

# RECOVER in Action: Status of Clinical Trial Protocols



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*An Initiative Funded by the National Institutes of Health*

# Understanding Long COVID



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# Potential Causes of Long COVID

- Long COVID is a set of multiple conditions with diverse clinical manifestations that can affect every major organ/tissue system, reflecting varied potential underlying and co-existing causes
- Examples of **hypothesized causes** that *may co-exist in the same patient*:
  - **Persistent virus or antigens**
  - **Reactivation of other viruses**
  - **Uncontrolled immune responses**
  - **Damage to wide range of organs and tissues** (e.g., nerves, heart, lungs, GI tract, brain)
  - **Injury to blood vessels and abnormal blood clotting**

**Diverse set of clinical conditions and varied underlying causes underscore the need for testing a broad portfolio of therapeutic agents**

1 [https://assets.researchsquare.com/files/rs-1139035/v1\\_covered.pdf?c=1640020576](https://assets.researchsquare.com/files/rs-1139035/v1_covered.pdf?c=1640020576)

2 <https://www.nature.com/articles/s41590-021-01113-x>

3 <https://www.nature.com/articles/s41586-021-03631-y.pdf>

4 <https://www.biorxiv.org/content/10.1101/2022.01.07.475453v1>

The collage features three overlapping research paper covers. The top cover is from Research Square, titled 'SARS-CoV-2 infection and persistence throughout the human body and brain'. The middle cover is from Nature Immunology, titled 'Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection'. The bottom cover is from Nature, titled 'Diverse functional autoantibodies in patients with COVID-19'. The collage is annotated with numbers 1, 2, 3, and 4 pointing to specific elements.

# About RECOVER



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# What is RECOVER?

A PATIENT-CENTERED, INTEGRATED,  
ADAPTIVE RESEARCH NETWORK



## SCIENTIFIC AIMS

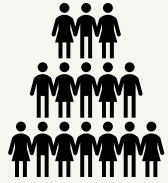
1 Understand the range of recovery and changes in our bodies over time.

2 Define risk factors, number of people getting Long COVID, and if there are specific, different Long COVID types.

3 Study how Long COVID progresses over time and how that may relate to other illnesses.

4 Identify possible treatments to help with Long COVID symptoms.

# RECOVER Progress and Future Directions



Largest diverse, deeply characterized clinical cohort of Long COVID patients



Insights on Long COVID prevalence, risk factors, impact, disparities from EHR



Robust longitudinal characterization of Long COVID patients



42+ studies to characterize pathophysiology of Long COVID



5 platform protocol clinical trials

## Future Directions

Interim analyses

Cross-validating EHR findings with clinical cohort data

Integrating wearable sensor data in adult cohort study

Mechanistic studies, risk stratification, biomarker identification

Anticipated launch of trials evaluating treatments in Summer 2023



# RECOVER Clinical Trials



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# RECOVER Clinical Trial Development and Design: Critical Inputs

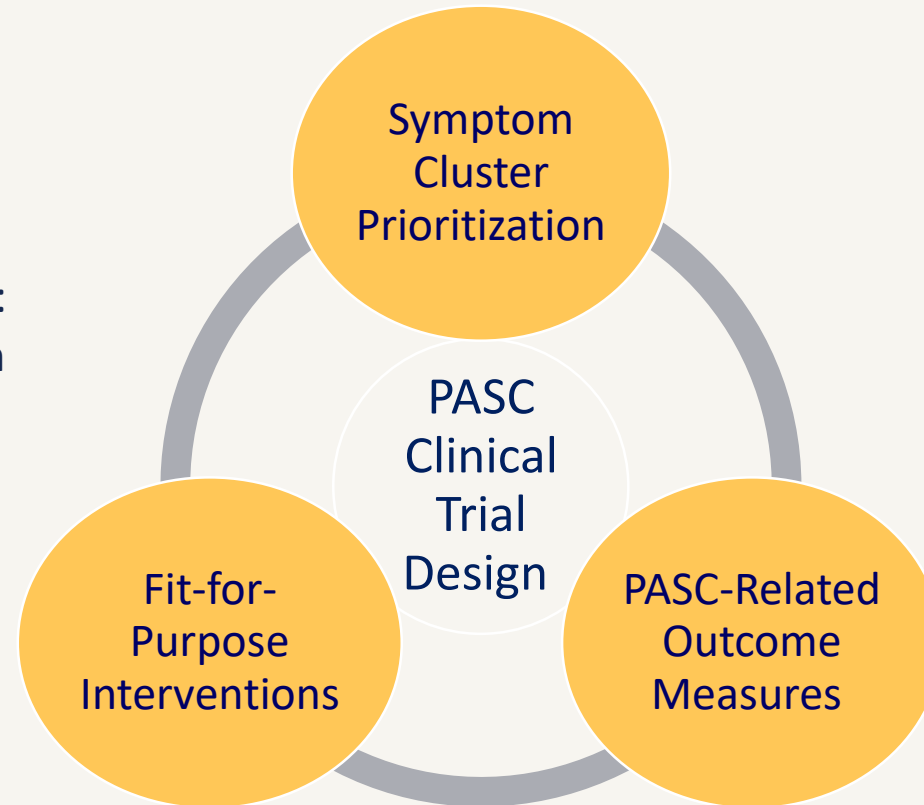
*Patients* • *Clinicians* • *Clinical Researchers*  
*FDA* • *OASH* • *CMS* • *PCORI* • *CDC*

*Input from* | *Partners and Governance*

**RECOVER cohort data** used to identify major symptom clusters

**Patient perspectives** informed:

- Symptom cluster prioritization
- Intervention prioritization
- Other trial concepts



Trial details solicited from broad research community

Industry collaborations underway with Public-Private Partnerships





# Defining Study Goals and Objectives



## Clinical Trials

### Goals

- Identify treatment strategies for Long COVID

### Objectives

- Investigate priority symptom clusters and their causes
- Test known and novel interventions across domains (drugs, devices, rehabilitation, etc.)
- Evaluate treatments to improve Long COVID symptoms



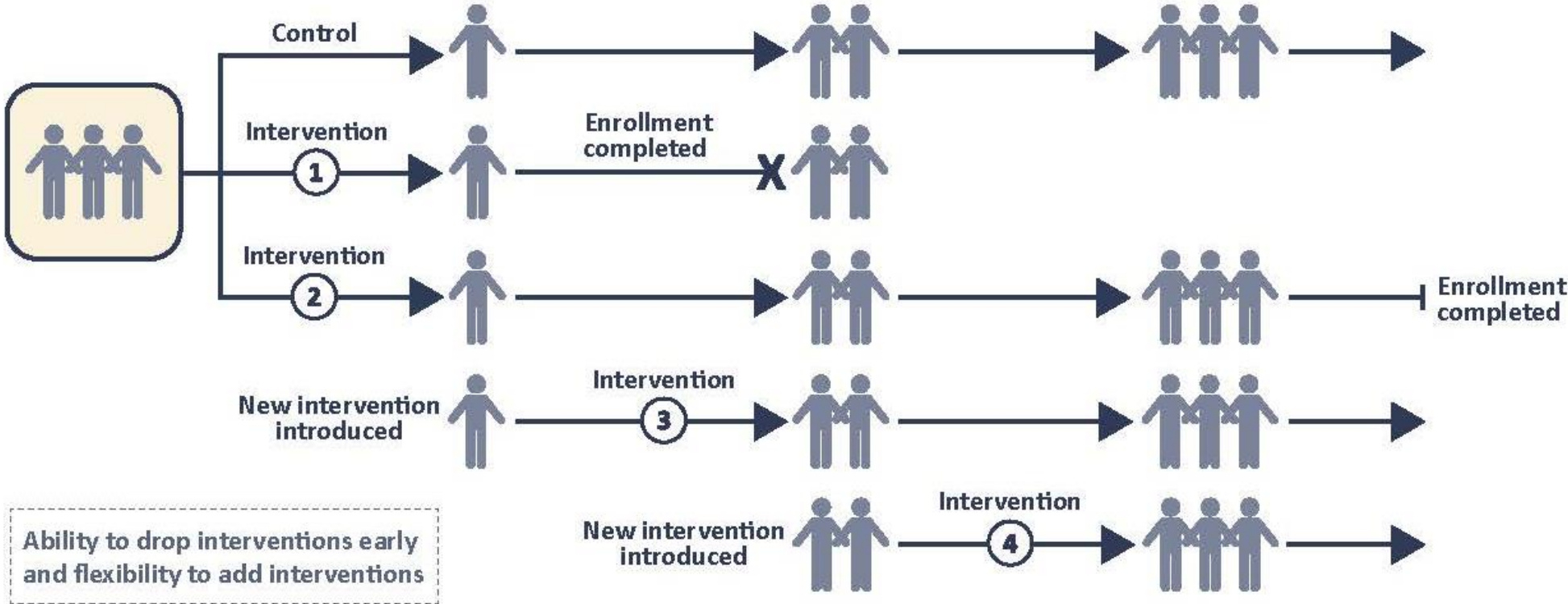
# PASC Platform Protocols for Clinical Trials Span Range of Dominant Symptom Clusters and Proposed Etiologic Pathways

- **Solicited clinical trial concepts and potential interventions** from clinical research community
- **5 platform protocols**
  - Spanning major PASC symptom clusters and proposed etiologic pathways
  - Protocols will be adapted/refined/expanded as needed due to new data, regulatory or other reviews
- **Interventions to treat PASC**

Evaluation and prioritization process includes cross-disciplinary teams of:

  - Research experts and patients drawn from RECOVER Consortium and
  - Other experts from external research community and regulatory groups
- **Successive rounds of interventions** could be tested based on findings and as new targets are identified
- **Interventions include:** drugs, biologics, devices, rehabilitation, CBT, and complementary and integrative medicine approaches

# Platform Clinical Trial Design



# Platform Protocol Clinical Trials Portfolio: *Comprehensive and Integrated Platform*

## **Integrated Infrastructure**

- sIRB
- DSMB
- Trial oversight
- Trial management
- Data analysis
- Large numbers of clinical enrolling sites under master service agreements with CT-DCC
- Long-term follow-up of participants

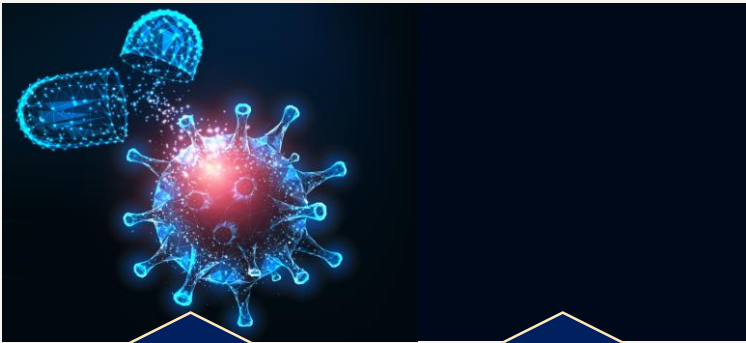
## **Functional Integration**

- Trial designs with some shared endpoints, controls, approach to patient inclusion
- Cross-disciplinary clinical expert protocol working groups
- Usage of common data elements
- Cross-cutting mechanistic studies using patient samples to inform identification of biomarkers, patient stratification, and new interventional targets

**These 5 platform protocols are *integrated* rather than siloed, disparate studies**

- **Achieves efficiencies**
- **Allows us to rapidly assess targeted therapeutics and pivot as needed to new treatment arms**
- **Maximizes knowledge gained from patient participation**
- **Enables cross-trial analysis and accelerated knowledge acquisition**

# RECOVER Clinical Trial Platforms Portfolio



**Viral  
Persistence  
and  
Reactivation**

**Immune  
Dysregulation**



**Neurologic/  
Cognitive  
Dysfunction**



**Autonomic  
Dysfunction**

**Sleep  
Disorders**



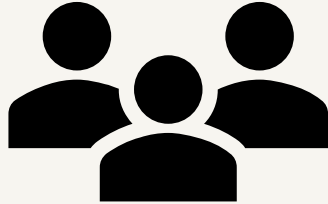
**Cardio-  
pulmonary/  
Exercise  
Intolerance  
and Fatigue**



# Protocol Working Groups

- **Each platform protocol has a Protocol Working Group that includes:**
  - Patient representatives
  - Scientific experts in the symptom area
  - Subject matter experts in interventions
  - Investigators who submitted interventions through the CT ROA process
  - Representatives from the RECOVER observational cohort hubs
- **Protocol Working Groups meet regularly** to develop the platform protocols and appendices

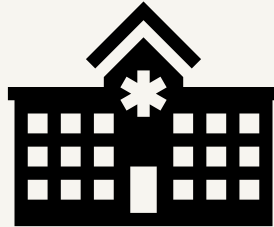
# Overview of Clinical Trials



## Total Participants

5 trials will enroll ~2,600 total participants

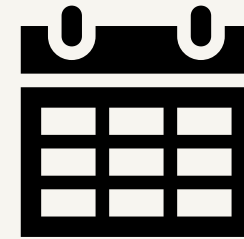
Recruitment will be based at sites for each platform protocol



## Total Sites

Each trial will include ~25-100 sites

Some sites may participate in multiple trials



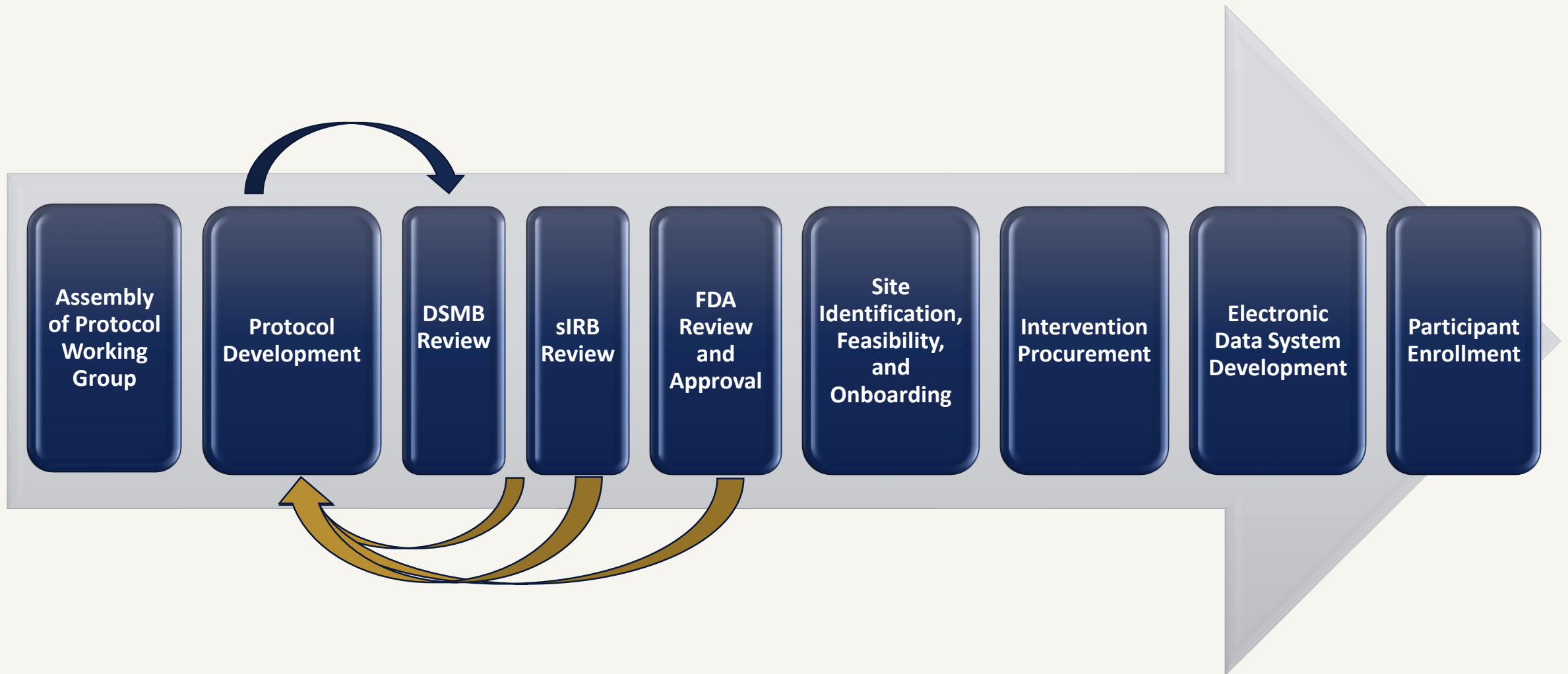
## Enrollment Plans

VITAL will begin in July 2023

Other trials will begin in Fall 2023



# Steps to Trial Enrollment





# RECOVER Clinical Trials





# RECOVER-VITAL

(Viral persistence and reacTivation, And immune dysreguLation)

**Key Question:** Does a study intervention improve outcomes for people with ongoing symptoms from PASC?



## Population

~900 adults with  
3 symptom clusters



## Intervention(s)

Antiviral drug



## Health Measures

- Patient-reported outcomes
- Performance-based outcomes
- Safety and tolerability



## Sites

Up to 100



## Launch

Summer  
2023





# RECOVER-NEURO (Cognitive Dysfunction)

**Key Question:** Does a study intervention improve outcomes for people with cognitive decline from PASC?



## Population

~315 adults with  
cognitive dysfunction  
from PASC



## Intervention(s)

Cognitive training



## Health Measures

- Patient-reported outcomes
- Performance-based outcomes
- Safety and tolerability



## Sites

Up to 45



## Launch

Late Summer  
2023





# RECOVER-SLEEP (Sleep Disturbances)

**Key Question:** Does a study intervention improve patient-reported outcomes for people with sleep disturbances from PASC?



## Population

~474 adults  
with sleep  
disturbances  
from PASC



## Intervention(s)

Pharmacologic and non-  
pharmacologic targeting  
hypersomnia and  
complex PASC-related  
sleep disturbances



## Health Measures

- Patient-reported outcomes
- Sleep outcomes
- Safety and tolerability



## Sites

Up to 100



## Launch

Fall 2023



# RECOVER-ENERGIZE

## (Exercise Intolerance and Fatigue)

**Key Question:** Does a study intervention improve outcomes for people with exercise intolerance symptoms from PASC?



### Population

~360 adults with exercise intolerance from PASC



### Intervention(s)

Cardiopulmonary rehabilitation



### Health Measures

- Patient-reported outcomes
- Performance-based outcomes
- Safety and tolerability



### Sites

Up to 50



### Launch

Fall 2023





# RECOVER-AUTONOMIC (Autonomic Dysfunction)

**Key Question:** Does a study intervention improve patient-reported outcomes for people with autonomic or immune-mediated symptoms from PASC?



## Population

~360 adults who experience autonomic dysfunction symptoms from PASC



## Intervention(s)

Pharmacologic, including immunotherapies, and non-pharmacologic



## Health Measures

- Patient-reported outcomes
- Performance-based outcomes on orthostatic intolerance
- Safety and tolerability



## Sites

Up to 75



## Launch

Winter 2023

# Next Steps



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# Updates will be posted to RECOVERCovid.org



## RECOVER: Researching COVID to Enhance Recovery

We're building a nationwide study population to support research on the long-term effects of COVID-19. Join the search for answers.

[LEARN MORE](#) →



Interested in volunteering for RECOVER studies? [Sign up](#) and be notified when studies open for enrollment.



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## What is PASC?


SARS-CoV-2 is a virus that can infect the body and is referred to as a SARS-CoV-2 infection. Recovery from SARS-CoV-2 infection can vary from person to person:

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## Taking a united approach toward recovery



### RECOVER Research Questions:

- What does recovery from SARS-CoV-2 look like for different groups?
- How many people continue to have symptoms?
- How many people develop new symptoms?
- What causes these health effects?

### Stay tuned and sign up for email updates.



To ensure this research is informed by patients, RECOVER will engage regularly with people who have experienced SARS-CoV-2 infection.

What types of updates would you like to receive?

- [Information about volunteering for RECOVER studies](#)
- [RECOVER updates and the latest research findings](#)
- [Announcements on related research funding, training, and technical assistance opportunities](#)

Together we can learn more. The more voices

recoverCOVID.org



# Questions





# RECOVER

Researching COVID to Enhance Recovery

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