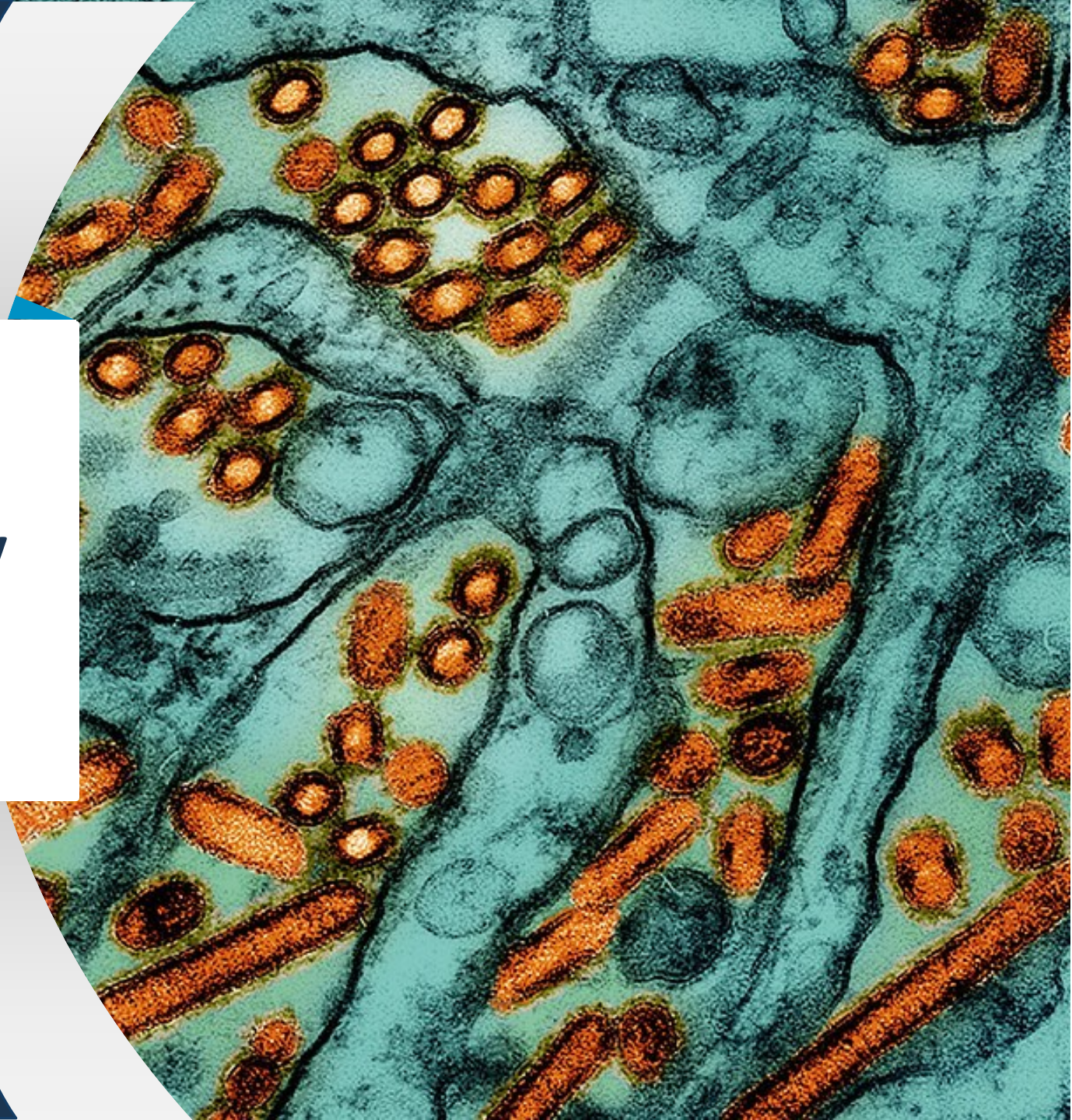
National Institute of Allergy and Infectious Diseases

RECOVER - Treating Long COVID: Future Clinical Trials Informed by Pathobiology and Symptoms

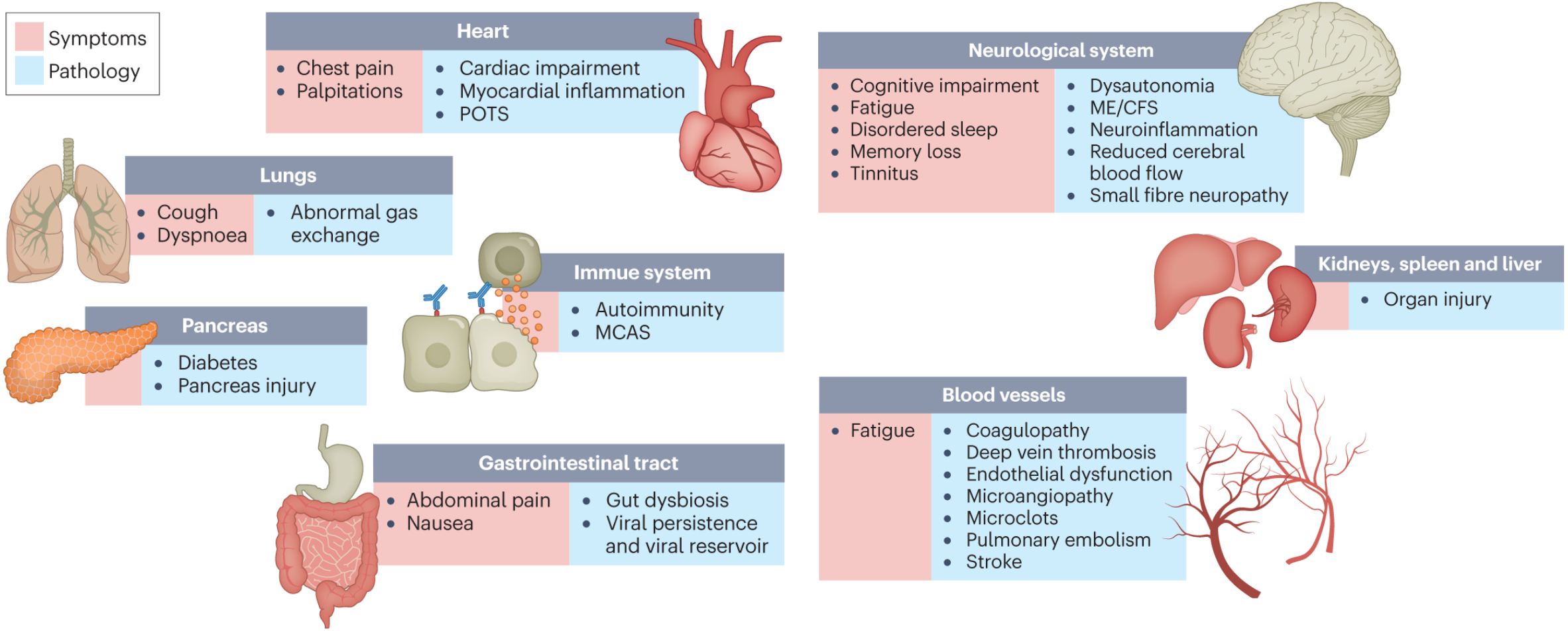
December 12, 2024



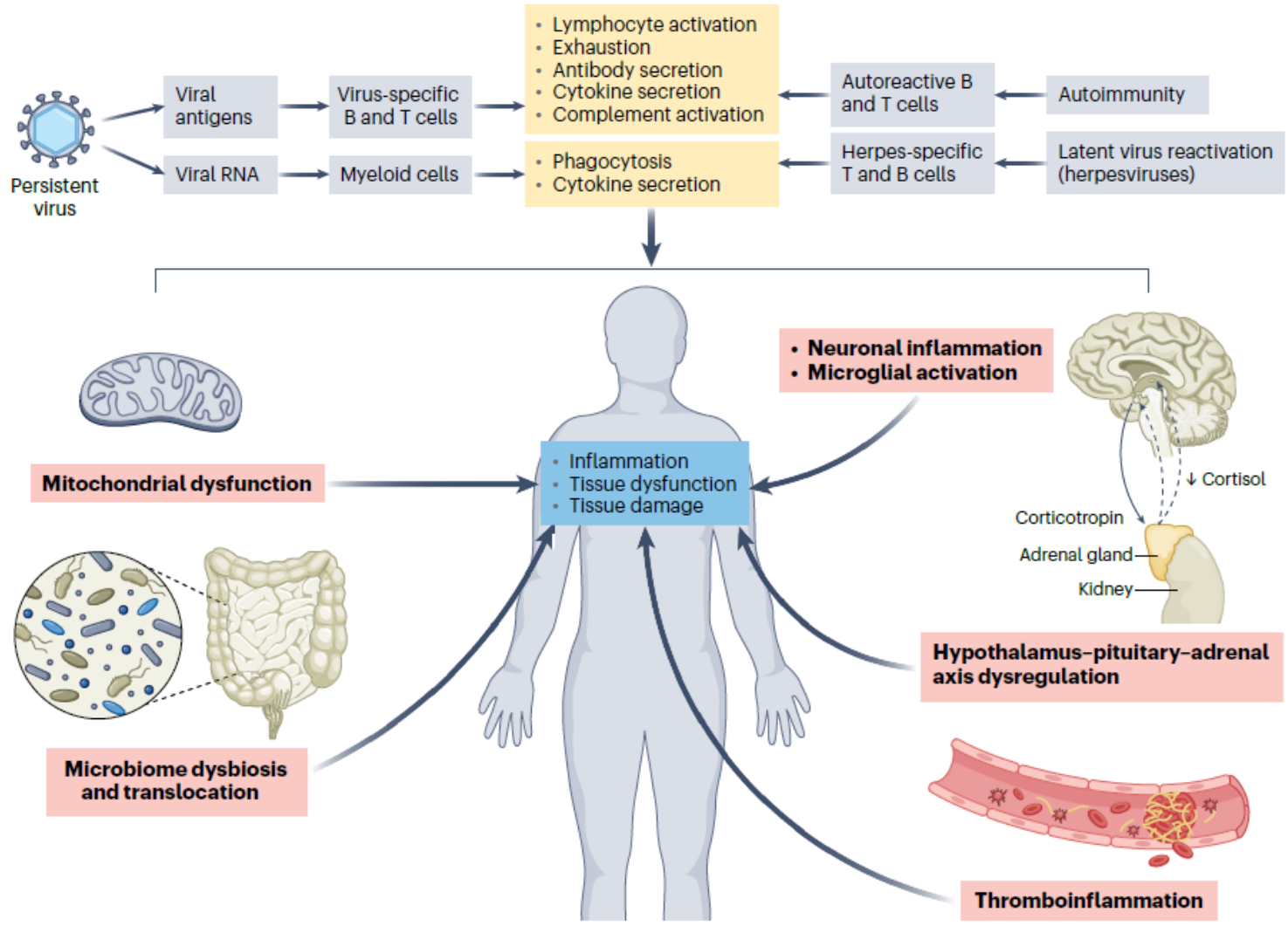
SARAH READ, MD, MHS

DEPUTY DIRECTOR, NIAID

Long COVID: Wide Multi-Symptom Clinical Spectrum



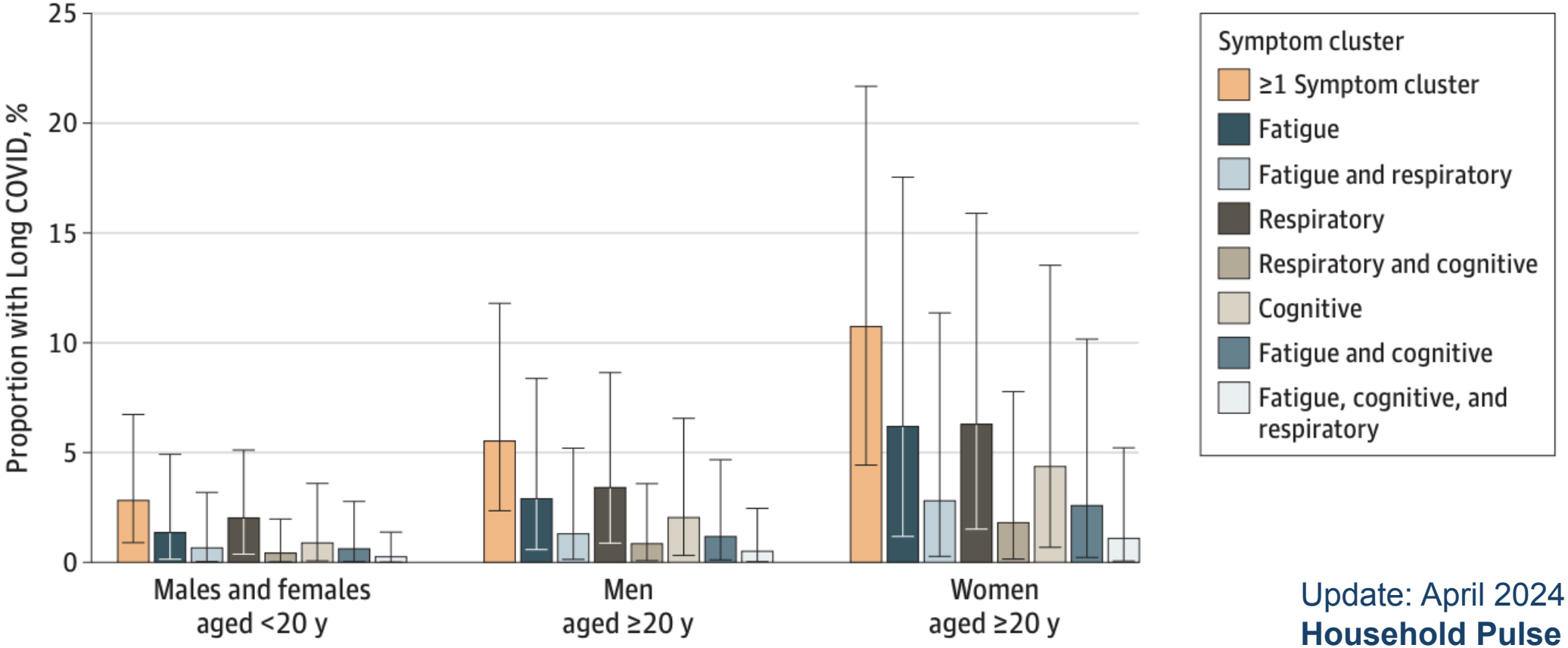
Long COVID



- Complex, multisystem disorder
- Cumulative incidence globally: ~400 million cases
- Annual economic impact: $1 trillion — about 1% of the global economy

How Prevalent is Long COVID?

Proportion of Individuals Who Survived Symptomatic SARS-CoV-2 Infection and Who Experienced at Least 1 of the 3 Long COVID Symptom Clusters in 2020 and 2021

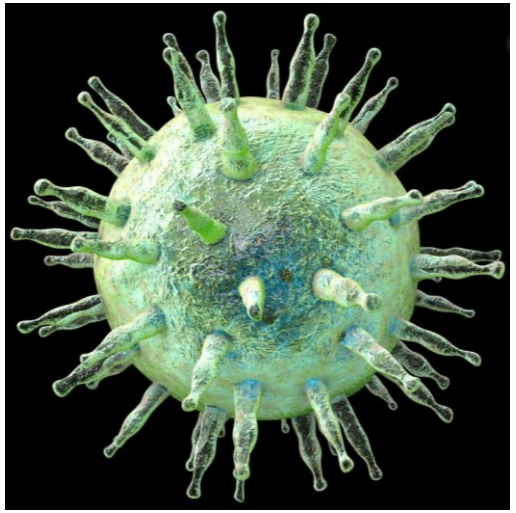


Global Burden of Disease Long COVID Collaborators. *JAMA,* October 2022

Update: April 2024: CDC et al **Household Pulse Survey** estimates 6.8% of adults in US currently experiencing Long COVID

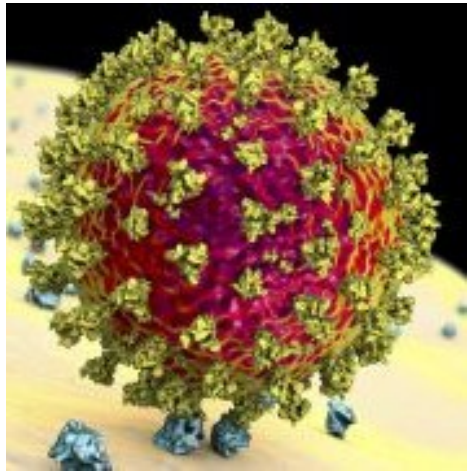
Pathogenesis of Long COVID – What do the Data Suggest?

Viral reactivation



EBV

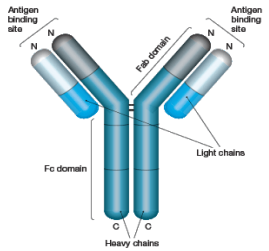
Persistent viral infection



SARS-CoV-2 antigen

Immune dysregulation

Macrophages



Antibodies / Autoimmunity

RECOVER
Researching COVID to Enhance Recovery

ANNOUNCEMENT

August 15, 2024 • recoverCOVID.org

Building on RECOVER's successes and lessons learned, RECOVER-TLC will test more potential treatments for Long COVID symptoms

NIH RECOVER-TLC Initiative

GOAL

Develop safe and effective therapeutic interventions for Long COVID and provide these to health care providers and their patients as rapidly as possible

KEY SCIENTIFIC AIMS

1. Identify pharmacologic and non-pharmacologic interventions to treat Long COVID
2. Build on findings from RECOVER cohorts, pathobiology studies, and clinical trials
3. Develop rapid, nimble clinical trials design with direct and transparent engagement with scientific, industry, and patient communities
4. Provide access and sharing of data with public and scientific communities

GUIDING PRINCIPLES

Patient-centered participants as partners

National scale with inclusive, diverse participation & community engagement

Platform protocols standardized methodologies, and common data elements

Adaptive approaches based on emerging science

NIAID-sponsored Clinical Trials

Experience and Resources:

- ❑ Large-scale, complex clinical trials
- ❑ Regulatory teams with long-standing FDA interactions
- ❑ Biostatistical support in clinical trial design and data analysis
- ❑ Product support and repositories
- ❑ DSMB capabilities
- ❑ Broad contract support
- ❑ Long-standing relationships with scientific and advocacy communities (i.e., HIV/AIDS)
- ❑ Medical Officers and Program Staff with extensive clinical trial expertise

Scientific Engagement

- Assess current RECOVER Clinical Trials landscape
- Determine what new approaches are needed for trials (e.g., ability to reach enrollment targets, sites participating, ability to achieve trial endpoints, etc.)
- Identify lessons learned to inform protocol design and launch of the new clinical trials program

Engagement & Transparency

How will RECOVER-TLC work?

First Steps

- ❑ Engage FNIH as strategic partner
- ❑ Engage partner ICs
- ❑ Kick-off, public meeting – engagement and transparency with the urgency of initiating new clinical trials
- ❑ Introduce structure of RECOVER-TLC

Oversight
&
Engagement

RECOVER-TLC Structure

Executive Committee (EC)

- Composition: NIH Director, NIAID Director, NHLBI Director, NINDS Director, FNIH President, input from community
  - Will review and make decisions on recommendations form the SOC of prioritized therapeutic interventions for entry into trials

Scientific Oversight Committee (SOC)

- Composition: NIH subject matter experts, academic leaders, community representatives
  - Will review list of prioritized therapeutic interventions and make recommendations for entry into trials to the EC

Scientific Engagement

RECOVER-TLC Scientific Working Groups

Scientific working groups will be formed with the assistance of FNIH

Each working group will be based on a specific mechanism to be targeted or could also be symptom-based if less mechanistic information is known

Examples: Neuro WG, Virology WG, Cardiovascular WG, etc.

The Scientific Working groups will work to help prioritize potential therapeutics and present to the Scientific Oversight Committee

Implementation
&
Management

RECOVER-TLC – Operations

The Clinical Operations Working Group will utilize established NIAID resources to design and conduct clinical trials using established mechanisms and pre-existing programs wherever available

- *Use what works and enhance only if needed*
- *Strategy to increase efficiency to reflect urgency*
- *Interact with Scientific Oversight and Executive Committees*

Community Engagement

- ❑ Critical in all components of RECOVER-TLC; ensuring bilateral communication
- ❑ Engage with community groups interacting with RECOVER, NIH OD, and ICs
- ❑ Establish Community Engagement Group to:
  - Provide feedback directly to Executive Committee
  - Participate in intervention prioritization
  - Participate in all Working Groups and Scientific Oversight Committee

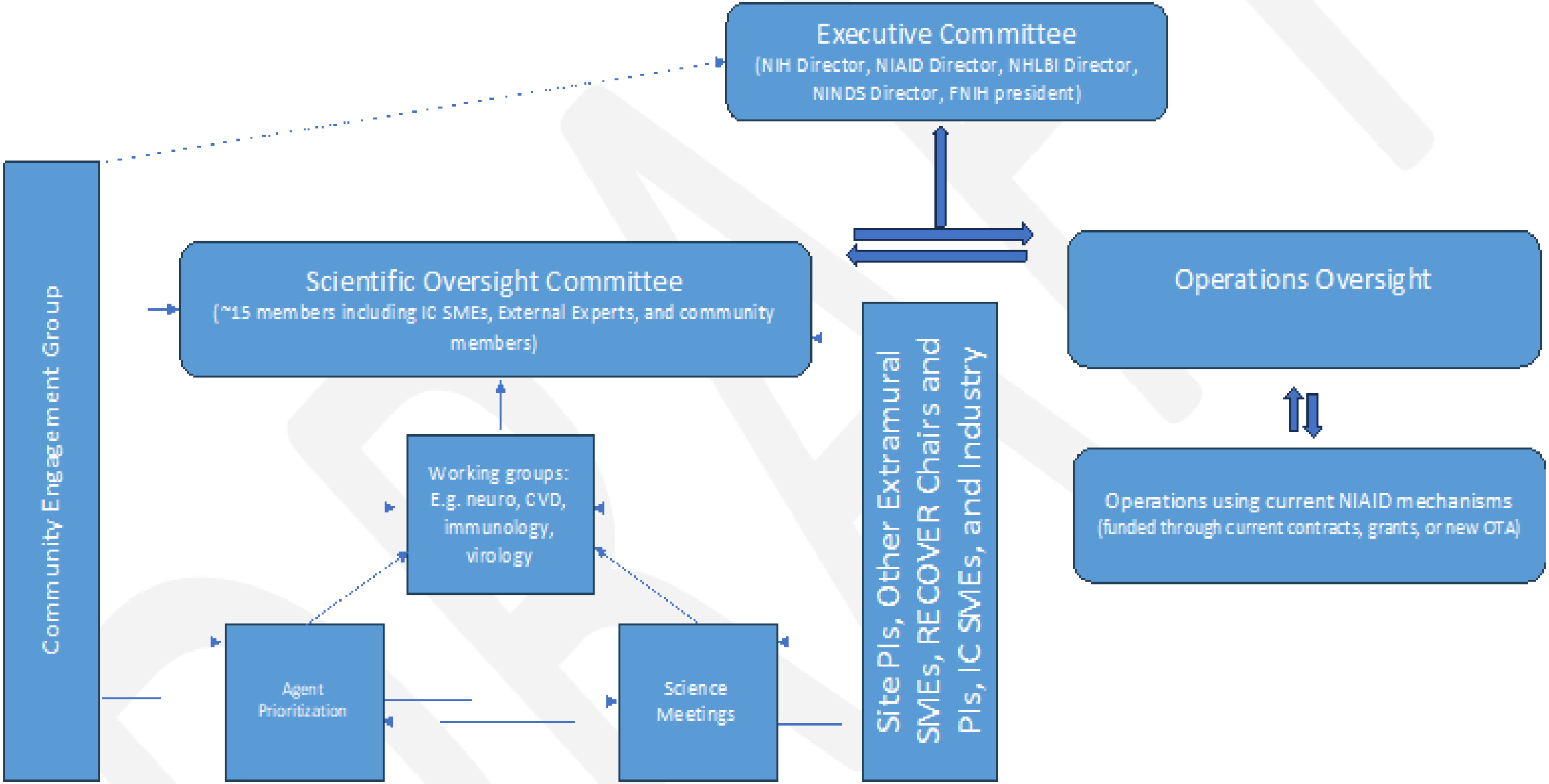
Clinical Trials

Clinical Trial Sites: Open to existing RECOVER sites, new sites identified through NIAID, NINDS, NHLBI, and other IC trial networks; must ensure enrollment of diverse populations; and international sites potentially

Protocols: Platform trial design using new protocol templates for rapid addition of other interventions; new intervention specific protocols developed collaboratively by Working Groups, Scientific Oversight Committee, and Operations Oversight group

Trial design: Sufficiently large to definitively assess safety and efficacy of potential interventions, with interim futility to stop trials; proof of concept/exploratory trials considered

Biospecimens: Testing using standardized, validated assays at site; shipped also to a new biorepository with clinical data; and available to inside and outside researchers


Executive Committee
(NIH Director, NIAID Director, NHLBI Director, NINDS Director, FNIH president)
Scientific Oversight Committee
(~15 members including IC SMEs, External Experts, and community members)
Operations Oversight
Community Engagement Group
Working groups: E.g. neuro, CVD, immunology, virology
Agent Prioritization
Science Meetings
Site PIs, Other Extramural SMEs, RECOVER Chairs and PIs, IC SMEs, and Industry
Operations using current NIAID mechanisms (funded through current contracts, grants, or new OTA)

October 11, 2024
Vol. LXXVI, No. 21

Printable PDF

IN THIS ISSUE

Experts Convene at NIH to Discuss Long Covid

FNIH CEO Dr. Julie Gerberding (c) speaks on a panel as NIH Director Dr. Monica Bertagnolli (l), Marrazzo and Baden look on.

PHOTO: CHIA-CHI CHARLIE CHANG

The National Institute of Allergy and Infectious Diseases (NIAID), in collaboration with the Foundation for the National Institutes of Health (FNIH), co-hosted a workshop titled, "RECOVER: Treating Long Covid (RECOVER-TLC)–Navigating the Pathway Forward." The three-day workshop took place in the John Edward Porter Neuroscience Research Center on NIH's campus in September.

There were 180 in-person and more than 1,200 virtual participants, including Long Covid researchers, healthcare providers, patients, advocacy organizations, industry partners, federal scientific agencies, and federal policymakers.

NIH Director Dr. Monica Bertagnolli, along with FNIH CEO Dr. Julie Gerberding gave welcoming remarks to open the meeting. NIAID Director Dr. Jeanne Marrazzo and Dr. Lindsey Baden, vice president of clinical research at the Brigham and Women's Hospital and Harvard Medical School, co-chaired the workshop.

Goals of the Workshop

High-level scientific review of clinical and mechanistic data, with strong emphasis on community input and implications for clinical trial design

Highlight opportunities for clinical trials based on what is known about mechanism, symptom burden and available interventions

Summarize core findings of workshop discussions and integrate into description of how this effort will move forward

Workshop Format

- ❑ Focus topics:
  - Pathobiology
  - Biomarkers
  - Epidemiology and cohort studies
  - Clinical trial designs
  - Interventional prioritization strategies
  - Endpoint selection
- ❑ Participants (180 in-person & >1,200 virtual):
  - RECOVER cohort and clinical trial PIs
  - U.S. and international researchers
  - Community and patient groups
  - Industry
  - NIH scientists and clinicians
  - USG agencies (FDA, CDC, DoD, VA, AHRQ, ASPR, OASH)

Workshop Outcomes

Communication and Structure

What We Heard

- Value to assembling this diverse group of people passionate about improving life for people living with infection-associated chronic conditions (IACC)
- Patient and community involvement is critical in all aspects of planning clinical trials
- Leadership should be accountable and transparent about the process
- RECOVER has advanced the science immeasurably & should be leveraged for future success

What We Will Do

- Provide forums for regular opportunities to continue this dialogue
- Ensure meaningful, real participation of patients and advocates at every step
- Provide regular (monthly) updates on progress
- Plan an annual meeting to review progress and strategy
- Finalize organizational set-up
  - Solicit interest and invite committee members
  - Define potential reviewers/content experts
  - Centralize leadership in NIAID OD

Selection of Clinical Trials

What We Heard

- Minimize exclusion criteria
- Ensure access for children/adolescents, reproductive aged women
- Where possible, include involvement of other IACCs
- Build on RECOVER infrastructure
- Expand access to all affected, despite severity of symptoms (homebound, bedbound) and access beyond 9-5 office hours

What We Will Do

- Assemble working groups w/ content expertise and lived experience
- Define rigorous, rapid review process
- Work closely w/ RECOVER team to maximize use of existing infrastructure in addition to utilizing other networks as needed
- Review sites to ensure access to populations we need; expand into rural communities utilizing emerging technologies
- Ensure accessibility of clinical sites or delivery of interventions/assessments to homebound, bedbound
- Assure accessibility to different populations/phenotypes; avoid unnecessary exclusions

Linking Interventions to Pathobiology

What We Heard

- RECOVER has a large biorepository
  - Unmet need to interrogate possible mechanisms
  - Needs to be leveraged for this immediately
- Other repositories exist
- Consider burden of specimen collection as people participate in clinical trials

What We Will Do

- Urgently investigate how existing specimens and data can be used to address top priority mechanistic questions ****that can inform next steps in clinical trial prioritization****
- Recognize diversity of expertise across disciplines (neurology, cardiology, immunology/allergy, rheumatology, pediatrics, Infectious diseases); establish multidisciplinary working group as needed

Involving People Living with Long COVID

What We Heard

- Community involvement is critical in all aspects of planning clinical trials from intervention selection, trial design, conduct, interpretation, dissemination, and implementation of findings
- Community needs recognition and support
- Recognize the pandemic's legacy of mistrust
- An opaque, top-down approach does not build trust or willingness to work together
- Providers are under-resourced to give evidence-based, comprehensive care

What We Will Do

- Include people with Long COVID in all aspects of clinical trial conduct, from review of the evidence to design and onward, including:
  - ❑ Community Engagement Group
  - ❑ Membership in all working groups, including those prioritizing interventions and on trial designs; key committees
- Support the development of community advocates
  - ❑ Look to other NIH networks that have done this successfully, including:
    - Community scholars programs
    - Mentorship programs, meeting sponsorship

Ongoing Activities Post-Workshop

Workshop report and manuscript in preparation

New portal for submissions of therapeutics and biologics

Assess and monitor ongoing long COVID clinical trials landscape

Establish prioritization process – criteria, triage and working group

Ongoing Activities Post-Workshop – RFI

Request for Information (RFI): Researching COVID to Enhance Recovery – Treating Long COVID (RECOVER-TLC)

Notice Number:
NOT-AI-25-007

Key Dates

Release Date:	October 28, 2024
Response Date:	February 01, 2025

Related Announcements

None

Issued by

National Institute of Allergy and Infectious Diseases (NIAID)

Purpose

To solicit input on aspects regarding the National Institutes of Health (NIH) RECOVER-TLC effort.

Background

Today, there are no approved therapies to treat Long COVID or its symptoms, leaving millions of patients suffering and waiting for answers. Trying to counter this public health crisis, the NIH announced the next phase of its Long COVID research program: Researching COVID to Enhance Recovery–Treating Long COVID (RECOVER-TLC) led by National Institute of Allergy and Infectious Disease (NIAID), in collaboration with National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Neurological Disorders and Stroke (NINDS). The goal of this initiative is to work rapidly, collaboratively, and transparently to advance treatments for Long COVID. RECOVER-TLC will apply lessons learned from the ongoing program, RECOVER, launched in 2021.

As an important first step, NIAID and the Foundation for NIH (FNIH) co-organized a hybrid workshop to introduce RECOVER-TLC and engage with scientific, patient, and industry communities on the new initiative. Moving forward, RECOVER-TLC will be assessing new ideas, identifying potential therapeutics, and conducting innovative clinical trials using platform study designs. Central to this initiative, RECOVER-TLC aims to have ongoing engagement to inform on various aspects of clinical trial planning and implementation.

Information Requested

NIAID seeks information or responses to the following topics:

1. Potential therapeutics for Long COVID
2. Interest in being involved on working groups (patients, caregivers, scientists, physicians, etc.)
3. Biomarkers to be used in Long COVID clinical trials
4. General feedback on RECOVER-TLC

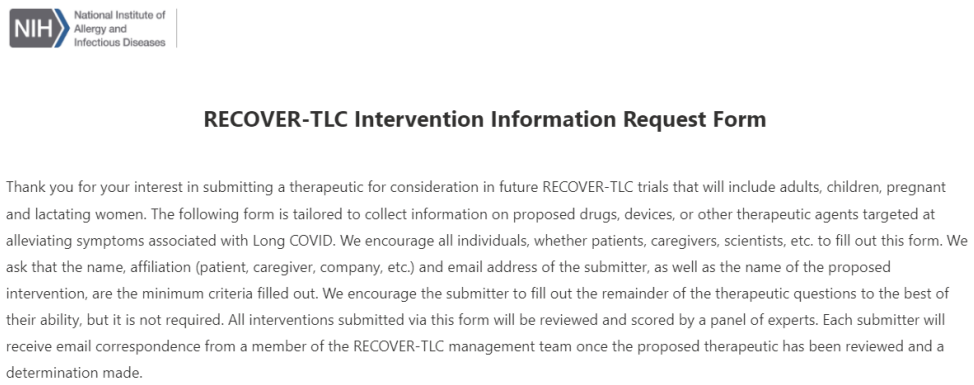
Information Requested:

- Potential therapeutics
- Nominations for Working Groups
- Biomarker suggestions
- General Feedback

Portal Overview

Portal to remain open for foreseeable future, with agents being reviewed on a rolling basis in waves

The portal was opened and announced to the public on **September 30th**


NIH National Institute of Allergy and Infectious Diseases

RECOVER-TLC Intervention Information Request Form

Thank you for your interest in submitting a therapeutic for consideration in future RECOVER-TLC trials that will include adults, children, pregnant and lactating women. The following form is tailored to collect information on proposed drugs, devices, or other therapeutic agents targeted at alleviating symptoms associated with Long COVID. We encourage all individuals, whether patients, caregivers, scientists, etc. to fill out this form. We ask that the name, affiliation (patient, caregiver, company, etc.) and email address of the submitter, as well as the name of the proposed intervention, are the minimum criteria filled out. We encourage the submitter to fill out the remainder of the therapeutic questions to the best of their ability, but it is not required. All interventions submitted via this form will be reviewed and scored by a panel of experts. Each submitter will receive email correspondence from a member of the RECOVER-TLC management team once the proposed therapeutic has been reviewed and a determination made.

Data was last pulled on **November 18th** and analyzed for key themes and insights

Metadata Overview

Data Pull Date Range: 9/30/2024 – 11/18/2024

49

Days worth of data submissions

313

Total Submissions

232

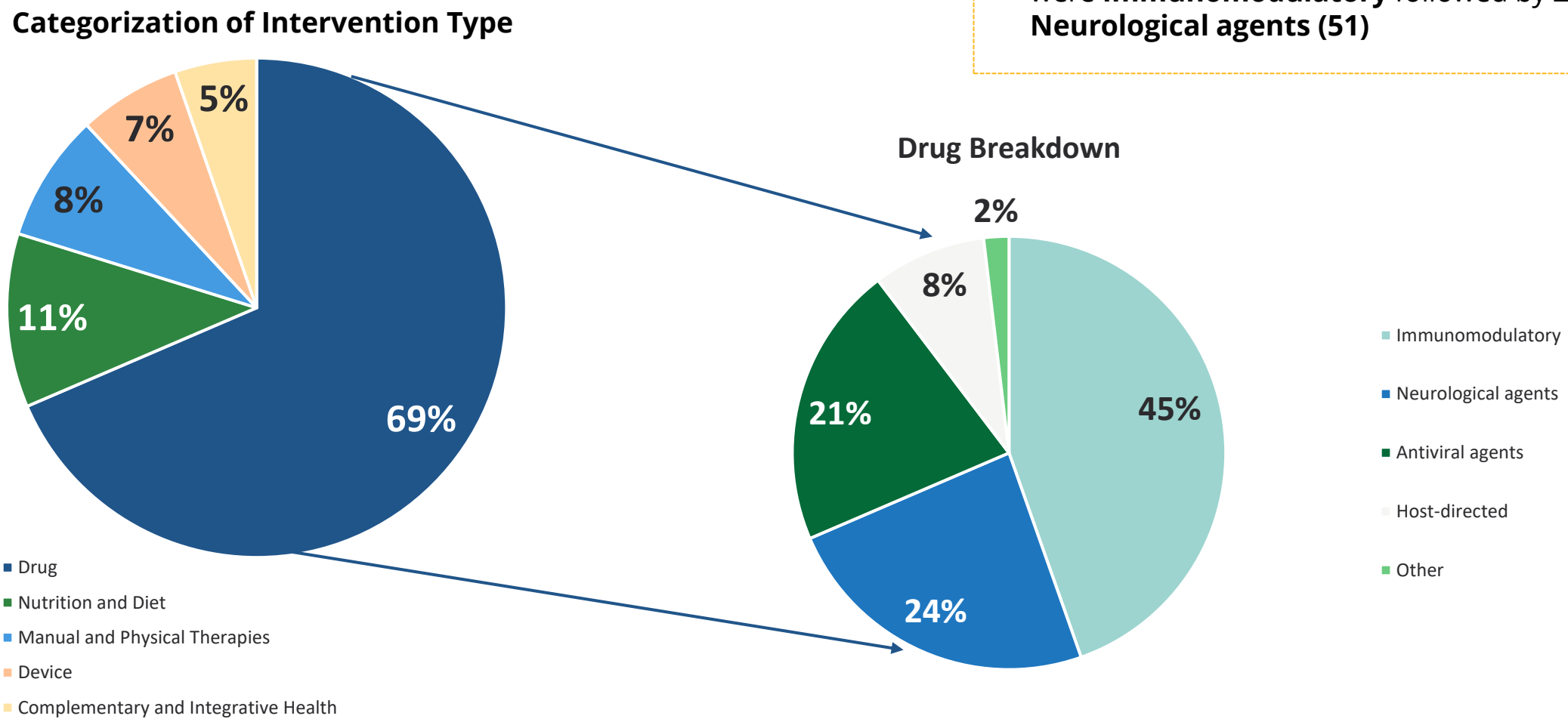
Distinct Respondents

Types of Drugs Submitted

What types of drugs were submitted?

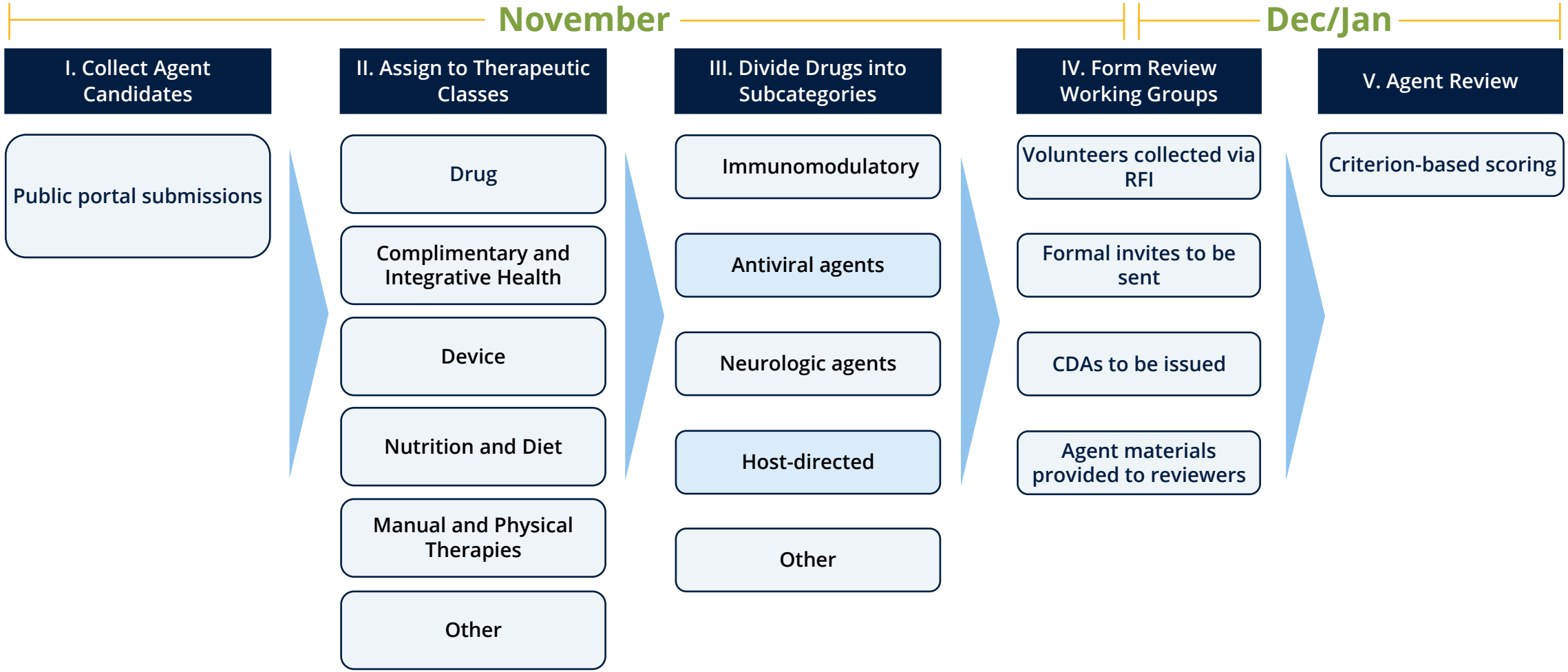
Key Insights

- Of the drug type submissions, **45%** or **95** total agents were **Immunomodulatory** followed by **24% Neurological agents (51)**



Agent Review Timeline: First Wave

Agents submitted to online portal to be reviewed on rolling basis



Scientific and Community Engagement

Ongoing Communication

- ❑ Annual meeting to:
  - Disseminate latest research and clinical findings
  - Review overall progress and state-of-the-science
- ❑ Periodic *blog posts*, *webinars*, and *newsletters* to share recent findings from RECOVER and this new Clinical Trials Program with scientific, clinical, and patient communities

Thank You!