Advancing Toward Recovery from Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

NIH RECOVER Initiative: Briefing for the Advisory Council to the Director (ACD)
December 9, 2021

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Understanding the Full Spectrum of PASC: A Multi-System Disorder

PASC: Refining a Case Definition

- Descriptions include: “persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms.”¹

- Potential overlap with other disorders and conditions (e.g., ME/CFS; Post-ICU).

¹Nalbandian et al. (2021)
PASC Recovery Trajectories: Incidence, Risk Factors and Sub-Phenotypes

PASC affects all ages and shows variable symptom persistence over time.

Likelihood of persistent symptoms for at least 5 weeks from presumed date of infection

![Bar chart depicting symptom likelihood for different age groups.]

- **Age Group**: 2 to 11 years, 12 to 16 years, 17 to 24 years, 25 to 34 years, 35 to 49 years, 50 to 69 years, 70 years and over.
- **Symptom probability**
- **Participants who tested positive**

![Graph showing pulmonary and respiratory symptoms over time.]

Pulmonary and Respiratory Symptoms

- Breathing difficulties (normal O2)
- Cough w mucus
- Coughing up blood
- Dry Cough
- Other respiratory, sinus issues
- Rattling of breath
- Shortness of breath
- Sneezing

![Graph showing neuropsychiatric and sensorimotor symptoms over time.]

Neuropsychiatric and Sensorimotor Symptoms

- Select sensorimotor symptoms
- Change of smell and taste
- Dizziness and balance issues
- Tremors
- Vibrating sensations
- Neuralgia

1. United Kingdom Office for National Statistics. (2021)
2. Davis et al. (2021)
Setting the Strategic Direction for RECOVER

**Goal**
Rapidly improve our understanding of and ability to predict, treat, and prevent PASC

**Key Scientific Aims**
1. Understand clinical spectrum/biology underlying recovery over time
2. Define risk factors, incidence/prevalence, and distinct sub-phenotypes of PASC
3. Study pathogenesis over time and possible relation to other organ dysfunction/disorders
4. Identify interventions to treat and prevent PASC

**Guiding Principles**
- Patient-centered, participants as partners
- Inclusive, diverse participation & community engagement
- Multi-disciplinary, trans-NIH collaborative teams and network
- Adaptive approaches based on emerging science
RECOVER’s Collaborative Approach

The RECOVER Initiative reflects diverse perspectives and multi-disciplinary experience in a national consortium to advance understanding, treatment, and prevention of PASC.

Collaborating Across RECOVER to Advance Key Scientific Aims

RECOVER Collaboration Essential For:

- Alignment with strategic direction
- Expertise across diverse domains
- Research protocol development
- Community engagement
- Continuous scientific prioritization
- Knowledge exchange
Working Together Across the Consortium

Unique perspectives and experiences from patients, researchers, and others will be included at every level of the Initiative.

NIH Institute Leadership

RECOVER Executive Committee

RECOVER Steering Committee

Research Working Groups
(e.g., study design, population science, community engagement)

Local Site Engagement Across the U.S.
(e.g., Community Advisory Boards)

RECOVER Research Consortium

Local Involvement

recoverCOVID.org
RECOVER’s Patient-Centered Approach

Patient perspectives are a critical element of the RECOVER Initiative and patient collaboration adds value to every element of the program.

Examples of Patient Involvement

- Representation Across Governance Structure
- 30+ Patients Participated in Common Protocol Design
- Participant Portal
- Social Media Outreach
- 400+ Attendees of Discussion on Patient Experience
- Mobile Health Platform for Patient-Reported Outcomes
- 200+ Direct Email Inquiries
- 4000+ Website Subscribers
RECOVER Components: A Comprehensive and Complementary Approach

**RECOVER Core Elements**

- Clinical Science Core
- Data Resource Core
- Biorepository Core

**Meta-Cohort Elements**

- RECOVER Enrolling Cohorts
- EHR/Health Systems Studies
- Autopsy-based Studies

**Data Resource Elements**

- Clinical
- Imaging
- Mobile and Digital Health
- EHR / Other Real-World Data
- Pathology

recoverCOVID.org
Achieving Depth and Breadth in RECOVER Enrolling Cohorts

Acute and post-acute cohort studies will **characterize the long-term effects of infection** and trajectory of recovery over time.

<table>
<thead>
<tr>
<th>ACUTE INFECTION COHORT</th>
<th>POST-ACUTE INFECTION COHORT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overview</strong></td>
<td></td>
</tr>
<tr>
<td>• Patients with confirmed acute SARS-CoV-2 infections</td>
<td>• PASC patients 4+ weeks after confirmed acute SARS-CoV-2 infection</td>
</tr>
<tr>
<td>• Prospective, nested PASC cases vs. controls</td>
<td>• Matched PASC case-control design</td>
</tr>
<tr>
<td></td>
<td>• Retrospective data capture</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
</tr>
<tr>
<td>9k, including 200+ pregnant persons</td>
<td>9k, including 2k pregnant persons</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td></td>
</tr>
<tr>
<td>1k</td>
<td>18k, including 800 with MIS-C</td>
</tr>
</tbody>
</table>

*Enrolling ~40,000 participants from 200+ sites across all 50 states*
# Building Diverse Adult and Pediatric Cohorts

Enriching enrollment of disproportionately affected communities by leveraging community engagement, multi-disciplinary partnerships across the NIH, and collaboration with patient groups.

<table>
<thead>
<tr>
<th></th>
<th>% U.S. Population</th>
<th>% U.S. COVID Cases</th>
<th>% Target Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entire¹</td>
<td>Pediatric²</td>
<td>Entire³</td>
</tr>
<tr>
<td>Hispanic / Latinx</td>
<td>18.5</td>
<td>26</td>
<td>27.3</td>
</tr>
<tr>
<td>Black</td>
<td>13.4</td>
<td>14</td>
<td>16.4</td>
</tr>
<tr>
<td>Asian</td>
<td>5.9</td>
<td>5</td>
<td>2.4</td>
</tr>
<tr>
<td>Native Hawaiian &amp; Pacific Islander</td>
<td>0.2</td>
<td>&lt;0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>American Indian / Alaska Native</td>
<td>1.3</td>
<td>1</td>
<td>1.4</td>
</tr>
</tbody>
</table>

¹United States Census Bureau (2019)  
²National Kids Count (2020)  
³Hollis et al. (2021)  
⁴Leidman et al. (2021)
Meta-Cohort Clinical Characterization: Tiered Assessment Strategy

Assessments tailored to stage of life will capture a broad spectrum of PASC recovery phenotypes with in-depth characterization using Common Protocols and Common Data Elements.

### Example Adult Tests from Common Protocol

<table>
<thead>
<tr>
<th>Tier</th>
<th>Title</th>
<th>Participants</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tier 1: Screening Tests</td>
<td>40k participants</td>
<td>Screening questionnaires, clinical assessments, labs (e.g., psychosocial factors, SDoH, basic clinical labs)</td>
</tr>
<tr>
<td>2</td>
<td>Tier 2: Clinical/Functional Tests</td>
<td>10k participants</td>
<td>Basic exams, labs, imaging, functional assessments (e.g., complete neurologic exam, pulmonary function tests, echocardiography)</td>
</tr>
<tr>
<td>3</td>
<td>Tier 3: Advanced Testing</td>
<td>5k participants</td>
<td>In-depth phenotyping exams, labs, imaging, functional assessments (e.g., complete ENT examination, Cardiac MRI, Chest CT)</td>
</tr>
</tbody>
</table>
Mobile Health Platform Facilitates Patient-Centered Approach

Platform will **collect and aggregate digital health data** to augment analysis of clinical data, which will drive better understanding of **PASC symptoms.**

**Platform Attributes**

- Outreach, engagement, and eConsent
- Timely assessment of symptoms, trajectory, and recovery
- Data from multiple sensor and device types
- Platform for self-management interventions
- Linkage to Telehealth in rural populations

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**Mobile Health Platform**

- Device-agnostic capture of person-centered data (e.g., electronic patient reported outcomes)

**Cohort Data Portal**

- Centralized data access for participants and researchers

**Data Resource Core Repositories**

- Integration of all RECOVER digital health data
EHR-based Data Assets Facilitate Research at Large Scale

Research that leverages EHR data will enable an ongoing complementary and bidirectional scientific interaction with enrolling cohorts to capture real-world facets of PASC.

Asset Attributes

- Incidence, prevalence, and risk factors over time
- Sampling of diverse populations to augment catchment of studies
- Longitudinal data capture with minimal participant burden
- Distinct sub-phenotypes of PASC to inform clinical approaches

Leverage Large Datasets

- Patient-Centered Research (PCORnet) – 32M+ records
- National COVID Cohort Collaborative (N3C) – 8M+ records

Data Resource Core Repositories

- Harmonize and synergize analyses across data assets

Rapid Data Analysis

- Cross-validation to enhance rigor and reproducibility
- In-depth analysis of unique clinical findings
NIH Cloud Platforms Aggregate and Harmonize RECOVER Data

Broad capture, harmonization, and continuous analysis of data will drive discovery and power research insights that address scientific aims.

**DATA HARMONIZATION**
- Mobile & Digital
- EHR
- Clinical
- Imaging

**CONTINUOUS DATA ANALYSIS**
- NIH Cloud Platforms
- Analytical Tools
- Data Ecosystem
- Workflows
- Secure Access
- AI

**INTEROPERABLE DATA FOR COLLABORATIVE STUDIES**
- Interoperable, shareable data for collaborative studies

**RESEARCH INSIGHTS**
- Novel Diagnostics
- Clinical Trials
- Pathogenic Mechanisms & Biomarkers
- Novel Diagnostics
- Clinical Trials
- Pathogenic Mechanisms & Biomarkers

**PASC Patients**

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To date, the NIH has obligated over $500M to support the RECOVER Initiative.
### Looking Ahead to RECOVER’s Next Phases

<table>
<thead>
<tr>
<th>Pathobiology and Pre-Clinical Research</th>
<th>Ancillary Studies</th>
<th>Clinical Trials</th>
</tr>
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<tbody>
<tr>
<td>• Elucidate pathogenic mechanisms, pathways, and targets</td>
<td>• Conduct deeper phenotyping and clinical characterization beyond core elements</td>
<td>• Execute interventional clinical trials (pharmacologic and non-pharmacologic)</td>
</tr>
<tr>
<td>• Develop animal models of PASC</td>
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**Continued Stakeholder and Community Engagement**