Long COVID Clinical Trials: Challenges and Opportunities

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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Zimmerman received grant funding from the Biogen Foundation to support a summer research training. (Updated June 5, 2023)

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Learning Objectives

After attending this presentation, learners will be able to:

- Explain the challenges associated with designing long COVID clinical trials
- Describe the breadth of the National Institutes of Health (NIH) effort to address long COVID through clinical trials

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Fundamental Components for Clinical Trials

- Important and well-defined clinical problem
  - Enough people affected
  - High burden (morbidity/mortality)
  - Adequate understanding of pathophysiology
- Identified intervention directed at pathophysiology
  - Supported by preliminary data
  - Widely available/accessible if proven successful
- Clinically meaningful and well-defined endpoint
  - Testable hypothesis
- Well-defined target population

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Long-COVID: Important and Well-Defined Clinical Problem

✓Affects millions of people worldwide
✓Devastating consequences
- Underlying pathophysiology remains poorly understood
- >200 waxing and waning symptoms described by patients after COVID-19
  - Is cognitive dysfunction in Long COVID the same as in other diseases? Which ones?
  - What defines and causes exercise intolerance? Is all EI in Long COVID the same?

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Identified intervention directed at known pathophysiology

✓Prior post-viral syndromes
- Limited efficacy of prior interventions

- Pathophysiology remains poorly understood

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Clinically meaningful and well-defined endpoint

- What type of measure?
  - Performance based measure
  - Patient reported outcome
  - Biomarker or other objective test
- Which measure?
  - Global impression of change
  - Symptom specific (which ones)
  - Does a known symptom measure have the same performance in those with Long COVID and similar symptoms (e.g., cognitive dysfunction)

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About RECOVER

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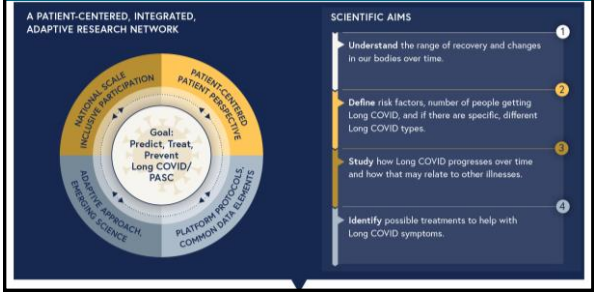
What is RECOVER?



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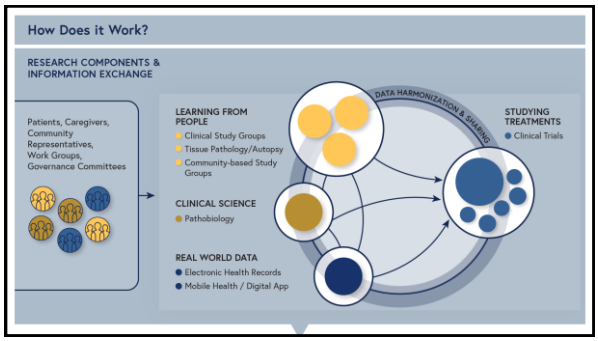
How Does it Work?
RESEARCH COMPONENTS & INFORMATION EXCHANGE
Patients, Caregivers, Community Representatives, Work Groups, Governance Committees
LEARNING FROM PEOPLE
Clinical Study Groups
Tissue Pathology/Autopsy
Community-based Study Groups
CLINICAL SCIENCE
Pathobiology
REAL WORLD DATA
Electronic Health Records
Mobile Health / Digital App
DATA HARMONIZATION & SHARING
STUDYING TREATMENTS
Clinical Trials

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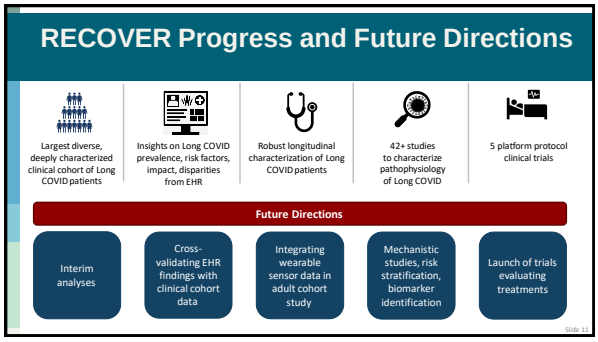
RECOVER Progress and Future Directions
Largest diverse, deeply characterized clinical cohort of Long COVID patients
Insights on Long COVID prevalence, risk factors, impact, disparities from EHR
Robust longitudinal characterization of Long COVID patients
42+ studies to characterize pathophysiology of 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
Launch of trials evaluating treatments

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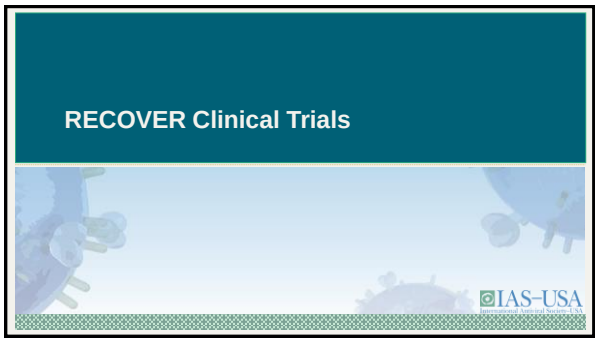
RECOVER Clinical Trials
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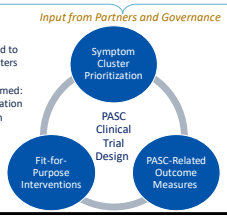
RECOVER Clinical Trial Development and Design: Critical Inputs

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

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Patient and community engagement

- **PASC Intervention Prioritization Committee (PIPP) Core Committee**
  - Patients sit on the committee and voice considerations such as the burden of administration, cost, insurance coverage (or lack thereof) and adverse effect profiles to deliberations on prioritizing PASC interventions.
  - Representatives also suggest therapies/interventions that they have seen work for themselves and many within the Long COVID community.
- **Clinical Trial Focus Areas and Proposal Review**
  - Patient representatives completed study questionnaires, surveys, and had discussions with the RECOVER team to help guide the clinical trials.
  - Patient representatives helped review proposals that were submitted in response to the NIH RECOVER Initiative Research Opportunity Announcement (ROA).
- **Protocol Development**
  - Patient representatives are integrated into the protocol working groups for each of the clinical trials.

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Impact of patient experience on Clinical Trial Development

- Align **unmet needs** of patients and communities with research goals
- Develop endpoints/outcomes most **meaningful to patients**
- Create **least burdensome** procedures, schedules, data collection methods...
- Eliminate/**decrease barriers** to recruitment and participation (increase access, acceptability, ability to participate if chosen)
- Increase understanding around **cultural beliefs and values**
- Create an **inclusive and supportive** research participant experience.
- Develop strategies for engagement and **distribution of findings** in patient and community environments.

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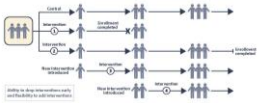
PASC Platform Protocols for Clinical Trials Span Range of Dominant Symptom Clusters and Proposed Etiologic Pathways

- **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



- **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

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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**

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RECOVER Clinical Trial Platforms Portfolio

Viral Persistence and Reactivation

Immune Dysregulation

Neurologic/ Cognitive Dysfunction

Autonomic Dysfunction

Sleep Disorders

Cardio-pulmonary/ Exercise Intolerance and Fatigue

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Definitions of the Clinical Trial Focus Areas

- **Viral persistence:** When the virus that causes COVID-19 stays in the body and causes the immune system to overreact.
- **Autonomic dysfunction:** Dizziness, fast heart rate, shortness of breath, problems digesting food, or other symptoms related to the autonomic nervous system.
- **Sleep disturbances:** Changes to sleep patterns or ability to sleep.
- **Cognitive dysfunction:** Trouble thinking clearly or brain fog.
- **Exercise intolerance and fatigue:** Changes in a person's activity and/or energy level that interferes with daily activities.

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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

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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
Beginning in coming months

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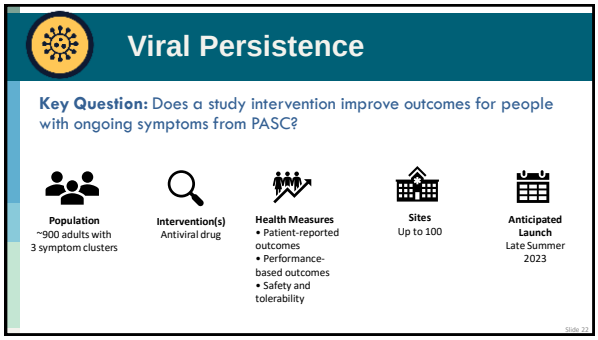
Viral Persistence
Key Question: Does a study intervention improve outcomes for people with ongoing symptoms from PASC?
Population
~900 adults with 3 symptom clusters
Intervention(s)
Antiviral drug
Health Measures
• Patient-reported outcomes
• Performance-based outcomes
• Safety and tolerability
Sites
Up to 100
Anticipated Launch
Late Summer 2023
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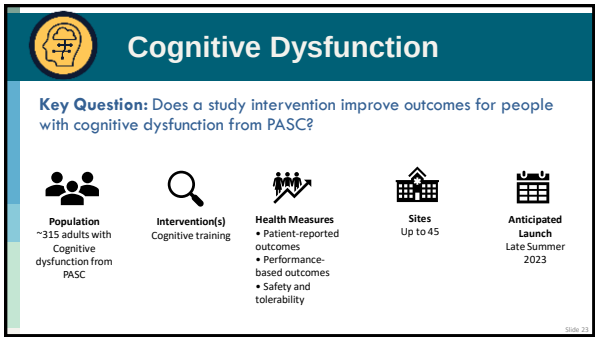
Cognitive Dysfunction
Key Question: Does a study intervention improve outcomes for people with cognitive dysfunction from PASC?
Population
~315 adults with Cognitive dysfunction from PASC
Intervention(s)
Cognitive training
Health Measures
• Patient-reported outcomes
• Performance-based outcomes
• Safety and tolerability
Sites
Up to 45
Anticipated Launch
Late Summer 2023
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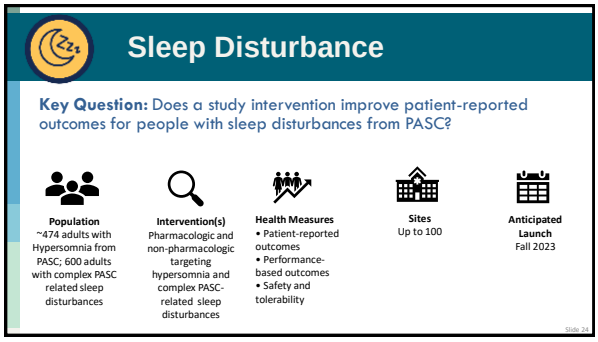
Sleep Disturbance
Key Question: Does a study intervention improve patient-reported outcomes for people with sleep disturbances from PASC?
Population
~474 adults with Hypersomnia from PASC; 600 adults with complex PASC related sleep disturbances
Intervention(s)
Pharmacologic and non-pharmacologic targeting hypersomnia and complex PASC-related sleep disturbances
Health Measures
• Patient-reported outcomes
• Performance-based outcomes
• Safety and tolerability
Sites
Up to 100
Anticipated Launch
Fall 2023
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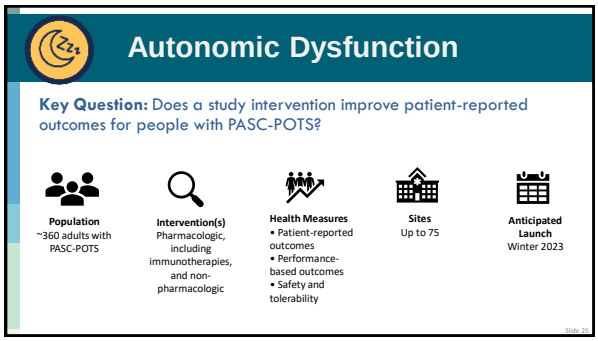
Autonomic Dysfunction
Key Question: Does a study intervention improve patient-reported outcomes for people with PASC-POTS?
Population
~360 adults with PASC-POTS
Intervention(s)
Pharmacologic, including immunotherapies, and non-pharmacologic
Health Measures
• Patient-reported outcomes
• Performance-based outcomes
• Safety and tolerability
Sites
Up to 75
Anticipated Launch
Winter 2023
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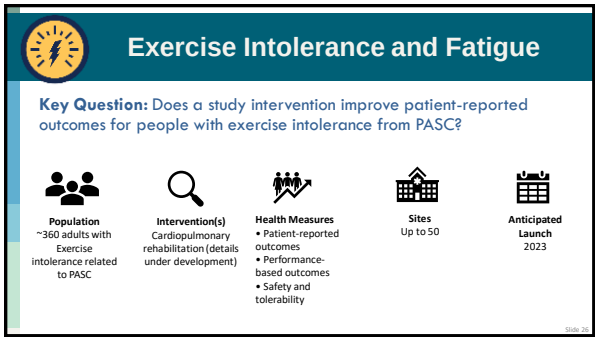
Exercise Intolerance and Fatigue
Key Question: Does a study intervention improve patient-reported outcomes for people with exercise intolerance from PASC?
Population
~360 adults with Exercise intolerance related to PASC
Intervention(s)
Cardiopulmonary rehabilitation (details under development)
Health Measures
• Patient-reported outcomes
• Performance-based outcomes
• Safety and tolerability
Sites
Up to 50
Anticipated Launch
2023
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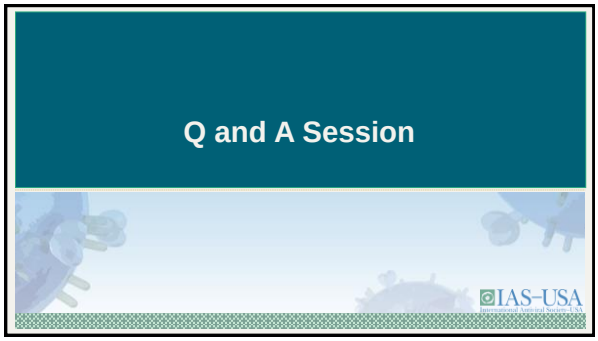
Q and A Session
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