Health's Office of Long COVID Research and Practice and the Long COVID Coordination Council **should lead the coordination and collaboration efforts** across federal, state, tribal, local, and territorial agencies and other relevant entities, including international organizations, **in the wide dissemination and implementation** of the 2024 NASEM Long COVID Definition

- **Update**

- **In no more than 3 years or when triggered by the emergence of relevant new knowledge**, the Office of the Assistant Secretary for Health's Office of Long COVID Research and Practice should convene a multi-disciplinary group, including individuals with lived experience, to reexamine and update the 2024 NASEM Long COVID Definition set forth in this report.

Concluding Remarks



- The committee hopes the 2024 NASEM Long COVID Definition will, first and foremost, benefit the Long COVID community by **creating a shared understanding of what Long COVID is and that it will lend added recognition to IACCs within the medical community and society at large.**
- The 2024 NASEM Long COVID Definition **reflects and promotes a more holistic and integrated approach to understanding disease.** Such an approach reflects a broader recognition of the complexities inherent in human health, including health disparities, social determinants of health, and the importance of including patient experience and knowledge in decision making.

Thank you!

Free PDF of the report and related materials:



Questions about the report?

Contact Lisa Brown, Study Director, at LBrown@nas.edu

