Title: NIH RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults

Short Title: Understanding the Long-term Impact of COVID-19 in Adults

Study ID: S21-01226

Sponsor: National Heart Lung and Blood Institute of the National Institutes of Health

Protocol Version: Version 3.0
### Revision history

<table>
<thead>
<tr>
<th>Revision #</th>
<th>Date</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>9/16/2021</td>
<td>Original release</td>
</tr>
<tr>
<td>1.1</td>
<td>10/08/2021</td>
<td>Revision to inclusion/exclusion criteria; revisions to appendices 2 and 3</td>
</tr>
<tr>
<td>2.0</td>
<td>10/18/2021</td>
<td>Revisions to appendices 2, 3 and 4</td>
</tr>
</tbody>
</table>
| 3.0        | 12/01/2021 | Footer: Added protocol version date.  
List of abbreviations: Added additional abbreviations.  
Section 4.1: Deleted risk for ventilation/perfusion scan since that procedure was previously removed.  
Section 7.1: Clarified inclusion criteria to include patients who will have positive SARS-Cov-2 infection-specific antibody testing  
Section 7.2: Added incarceration as an exclusion criterion.  
Section 7.3: Added language regarding enrollment in the pediatric protocol  
Section 9.7: Added text about the data management plans from the Data Resource Core, including two new figures  
Section 13.3.2: Revised to indicate the study will be posted on clinicaltrials.gov  
Section 13.6: Added an opt-in for future genetic testing  
Section 15.3: Clarified that participant compensation is site-specific  
Appendix 1:  
- Schedule of Assessments revised to provide more detail;  
- Clarified assessment schedule for subjects > 48 months post-infection.  
Appendix 3:  
- Removed procalcitonin from Tier 2 and moved EKG from Tier 1 to Tier 2  
- Added the NIH Toolbox picture sequence age 7+ v2.1+ as a Tier 3 procedure (inadvertently removed in previous version);  
- Deleted ENT as a Tier 3 procedure, since it’s in Tier 2.  
Appendix 4: Added one laboratory study – Anti-Mullerian hormone. |
Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

___________________________________________  ____________________
Signature of Site Principal Investigator    Date
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event/Adverse Experience</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 2019</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>DRC</td>
<td>Data Resource Core</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
</tr>
<tr>
<td>EDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EHD</td>
<td>Electronic Health Database</td>
</tr>
<tr>
<td>EHR</td>
<td>Electronic Health Record</td>
</tr>
<tr>
<td>ETL</td>
<td>Extract, Transform, Load</td>
</tr>
<tr>
<td>FISMA</td>
<td>Federal Information Security Modernization Act of 2002</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act of 1996</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
</tr>
<tr>
<td>I2b2 Data Hub</td>
<td>Implementing Informatics from Bench to Bedside – Data Hub for all PASC datatypes harmonized into a common data model</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>MOP</td>
<td>Manual of Operations and Procedures</td>
</tr>
<tr>
<td>N</td>
<td>Number (typically refers to subjects)</td>
</tr>
<tr>
<td>NHLBI</td>
<td>National Heart, Lung and Blood Institute</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>OHRP</td>
<td>Office for Human Research Protections</td>
</tr>
<tr>
<td>OHSR</td>
<td>Office of Human Subjects Research</td>
</tr>
<tr>
<td>OSMB</td>
<td>Observational Study Monitoring Board</td>
</tr>
<tr>
<td>PASC</td>
<td>Post-Acute Sequelae of COVID-19</td>
</tr>
<tr>
<td>PBC</td>
<td>PASC Biorepository Core</td>
</tr>
<tr>
<td>PHI</td>
<td>Personal Health Information</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PII</td>
<td>Personal Identifiable Information</td>
</tr>
<tr>
<td>REDCap</td>
<td>Research Electronic Data Capture</td>
</tr>
<tr>
<td>REDCap Central</td>
<td>Research Electronic Data Capture Central dataset</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>UUID</td>
<td>Universally Unique Identifiers</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Table of Contents

1  PROTOCOL SUMMARY .........................................................................................................................9
2  KEY ROLES ........................................................................................................................................11
3  INTRODUCTION, BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE .........................12
   3.1  BACKGROUND INFORMATION AND RELEVANT LITERATURE ....................................................12
   3.2  RATIONALE AND STUDY SIGNIFICANCE ....................................................................................12
4  POTENTIAL RISKS AND BENEFITS ..............................................................................................12
   4.1  KNOWN POTENTIAL RISKS ........................................................................................................12
   4.2  KNOWN POTENTIAL BENEFITS ..................................................................................................15
5  OBJECTIVES AND PURPOSE .........................................................................................................15
6  STUDY DESIGN ..................................................................................................................................16
   6.1  STUDY DESIGN ..............................................................................................................................16
   6.2  CHARACTERISTICS OF THE STUDY POPULATION ....................................................................17
   6.3  RECRUITMENT AND RETENTION ...............................................................................................17
   6.3.1  Recruitment Strategy and Procedures ......................................................................................17
   6.3.2  Retention Strategy ....................................................................................................................18
7  STUDY ENROLLMENT AND WITHDRAWAL ....................................................................................19
   7.1  INCLUSION CRITERIA ....................................................................................................................19
   7.1.1  Change in Eligibility Status ....................................................................................................20
   7.2  EXCLUSION CRITERIA ..................................................................................................................20
   7.3  VULNERABLE POPULATIONS ......................................................................................................20
   7.4  SUBJECT WITHDRAWAL .............................................................................................................21
   7.5  PREMATURE TERMINATION OR SUSPENSION OF STUDY ..........................................................21
8  STUDY SCHEDULE ..........................................................................................................................21
   8.1  OVERVIEW OF STUDY SCHEDULE ............................................................................................21
   8.2  BASELINE/ENROLLMENT VISIT ..................................................................................................22
   8.3  FOLLOW-UP VISITS ......................................................................................................................22
9  STUDY PROCEDURES/EVALUATIONS ............................................................................................22
   9.1  TIER 1 ASSESSMENTS ..................................................................................................................22
   9.2  TIER 2 ASSESSMENTS ..................................................................................................................22
   9.3  TIER 3 ASSESSMENTS ..................................................................................................................22
   9.4  BIOSPECIMEN BANKING ............................................................................................................22
   9.5  DATA SOURCES ............................................................................................................................23
   9.6  DATA COLLECTION ......................................................................................................................23
   9.7  DATA MANAGEMENT ....................................................................................................................24
   9.7.1  Data Transfer from Enrolling Sites to DRC .............................................................................24
   9.7.2  Data Transfer from PASC Biorepository Core (PBC) to and from DRC ...................................25
   9.7.3  Data Transfer Within DRC .....................................................................................................25
   9.7.4  Harvard Medical School (HMS) AWS Cloud Environment .....................................................26
1 Protocol Summary

<table>
<thead>
<tr>
<th>Title</th>
<th>NIH RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Title</td>
<td>Understanding the Long-term Impact of COVID-19 in adults</td>
</tr>
</tbody>
</table>

**Brief Summary**

This is a combined retrospective and prospective, longitudinal, observational meta-cohort of individuals who will enter the cohort with and without SARS-CoV-2 infection and at varying stages before and after infection. Individuals with and without SARS-CoV-2 infection and with or without PASC symptoms will be followed to identify risk factors and occurrence of PASC. This study will be conducted in the United States and subjects will be recruited through inpatient, outpatient, and community-based settings. Study data including age, demographics, social determinants of health, medical history, vaccination history, details of acute SARS-CoV-2 infection, overall health and physical function, and PASC symptom screen will be reported by subjects or collected from the electronic health record using a case report form at specified intervals. Biologic specimens will be collected at specified intervals, with some tests performed in local clinical laboratories and others performed by centralized research centers or banked in the Biospecimen Repository. Advanced clinical examinations and radiologic examinations will be performed at local study sites with cross-site standardization.

**Objectives**

- Characterize the incidence and prevalence of sequelae of SARS-CoV-2 infection.
- Characterize the spectrum of clinical symptoms, subclinical organ dysfunction, natural history, and distinct phenotypes identified as sequelae of SARS-CoV-2 infection.
- Define the biological mechanisms underlying pathogenesis of the sequelae of SARS-CoV-2 infection.

**Methodology**

Ambidirectional longitudinal meta-cohort study (combined retrospective and prospective) with nested case-control studies.

**Endpoint**

Primary Endpoints: Presence of candidate PASC symptoms over time (incidence and prevalence).

Secondary Endpoints: Biological and recovery trajectories from SARS-CoV-2 infection; organ injury; incident clinical disease.

**Study Duration**

Four years

**Subject Duration**

Up to four years
**Population**

Infected: Individuals at least 18 years of age meet WHO criteria for suspected, probable or confirmed SARS-CoV-2 infection on or after March 1, 2020.

Uninfected: Individuals at least 18 years of age who have never met any of the WHO criteria for suspected, probable or confirmed SARS-CoV-2 infection.

**Number of subjects**

15,000 total subjects with SARS-CoV-2 infection and 2,680 total subjects without SARS-CoV-2 infection.

**Statistical Analysis**

A flexible study design is proposed to allow modifications to PASC case definition, tiered phenotyping assessments, comparator groups, and/or statistical plan after its initiation to optimize public health impact without undermining validity and integrity of study findings. Modifications in study design may be based on analyses of structured cohort data, unstructured cohort EHR data, and other cohort EHR data.
2 Key Roles

Principal Investigators

Stuart Katz, MD MS
Helen L. and Martin S. Kimmel Professor of
Advanced Cardiac Therapeutics
Director Heart Failure Programs
NYU Grossman School of Medicine
Leon H. Charney Division of Cardiology
530 First Avenue, Skirball 9R
New York, NY 10016
212-263-3946

Andrea B. Troxel, ScD
Professor and Director, Division of Biostatistics
Department of Population Health
NYU Grossman School of Medicine
180 Madison Avenue, Suite 5-55
New York, NY 10016
Tel (646) 501-3654

Leora Horwitz, MD
Associate Professor, Department of Population
Health at NYU Grossman School of Medicine
Associate Professor, Department of Medicine at
NYU Grossman School of Medicine
Director, Center for Healthcare Innovation and
Delivery Science
Director, Division of Healthcare Delivery Science
550 1st Avenue, Suite 1803
New York, NY 10016

Clinical Science Core

Stuart Katz, MD MS
Helen L. and Martin S. Kimmel Professor of
Advanced Cardiac Therapeutics
Director Heart Failure Programs
NYU Grossman School of Medicine
Leon H. Charney Division of Cardiology
530 First Avenue, Skirball 9R
New York, NY 10016
212-263-3946

Andrea B. Troxel, ScD
Professor and Director, Division of Biostatistics
Department of Population Health
NYU Grossman School of Medicine
180 Madison Avenue, Suite 5-55
New York, NY 10016
Tel (646) 501-3654

Leora Horwitz, MD
Associate Professor, Department of Population
Health at NYU Grossman School of Medicine
Associate Professor, Department of Medicine at
NYU Grossman School of Medicine
Director, Center for Healthcare Innovation and
Delivery Science
Director, Division of Healthcare Delivery Science
550 1st Avenue, Suite 1803
New York, NY 10016

Contact Principal Investigator

Andrea S Foulkes, ScD
Director, Biostatistics, Massachusetts General
Hospital
Professor of Medicine, Harvard Medical School
Professor, Department of Biostatistics, Harvard
TH Chan School of Public Health
50 Staniford Street, Suite 560 | Boston, MA
02114 | +1 (617) 724-8208
3 Introduction, Background Information and Scientific Rationale

3.1 Background Information and Relevant Literature

COVID-19 is a global pandemic currently affecting the US, yet little is known about risk factors for illness, including more severe illness and indicators of recovery. Since its nascence in China’s Wuhan province in late 2019, the outbreak has evolved with startling rapidity with approximately 177 million people infected with COVID-19, resulting in at least 3.8 million deaths globally.1 COVID-19 positive cases are identified with COVID-19 polymerase chain reaction test or an antigen test using saliva, nasopharyngeal or bronchial samples.1,2 Fever, chills, cough, shortness of breath, fatigue, muscle aches, loss of taste and/or smell, nausea, diarrhea, and other symptoms are typical of the acute phase of the disease.3,4 COVID-19 multi-organ manifestations are now well-documented5-8, and even after recovery from acute illness, more than 70% of those infected report a diverse array of persistent mild to severe symptoms and diseases, from fatigue and persistent loss of taste or smell to stroke, renal failure, myocarditis, neurological syndromes, COVID-associated thrombosis, and pulmonary fibrosis.3,9-17 Persistent or new symptoms after COVID infection are now termed post-acute sequelae of SARS-CoV-2 (PASC). The underlying pathophysiology of persistent symptoms after COVID-19 infection is unknown but has been proposed to be attributable to viral persistence, complications from critical illness related to prolonged intubation, prolonged bed rest, and malnutrition or impacts of pandemic-related disruptions on health.16

The goal of this study is to identify, evaluate, and characterize the heterogeneity in the pace and extent of recovery after acute COVID-19 infection, the clinical course of PASC symptoms in subjects who have recovered from acute infection, and the risk factors associated with the severity of the clinical course of PASC. This prospective longitudinal observational cohort study will focus on the biological differences that distinguish those who recover quickly from those who develop PASC symptoms and the long effects of COVID-19 infection, while explicitly considering racial/ethnic disparities in risks and outcomes. Data acquired from this study will provide accurate and quantifiable measures for PASC symptoms in selected case and control populations and allow for comparisons among groups to provide clues on PASC progression and complete recovery.

3.2 Rationale and Study Significance

This research study will ascertain information about subjects who have recovered from COVID-19 infections and define and categorize the clinical spectrum and risk factors for PASC. Data generated from this study will also serve to understand the long-term effects of COVID-19 infection and treatment options for affected individuals.

4 Potential Risks and Benefits

4.1 Known Potential Risks

This study includes patient-reported questionnaires, data extraction from electronic health records (EHR) and claims data, basic clinical examinations, blood draws, and radiology studies. We describe the risks of each in turn. Some patients (maximum of 20%) will be asked to undergo moderate risk procedures; these patients will be separately consented for those procedures. Clinical consent will be obtained for procedures that require clinical consent, such as colonoscopy, endoscopy, bronchoscopy, and right heart catheterization.

Risks of survey completion: While we anticipate no risk greater than that found in everyday life from survey completion, we understand that completing questionnaires about the COVID-19 experience could cause subjects to become upset or frustrated. To minimize risk, staff will be trained to let subjects know that they can stop the line of questioning at any point and ask for the subject to notify them if and/or when they are ready to resume the questioning.
Additionally, loss of confidentiality for the subjects’ answers is another potential risk. Loss of confidentiality could result in damage to a patient’s financial standing, employability, insurability, or reputation. The aforementioned risk is significantly minimized through the use of a secure, encrypted, password-protected database such as i2b2 Data Hub REDCap Central residing in a protected cloud environment. Minimal necessary access to the REDCap database will be granted only to study and research personnel. The REDCap Central database and the i2b2 Data Hub will meet compliance with FISMA-Moderate federal standards.

PHI that may link subjects to the data will be stored in REDCap Central. In the databases used for analyses, such as the i2b2 Data Hub, there will be a HIPAA-defined coded Limited Data Set. Universally Unique Identifiers (UUIDs) will be generated from PHI to maintain unique, non-duplicated subject identifiers across the analysis databases used in the study (see section 13.4.2).

Any PHI that may link subjects to the data will be stored in a separate location.

**Risks of mobile health technology:** Use of commercial products and devices made by third party companies, including wearable fitness trackers, wearable sleep monitors, mobile apps, websites, web apps and types of computer software that permit screen sharing, record keystrokes, gain access to device files and/or use location tracking technology, may be associated with loss of privacy and risk of breach of confidentiality. These products and devices will only be used to collect study data with IRB approval and if the subject has agreed to all applicable Terms of Service and EULAs. Any newly created mobile health platforms will be assessed and cleared before use in this study.

**The following protocol elements pose no appreciable risk:**
- Clinical examinations (e.g., vital signs, height and weight, physical examination)
- Collection of urine, stool and saliva
- Electrocardiogram
- Home activity monitoring
- Sleep studies
- Ultrasound studies

**Phlebotomy:** Having blood taken poses minimal risks like lightheadedness or feeling faint. Redness, pain, bruising, bleeding or (rarely) infection may occur at the site of a puncture during blood collection.

**Risk of COVID-19 Nasal Swab:** The nasal swab test may be uncomfortable and may cause a small proportion of people to gag, cough or have a nosebleed.

**Mental and behavioral screening:** The tests of memory, attention, and thinking may be frustrating or stressful for some people. Subjects may stop the questions at any time.

**Vision testing:** There is minimal medical risk from the tests of vision, measuring eye pressure or retinal thickness or eye photography. The eye drops used to dilate patients’ eyes may sting, or cause glare and blurry vision for several hours. Some people are allergic to eye drops. Some people have a temporary increase in eye pressure which would make the eye become red or painful. These problems will be treated if they occur.

**6-minute walk test, spirometry and plethysmography lung volumes:** Some patients may get tired or short of breath or have palpitations during these tests. There is minimal medical risk from these tests.

**Tilt table test and cardiovagal testing:** Some patients may feel lightheaded or weak or may faint during these tests. If so, the patient will immediately be laid flat and monitored until improvement. We will exclude pregnant women from tilt table testing.
Local Lidocaine administration: Several study procedures (including the nerve conduction study, electromyography, skin and muscle biopsies, lumbar puncture, and right heart catheterization) include use of lidocaine locally, which can occasionally cause redness or swelling. Some people are allergic to lidocaine. Symptomatic allergy will be treated at the study site. Anaphylactic reaction is extremely rare.

CT Scans and X Rays: CT scans and x-rays involve radiation. We estimate the additional amount of radiation that a patient will receive as a result of participating in this study will likely be a maximum of approximately 22 mSv over four years, which is comparable to 7 times the yearly dose from natural environmental radiation in the US (3.1 mSv). The risk of this level of radiation is thought to be very low but may involve a low risk of cancer. Some CT scans use gadolinium, a contrast dye. Risks of contrast dye include allergic reaction and kidney damage. Kidney damage is usually mild and temporary; people with impaired kidney function at baseline are at higher risk and will be excluded from participation in CT scanning with contrast. We will exclude pregnant women.

MRI/MRV/MRA: MRI does not involve high-energy radiation but poses risk for people with metal implants, which may cause burns if the patient is not properly excluded from having the study. Patients may experience claustrophobia, hear loud noises, feel warm or hot, or experience tingling during the MRI. Very rarely, patients may experience burns even without metal in the body. Some subjects may have allergies to the gadolinium dye used to generate MRI contrast images. In rare situations, MRI dye can cause nephrogenic systemic fibrosis; this is typically seen in patients with severe kidney problems, who will be excluded from participation. These risks are minimized through completion of a patient questionnaire and laboratory testing prior to MRI to identify patients who cannot safely undergo MRI. We will exclude pregnant women from MRI studies with contrast.

Nerve conduction study (NCS) and electromyography (EMG): Either of these tests may cause mild patient discomfort because of the electrical signals (NCS) and tiny needles (EMG) used in the studies. Rarely, bruising or bleeding may occur at EMG sites.

Skin and muscle biopsies: Risks of biopsy include bleeding, bruising or infection. We will exclude pregnant women.

Lumbar puncture: Risks of lumbar puncture include bleeding, headache (3%) or infection. Very rarely, headaches may persist for a week or be sufficiently severe as to require a blood patch for treatment. In extremely rare cases, bleeding can compress the spinal cord, requiring surgical removal of the clot. We will exclude pregnant women.

Bronchoscopy: Risk from fiberoptic bronchoscopy is primarily post-procedure fever, which is transient and occurs in 5% of patients. Pneumonia is a rare complication; pneumothorax is even rarer. To minimize risk, we will not perform the test on anyone with FEV1 < 50% or with abnormal clotting function and will check a post-procedure chest X ray. There is risk from lidocaine used for local anesthesia of vocal cords, trachea, and airways, where excess lidocaine can induce seizures and even death; we will place strict limits on total lidocaine dosage to avoid this risk. We will exclude pregnant women.

Right heart cardiac catheterization: Bruising may occur at the injection site and, in rare cases, infection or occlusion may also occur. If the catheter is inserted in a vein in the neck, there is a very low risk of lung collapse resulting in in-patient hospitalization. The catheterization can lead to abnormal heart rhythms. In very rare cases, therapy may be necessary. Serious changes may require treatment with emergency defibrillation (application of electrical shock to the heart). We will exclude pregnant women.

Cardiac imaging with meta-iodobenzylguanidine: MIBG is an FDA approved radioactive substance that is equivalent to about 15 months of normal background radiation. It may cause blood pressure to increase
after injection. Subjects will be monitored for 30-60 minutes after the procedure. We will exclude pregnant women.

**Gastric emptying study:** The radioactive substance used is a gastric emptying study is not harmful, is not absorbed through the gastric tract but excreted. We will exclude pregnant women.

**Upper endoscopy:** Upper endoscopy is safe and very rarely may cause bleeding from biopsy sites or result in a puncture of the esophagus, stomach or small intestine that may require surgery to repair. Sedation may slow the breathing or lower the blood pressure; these can be treated with oxygen or fluids and a lower dose of sedation. We will exclude pregnant women.

**Colonoscopy with or without biopsy:** Colonoscopy procedures are safe and very rarely may cause a puncture of the colon requiring antibiotics, hospitalization and possibly surgery to repair. Sedation may slow the breathing or lower the blood pressure; these can be treated with oxygen or fluids and a lower dose of sedation. People may experience nausea, vomiting, bloating or pain while doing the bowel preparation. Serious side effects are rare. We will exclude pregnant women.

**Risk of incidental findings:** Tests performed by certified clinical laboratories or research laboratories may provide results that indicate a clinically significant or medically actionable condition might be present. In these circumstances, the Principal Investigator or other designated licensed medical professional at each site will determine if further testing is necessary and will contact participants as detailed in section 13.4.3.

**Risk of genetic testing:** There is a risk of discovering potentially pathogenic genetic variants of uncertain clinical significance during the study. Results are defined as clinically actionable according to the standards and guidelines defined by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMB-AMP guidelines). The WGS studies will be performed in a CLIA-approved lab. All disclosure of clinically actionable genetic results at the end of the study will be guided by the PASC Biospecimens Committee. The consent form will inform participant of the potential for actionable results and will ask participants whether they would like to be informed at the end of the study about the presence of actionable potentially pathogenic genetic variants. For participants who elect to be informed of their genetic results, the genetic variant discovered will be shared with the site PI or designated study personnel, who will use their local process and policies for re-identification of the participant and referral if needed for evaluation, which may include involvement of their local genetics team and/or the participant’s cardiologist or other caregivers.

There is some chance that analysis of the relationship of genetic findings to outcomes could cause psychological distress. Some people involved in genetic studies feel anxious about the possibility of carrying (or their child carrying) an altered gene that may place them at risk or that might be passed on to subsequent generations.

### 4.2 Known Potential Benefits

There are no known potential benefits to this study to subjects, but there is a potential benefit to public health. Healthcare physicians may have a better understanding of how to meet the needs of COVID-19 survivors more effectively.

### 5 Objectives and Purpose

The purpose of this study is to characterize the spectrum of PASC symptoms and define the incidence, prevalence, and underlying mechanism of PASC in the adult across multiple sites in the United States. The specific aims are to:

- Characterize the incidence and prevalence of PASC, including clinical and biological features, severity, and distinct sub-phenotypes, following COVID-19 infection
• Characterize the clinical course and recovery of sequelae over time and determine associated risk factors for PASC among COVID-19 infected individuals and compared them to uninfected individuals.
• Define the pathophysiology of and mechanisms of post-acute sequelae, including direct and indirect causal effects of COVID-19 infection, and potential modifiers (e.g., sex, age, and race/ethnicity).

We hypothesize that this study will elucidate risk factor(s) that contribute to PASC progression.

6 Study Design

6.1 Study Design

This is an ambi-directional longitudinal meta-cohort study (combined retrospective and prospective) to determine the clinical spectrum, progression, prevalence, and incidence of PASC (COVID-19). Individuals with and without COVID-19 infection will be enrolled at varying stages during and after infection (Fig 1).

We will include subjects who meet our inclusion and none of the exclusion criteria and analyze the core set of questions on demographics, comorbidity, COVID-19 vaccination status, acute COVID-19 clinical course, current clinical condition/symptom, and outcomes as tiered testing.

Many of the participating health centers use utilize electronic health record (EHR) systems. This facilitates the pooling of data to ask and answer numerous research questions applicable to the care of subjects with or at risk for COVID-19. Data will be entered into the secure HIPAA compliant REDCap database for analysis and storage.
Subjects with abnormal findings on Tier 1 evaluations will be asked to undergo Tier 2 (Appendix 3: Tier 2 questions, tests and procedures) and in some cases Tier 3 testing (Appendix 4: Tier 3 tests and procedures). The study procedures in which subjects participate is dictated by their symptoms. We anticipate that approximately 30% of enrollees will undergo Tier 2 testing and 20% of enrollees will undergo Tier 3 testing for any given symptom, including both those with relevant symptoms and a random sample of SARS-CoV2 infected and uninfected subjects without relevant symptoms. Procedures in Tier 3 will only be performed concurrently when clinically appropriate. Complete information regarding how tests will be assigned will be in the Manual of Procedures.

6.2 Characteristics of the Study Population

**Number of Subjects:** 17,680 subjects with and without existing subject records.

**Age of Subjects:** 18 years and above.

**Racial and Ethnic Origin:** Expected overall recruitment by race/ethnicity will be 53% non-Hispanic Whites, 16% non-Hispanic Blacks, 27% Hispanic/Latinx, and 4% Asian Americans, Native Hawaiians, Pacific Islanders, American Indians, and Native Alaskans with equal distributions between male and female populations.

**Severity of Illness:** Targeted distribution will be 25% hospitalized for index COVID-19 infection; 75% not hospitalized.

**Pregnancy status:** Targeted enrollment will be 1,867 infected and 583 uninfected at the time they were pregnant.

6.3 Recruitment and Retention

6.3.1 Recruitment Strategy and Procedures

Recruitment of people with and without SARS-CoV-2 infection will be stratified to ensure adequate representation by sex and race/ethnicity as described in section 6.2. For patients with SARS-CoV-2 infection recruited during or after acute infection, priority will be placed on recruiting patients from lists of SARS-CoV-2 infected patients to ensure that (a) potential patients were identified prior to study enrollment to minimize bias associated with self-referral, and (b) enrollment response rates can be generated from known denominators. If lists are large, recruitment can be phased using random sampling and adequate “working of recruitment lists” to maximize generalizability. Attempts will be made to include a diversity of sites of care (e.g. not only from a post-COVID clinic or only from patients cared for in academic medical centers) and severity of illness (i.e. not only from hospitalized patients). For patients without SARS-CoV-2 infection, patients will be randomly sampled and recruited from known lists of potential study subjects in similar communities, demographics, and sites of care as those being recruited into the SARS-CoV-2 positive cohort. Recruitment will be stratified to match the SARS-CoV-2 positive group in terms of racial/ethnic diversity, index time point, and proportion of patients not hospitalized, hospitalized but not in the intensive care unit, and those hospitalized in the intensive care unit.

Self-referral patients will be accepted but cannot account for more than 15% of enrolled patients to minimize selection bias.

For patients enrolled after acute infection, preference should be given to those who have data and/or biospecimens collected before or during the acute phase available to the investigators, though efforts should still be made in such cases to recruit an unbiased sample of such patients (for instance, by oversampling this group for underrepresented minority patients or those in communities not already well-represented in the cohort).
If the subject has provided prior consent to be contacted for research at their study site institution, the site study team may create a query in the local EHR system to identify potential subjects based on study entry criteria (age, and history of prior diagnosis or testing related to COVID-19). Institutions may also partner with local health departments to obtain complete case lists of people with positive tests in a geographic area. A secure email will be sent to potential subjects to solicit interest in the study, with instructions for contact of the study team if interested to participate. This email will be provided to the IRB for review and approval before use in the study. Once contacted by the potential subject, the study Principal Investigator or designated study staff members will provide additional IRB-approved information to the subject as described below and may schedule a study visit. The EHR query or public health department query may be repeated for the duration of the 4-year study. All query responses will be deleted at the end of the study.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to site Principal Investigator or designated study team member.

Any recruitment information sent by email will utilize secure encrypted email platform. Once potential subjects have been identified, the study team may need to notify the treating physician that they have patients eligible to participate.

If notification to the treating physician is necessary, one or more of the following methods will be used to notify the treating physician:

1. The treating physician will be given a list, advertisement, letters or oral script to use when contacting potential subjects
2. The treating physician and site Principal Investigator will send a letter to all potential subjects (letter must have both names)
3. If the treating physician agrees, the study team will directly contact potential subjects on behalf of TP by letter, phone, email, or an electronic medical record patient portal.

Once contact is made, approved recruitment language will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

Social media platforms, websites, conventional mass media (radio and print publications), flyers or other advertising may also be used for recruitment purposes. All recruitment materials or text for any of these platforms will be submitted to the IRB for approval prior to use.

6.3.2 Retention Strategy

Participant retention may be promoted by providing educational materials related to PASC symptom management, by creation of a patient web portal to provide access to study personnel for questions, and by using feedback received from participants to enhance participant experience. Additional efforts may be made to minimize attrition: 1) reminder calls for assessments, rescheduled if missed; 2) maintaining contact information (e.g., updating at each contact, obtaining alternate contacts, re-connecting in primary care), and maintaining ongoing contact with all participants during the study. All materials used for participant retention will be provided to the IRB for review and approval before use in the study.

Contacts with participants may include: reminders for completion of study surveys, reminders for study appointments, a post-visit thank-you card or call, a quarterly newsletter, a birthday or greeting card, and a holiday or end-of-year card. We aim to design both culturally and religiously appropriate contact documents. Therefore, these contacts will be initiated by each site and will be conducted in the language of choice of the participant. In addition, because some religions (e.g. Jehovah’s Witnesses) may not celebrate birthdays or holidays, specialized cards will be designed to accommodate these participants. Newsletters and cards sent to RECOVER respondents will be targeted for a 5th grade reading-level.
Participant response burden may be monitored in real-time during the study. If burden is found to be excessive, it may be reduced by altering the data collection strategy, such as by increasing the interval of assessments to 6 months instead of 3 months; reducing the number of data elements collected (eliminating rare symptoms); pre-filling prior responses to reduce data entry time for patients; tightening criteria for Tier 2 and Tier 3 data collection; increasing the availability of home-based Tier 2/3 assessments; and/or increasing participant reimbursement. All such modifications will be approved by the IRB before implementation.

Recruitment and retention data will be monitored on an ongoing basis to compare target versus actual recruitment rates by site (stratified by race/ethnicity, hospitalization status and acute infection at enrollment); compare the number of expected surveys completed and biospecimens collected to target; and to review participant retention reports indicating the number of participants active, completed, and lost to follow-up.

7 Study Enrollment and Withdrawal

7.1 Inclusion Criteria

- Patients will be eligible for inclusion if they are at least 18 years of age and have reached the age of majority in their state of residence
- Infected individuals will have suspected, probable, or confirmed SARS-CoV-2 infection as defined by WHO criteria within 24 months of enrollment, or positive SARS-CoV-2 infection-specific antibody testing

Adults with suspected SARS-CoV-2 infection

An adult qualifies as having suspected SARS-CoV-2 infection if meeting criteria a, b or c below:

a) Patients who meet the following clinical criteria plus one of the epidemiological criteria:

**Clinical criteria:** Acute onset of fever and cough OR acute onset of any three of more of the following signs or symptoms: fever, cough, general weakness /fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia-nausea/vomiting, diarrhea, altered mental status.

**Epidemiological criteria:**

i. Residing or working in an area with a high risk of transmission of virus: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons; anytime within the 14 days before symptom onset; or

ii. Residing or travel to an area with community transmission anytime within the 14 days before symptom onset; or

iii. Working in any health care setting, including within health facilities or within the community; anytime within the 14 days before symptom onset.

b) A patient with severe acute respiratory illness: (acute respiratory infection with history of fever or measured fever of ≥38°C; and cough; with onset within the last 10 days; and requires hospitalization).

c) An asymptomatic person not meeting epidemiologic criteria with a positive SARS-CoV-2 Antigen-RDT.

Adults with probable SARS-CoV-2 infection

An adult qualifies as having probable SARS-CoV-2 infection if meeting any one of a-d below:

a) A patient who meets clinical criteria for suspected SARS-CoV-2 AND is a contact of a probable or confirmed case or linked to a COVID-19 cluster;

b) A suspect case with chest imaging showing findings suggestive of COVID-19 disease;

c) A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause;
d) Death, not otherwise explained, in an adult with respiratory distress preceding death AND was a contact of a probable or confirmed case or linked to a COVID-19 cluster

**Adults with confirmed SARS-CoV-2 infection**

An adult qualifies as having confirmed SARS-CoV-2 infection if meeting any one of a-d below:

a) Any person with a positive Nucleic Acid Amplification Test (NAAT);

b) Any person with a positive SARS-CoV-2 Antigen-RDT AND meeting either the probable case definition or suspect criteria A OR B;

c) An asymptomatic person with a positive SARS-CoV-2 Antigen-RDT who is a contact of a probable or confirmed case

d) Any person with a positive SARS-CoV-2 nucleocapsid protein antibody test OR a positive SARS-CoV-2 spike protein antibody test IF not vaccinated

**Adults with no SARS-CoV-2 Infection**

- Does not meet WHO criteria for a suspected, probable, or confirmed case of SARS-CoV-2 infection, AND
- Documented negative SARS-CoV-2 testing from a respiratory specimen (PCR or antigen testing) at the time of enrollment/screening and negative SARS-CoV-2 nucleocapsid protein antibody and spike protein antibody test (if not vaccinated) at the time of enrollment, AND
- Live in the same communities or recruited from the same sources as those in the SARS-CoV-2 infected cohort, AND
- Either not hospitalized for any reason in prior 3 months, or hospitalized (with or without ICU stay) within the prior 3 months
- Note: uninfected individuals may participate independent of their vaccination status

### 7.1.1 Change in Eligibility Status

Uninfected individuals who develop SARS-CoV-2 infection during the study period will be designated as SARS-CoV-2 infected at the time of infection and will be considered to have been enrolled prior to SARS-CoV-2 infection.

### 7.2 Exclusion Criteria

- Individuals who have not yet reached the age of majority
- Unable to provide consent
- Individuals in hospice care
- Any serious medical condition which would prevent long-term participation
- Individuals participating in the study NIH RECOVER-Pediatric: Understanding the long-term impact of COVID on children and families
- Incarcerated individuals

Note that participation in other observational or intervention studies while participating in RECOVER is not an exclusion criterion.

### 7.3 Vulnerable Populations

Data from pregnant women will be included as part of the study as it is important to understand COVID-19 in all populations. The study cannot be conducted without the group because pregnant women represent a portion of the population affected by COVID-19 and their responses to COVID-19 disease may be different from that of the general population. No inducements, monetary or otherwise, will be offered to terminate a pregnancy. Individuals engaged in the research will have no part in any decisions as to the timing, method or procedures used to terminate a pregnancy. Individuals engaged in the research will have no part in determining the viability of a neonate. Women who were pregnant while they had COVID-19 will be offered the opportunity to enroll their infants (once born) in the NIH RECOVER-Pediatric: Understanding the long-
term impact of COVID on children and families study if they are being enrolled at a site that also supports the pediatric study. Agreement to participate in the pediatric protocol is not required for participation in the adult protocol. Similarly, agreement to participate in the pediatric protocol does not require participation in the adult protocol. This option will only be available to the participants at the maternal fetal medicine sites in the RECOVER Network only and is consistent with the pediatric protocol. At these sites, women who had covid while pregnant and gave birth before enrolment in RECOVER, will have their medical information during pregnancy collected and used in this protocol.

7.4 Subject Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request. The subject will provide a written notice of withdrawal (either via letter or e-mail) to the study site PI, after which data and biospecimens of the subject will be destroyed. Once the subjects withdraw participation, no more information will be collected. However, in cases when the data removal will affect the integrity of the study, all previously collected data will not be removed. Subjects will be informed about this during consenting process. Data that have already been distributed to the i2b2 Data Hub will not be removed or destroyed.

7.5 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the NIH Sponsor and site investigators. If the study is prematurely terminated or suspended, the site PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:
- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor and/or IRB.

8 Study Schedule

8.1 Overview of Study Schedule

Data will be collected at baseline and then following the study schedule, which starts at time of infection or of enrollment or equivalent event (i.e. hospitalization, negative COVID-19 test), for those who are uninfected. Subjects enrolling after infection will follow the study schedule corresponding to their time since infection. Collection will be tiered such that all enrolled patients will undergo Tier 1 data collection, and those with abnormal findings on Tier 1 collection will progress to more intensive, invasive or costly Tier 2 and Tier 3 data collection. We anticipate that approximately 30% of enrollees will undergo Tier 2 testing and 20% of enrollees will undergo Tier 3 testing for any given symptom, including both those with relevant symptoms and a random sample of SARS-CoV-2 infected and uninfected subjects without relevant symptoms. All patients will undergo at least one in-person visit at baseline, which can be provided at home if provision is made for home blood and biospecimen collection.

Home Visits

Some study testing or procedures may be conducted through home visits to alleviate travel burden for subjects. These home study visits will be conducted by members of the clinical research study staff and will follow COVID safety protocols for the duration of the visit. As only research staff will be performing these
visits, responses and specimens collected will be strictly confidential. These study visits will be strictly for
data and/or specimen collection and all research tests and procedures which may be performed through home visits are indicated in Appendix 2-4.

8.2 Baseline/Enrollment Visit
A core set of questions on demographics, comorbidity, SARS-CoV-2 vaccination status, acute SARS-CoV-2 clinical course and current clinical condition/symptom inventory will be answered by the patient upon enrollment (survey instruments attached separately). Additional modules on demographics, social determinants and habits will be made available to the patient to complete once the core set is completed (survey instruments attached separately). Following completion of the core questions, a minimal physical examination will be performed, including collection of height, weight, vital signs (including orthostatic vital signs) and measurement of waist circumference. Additional clinical examinations will be performed at that time as indicated by patient responses to the symptom questionnaires. This visit will also include collection of blood, urine, saliva and stool both for initial clinical testing and banking (see below), and/or retrieval of specimens already banked for the patient during acute COVID. If enrollment occurs at time of acute COVID-19 and the patient is too ill to participate in the complete baseline assessment or assessment is not safe for research personnel, some patient-reported elements may be deferred until recovery but should then be completed as close to the acute infection as possible. Should a patient lose capacity to consent or participate in research during the study, all research activities will be paused. Research activities will only resume once a member of the clinical team caring for the patient deems the patient capable of consent or participation. See Appendix 1 for schedule of assessments.

8.3 Follow-up Visits
A current symptom inventory (see 19.2) will be collected at 3 month intervals, with further physical examination, blood/specimen and radiologic testing conducted in a subset per protocol (see Appendix 3: Tier 2 questions, tests and procedures and Appendix 4: Tier 3 tests and procedures).

9 Study Procedures/Evaluations

9.1 Tier 1 Assessments
Tier 1 assessments are listed in Appendix 2: Tier 1 questions, tests and procedures.

9.2 Tier 2 Assessments
Tier 2 assessments are listed in Appendix 3: Tier 2 questions, tests and procedures.

9.3 Tier 3 Assessments
Tier 3 assessments are listed in Appendix 4: Tier 3 tests and procedures.

9.4 Biospecimen Banking
The following biospecimens will be collected for banking at baseline, at 3 and 6 months after infection (if enrolled during that time period), and then yearly:
- Nasal swabs in freeze medium
- Blood
  1. 4 x 8 ml CPT tubes – for peripheral blood mononuclear cell (PBMC) collection
  2. 2 x 8.5 ml SST tubes – for serum collection
  3. 1 x 2.5 ml PAXgene tube – for mRNA
- Blood specimens will be replaced by serum collected via Mitra, TAP or other similar product for patients who cannot undergo phlebotomy
The following additional biospecimens will be collected on a different schedule:

- Saliva (on enrollment only)
- Stool and urine (on enrollment and at year 2)

For patients undergoing Tier 3 invasive testing through additional consent, or undergoing additional tests as part of routine clinical care, residual samples collected for clinical purposes will whenever possible be collected and sent to the biospecimen core, including:

- Cerebrospinal Fluid (CSF)
- Biopsy specimens
- Bronchoalveolar lavage (BAL)
- Lymph node aspirants

### 9.5 Data Sources

Data sets obtained directly from the subject, or from the subject’s EHR or existing registries, will be stored in REDCap Central and the i2b2 Data Hub, which will collect and harmonize subjects’ data from disparate sources and make it available for reporting and analysis by RECOVER cores, coordinating centers, and OSMB as needed.

### 9.6 Data Collection

Demographic data points that will be collected include name, date of birth, current address, sex assigned at birth, ethnicity, race, COVID-19 status, COVID-19 vaccination status, COVID-19 vaccine received if applicable, medical history during COVID-19 hospitalization, and/or treatment, pregnancy status, medical history, and health status before COVID-19. See Table 1 for PHI elements.

### Table 1. PHI that will be collected for this study

<table>
<thead>
<tr>
<th>Protected Health Information (HIPAA Identifiers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Names</td>
</tr>
<tr>
<td>2. Street Address</td>
</tr>
<tr>
<td>3. Any of the following: City, State, Zip Code</td>
</tr>
<tr>
<td>4. Date of Birth</td>
</tr>
<tr>
<td>5. For those 90 or older: Any element of date (including year) indicative of age, or recording actual age (i.e., rather than recording age as “90 or older”)</td>
</tr>
<tr>
<td>6. Telephone numbers</td>
</tr>
<tr>
<td>7. Fax numbers</td>
</tr>
<tr>
<td>8. Electronic mail addresses</td>
</tr>
<tr>
<td>9. Social security numbers</td>
</tr>
<tr>
<td>10. Medical record numbers</td>
</tr>
<tr>
<td>11. Health plan beneficiary numbers</td>
</tr>
</tbody>
</table>
9.7 Data Management

The study staff and the Data Resource Core (DRC) will collaborate to develop the electronic data capture (EDC) system before the commencement of the research study and will utilize REDCap between systems for secure transfer and recording of study data. EDC data will be stored in REDCap, a secure HIPAA compliant electronic data capture system and then transferred via secure file transfer, first from the study site to REDCap Central and then to the i2b2 Data Hub, where it will be harmonized with additional data types. Both REDCap Central and the i2b2 data hub will reside in a FISMA-moderate compliant cloud environment. Access to this aggregated study database will be limited to HIPAA-certified investigators who have been approved for participation in this study.

If any information is shared with external interested site(s), data use agreements will be established.

9.7.1 Data Transfer from Enrolling Sites to DRC

Recruiting sites will not send any PHI to the DRC except date of birth (DOB) and five digit zip code. Each site will collect and retain subject identifiers in HIPAA-compliant databases such as local REDCap. These will be linked to the central REDCap database through a participant ID (RpID). In order to allow future linkage of study data to other national datasets without transferring PHI to the DRC, each recruiting site will use the commercial application Datava to generate a deidentified participant key (known as a hash, or token) via a privacy-preserving record linkage (PPRL) methodology embedded in the software. Datavant's de-identification engine performs two functions: (i) removal of PII (personally identifiable information) from a participant’s record and (ii) generation of multiple encrypted tokens that can be substituted for RpIDs. These tokens are irreversible and specific for a given study site, which retains the ability to view PII from its own participants. Tokens can be used to link a participant’s record in one repository with a record from the same participant in a different repository, without ever exposing the PII. Over years of implementations, QA testing protocols have shown that Datavant’s technology generates tokens in a manner that facilitates linking of participant PHI across disparate data sources while maintaining privacy. The token generation process is summarized graphically in Figure 2.

Figure 2: Token generation process

Sites will send RECOVER study data (surveys, clinical laboratory results, etc.) to the DRC via REDCap electronic case report forms (eCRFs). REDCap automatically generates a RECOVER Participant ID (RpID), and the only other PII associated with study data are the participant’s date of birth and zip code. The
eCRFs and PII are submitted to “REDCap Central,” a FISMA-Moderate repository located at Harvard Medical School (HMS) and managed by HMS personnel. Summarizing, REDCap Central holds each RECOVER participant’s study data and three PII data elements: DOB, ZIP Code and RpID.

Figure 3: Data transfer in RECOVER

9.7.2 Data Transfer from PASC Biorepository Core (PBC) to and from DRC

Data Transfers from PBC to i2B2

The DRC will import data from the PBC’s specimen system (LIMS) directly into i2b2 using secure file transfer and will create ontologies to represent those data in i2b2 so they can be used for analysis. Quality assurance processes will ensure that the extract, transform and loading (ETL) process is accurate. Monitoring and reporting systems will be created to track the data.

Data Transfers from REDCap to PBC

To enable PBC to link specimen collection information with specimens, REDCap will export a file to a secure server hosted at PBC via secure file transfer protocol. This file will include the participant ID/Kit ID mapping and will include all specimen-specific information captured into REDCap Central.

9.7.3 Data Transfer Within DRC

Data Transfers from REDCap to i2b2 Data Hub

Data from REDCap electronic Case Report Forms (eCRFs) and some fields from Informed Consent Forms (ICFs) will be loaded from REDCap into the i2b2 hub. The i2b2 hub will serve as the analytic database for the study. In order to be usable, all data loaded into the i2b2 Data Hub will first be extracted and
transformed into the i2b2 star schema format. Quality assurance processes will ensure that the ETL process is accurate. Monitoring and reporting systems will be created to track the data.

9.7.4 Harvard Medical School (HMS) AWS Cloud Environment
RECOVER systems, including REDCap Central (all cohorts), the i2b2 Data Hub, and statistical analysis tools such as R, SAS, SQL Server, SHRINE, and Gitlab will reside on a FISMA Moderate compliant infrastructure. i2b2 will be the primary software component used to centrally store all data and provide investigator tools for querying, reporting and extraction of analysis data sets.

The REDCap Central environment is managed by HMS. It is developed on an existing fully authorized FISMA Moderate environment in Amazon Web Services (AWS) currently in use to support the NHLBI BioData Catalyst (BDC) project, as authorized by the NHLBI in March, 2021. This environment leverages all the management and security systems, controls, change control methodologies, training, documentation, and 3rd party security testing (e.g., Penetration Testing) and assessments (e.g., 3PAO reviews) in place for the HMS BDC project.

9.7.5 Data Storage
Data will be stored in a cloud infrastructure. To comply with the government’s Cloud Smart policy, all PHI will live within a FISMA Moderate cloud environment that has received an ATO from NHLBI based on review by NHLBI’s cybersecurity office.

9.7.6 Data Destruction
When participants withdraw from the study, their data will be destroyed in REDCap using standard REDCap functionality. The record, including its participant ID, will persist, as will records of ICFs that were signed, and the withdrawal record. All other data will be destroyed from REDCap. It will not be possible to restore this data once it is destroyed.

Per the study protocols, data that are stored in the i2b2 Data Hub will not be destroyed at the time of withdrawal.

When the study ends, all data will be de-identified in REDCap Central. The data in the i2b2 Data hub will persist in its existing de-identified form.

9.7.7 Data Integrity
Detailed Quality Control programs will be deployed to ensure and audit data integrity. The DRC team has extensive experience standing up and maintaining operational i2b2 instances (e.g., the MGB Biobank Portal, operational since 2015), including QC controls.

9.7.8 Security Management
Data will be stored in cloud infrastructure. To comply with the government’s Cloud Smart policy, all PHI will live within a FISMA Moderate cloud environment that has received an ATO from NHLBI, which includes network firewalls and systems for access control, change control, continuous monitoring, and training. A System Security Plan, which will be reviewed and approved by NHLBI as part of the ATO, describes the cybersecurity and IT management plan in detail.

10 Safety and Adverse Events

10.1 Definitions
Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
• Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
• Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm)

Adverse Event
An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study (excluding endpoints determined to be due to SARS-CoV-2 infection, section 10.3). Intercurrent injuries should be regarded as adverse events. Abnormal results of research procedures are considered to be adverse events if the abnormality:
• results in study withdrawal
• is associated with a serious adverse event
• is associated with clinical signs or symptoms
• leads to additional treatment or to further diagnostic tests
• is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:
• fatal
• life-threatening
• requires or prolongs hospital stay
• results in persistent or significant disability or incapacity
• a congenital anomaly or birth defect
• an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject’s personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.
10.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of REDCap Central. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed until resolution. Any serious adverse event that occurs after the study period and is considered to be possibly related to study participation will be recorded and reported according to the same criteria as other serious adverse events.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

Since the subjects in the study have known acute and post-acute SARS-CoV-2 infections, known manifestations of acute and post-acute SARS-CoV-2 infection will be recorded as endpoints rather than AE and SAE. These known events include:

- Upper respiratory infection
- Fever
- Flu-like symptoms
- Pneumonitis
- Respiratory failure
- Psychosis and delirium
- Multi-system inflammatory syndrome
- Multisystem organ failure
- Arterial thromboembolic events including stroke and myocardial infarction
- Venous thromboembolic events including deep vein thrombosis, CNS venous thrombosis, and pulmonary embolism
- Myocarditis
- Cholelithiasis and cholecystitis
- Acute kidney failure
- Autonomic dysfunction
- Headache
- Hair loss
- Tooth loss
- Tinnitus
- Loss of smell and taste
- Fatigue
- Malaise
- Muscle pain and weakness
- Bone pain
- Generalized pain
- Anxiety
- Depression
- Neurological symptoms (loss of concentration, loss of memory)
- Palpitations
- Shortness of breath
- Cough
Poor appetite
Nausea, vomiting, diarrhea, abdominal pain
Glucose intolerance
Skin Rash
Thirst
Raynaud’s phenomenon
COVID (chilblain-like) toes

Investigators will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:
- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others

For Narrative Reports of Safety Events
If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:
- Study identifier
- Study center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

10.3.1 Investigator Reporting: Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULH IRB reporting requirements, though investigators at participating sites are responsible for meeting any additional local requirements and/or those of the relevant sIRB.

Report Promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:
- Unanticipated problems including adverse events that are unexpected and related
  - Unexpected: An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.
  - Harmful: either caused harm to subjects or others, or placed them at increased risk

Other Reportable events:
The following events also require prompt reporting to the IRB, no later than 5 working days:
- **Complaint of a research subject** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - one or more subjects were placed at increased risk of harm
  - the event has the potential to occur again
  - the deviation was necessary to protect a subject from immediate harm
• **Breach of confidentiality**
• **Incarceration of a subject** when the research was not previously approved under Subpart C of the Federal Code and the investigator believes it is in the best interest of the subject to remain on the study.
• **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency (e.g. analysis indicates study procedures are of no value, or new study procedures are to be added, or study procedure frequencies will be changed)

**Reporting Process**
The reportable events noted above will be reported to the IRB using a Reportable New Information submission and will include a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution, and need for revision to consent form and/or other study documentation. Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

11 **Study Oversight**

11.1 **Monitoring Board**
Oversight of data and safety is provided by a RECOVER Observational Safety Monitoring Board (OSMB) appointed by the National Heart, Lung and Blood Institute (NHLBI). A charter of the OSMB will be submitted for IRB review before starting enrollment. The OSMB will meet at least twice a year to review data on AEs, unanticipated events, patient-reported outcomes, data quality, and study recruitment as described in the committee charter, and make recommendations about study conduct to the NHLBI. As the Adult PASC Investigator Consortium study does not involve any interventions, an early stopping rule for efficacy or futility is not indicated.

11.2 **Data Safety Monitoring Plan**
The Data and Safety Monitoring Plan for this trial will follow recommended monitoring principles for an observational study of a vulnerable population. Oversight of data and safety is provided by the RECOVER Observational Safety Monitoring Board appointed by NHLBI. The OSMB will be composed of experts in longitudinal research (adult and pediatric populations), clinical experts in adult and pediatric manifestations of COVID-19, biostatistics, bioethics, and patient/caregiver representatives. The OSMB will also appoint ad hoc members with subspecialty expertise in the diverse array of clinical manifestations of PASC. The OSMB will meet at least twice a year to review data on AEs, adverse reactions, suspected adverse reactions, unanticipated events, patient-reported outcomes, data quality, and study recruitment, and make recommendations about study conduct to the NHLBI. As the PASC study does not involve any interventions, an early stopping rule for efficacy or futility is not indicated.

After each OSMB meeting, the OSMB determination letter and a summary report of adverse events will be prepared within 30 days and will be distributed by NHLBI staff to each principal investigator and study coordinator for review. The summary report will contain the following information:

- A statement that a OSMB review of outcome data, adverse events, and information relating to study performance across all centers took place on a given date.
- A statement as to whether or not the frequency of adverse events exceeded what was expected and indicated in the informed consent.
- A statement that a review of recent literature relevant to the research took place.
- The OSMB’s recommendation with respect to progress or need for modification of the protocol or informed consent. If the OSMB recommends changes to the protocol or informed consent, the rationale for such changes and any relevant data will be provided.
- A statement that if safety concerns are identified, the NHLBI Program Official will communicate these promptly to the investigators.
12 Statistical Considerations

The analysis will integrate retrospective and prospective data on individuals at multiple stages, including pre-infection, acute infection, and long-term progression and recovery. Characterizing the incidence and prevalence of PASC will be achieved by estimating the incidence of PASC phenotypes among subjects with COVID-19 infection, compared with uninfected individuals followed over the same time.

To characterize the clinical course, recovery, and risk factors of PASC, PASC positive individuals will be compared with infected PASC negative individuals and uninfected individuals to characterize patterns. To define the pathophysiology and mechanisms of PASC, we will estimate the direct and indirect effects of COVID-19 infection and its severity on the development of PASC. Longitudinal data models such as generalized estimating equations, generalized linear mixed models, and functional principal component analysis will be used to characterize patterns of outcomes and develop analysis models.

12.1 Hypotheses to be Tested

- The incidence proportion between infected and uninfected individuals will be greater than 1.10.
- Risk factors related to demographics, social determinants of health, and co-morbid conditions will be associated with increased risk for development of PASC symptoms after SARS-CoV-2 infection.
- Direct and indirect effects of SARS-CoV-2 infection on organ function will mediate clinical and subclinical manifestations of PASC.

12.2 Sample Size Determination

The following factors were considered in determining the sample size:

- Expected frequency of PASC in the SARS-CoV-2 infected population. Population estimates from studies with selection bias currently range from 25-70%; we used 25% as a conservative estimate.
- The desire for the cohort distribution to include a diverse population, with overrepresentation from non-Hispanic Black, Hispanic and Asian populations relative to general population prevalence to account for a higher rate of SARS-CoV-2 infection and PASC in these populations.
- The desire to be able to perform subgroup analyses based on characteristics such as age, sex, race/ethnicity, pregnancy, vaccination status and combinations thereof.

Table 2 shows minimal detectable effect sizes for the key study questions both for the full study sample (Tier 1 N=17,680; Tier 2 N=5,304 and Tier 3 N=3,536) and for subgroups of 25% thereof. These sample sizes for Tier 2 and Tier 3 assume that 25% of infected subjects will have abnormal symptoms. It is further assumed that all infected subjects with abnormal symptoms will progress to Tier 2 and 5.6% of infected subjects without symptoms will progress to Tier 2. Among uninfected subjects, 26.8% will progress to Tier 2. 68% of infected subjects with abnormal symptoms will progress to Tier 3, and 3.8% of infected subjects without symptoms will progress to Tier 3. Among uninfected subjects, 18.2% will progress to Tier 3. The infected cohort is expected to include 1,867 pregnant individuals and the uninfected cohort is expected to include 583 pregnant individuals.
### Table 2: Sample size calculations

<table>
<thead>
<tr>
<th>Tier</th>
<th>Comparison groups</th>
<th>Effect of interest</th>
<th>Assumptions</th>
<th>Min detectable ES*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Full sample</td>
<td>25% subgroup (e.g. inpatients, Hispanic individuals, etc)</td>
</tr>
<tr>
<td>1</td>
<td>Infected</td>
<td>Difference in risk of PASC between infected and uninfected</td>
<td>Risk of PASC in infected: 25%</td>
<td>3.4% 6.7%</td>
</tr>
<tr>
<td>1</td>
<td>Infected w/ RF</td>
<td>Risk difference for PASC in infected with RF vs. without RF</td>
<td>Prevalence of RF: 20%, risk of PASC in infected, RF+: 30%</td>
<td>3.5% 6.9%</td>
</tr>
<tr>
<td>1</td>
<td>Pregnant infected</td>
<td>Risk difference for PASC in pregnant infected versus non-pregnant infected</td>
<td>Risk of PASC in non-pregnant infected: 25%</td>
<td>4.1% 8.0%</td>
</tr>
<tr>
<td>1</td>
<td>PASC+ w/ RF</td>
<td>Difference in proportion who recover from PASC for those with and without a risk factor</td>
<td>Prevalence of RF: 20%, probability of recovery in PASC+ w/out RF: 0.50</td>
<td>7.8% 15.5%</td>
</tr>
<tr>
<td>2</td>
<td>PASC+</td>
<td>Precision of rate of feature</td>
<td>Rate of 50% (conservative)</td>
<td>± 2.1% ± 4.2%</td>
</tr>
<tr>
<td>2</td>
<td>Infected</td>
<td>Difference in proportion with a feature in between infected and uninfected individuals</td>
<td>Rate of 50% with feature in infected</td>
<td>7.7% 15.3%</td>
</tr>
<tr>
<td>2</td>
<td>PASC+</td>
<td>Difference in proportion with a feature, PASC+ vs. PASC-</td>
<td>Rate of 50% with feature in PASC+ (conservative); Risk of PASC in acute: 10%</td>
<td>8.3% 16.3%</td>
</tr>
<tr>
<td>3</td>
<td>PASC+</td>
<td>Precision of rate of feature</td>
<td>Rate of 50% (conservative)</td>
<td>± 2.6% ± 5.1%</td>
</tr>
<tr>
<td>3</td>
<td>PASC+</td>
<td>Difference in proportion with a feature, PASC+ vs. PASC-</td>
<td>Rate of 50% in PASC+ (conservative)</td>
<td>10.0% 19.7%</td>
</tr>
</tbody>
</table>

ES: effect size; RF: risk factor

### 12.3 Statistical Methods

#### 12.3.1 Methods of Data Collection

Structured data elements will be collected remotely through a mobile or web-based platform, by telephone with study personnel, by home visit by study personnel, or (if no other option) by return of written questionnaire by postal mail.

Biospecimen collection will be handled as follows:
1) Biorepository will ship complete kits including collection tubes and aliquot tubes for each subject and each time point, all prelabeled with a kit ID. All collection tubes will be prelabeled.
2) Site will associate the kit ID with the subject ID.
3) Site will obtain specimens during in person visit (except stool, Mitra, or via home visit if arranged by site).
4) SST tubes will be centrifuged by each site then aliquoted by each site into matrix tubes (3 aliquots of 1 cc each per tube); the matrix tubes are provided by biorepository core. Aliquoted samples will be stored in a -80 freezer until shipped on dry ice. Shipping supplies will be provided with each kit for monthly batch shipping.
5) CPT tubes will be centrifuged locally, refrigerated (not frozen) and shipped day of collection. Biorepository will be responsible for processing, cell counts, aliquoting, slow freezing and storage in liquid nitrogen.
6) Urine and saliva will also be collected, refrigerated and shipped day of collection. Biorepository will aliquot the urine and freeze both saliva and urine.
7) Samples will be collected from study sites by Mayo via courier service or FedEx.

Off-protocol clinically obtained samples including cerebrospinal fluid, bronchoalveolar lavage specimens, procedural biopsies, and surgical pathology specimens will be tracked and either transferred from study site biorepository to the central RECOVER biorepository or linked by the patient ID to the institutional RECOVER biorepository for future access.

12.4 Strategies for Study Modifications
This protocol is designed to be pragmatic and flexible in design. We will undertake the following procedures to guide protocol modifications over time:

1) The frequency of PASC will be monitored in real-time during the study. If the incidence or prevalence is found to be higher or lower than planned, recruitment strategies will be altered to deliberately undersample/oversample PASC cases.
2) Subject response burden will be monitored in real-time during the study. If burden is found to be excessive, it will be reduced by altering the data collection strategy, such as by increasing the assessment interval; reducing the number of data elements collected; increasing the availability of home-based assessments; and/or increasing subject reimbursement.
3) Free text responses to interval assessments will be monitored in real-time during the study. If a new symptom or outcome is being reported at a frequency >15% by subjects, the symptom will be added to the data collection tool.
4) Data elements may be modified based on ongoing analysis by DRC; data elements that are not informative to PASC definition models may be removed, with substitution by new data elements.
5) PASC definition will be revised in an iterative manner based on existing PASC data, medical literature, and feedback from patient representatives, subjects, and the scientific community. Updated PASC definitions may be used to implement a strategy to modify deeper phenotyping.
6) Tier 2 and Tier 3 assessments will be evaluated for futility at pre-specified intervals; protocol assessments will be adjusted accordingly, and may include elimination of some assessments and introduction of other new assessments.

12.5 Overview of Analytic Approach to Aims
A statistical analysis plan will be included as an amendment in the future.

Aim 1 is to characterize the incidence and prevalence of long-term sequelae, including clinical and biological features, severity and distinct sub-phenotypes, following SARS-CoV-2 infection. This will be achieved by estimating the incidence of PASC phenotypes among subjects with SARS-CoV-2 infection or born to a mother with SARS-CoV-2 infection who are free of PASC-like symptoms and/or diagnoses prior to SARS-CoV-2 infection, compared with uninfected individuals free of PASC-like symptoms prior to the...
pandemic followed over the same time interval. To identify PASC phenotypes, sub-phenotypes and severity based on clinical and biologic features, we will statistically compare the incidence among infected and uninfected individuals. Supervised and unsupervised approaches will be applied to characterize sub phenotypes.

Aim 2 is to characterize the clinical course and recovery of acute and post-acute sequelae over time and to determine associated risk factors for PASC among SARS-CoV-2 infected, PASC positive individuals compared to infected PASC negative individuals and compared to uninfected individuals. We will characterize the patterns of outcomes of acute and post-acute sequelae over time using longitudinal data methods (e.g., general estimating equations and generalized linear mixed models) and functional principal component analysis. Longitudinal trajectories will be compared statistically between infected and uninfected individuals. We will additionally estimate and test the association of pre-infection and peri-infection risk and resiliency factors (e.g., social determinants of health, demographic, behavioral, biological factors and preexisting clinical and subclinical disease) prior to and following SARS-CoV-2 infection with the presence, severity and time to resolution of acute and post-acute sequelae using standard longitudinal and time-to-event models. We will also estimate the incidence and prevalence of subclinical organ injury/disease after SARS-CoV-2 infection and compare the prognostic significance of subclinical organ injury/disease for incident clinical disease among SARS-CoV-2 infected versus uninfected individuals.

Aim 3 will define the pathophysiology of and mechanisms associated with the development of acute and post-acute sequelae, including the direct and indirect effects of SARS-CoV-2 infection on symptom onset and potential modifiers. We will estimate the direct and indirect effects of SARS-CoV-2 infection on the development of acute and post-acute sequelae, including potential mediation by post-traumatic responses (e.g., severe disease).

12.6 Data Management Plan

12.6.1 Data Sources

There are three primary sources of data for the RECOVER cohort studies initiative:

- Prospective observational cohort studies
  - Adult cohort sites
  - Pediatric cohort sites
  - Pregnancy cohort sites
- RECOVER biorepository core
- Data repositories
  - Imaging
  - Pathology
  - Other

12.6.2 Data Categories

RECOVER study data may be divided into two broad categories: structured and unstructured. Structured data can be simple (e.g., surveys/lab tests) or complex (e.g., sleep studies). REDCap will be used to capture structured data electronically. REDCap will include PHI data, which will be used to create the universally unique identifiers (UUIDs), that will enable centralized coordination of biospecimen collection information and other data types.

12.6.2.1 Data Types

RECOVER study data may be divided into at least 12 different operational data types.

1. Patient questionnaires (in-person or submitted online; Structured)
2. Clinical site historical data (extant data; Structured->Complex)
3. Clinical site historical data (extant data; Unstructured)
4. EHR repository data (Structured->Complex)
5. Lab test results (Structured->Complex)
   i. Hospital
   ii. Commercial
   iii. Home
6. RECOVER biorepository inventory data (Biospecimens, slides; Structured->Complex)
7. Neuropsychological assessment data (Complex/Structured)
8. Functional assessment data (e.g. exercise testing, pulmonary/liver/kidney function; Structured->Complex)
9. Mobile health/wearable devices and computer software (i.e. fitness trackers, sleep monitors, Zio patch)
10. Advanced imaging data (CT and MRI; Unstructured)
11. Vaccination status data (Structured)
12. Physical exam and physiological testing data (e.g. PFTs, tilt table; Structured->Complex)

12.6.3 Electronic Data Capture (EDC) Methods
A uniform electronic data capture system will be used. Details will be found in the manual of operations.

12.6.4 Source Documents and Access to Source Data/Documents
Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

The study electronic case report form (eCRF) is the primary data collection instrument for the study. However, in some cases paper CRFs may be completed by subjects who cannot access surveys online or prefer paper. Data from these CRFs will be transferred into the eCRF by study staff. All data requested on the eCRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, insert “N/D.” If the item is not applicable to the individual case, insert “N/A.” Records will be retained of the date and time of any changes to data entered after initial completion.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

13 Ethics/Protections of Human Subjects

13.1 Ethical Standard
The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.
13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented subjects need to be re-consented.

13.3 Informed Consent Process

When the enrollment visit is completed in person, informed consent will be obtained and documented in writing before participation in study procedures. When the enrollment visit is completed remotely, electronic consent will be used. Study sites will identify potential subjects in their available recruitment pools (extant cohorts, clinical cohorts, acute cohorts, and/or post-acute cohorts). The research study will be explained in lay terms to each potential research subject in their preferred language. The overall common consent document will include:

1) consent for participation in all minimal risk RECOVER Tier 1, 2 and 3 activities;
2) consent for recontact for future participation in research;
3) consent for sharing identifiable data with the secure REDCap Central database;
4) consent to obtain and link data from electronic health records, regional health information exchanges, claims data and the National Death Index;
5) consent for sharing of deidentified data and specimens through RECOVER databases and specimen repositories (in addition to other NIH-designated repositories).
6) optional return of genetic information

Separate procedural consent will be obtained at the relevant time for any Tier 3 activities that are more than minimal risk.

Separate consent will be obtained by the pediatric study team from a person who was pregnant while infected with COVID-19 for the infant to participate in the pediatric study, if applicable.

The potential subject will provide informed consent before undergoing any study procedures. The consent process may be conducted by telephone, Webex video conference, or in person. The investigator or suitable designated delegate will conduct a meeting with the study candidate all the required elements of informed consent and to address all questions about the study. Comprehension of the study procedures and risks will be confirmed with standardized questions to the subject. Subjects will be provided information on how to contact an appropriate individual for pertinent questions about the research and their rights and whom to contact in the event that they sustain a research-related injury.

Documentation of consent will be recorded electronically via REDCap or an equivalent compliant system. Subjects will be sent the link to the consent form via encrypted email, and subjects will be given the phone number of a study team member to call after they have reviewed the consent. The study team member will then explain the consent to the subject, and ask if the subject has any questions. The subject will then electronically sign the informed consent document. Study personnel will verify identification before sanctioning an individual's electronic signature. An electronic or printed signed copy will be provided to the subject and a copy of the subject's consent to participate will be kept on a password-protected and secure drive at each study site.

Every site's eConsent link will be sent to the IRB for review before use in the study. Language consistency with the IRB-approved consent must be reviewed and approved by the IRB before eConsent is initiated.

If a subject is unable to provide an electronic signature during a remote visit, he or she will be required to sign a paper copy of the informed consent in the presence of a witness. The signature and date of the
witness will also be required on the paper copy. A separate record of the required elements of the ICF process will be documented in the subject’s study record.

13.3.1 Consent and Other Informational Documents Provided to Subjects

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention. The following consent materials are submitted with this protocol:

- Informed consent form adult subjects (Tiers 1 and 2)
- Informed consent form adult subjects (Tier 3)

13.3.2 Posting to ClinicalTrials.gov

The proposed study will be posted on clinicaltrials.gov.

13.4 Subject and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Investigators in this research will take all reasonable measures to protect the confidentiality of the medical records of patients and their families. Measures to protect confidentiality are as follows:

13.4.1 Storage of Study Materials

Investigators will take all reasonable measures to protect the confidentiality of the study subjects through the measures used in all PASC studies, including storage of study materials in locked, secure locations accessible only to study investigators, knowledge of the subject’s name only at the local institution, use of a UUID with no personal identifiers in the study database, and use of secure password protected computer access and encrypted transmission of patient information.

13.4.2 Hashed Identifiers

A unique subject hashed identifier, called a universal unique identifier (UUID), will be assigned to each study participant. The hashed identifier is a universal subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII) and at the same time be able to match participants across labs, databases, or research studies, while preventing multiple different identifiers for the same subject.

13.4.3 Reporting of Genetic Testing

At the end of the study, clinically actionable results of any whole genome sequencing performed during this study may be returned to the subject, if the subject has indicated on the consent form that s/he would like results returned. Clinically actionable means findings or results that would prompt clinical action by the subject’s medical provider because there is an established medical/therapeutic intervention, preventative approach, or other actions (e.g., changes in medication) available that could have the potential to change the clinical course of the subject’s disease or provide important pharmacogenetic information that is likely to impact future care.
Clinical genetic testing targeting known disease-associated variants will not be performed. There is a reasonable possibility that no findings will result from this research effort. If findings are detected, it may be years before any utility of these findings is realized. Further, if samples are “anonymized” prior to release to other investigators for future research, it may not be possible to trace the results back to the subject.

Genetic counseling will be offered to the subject and subject family to explain the results of genetic testing.

13.4.3.1 Reporting of Incidental Findings
Tests performed by certified clinical laboratories that are analytically valid and either clinically significant or medically actionable will be recorded in the participant medical record and will be reviewed by the Principal Investigator or other designated licensed medical professional at each site. If the Principal Investigator or licensed designee determine that the result is clinically significant or medically actionable, the participant will be contacted by telephone or in-person to explain the test findings within one week of the return of the test results. The participant will also be advised to follow up with their primary care physician. The results of incidental findings will be shared with subjects consistent with state and local regulation. Any additional testing ordered by the primary care physician will be paid by the participant or their insurance company.

Tests performed in research laboratories may provide results that indicate a clinically significant or medically actionable condition might be present. In such cases, the Principal Investigator or other designated licensed medical professional at each site will determine whether additional testing in a certified clinical laboratory is warranted. If the participant has requested return of incidental information from research laboratory testing, the Principal Investigator or other designated licensed medical professional at each site will order the testing at a certified clinical laboratory (costs billed to the grant). The results from the certified laboratory will be available in the participant medical record. If the Principal Investigator or licensed designee determine that the result from the certified clinical laboratory is clinically significant or medically actionable, the participant will be contacted by telephone or in-person to explain the test findings within one week of the return of the test results. The participant will also be advised to follow up with their primary care physician. Any additional testing ordered by the primary care physician will be paid by the participant or their insurance company.

13.4.4 Certificate of Confidentiality
Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, or representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject’s contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

To help us protect the privacy of subjects participating in the RECOVER cohort study, a Certificate of Confidentiality is issued by the National Institutes of Health (NIH). With this Certificate, the researchers of this study cannot be forced to disclose information that may identify a subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding. The Certificate cannot be used to resist a request for information from the United States government when it is used for evaluating federally funded study projects or for information that must be disclosed to meet the
requirements of the Food and Drug Administration (FDA). A Certificate of Confidentiality does not prevent a subject or his/her family from voluntarily releasing information about the subject's involvement in this research. If an insurer, employer, or other person obtains a subject's or family's written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

This study is a genome-wide association study and will comply with the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted GWAS, which calls for investigators funded by the NIH for GWAS to 1) share de-identified genetic (genotypic and phenotypic) data through a centralized NIH data repository; and 2) submit documentation that describes how the institutions have considered the interests of the research subjects, such as privacy and confidentiality. Submission of data to the NIH GWAS repository will be consistent with the permissions and limitations delineated on the study consent signed by study subjects. Information from DNA analyses and clinical studies or medical records may be placed into a central data repository in the future, such as the National Center for Biotechnology Information repository. Data and samples will be de-identified before submission to this or any other central repository. Note that “true” genetic testing in a certified laboratory for the purpose of diagnosing subjects' predisposition to conditions they don’t currently know they have will not be performed.

13.5 Research Use of Stored Human Samples, Specimens or Data

- Intended Use: Samples and data collected under this protocol may be used to study mechanisms and clinical manifestations of SARS-CoV-2 infection. It is anticipated that DNA testing will be performed in the future.
- Storage: Access to stored samples will be limited with policies and procedures requiring multiple reviews prior to release of any samples for analysis. Samples and data will be stored using UUID codes assigned by the investigators until the aliquots are used up. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using i2b2 at the PASC Investigator Consortium Data Resource Core. Each specimen will be labeled and tracked with a UUID.
- Disposition at the completion of the study: All stored samples will be sent to the RECOVER biorepository at Mayo Clinic. Study subjects who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.6 Future Use of Stored Specimens

Data collected for this study will be stored at the RECOVER biorepository at Mayo Clinic. After the study is completed, de-identified, archived data will remain at the biorepository, under the supervision of PI Dr. Mine Cicek, for use by other researchers including those outside of the study as determined by the policies and procedures of the RECOVER ancillary studies committee. The specimens will be retained indefinitely or until used up by future analyses. Permission to transmit data to the RECOVER Mayo Clinic biorepository will be included in the informed consent as an individual opt in component of the overall consent. Specific consent opt in will also be included for permission to conduct future genetic testing. Participant responses to these parts of the consent will be individually tracked in REDCap. Subjects who do not provide consent for biorepository or for genetic analyses will not have samples sent to the biorepository. Only individuals authorized by Mayo will have access to the samples. Samples will be identified by code and only the Data Resource Core will have access to the linking key between subject ID and subject identity.

With the subject's approval and as approved by the NYU sIRB and consortium central IRBs, de-identified biological samples will be stored at the RECOVER biorepository at Mayo Clinic. These samples could be used for research into the causes of long-term sequelae of SARS-CoV-2 infection, its complications and other conditions for which individuals with co-morbid conditions may be at increased risk, and to improve treatment. The RECOVER biorepository at Mayo may also be provided with a UUID that will allow linking the biological specimens, following study completion, with the phenotypic data from each subject, maintaining the masking of the identity of the subject.
During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed as samples will be fully anonymized and cannot be traced back to the subject.

When the study is completed, access to study data and/or samples will be provided through the RECOVER biorepository at Mayo Clinic as determined by the policies and procedures of the RECOVER investigator consortium ancillary studies committee and NIH Sponsor.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the study staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each subject enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the subject’s official electronic study record.

Clinical data and clinical laboratory data will be entered into the REDCap Central database, and then a HIPAA defined coded limited data set with UUID linkage and stored in the i2b2 data system (i2b2 Data Hub) provided by the RECOVER PASC Consortium Data Resource Core at Massachusetts General Hospital. A central instance of REDCap will be used for capture of structured data. The data capture system meets Federal data security requirements and includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. At the end of the study, all identifiers will be removed from the central REDCap database. Identifiers may remain in the local site research database if the participant has provided consent for contact for future research.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close out or 5 years after final reporting/publication. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the study protocol or MOP requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations associated with change in risk to subjects or compromise of scientific integrity of the study must be addressed in study source documents,
reported to RECOVER program scientific directors at NIH, the Clinical Science Core, and the RECOVER PASC DRC at Massachusetts General Hospital. Protocol deviations that do not impact risk or scientific integrity must be recorded on note to file and reported to the OSMB at 6-month intervals. Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

15 Study Finances

15.1 Funding Source

This study is financed through a grant from the Other Transactional Authority (OTA) of the US Federal Government. The study is overseen by the National Institutes of Health, National Heart Lung and Blood Institute (NHLBI).

15.2 Costs to the Subject

There are no costs to the subject related to participation in the study. The OTA grant will pay for all study related procedures and costs.

15.3 Subject Reimbursements or Payments

Sites will offer patients a nominal reimbursement for participation in the remote interval assessments (amounts to be determined by each enrolling site) and more substantial reimbursement for participation in each more invasive or time-consuming Tier 2 and Tier 3 tests (amounts to be determined by each enrolling site). Site compensation amounts will be reviewed and approved by local IRBs.

16 Study Administration

16.1 Study Leadership

The scientific leadership for the study and oversight of sites participating in the study is provided by the RECOVER Clinical Science Core (CSC) at the NYU Grossman School of Medicine. The RECOVER CSC collaborates with the RECOVER Data Resource Core at Massachusetts General Hospital for data management and data storage at the RECOVER biorepository at Mayo Clinic for biospecimen storage. The activity of the RECOVER Cores is overseen by a Steering Committee composed of the Core PIs, NIH Scientific Program leads, and Chairs of RECOVER PASC Consortium study committees, an Executive Committee composed of NIH Institute leadership and Centers for Disease Control leadership, and an OSBM composed of experts in longitudinal observation studies, epidemiology, bioethics, and biostatistics. The Steering Committee, Executive Committee and OSMB will meet at a minimum of twice yearly.

17 Conflict of Interest Policy

All recipient institutions and investigators in the PASC consortium will comply with the requirements of 42 CFR 50, Subpart F, "Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought" (FCOI Regulation), as implemented in the 2011 Final Rule for grants and cooperative agreements.
The requirements promote objectivity in research by establishing standards that provide a reasonable expectation that the design, conduct, or reporting of research funded under PHS grants or cooperative agreements will be free from bias resulting from any conflicting financial interest of an investigator. An "investigator" is someone defined as the PD/PI and any other person, regardless of title or position who is responsible for the design, conduct, or reporting of research funded by PHS, or proposed for such funding which may include, for example, collaborators or consultants.

Each Institution shall maintain an up-to-date, written, enforced policy on financial conflicts of interest that complies with the regulation and make the policy available via a publicly accessible Web site.

These FCOI requirements do not apply to Federal employees or Federal agencies. Federal agencies have their own set of rules governing financial conflicts of interest for employees.

When submitting a grant application, the signature of the Authorized Organization Representative (AOR) will certify each PASC Consortium applicant institution's compliance with the requirements of 42 CFR 50, Subpart F, including that:

- There is in effect at the Institution an up-to-date, written and enforced administrative process to identify and manage Financial Conflicts of Interest (FCOI) with respect to all research projects for which NIH funding is sought or received;
- The Institution shall promote and enforce Investigator compliance with the regulation's requirements including those pertaining to disclosure of Significant Financial Interests;
- The Institution shall identify and manage FCOIs and provide initial and ongoing FCOI reports to the NIH consistent with this subpart;
- When requested, the Institution will promptly make information available to the NIH/HHS relating to any Investigator disclosure of financial interests and the Institution's review of, and response to, such disclosure, whether or not the disclosure resulted in the Institution's determination of an FCOI;
- The Institution shall fully comply with the requirements of the regulation.
18 References


19 Appendices

19.1 Appendix 1: Schedule of assessments

* COVID Treatment not collected on uninfected controls.
Note that the 36-48m schedule will be repeated for subjects who are more than 48 months after infection while the study is still ongoing

<table>
<thead>
<tr>
<th>Category</th>
<th>Element</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Name and contact information</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Demographics</td>
<td>Alternate contacts</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Demographics</td>
<td>Date of birth</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Demographics</td>
<td>Race and ethnicity</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Demographics</td>
<td>Biological sex</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Demographics</td>
<td>Gender identity</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Demographics</td>
<td>Sexual orientation</td>
<td>Once, on enrollment</td>
</tr>
</tbody>
</table>

19.2 Appendix 2: Tier 1 topics, tests and procedures (see CRFs for specific questions and data fields)

All Tier 1 questions, tests and procedures may be done using home visits. All Tier 1 questions, tests and procedures may be done in pregnant populations. This includes the 30 second sit-to-stand, active standing test and electrocardiogram procedures which are no more than minimal risk. As the 30 second sit-to-stand and active standing test procedures involve sitting and standing for brief periods of time while blood pressure is taken, it does not pose a risk to pregnant individuals.
<table>
<thead>
<tr>
<th>Category</th>
<th>Element</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Marital status</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Education</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Number of people in household</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Homelessness</td>
<td>At infection and every 3 months thereafter, if address changes</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Description of living place</td>
<td>At infection and every 3 months thereafter, if address changes</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Community cohesion</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Primary language</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Fluency in English</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Birthplace</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Financial insecurity</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Employment</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Income in 2019</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Access to health care</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Health insurance</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Loss of insurance because of COVID pandemic</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Hunger Vital Sign</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Discrimination</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Category</td>
<td>Element</td>
<td>Interval</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Social support</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Social determinants</td>
<td>Alcohol and substance use</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Baseline disability</td>
<td>Baseline disability</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Acute COVID</td>
<td>Diagnosis method</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Acute COVID</td>
<td>Site and level of care for initial infection</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Acute COVID</td>
<td>Treatments received for initial infection</td>
<td>Once, on enrollment</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Pregnancy status</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Pregnancy outcomes</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Vaccination status and vaccine details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Immunocompromised condition and specific types</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Rheumatologic, autoimmune or connective tissue disease and specific types</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Diabetes and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Kidney disease and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Active cancer and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Dementia or cognitive impairment and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Central nervous system infection, inflammatory disease or demyelinating disease and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Seizure disorder</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Neuromuscular disease and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Movement disorder and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Cardiovascular disease and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Stroke or bleed and specific type</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Asthma</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Chronic obstructive pulmonary disease</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Category</td>
<td>Element</td>
<td>Interval</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Other chronic lung disease</td>
<td>At infection and every 3 months</td>
</tr>
<tr>
<td>Category</td>
<td>Element</td>
<td>Interval</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Headache details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Chest pain details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Shortness of breath or trouble breathing and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Cough</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Palpitations, racing heart, arrhythmia, skipped beats</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Swelling of lower legs and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Gastrointestinal symptoms and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Bladder problems and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Nerve problems and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Problems with anxiety, depression, stress, or trauma-related symptoms like nightmares or grief</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Depression screen and assessment</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Anxiety screen and assessment</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Stress</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>PTSD screen and assessment</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Prolonged grief screen and assessment</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Problems thinking or concentrating and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Problems with sleep and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Faint, dizzy, &quot;goofy,&quot; difficulty thinking soon after standing up from a sitting or lying position and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Color changes in your skin, such as red, white or purple and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Skin rash</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Changes in sweating</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Excessively dry eyes</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Category</td>
<td>Element</td>
<td>Interval</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Excessively dry mouth</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Excessive thirst</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Vision problems (blurry, light sensitivity, difficulty reading or focusing, floaters, flashing lights, &quot;snow&quot;) and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Problems with hearing (hearing loss, ringing in ears) and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Hair loss</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Problems with teeth or gums</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Change in menstruation or menopause and details</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Changes in desire for, comfort with or capacity for sex</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Post-COVID utilization</td>
<td>Hospitalization since COVID or last assessment</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Post-COVID utilization</td>
<td>Emergency department visit since COVID or last assessment</td>
<td>At infection and every 3 months thereafter</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Height, weight, BMI</td>
<td>0, 6 months after infection then yearly</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Waist circumference (cm)</td>
<td>0, 6 months after infection then yearly</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Seated vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation)</td>
<td>0, 6 months after infection then yearly</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>30 second sit to stand</td>
<td>0, 6 months after infection then yearly</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Active standing test</td>
<td>0, 6 months after infection then yearly</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Wearable with continuous remote monitoring for ECG, RR, SpO2, sleep fragmentation, actigraphy</td>
<td>Every six months</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Comprehensive metabolic panel with cystatin-C</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Complete blood count with differential</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Lipid panel</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Hemoglobin A1c</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Coagulation panel</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>D-dimer</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Category</td>
<td>Element</td>
<td>Interval</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Troponin</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>NT-pro BNP</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Thyroid panel</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>25-hydroxy vitamin D</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Urinalysis</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Urine microalbumin and creatinine</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Anti-nuclear antibody</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Anti-CCP</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Rheumatoid factor</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>hsCRP</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>EBV DNA PCR</td>
<td>0, 6 months after infection then yearly if abnormal</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>SARS-CoV-2 antibody</td>
<td>On enrollment for uninfected controls and positives without confirmatory test</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>SARS-CoV-2 NAAT</td>
<td>On enrollment for uninfected controls</td>
</tr>
</tbody>
</table>

19.3 Appendix 3: Tier 2 questions, tests and procedures

These questions may be asked of or tests may be conducted on ~30% of patients, including those meeting trigger criteria plus a random sample of those not meeting criteria. Tests and procedures will occur not more than once a year for a maximum of four times, if indicated. Indications for each question and test are specified in the manual of operations.

All Clinical assessments, laboratory studies and procedures may be done by pregnant populations except CT scanning. All remaining radiological procedures do not involve radiation and pose no risk to pregnant individuals.

(+Questions, tests and procedures which may be completed at home visits.)

<table>
<thead>
<tr>
<th>Category</th>
<th>Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>Home sleep test+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>6 minute walk test+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Neurologic exam</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Rehabilitation exam</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>ENT exam</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Mini International Neuropsychiatric Interview (MINI)</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Vision screen+</td>
</tr>
</tbody>
</table>
### 19.4 Appendix 4: Tier 3 tests and procedures

These questions and tests may be performed on ~20% of subjects. Tier 3 tests and procedures that are more than minimal risk (indicated with an asterisk) will not be performed more than once for the entire duration of the study. Triggers for each question and test are specified in the manual of operations.

All clinical assessments and laboratory studies may be done in pregnant populations. The full cardiopulmonary exercise testing, and facility-based sleep study may also be done in pregnant individuals as these pose no more than minimal risk.

(*Greater than minimal risk) (+Questions, tests and procedures which may be completed at home visits.)

<table>
<thead>
<tr>
<th>Category</th>
<th>Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>Smell Test+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>NIH Toolbox oral reading recognition test age 3+ v2.0+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>NIH Toolbox picture vocabulary test age 3+ v2.0+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>NIH Toolbox auditory verbal learning test (Rey) 8+ v2.0+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>NIH Flanker inhibitory control and attention test age 12+ v2.1+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>NIH Toolbox pattern comparison processing speed test age 7+ v2.1+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>NIH Toolbox picture sequence age 7+ v2.1+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Anti dsDNA antibody+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Ro antibody+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>La antibody+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Smooth muscle antibody+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>RNP antibody+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>ACTH and cortisol+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Hepatitis B and C testing+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Cytokine panel (IL2 receptor; IL 1beta, 2, 4-6, 8, 10, 13, 17; interferon gamma, TNF alpha)+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>ICAM-1+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Insulin c-peptide+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Oral glucose tolerance test (time points 0, 60, 120 min)</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Fecal WBC</td>
</tr>
<tr>
<td>Radiology</td>
<td>Volumetric non contrast chest CT (with inspiratory/expiratory scans)</td>
</tr>
<tr>
<td>Radiology</td>
<td>Dual energy chest CT with contrast</td>
</tr>
<tr>
<td>Radiology</td>
<td>Resting transthoracic echocardiography + strain imaging</td>
</tr>
<tr>
<td>Radiology</td>
<td>Renal ultrasound</td>
</tr>
<tr>
<td>Radiology</td>
<td>Fibroscan</td>
</tr>
<tr>
<td>Procedure</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Procedure</td>
<td>Pulmonary function tests (no medication hold) with lung volumes, resting SpO2 and single breath diffusion capacity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>Complete eye examination including optical coherence tomography</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Complete neurocognitive testing+</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td>Endopat testing</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Supine and upright plasma catecholamine testing+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Serum protein immunofixation eletropheresis+</td>
</tr>
<tr>
<td>Category</td>
<td>Element</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Serum B12 with metabolites+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>CPK, aldolase, myositis panel+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Neurofilament light chain+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Fecal SARS-CoV-2 viral load (viral RNA and/or antigen) +</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Fecal calprotectin+</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Total Tau (single molecule array SIMOA) +</td>
</tr>
<tr>
<td>Laboratory study</td>
<td>Anti-Mullerian hormone</td>
</tr>
<tr>
<td>Radiology</td>
<td>MRI brain with and without gadolinium</td>
</tr>
<tr>
<td>Radiology</td>
<td>Cardiac imaging with meta-iodobenzylguanidine (mIBG)*</td>
</tr>
<tr>
<td>Radiology</td>
<td>Cardiac MRI, with and without gadolinium contrast*</td>
</tr>
<tr>
<td>Radiology</td>
<td>Gastric emptying study*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Nerve conduction study*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Electromyography*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Skin biopsy*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Muscle biopsy*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Lumbar puncture*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Facility-based sleep study</td>
</tr>
<tr>
<td>Procedure</td>
<td>Tilt table testing</td>
</tr>
<tr>
<td>Procedure</td>
<td>Cardiovagal innervation testing</td>
</tr>
<tr>
<td>Procedure</td>
<td>Full cardiopulmonary exercise testing</td>
</tr>
<tr>
<td>Procedure</td>
<td>Bronchoscopy*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Right heart catheterization*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Upper endoscopy*</td>
</tr>
<tr>
<td>Procedure</td>
<td>Colonoscopy with or without biopsy*</td>
</tr>
</tbody>
</table>