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 7.0

Revision history

Revision #	Date	Changes
1.0	9/16/2021	Original release
1.1	10/08/2021	Revision to inclusion/exclusion criteria; revisions to appendices 2 and 3
2.0	10/18/2021	Revisions to appendices 2, 3 and 4
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.
4.0	01/27/2022	Section 4.1: * clarified that pregnant women can not undergo cardiopulmonary exercise testing

		* added language regarding risks to bronchoscopy, right heart cardiac catheterization, upper endoscopy, colonoscopy * removed text allowing return of research laboratory results * clarified risk of genetic testing language Section 6.3.1: Added that subjects may receive information about the study through videos, slides, pamphlets or website information. Section 8.4: Added new section permitting one-time off schedule visits during on-study infections Section 9.6: Clarified which PHI elements are in the central database and which are retained locally by sites Section 9.7.6: Noted that only data that have already been shared for research will not be destroyed if a subject withdraws from the study Section 12.1: Updated hypotheses to be tested according to latest version of statistical analysis plan Table 2: Added an additional row for sample size calculations; corrected data in one other row Section 12.3.1: Corrected number of aliquots that can be collected per SST tube Section 12.5: Removed analytic details and referred instead to more detailed SAP (included as attachment) Section 13.3.1: Added that materials such as videos, slide presentation and scripts may be used to aide in the consent process. Section 13.4.3.1: Removed option to return research lab results Appendix 2: Corrected table to indicate Tier 1 lab tests are performed at 0, 3, 6 months Appendix 3: Clarified which procedures pregnant women cannot do; moved fecal viral load to Tier 2 Appendix 4: Clarified which procedures pregnant women cannot do; indicated which procedures may be performed under sedation
5.0	03/22/2022	Section 4.1: Added risk of brain infection to Lumbar Puncture Section 7.1: Updated the recruitment window from 24 to 36 months Section 7.2: Amended exclusion criteria to exclude some types of pregnant subjects from adult cohort sites Section 8.1: Added that uninfected pregnant individuals begin study schedule on delivery date Section 9.4: Removed option for MITRA or other home blood collection device

		Section 10.3.1: Changed IRB reporting deadline from 5 to 10 days Section 10.4: Section added to describe process for ensuring participant safety when survey response indicates suicidal ideation Section 14.3 Changed IRB reporting deadline from 5 to 10 days; clarified type of protocol deviations to be reported to OSMB Appendix 1: Added figure legend. Indicated that Office visit, labs, biospecimens may be collected at 48 months after infection and thereafter if participant is still within study follow up period Appendix 2: Replaced “infection” with “enrollment” throughout Appendix 3: Added that women <3 months post-partum can not have any tests that pregnant women can not have Appendix 4: Specified methylmalonic acid to be drawn with serum B12; added that women <3 months post-partum or breastfeeding can not have any tests that pregnant women can not have
5.1	03/28/2022	Appendix 2: Corrected clinical assessment and laboratory timeline to start from infection not enrollment
6.0	8/11/2022	Protocol Summary: Revised the earliest date of possible infection from March to January, 2020 Section 4.1: Removed reference to lung plethysmography Section 6.1: Revised Figure 1 to include acute reinfected participants Section 6.3.1: Removed 15% cap on self-referral participants Section 6.3.2: Added additional retention strategies Section 7.1: Added note that participants should be willing to participate in the overall protocol and should expect to be available for the duration of the study to meet inclusion criteria; added several clarifications to inclusion criteria to match MOP. Section 7.3.2: Added section on Prisoners to indicate long-term incarcerated subjects are not eligible. Section 7.3.3: Added section on “Inclusion of Students and Employees in Research” to clarify the measures taken to include these vulnerable populations if passively recruited. Section 7.4: Added section “Loss to Follow-Up” to document how sites should proceed if participants cannot be reached or choose not to continue with participation Section 7.5: Clarified “Subject Withdrawal” to differentiate withdrawal of consent from cessation of participation or loss to follow-up.

		Section 8.1: Added instructions for starting study schedule at time of acute reinfection (enrollment) for previously infected participants enrolling during an acute infection. Section 9.4: Revised the biospecimen tube protocol to include the reduction in CPT tubes and addition of sodium citrate and EDTA tubes. Added instructions for biospecimen collection for acute on-study reinfection. Section 9.7: New section on reading centers Section 10.1: Revised definition of adverse event for clarity to clearly exclude data collected as potential PASC outcomes; additional textual clarifications Section 10.2: Clarified recording of adverse events in REDCap Section 10.3: Clarified reporting of new information to the IRB Section 12.3.1: Removed details of biospecimen processing in favor of referral to biospecimen MOP Section 14.3: Noted that protocol deviations captured by data reports do not need to be individually filed in REDCap Appendix 1: Changed the color of the comorbidity row to indicate participation completion only. Clarified that the post-48 month study schedule repeats starting at 39 month schedule Appendix 2: Moved ANA, anti-CCP, RF, EBV to Tier 2; removed reference to lung volumes Throughout: Revised minor formatting and grammatical errors
6.1	9/29/2022	Section 6.3.1: Added waiver of authorization language
7.0	12/15/2022	Section 4.1: Added risks of oral glucose tolerance test and pulmonary function test Sections 4.1, 8.2 and 9.4: Added collection of tears as a biospecimen Section 9.8: Added section on the mobile health platform Section 9.9: Revision of data management section to include that data will also be collected from wearable devices. Section 9.9.4: Added subsection on FISMA moderate environments Section 10.1: Revision of definition of adverse event to align with revised NYULH IRB policy manual Section 10.3: Revision of reporting requirements of reportable new information to align with revised NYULH IRB policy manual Section 13.3: Added that group information sessions are allowed.

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

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

SOP	Standard Operating Procedure
US	United States
UUID	Universally Unique Identifiers
WHO	World Health Organization

1 Table of Contents

1 Protocol Summary

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
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 January 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 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, MHS Professor, Department of Population Health at NYU Grossman School of Medicine 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 Data Resource Core	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-documented [5-8], 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, tears, 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: Some patients may get tired or short of breath or have palpitations during these tests. There is minimal medical risk from these tests.

Pulmonary function tests (PFTs): Some people may feel dizzy or lightheaded during the test. If patients are given the medicine albuterol during this test, they may have side effects. Side effects of albuterol include feeling nervous, shakiness, headache, sore throat or nostrils, and muscle aches. More serious, but less common, side effects of albuterol include a fast heartbeat or feeling like their heart is pounding

Oral glucose tolerance test: There is minimal medical risk from this test. After drinking the sugary liquid, patients may have some side effects. Side effects may include feeling sick to their stomach (nausea), feeling sweaty, or feeling dizzy or like they might faint. People with diabetes may have high blood sugar after the test. They may need to take a dose of their regular diabetes medicine after the test if their blood sugar is high.

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.

Sedation administration: Several study procedures (including bronchoscopy, right heart cardiac catherization, upper endoscopy and colonoscopy with or without biopsy) include the use of sedation, which may slow the breathing or lower the blood pressure or cause transient cognitive impairment; these can be treated with oxygen or fluids and a lower dose of sedation.

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, including low risk of developing brain 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. There may also be risks associated with the use of sedation. 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). There may also be risks associated with the use of sedation. 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.

Cardiopulmonary exercise testing: Complications of exercise testing are rare. Major complications of exercise testing may include abnormal heart beats (arrhythmias), change in blood pressure (for example, too high or too low), heart attack (myocardial infarction), muscle, bone, or joint injury, or death. These complications happen in less than 1 in every 5,000 to 10,000 tests, with death estimated at 1 in every 20,000 tests. 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. There may also be risks associated with the use 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. There may also be risks associated with the use 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 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. The consent form will inform the participant of the potential for actionable results and will ask participants whether they would like to be informed 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 factors(s) that contribute to PASC progression.

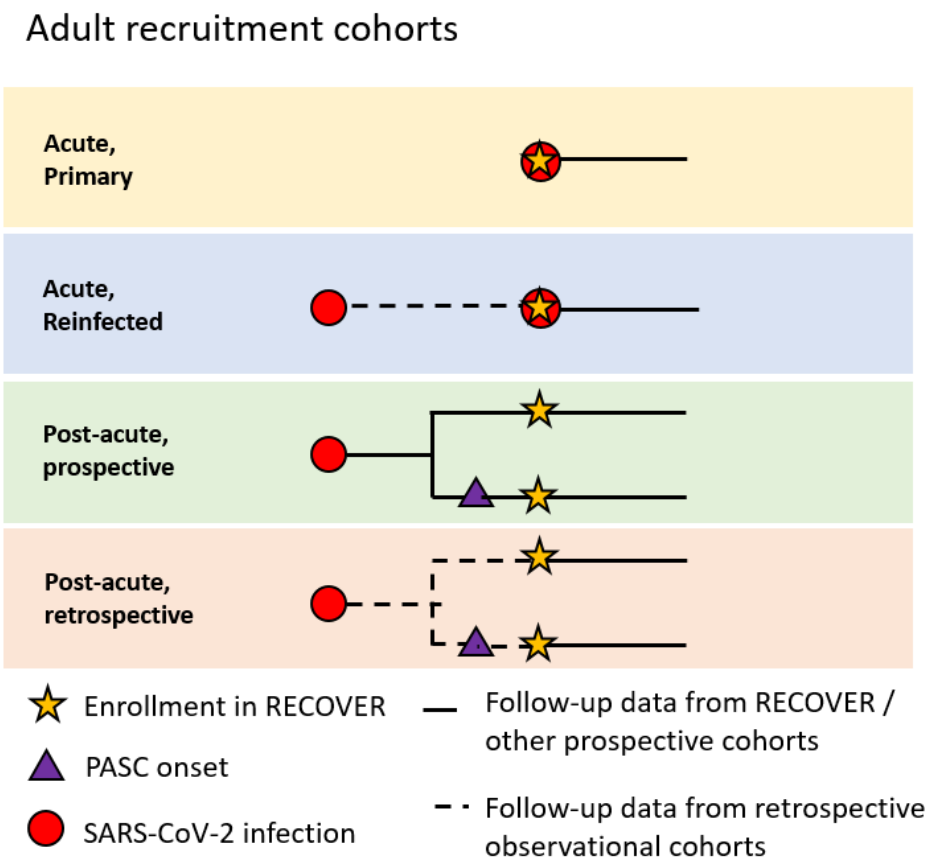
6 Study Design

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 first 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.

Figure 1: Enrollment plan for people with infection



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 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 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.

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 de-identified and retained per section 14.2. A waiver of authorization will be in place at participating sites so study teams can review patient medical records to identify potential subjects who meet eligibility criteria.

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.

Additional information sent to or available to subjects prior to enrollment may include videos, slide presentations, pamphlets, or website information that provide a general overview of the study and/or more details about the informed consent form. Subjects may view these materials prior to in-person discussion. All materials will be submitted to the IRB for approval prior to their use. 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, through newsletters or other periodic outreach, through personalized periodic contact (e.g., birthday greetings), by rollout of a mobile application, 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 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 reviewed for health literacy to ensure comprehension among participants of varying literacy levels.

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 overall study 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 study-wide. Individuals at risk of withdrawing from the study because of burden may, on a case-by-case basis, be offered: the option to skip an interval assessment (e.g. if traveling); the option to skip a survey instrument that is not the PASC symptom survey; the option to increase the interval of assessments to 6 months; home-based Tier 2/3 assessments where feasible; or, if no other strategy is acceptable, the option to return for a final assessment only.

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 must have suspected, probable, or confirmed SARS-CoV-2 infection as defined by WHO criteria within 36 months of enrollment, or positive SARS-CoV-2 infection-specific antibody testing, to meet inclusion criteria
- Participants must be willing to generally comply with the overall protocol (e.g. can not agree to participate only for survey collection) and must expect to be available for the duration of the study.

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.
Note: Signs separated with a slash (/) are counted as one sign, in which the slash means “OR” (i.e., participants may have anorexia and/or nausea and/or vomiting; any combination of these symptoms counts as one of three symptoms needed to meet clinical criteria).

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 and within households or within the community; anytime within the 14 days before symptom onset.

Note: For purposes of this protocol, we define “community transmission” as any county with at least substantial community transmission according to the CDC definition (50 or more cases per 100,000 in the past 7 days). If the participant has traveled to or from another country, use the most granular data available to determine transmission in that area. Historical data about community transmission levels can be found in the MOP.

b) A patient with severe acute respiratory illness: (acute respiratory infection with history of fever or measured fever of ≥38C°; and cough; with onset within the last 10 days; and requires hospitalization).
c) A person with a positive SARS-CoV-2 Antigen-RDT who is asymptomatic or meets some but not all clinical or epidemiologic criteria.

Note: A patient who meets criteria for suspected SARS-Cov-2 infection who had a negative test at the time does NOT qualify as an infected case.

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 (Not applicable to the RECOVER adult protocol)

Note: A patient who meets criteria for probable SARS-Cov-2 infection who had a negative test at the time does NOT qualify as an infected case.

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) OR positive SARS-CoV-2 antibody test*;
b) Any person with a positive SARS-CoV-2 Antigen-RDT (including home-administered rapid test) 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 (including home-administered rapid test) 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

*This protocol modifies the WHO criterion a to add detectable SARS-CoV-2 antibody as a qualifying test

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
- Has negative NAAT SARS-CoV-2 testing from a respiratory specimen performed at the time of enrollment/screening AND
- Has a negative SARS-CoV-2 nucleocapsid protein antibody and spike protein antibody test (spike only if not vaccinated) performed at the time of enrollment, AND
- Lives in the same communities or recruited from the same sources as those in the SARS-CoV-2 infected cohort

Note: uninfected individuals may participate independent of their vaccination status

7.1.1 Change in Infection 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 as children in the study NIH RECOVER-Pediatric: Understanding the long-term impact of COVID on children and families; individuals participating as caregivers are eligible for inclusion in the adult protocol
- Incarcerated individuals
- For adult cohort sites only: individuals who were pregnant at the time of their COVID infection or qualifying negative test, and whose pregnancy is ongoing.
- For adult cohort sites only: individuals who were pregnant at the time of their COVID infection or qualifying negative test, and whose pregnancy is completed and resulted in a live birth.
    - Individuals who were pregnant at the time of COVID or qualifying negative test and who did not have a live birth remain eligible for inclusion at adult cohort sites.
    - Individuals who were pregnant at the time of COVID or are currently pregnant, regardless of pregnancy outcome, remain eligible for inclusion at pregnancy cohort sites

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

7.3 Vulnerable Populations

7.3.1 Pregnant Participants

Data from pregnant participants 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 participants 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. Participants 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 pregnancy sites in the RECOVER Network and is consistent with the pediatric protocol. At these sites, participants 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.

7.3.2 Prisoners

Long-term incarcerated individuals will not be enrolled in the study. If an enrolled participant becomes incarcerated, the IRB should be notified immediately. If the incarceration is short-term (i.e., less than 90 days), the participant can remain in the study.

7.3.3 Students and Employees

Students and employees recruited as research subjects are more vulnerable to coercion or undue influence. Students may feel their participation in research is necessary as part of their academic requirements, or that failing to participate will negatively impact their relationship and

academic/professional opportunities with the instructor/investigator. Employees may feel unable to exercise free choice in their decision to participate, due to belief that their decision may affect (favorably or unfavorably) their performance evaluations, advancement opportunities, or other employment-related decisions. The appearance of coercion and undue influence of employees/students must be minimized in recruitment methods, including the informed consent process, and other procedures. The informed consent process must include a discussion stating that the subject's decision to participate will not impact the status of employment, academic status, and/or grades respective to the target subject population.

Students or employees will not be specifically targeted for participation in this protocol, but will also not be excluded based on these protected statuses. Passive recruitment methods, such as those that require the employee/student to reach out regarding participation include, but are not limited to: an unassociated, non-supervisory recruiter; IRB approved flyers; site-wide e-mails to specific groups that encourage those interested to reach out for information. All prospectively enrolled students or employees will be informed of the specific risks to privacy and confidentiality that may be compromised prior to signing consent. This information may include sensitive topics included in the RECOVER protocol including, but not limited to, comorbidities, mental health, sexual behavior, and/or drug/alcohol use.

7.4 Loss to Follow-up

Subjects may be considered lost to follow-up if they have missed at least three consecutive study visits and are not responsive to the site's contact attempts or offers to reduce participant burden (see **Retention Strategy**). For each missed visit, the site should attempt to contact the participant through at least three different methods at different times. Contact methods include, but are not limited to, email, phone calls, certified letters, and/or contacting their emergency contact. An IRB-approved appointment reminder letter can be used for this purpose. If a participant contacts or returns to the site even after multiple missed follow-up visits, they should be given the option to resume participation in the study. If a participant is lost to follow-up or declines future visits, their data will be retained for future use unless they provide written documentation to withdraw their consent (see Error! Reference source not found.); however, no additional data will be collected.

Should a study participant return after a period of no contact, study staff should conduct the closest visit based on their schedule.

7.5 Subject Withdrawal

Subjects are free to stop participating in the study at any time upon request. However, if the subject desires to withdraw consent from participation, this includes destruction of collected data and biospecimens. The subject must provide a written notice of withdrawal of their consent (either via letter or e-mail) to the study site PI clearly stating that they wish all eligible data,biospecimens (if collected) to be destroyed. Once the subjects withdraw their consent to participate, 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. Subjects may not re-enroll in the study once they have withdrawn their consent, and deleted data cannot be reversed.

7.6 Premature Termination or Suspension of the Study or a Participant

This study or a participant may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for 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
- 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 first infection for those enrolled during first infection or after their first infection without an active infection at time of enrollment; at time of reinfection if enrolled during an acute infection; or at time of negative COVID-19 test, for those who are uninfected. Uninfected pregnant individuals will begin the study schedule on their delivery date. See Table 1. Collection will be tiered such that all enrolled patients will undergo Tier 1 data collection, and those with abnormal findings on Tier 1 collection may 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 annually, which can be provided at home if provisions are made for home blood and biospecimen collection.

Table 1: Index date and study schedule date, by enrollment type

Enrollment Category	Index Date	Study Schedule Start Date
Acute Infected (First Infection)	**First** positive SARS-CoV-2 test result date or, if test not available, date of COVID symptom onset	Same as Index Date
Acute Infected (Reinfected)	**First** positive SARS-CoV-2 test result date or, if test not available, date of COVID symptom onset	**Most recent** positive SARS-CoV-2 test result date or, if test not available, date of COVID symptom onset
Acute Uninfected	Qualifying negative SARS-CoV-2 test result date	Same as Index Date
Post-Acute Infected	**First** positive SARS-CoV-2 test result date or, if test not available, date of COVID symptom onset	Same as Index Date
Post-Acute Uninfected	Qualifying negative SARS-CoV-2 test result date. For pregnancy sites **only**, index date is the prior delivery date.	Same as Index Date

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 or contracted clinical examiners (such as Exam One) and will follow COVID safety protocols for the duration of the visit. As only delegated 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: Tier 1 topics, tests and procedures (see CRFs for specific questions and data fields), Appendix 3: Tier 2 questions, tests and procedures, and Appendix 4: Tier 3 tests and procedures.

8.2 Baseline/Enrollment Visit

A core set of questions on demographics, habits, social determinants of health, comorbidity, medications, 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. 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, tears, 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 19.1Appendix 1: Schedule of assessments for schedule of assessments.

8.3 Follow-up Visits

A current symptom inventory (Appendix 2: Tier 1 topics, tests and procedures (see CRFs for specific questions and data fields)) 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). See MOP for details of how tests are selected and conducted.

8.4 One time Visits

Participants who develop COVID while enrolled in the study may be eligible for a one-time off-schedule study visit that will follow the protocol for month 0 (acute infection) visit, if the infection is identified within the acute infection window, and if it is the first repeat infection while in the study. See MOP for details of handling of on-study infections in previously uninfected vs infected participants.

9 Study Procedures/Evaluations

9.1 Tier 1 Assessments

Tier 1 assessments are listed in Appendix 2: Tier 1 topics, 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 index date (or enrolled date if acute reinfected) if enrolled during that time period, and then yearly, if the participant has consented to provide biospecimens:

- Nasal swabs in freeze medium
- Blood
    1. 2 x 8.0 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
    4. 2 x 2.7 mL Sodium citrate tubes – for plasma collection
    5. 1 x 10.0 mL EDTA tube – for plasma and white blood cells (WBCs) collection

The following additional biospecimens will be collected on a different schedule:

- Saliva (on enrollment only, if the participant has consented to genetic testing)
- Stool and urine (on enrollment and at year 2)
- Tears (schedule to be determined)

Patients undergoing the Oral Glucose Tolerance Test who have also consented to provide additional biospecimens for future research will have the following samples collected and sent to the biospecimen core. These samples are taken from the SST tubes that are collected for central lab assessments; no additional volume will be collected solely for biospecimens.

- 4 x 1.4mL matrix tubes for PBC aliquoting

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

The following biospecimens will be collected for banking at the one-time on-study reinfection visit if the participant has consented to provide biospecimens:

- Nasal swabs in freeze medium
- Blood
    1. 2 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
    4. 2 x 2.7 ml Sodium citrate tubes – for plasma collection
    5. 1 x 10 ml EDTA tube – for plasma and white blood cells (WBCs) collection
- Stool and urine

If saliva was previously collected it does not need to be repeated for this one-time reinfection visit.

Table 2: Biospecimen collection schedule

Biospecimen	Baseline	On Study Reinfection	3M	6M	12M	24M	36M	48M
Nasal Swab	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blood	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Saliva	Yes*	Only if not previously collected*	No	No	No	No	No	No
Stool	Yes	Yes	No	No	No	Yes	No	No
Urine	Yes	Yes	No	No	No	Yes	No	No

*if participant has agreed to genetic testing

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, in the mobile health platform 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 centrally and included in the main study database include date of birth, zip code, 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. Sites will retain other PHI elements locally in a HIPAA-compliant manner for purposes of follow up and data retrieval. See Table 3 for PHI elements that may be collected locally.

Table 3. PHI that will be collected for this study

Protected Health Information (HIPAA Identifiers)	
1	Names
2	Street Address
3	Any of the following: City, State, Zip Code
4	Date of Birth
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")
6	Telephone numbers
7	Fax numbers
8	Electronic mail addresses
9	Social security numbers
10	Medical record numbers
11	Health plan beneficiary numbers

9.7 Reading Centers

For some Tier 2 and Tier 3 procedures, reading centers will be utilized to develop and implement standardized protocols and case report forms, train site study staff, monitor site performance for safety, analyze and interpret the readings/scans/tissue, and implement quality control and quality assurance programs. Selection criteria for the reading centers will take into account the experience of the center in clinical interpretation and collaboration with investigators in multisite clinical research.

9.8 Mobile Health

The Mobile Health Platform (MHP) and Mobile Health Data Repository (MHDR) teams will implement a mobile health program to augment data collected by this study and to promote participant engagement and retention. Participation in the mobile health program is optional.

The Mobile Health Program includes the following components:

- **Mobile application** – A secure smartphone application developed and managed by the MHP team (CareEvolution) will be deployed to participants who elect to use it. This application will enable participants, at their sole discretion, to report a new COVID infection, to share data from their cell phones and/or a wearable devices, such as a Fitbit or an iWatch, ~~and~~ to share their electronic health records, and to track their symptoms. Prior to downloading the application, participants will be provided an IRB-approved mobile health information sheet that describes the mobile health program, including information about the vendor, terms of use, and how to stop using the app. The purpose of the information sheet is to ensure that the participant is informed on the key points of the program. Once the participant agrees to be part of the MHP, study staff will send them an email or, if they consented to received text messages, study staff will send them a text message with a link to download the application. From there, the participant will be able to download the app, NOTE: Study participants previously will have signed a consent form that includes a description of data that may be collected by the MHP.
- **Mobile Health Data Repository (MHDR).** The MHP team will transfer mobile health data to the MHDR team (Sage BioNetworks). The MHDR team is responsible for harmonizing, curating and analyzing mobile health data before it is transferred to the RECOVER Data Resource Core (DRC).

9.9 Data Management

There will be two tools to collect study data. The first is an electronic data capture (EDC) system called REDCap. This secure HIPAA compliant electronic data capture system will enable study coordinators to record participant data. The second is a secure app that participants will be able to download to their mobile dervices. This mobile app will record information that participants provide and will enable the collection of wearable device data and the collection of electronic health data. The mobile health data will be transferred to a platform managed by the MHDR team, where it will be harmonized and curated.

Both the REDCap data and the mobile data will be transferred to the DRC, where it will be harmonized with additional data types.

All RECOVER tools for capturing and harmonizing data reside in FISMA-moderate compliant cloud environments. Access to this aggregated study database will be limited to HIPAA-certified investigators who have been approved for participation in this study.

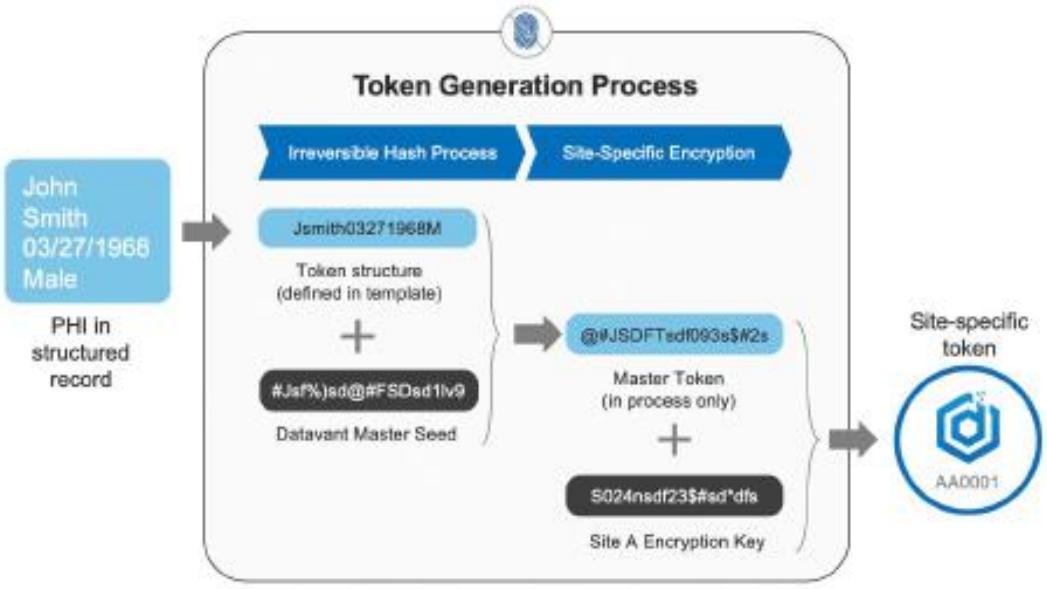
If any information is shared with external interested site(s), data use agreements will be established.

9.9.1 Data Transfer from Enrolling Sites to DRC

Recruiting sites will not send any PHI to the DRC except date of birth (DOB) and 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). Recruitment sites may enter identifiers in REDCap Central. 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.

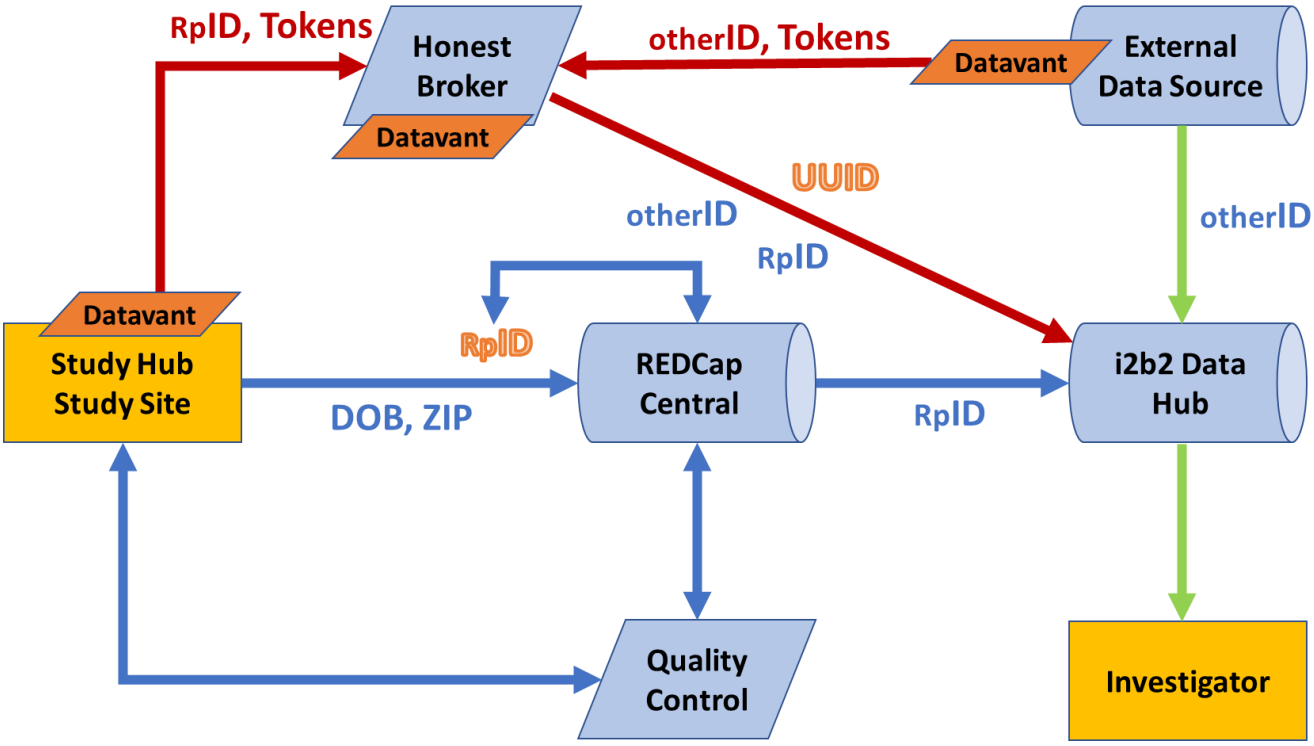
Figure 2: Token generation process



:

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



9.9.2 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 extxract, 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.

9.9.3 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.

9.9.4 FISMA moderate environments

All software in use as part of the study is hosted on secure, FISMA-moderate cloud environments. These environments leverage all the management and security systems, controls, change control methodologies, training documentation, and third party security testing (e.g. penetration testing) and assessments (e.g. 3PAO reviews) that are required to obtain a FISMA authority to operate (ATO).

- **Mass General Brigham FISMA Azure cloud environment** – Hosts i2b2, which enables data harmonization. In the future, REDCap Central and all statistical analysis tools will be migrated to this environment.
- **Harvard Medical School FISMA AWS cloud environment** – REDCap and statistical analysis tools, such as R, SAS, and SQL Server have been hosted at Harvard Medical School. These tools will transition to the Mass General Brigham FISMA cloud environment in 2023 and at this point the Harvard Medical School FISMA cloud environment will be retired from the RECOVER study.
- **Mobile Health Platform (MHP) FISMA cloud environment** – Hosts the mobile app and the coordinator console.
- **Mobile Health Data Repository (MHDR) FISMA cloud environment** – Hosts the mobile health data pipelines and the data portal that enables investigators to access mobile health data.

9.9.5 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.

9.9.6 Data Destruction

When participants withdraw consent from the study and ask for their data to be destroyed, 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 consent 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 that have already been used for research will not be destroyed at the time of consent 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.

9.9.7 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.

9.9.8 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 event, incident, experience, outcome, or new information that meets **all** of the following criteria:

- unexpected in nature, severity, or frequency given the information provided in research-related documents and characteristics of the subject population being studied; and
- is related or possibly related to participation in the research; and
- suggests that the research caused harm to subjects or others or places subjects or others at increased risk of harm (including physical, psychological, economic, or social harm). than was previously known or recognized

Please refer to 10.3 for reporting requirements.

Adverse Event
An **adverse event** (AE) is defined as any physical and psychological harm occurring to subjects during the course of participating in research, whether or not it is related to participation in the research (**excluding** symptoms, signs and co-morbidities already captured in the PASC symptom, co-morbidity, laboratory results or procedure results forms), or an adverse consequence of a study-related procedure. An AE can be any unfavorable or unintended event that is temporally related to the research.

Known manifestations of acute and post-acute SARS-CoV-2 infection will be recorded as endpoints on the PASC symptom, co-morbidity, laboratory results or procedure results forms in REDCap, rather than as AEs or SAEs, even if occurring in uninfected individuals.

Serious Adverse Event
Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal, OR
- life-threatening, OR
- requires or prolongs hospital stay, OR
- results in persistent or significant disability or incapacity, OR
- a congenital anomaly or birth defect, OR
- 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 participant, 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 a serious adverse event.

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 and is not captured in existing RECOVER study forms as detailed above.

Post-study Adverse Event
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.

10.2 Recording of Adverse Events in REDCap

At each contact with the participant, the investigator will seek information on adverse events. Information on all adverse events will be recorded immediately in the adverse event form in REDCap Central, unless the

event is captured on another form in REDCap Central. Related signs, symptoms, and abnormal diagnostic procedures results should be recorded as a single event/diagnosis in REDCap Central. Note that while AEs and SAEs should be recorded in REDCap whether related to the study or not, only related events need prompt IRB reporting (see Section 10.3).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study participation is not the cause. Thus, only events that are related to study participation need to be followed until resolution or stabilization.

10.3 Reporting New Information to the IRB

Federal regulations require timely filing of unanticipated problems posing risks to subjects or others to the local IRB. These events are:

- unexpected, AND
- related to study participation, AND
- serious or involve risks to subjects or others

This section also describes the NYULH IRB reporting requirements for other types of events, though investigators at participating sites are responsible for meeting any additional local requirements and/or those of the relevant sIRB. The following categories of events are considered reportable and require a submission to the IRB using the Reportable New Information e-submission form.

1. New or Increased Risk

Information arising from the study that indicates a new or increased risk or safety issue. For example:

- New information (e.g., an interim analysis, safety monitoring report, publication in the literature, sponsor report, or investigator finding) indicates an increase in the frequency or magnitude of a previously known risk or uncovers a new risk.
- Protocol violation that harmed subjects or others, or that indicates subjects or others might be at increased risk of harm.
- Complaint of a subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm.

2. Unexpected Harm to a Subject or Other Individual

Any harm experienced by a subject or other individual(s) that, in the opinion of the investigator, is unexpected and related or possibly related to the research procedures. Harms can include psychological, economic, legal, and other non-physical harms.

- A harm is “unexpected” when its specificity or severity is inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population
- A harm is “probably related” to the research procedures if, in the opinion of the investigator, the research procedures more likely than not caused the harm

Examples of harm include:

a. Death of a Research Subject. Investigators are required to report deaths of research participants to the IRB if the death was unanticipated and related or probably related to participation in the study.

b. Adverse Events. Only Unanticipated Adverse Events that are related to the research need to be reported to the IRB. As described above, RNI includes events that may increase risks or cause harm.

3. Non-Compliance
Non-compliance with federal regulations governing human research, NYU Langone Health's HRP policies, or with IRB requirements or determinations, or allegations of such non-compliance.

4. Audits
External audits, inspections, or inquiries by a federal agency and any resulting reports (e.g., FDA Form 483).

5. Reports
Written reports of study monitors, reports to/from a study sponsor or other information that indicates a change to the risks or potential benefits of the research.

6. Researcher Error
Failure to follow the protocol due to the action or inaction of the investigator or research staff.

7. Breach of Confidentiality
Breach of subject or patient confidentiality, data breach, or data incident. Any unauthorized disclosure of subject's personally identifiable information.

8. Unreviewed Change
Any change in the IRB-approved study protocol that was taken without prior IRB review to eliminate immediate hazard to subjects must be reported. This would include protocol violations and deviations.

A protocol violation refers to an accidental or unintentional change to the IRB-approved protocol that harmed subjects or others, or that indicates subjects or others may be at increased risk of harm. Examples: subject received the wrong dose of study medication.

9. Incarceration
Investigators must report to the IRB when a subject who is enrolled in a study that is not IRB-approved to involve prisoners becomes incarcerated and the study team plans to continue study activities with prisoners while incarcerated.

10. Complaint
Complaints made by a subject that are related to the study and either indicate increased risk and/or that cannot be resolved by the research team must be reported.

11. Suspension or Termination
Principal Investigators must report premature suspension or termination of the research by the sponsor, investigator, or institution.

10.3.1 When to Report Events

Report promptly, but no later than 5 calendar days from the time the investigator becomes aware of the event:

- **Unanticipated Problems Involving Risk to Subjects or Others** (see Section 10.1 for definition), if the event requires immediate intervention to prevent serious harm to subjects or others, or the subject suffered serious harm.
- **Death of a Participant**, if it is unexpected and related to a study procedure

For all other reportable events listed above, report promptly, but no later than 10 calendar days from the time the investigator becomes aware of the event:

The IRB will accept other reports when the Principal Investigator is unsure whether the event should be reported. The Principal Investigator should first contact IRB Operations by email or telephone to determine if the reporting is necessary under this Policy.

Events that do not meet the above criteria for immediate reporting should be summarized and reported to the IRB at the time of continuing review.

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 reporting category above, 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.

10.4 Participant Mental Status

Survey questions may ask about the mental status of participants, including suicidal ideation. The CSC will receive an alert when a response suggesting possible thoughts of suicidality is submitted. Upon receipt, CSC staff will communicate with site study staff to confirm accuracy of the response and verify appropriate measures are taken to ensure participant safety.

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 following hypotheses will be addressed in the analytic approach to Aim 1:

- Hypothesis 1a: Clinically meaningful PASC cases and sub-phenotypes will be discernable based on a combination of candidate PASC symptoms, and potentially other clinical features.
- Hypothesis 1b: Cumulative incidence of long-term sequelae differs between SARS-CoV-2 infected and uninfected individuals, overall and stratified by hospitalization.
- Hypothesis 1c: Incidence rate of long-term sequelae differs between SARS-CoV-2 infected and uninfected individuals, overall and stratified by hospitalization
- Hypothesis 1d: The point prevalence of long-term sequelae differs between SARS-CoV-2 infected and uninfected individuals, overall and stratified by hospitalization.
- Hypothesis 1e: The severity of long-term sequelae differs between SARS-CoV-2 infected and uninfected individuals, overall and stratified by hospitalization.

The following hypotheses will be addressed in the analytic approach to Aim 2:

- Hypothesis 2a: The risk of PASC among infected individuals will vary by: demographic and clinical characteristics, vaccine status at the time of infection, severity of disease (including hospitalization and admittance to ICU), drug exposures, pregnancy during acute infection and calendar time.
- Hypothesis 2b: The rate of recovery from PASC among individuals with PASC will vary by: (i) demographic and clinical characteristics and vaccine status at the time of infection, and (ii) severity of disease (including hospitalization and admittance to ICU), drug exposures, and pregnancy during acute infection.

The following hypotheses will be addressed in the analytic approach to Aim 3:

- Hypothesis 3a: PASC and PASC sub-phenotypes will be associated with concurrent and subsequent abnormal laboratory results and other clinical and subclinical features.
- Hypothesis 3b: The association between PASC and PASC sub-phenotypes with concurrent and subsequent abnormal laboratory results and other clinical and sub-clinical features will be modified by demographic factors, including sex, age and race/ethnicity.
- Hypothesis 3c: Recovery from PASC will be associated with laboratory results and other clinical and subclinical features.
- Hypothesis 3d: The association between SARS-CoV-2 infection and PASC and PASC sub-phenotypes will be mediated by abnormal laboratory results and other clinical and sub-clinical features.

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

Tier	Comparison Group	Comparison Group	Effect of Interest	Assumptions	Min. Detectable ES* Full Sample	Min. Detectable ES* 25% subgroup (e.g. inpatients, Hispanic individuals, etc)
1	Infected	Uninfected	Difference in risk of PASC between infected and uninfected	Risk of PASC in infected: 25%	3.4%	6.7%

1	Infected w/ RF	Infected w/out RF	Risk difference for PASC in infected with RF vs. without RF	Prevalence of RF: 20%, risk of PASC in infected, RF+: 30%	3.5%	6.9%
1	Pregnant infected	Non-pregnant infected	Risk difference for PASC in pregnant infected versus non-pregnant infected	Risk of PASC in non-pregnant infected: 25%	4.1%	8.0%
1	PASC+ w/ RF	PASC+ w/out RF	Difference in proportion who recover from PASC for those with and without a risk factor	Prevalence of RF: 20%, probability of recovery in PASC+ w/out RF: 0.50	7.8%	15.5%
2	PASC+	PASC+	Precision of rate of feature	Rate of 50% (conservative)	± 2.1%	± 4.2%
2	Infected	Uninfected	Difference in proportion with a features in between infected and uninfected individuals	Rate of 50% with feature in infected	7.7%	15.3%
2	PASC+	PASC-	Difference in proportion with a feature, PASC+ vs. PASC-	Rate of 50% with feature in PASC+ (conservative); Risk of PASC in acute: 10%	8.3%	16.3%
3	PASC+	PASC+	Precision of rate of feature	Rate of 50% (conservative)	± 2.6%	± 5.1%
3	Infected	Uninfected	Difference in proportion with a feature, infected vs. uninfected-	Rate of 50% in PASC+ (conservative)	11.1%	21.7%
3	PASC+	PASC-	Difference in proportion with a feature, PASC+ vs. PASC-	Rate of 50% in PASC+ (conservative)	11.8%	23.1%

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 following the RECOVER Adult Standard Collection Workflow Manual of Operating Procedures or RECOVER Adult Local Collection Workflow Manual of Operating Procedures and associated reference materials. Either central or local processing is acceptable if procedures are followed.

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

The complete analytic approach to aims is detailed in the statistical analysis plan, included as a separate attachment.

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
  - Autopsy 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). Once potential subjects are identified through standard processes by the study team,the research study will be explained in lay terms to each potential research subject in their preferred language, either one-on-one or in a group session. If through a group information session, no patient identifiers will be collected during the session. In addition, if using a group session, potential subjects must have an opportunity to meet individually with study staff after the group session to ask questions and provide written consent in a private setting. The option to use group information sessions will help with (1) meeting recruitment goals in a timely manner; (2) overcoming the challenges of patients not showing up for screening appointments; and (3) scheduling more than one subject visit per time slot.

The overall common consent document(s) will include:

1) consent for participation in all minimal risk RECOVER Tier 1, 2 and 3 activities;
2) consent for sharing identifiable data with the secure REDCap Central database;
3) consent to obtain and link data from electronic health records, regional health information exchanges, claims data and the National Death Index;
4) consent for sharing of deidentified data and specimens through RECOVER databases and specimen repositories (in addition to other NIH-designated repositories).
5) optional collection of biospecimens
6) If biospecimens are collected, additional optional collection of genetic sample for testing and optional consent for 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); combined (Main) and as stand-alone documents
- Informed consent form adult subjects (Tier 3)

Materials such as videos, slide presentations and scripts may be used to aide in the informed consent process. All materials will be submitted to the IRB for approval prior to their use.

13.3.2 Posting to ClinicalTrials.gov

The proposed study is 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

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.

13.4.3.1 Reporting of Clinically Actionable 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.

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 a 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 Data Resource Core (DRC). 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 as soon as possible, but in all cases within 10 working days of identification of the protocol deviation. Certain protocol deviations can be determined by periodic reports developed by the DRC so do not have to be reported separately (e.g. missed follow-up visits or missed procedures). 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 through REDCap, and then reported by the Clinical Science Core to the RECOVER program scientific directors at NIH, and where relevant to the RECOVER DRC. Protocol deviations that impact risk or scientific integrity will be 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 DRC 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 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

1. Worldometer. Coronavirus Cases. 2021; https://www.worldometers.info/coronavirus/?utm_campaign=homeAdUOA?Si. Accessed June 17th, 2021.
2. Carbone M, Lednicky J, Xiao S-Y, Venditti M, Bucci E. Coronavirus 2019 Infectious Disease Epidemic: Where We Are, What Can Be Done and Hope For. *J Thorac Oncol.* 2021;16(4):546-571.
3. Nasserie T, Hittle M, Goodman SN. Assessment of the Frequency and Variety of Persistent Symptoms Among Subjects With COVID-19: A Systematic Review. *JAMA Network Open.* 2021;4(5):e2111417-e2111417.
4. Higgins V, Sohaei D, Diamandis EP, Prassas I. COVID-19: from an acute to chronic disease? Potential long-term health consequences. *Critical Reviews in Clinical Laboratory Sciences.* 2020:1-23.
5. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nature Medicine.* 2020;26(7):1017-1032.
6. Wadman M, Couzin-Frankel J, Kaiser J, Matacic C. A rampage through the body. *Science (New York, NY).* 2020;368(6489):356-360.
7. Barth RF, Xu X, Buja LM. A Call to Action: The Need for Autopsies to Determine the Full Extent of Organ Involvement Associated With COVID-19. *Chest.* 2020;158(1):43-44.
8. Hannah E. Davis GSA, Lisa McCorkell, Hannah Wei, Ryan J. Low, Yochai Re'em, Signe Redfield, Jared P. Austin, Athena Akrami. Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. *medRxiv.* 2020.
9. Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterization of post-COVID-19 manifestations. *Int J Clin Pract.* 2021;75(3):e13746-e13746.
10. Türktaş H, Oğuzülgen İ K. [Post-COVID-19 pulmonary sequla: longterm follow up and management]. *Tuberkuloz ve toraks.* 2020;68(4):419-429.
11. Asly M, Hazim A. Rehabilitation of post-COVID-19 subjects. *Pan Afr Med J.* 2020;36:168-168.
12. Davido B, Seang S, Barizien N, Tubiana R, de Truchis P. 'Post-COVID-19 chronic symptoms' - Author's reply. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases.* 2021;27(3):495-496.
13. Tarawneh O, Tarawneh H. Immune thrombocytopenia in a 22-year-old post-Covid-19 vaccine. *American journal of hematology.* 2021;96(5):E133-e134.
14. Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. *Journal of the neurological sciences.* 2020;419:117179.
15. Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in 'long COVID': rationale, physiology, and management strategies. *Clinical medicine (London, England).* 2021;21(1):e63-e67.
16. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nature Medicine.* 2021;27(4):601-615.
17. Health F. *A Detailed Study of Subjects with Long-Haul COVID -An Analysis of Private Healthcare Claims.* A FAIR Health White PaperJune 15, 2020.

19 Appendices

19.1 Appendix 1: Schedule of assessments

		Time Point after index date															
eCRF	Baseline	3m	6m	9m	12m	15m	18m	21m	24m	27m	30m	33m	36m	39m	42m	45m	48m
Enrollment	●																
Tier 1-2 Consent	●																
Identity	●																
Visit	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Comorbidities	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
COVID Treatment*	●																
Medications	●																
Change in Medications		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Demographics	●																
PASC Symptoms	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Vaccine	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
SDoH	●																
SDoH Follow-up		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Alcohol/Tobacco	●																
Alcohol/Tobacco Follow-up		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Disability	●																
Pregnancy	●																
Pregnancy Follow-up		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tier 1 office visit	●		●		●				●				●				●
Biospecimens	●	●	●		●				●				●				●
Lab Results	●	●	●		●				●				●				●
Tier 2/Tier 3 Tests																	

Legend

- ● Completed by research coordinator
- ● Completed by participant
- ● Completed by research coordinator with review/validation by participant

* COVID Treatment not collected on uninfected controls.

The 39-48m schedule will be repeated for subjects who are more than 48 months after infection while the study is still ongoing

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.

Category	Element	Interval
Demographics	Name and contact information (retained locally)	At enrollment and every 3 months thereafter
Demographics	Alternate contacts (retained locally)	At enrollment and every 3 months thereafter
Demographics	Date of birth	Once, on enrollment
Demographics	Race and ethnicity	Once, on enrollment
Demographics	Biological sex	Once, on enrollment
Demographics	Gender identity	Once, on enrollment
Demographics	Sexual orientation	Once, on enrollment
Demographics	Marital status	At enrollment and every 3 months thereafter
Social determinants	Education	Once, on enrollment
Social determinants	Number of people in household	Once, on enrollment
Social determinants	Homelessness	At enrollment and every 3 months thereafter
Social determinants	Description of living place	At enrollment
Social determinants	Community cohesion	Once, on enrollment
Social determinants	Primary language	Once, on enrollment
Social determinants	Fluency in English	Once, on enrollment
Social determinants	Birthplace	Once, on enrollment
Social determinants	Financial insecurity	At enrollment and every 3 months thereafter
Social determinants	Employment	At enrollment and every 3 months thereafter
Social determinants	Income in 2019	Once, on enrollment
Social determinants	Access to health care	Once, on enrollment
Social determinants	Health insurance	At enrollment and every 3 months thereafter
Social determinants	Loss of insurance because of COVID pandemic	Once, on enrollment
Social determinants	Hunger Vital Sign	Once, on enrollment
Social determinants	Discrimination	Once, on enrollment
Social determinants	Social support	Once, on enrollment
Social determinants	Alcohol and substance use	At enrollment and every 3 months thereafter
Baseline disability	Baseline disability	Once, on enrollment

Category	Element	Interval
Acute COVID	Diagnosis method	Once, on enrollment
Acute COVID	Site and level of care for initial infection	Once, on enrollment
Acute COVID	Treatments received for initial infection	Once, on enrollment
Pregnancy	Pregnancy status	At enrollment and every 3 months thereafter
Pregnancy	Pregnancy outcomes	At enrollment and every 3 months thereafter where relevant
Vaccination	Vaccination status and vaccine details	At enrollment and every 3 months thereafter
Comorbidity	Immunocompromised condition and specific types	At enrollment and every 3 months thereafter
Comorbidity	Rheumatologic, autoimmune or connective tissue disease and specific types	At enrollment and every 3 months thereafter
Comorbidity	Diabetes and specific type	At enrollment and every 3 months thereafter
Comorbidity	Kidney disease and specific type	At enrollment and every 3 months thereafter
Comorbidity	Active cancer and specific type	At enrollment and every 3 months thereafter
Comorbidity	Dementia or cognitive impairment and specific type	At enrollment and every 3 months thereafter
Comorbidity	Central nervous system infection, inflammatory disease or demyelinating disease and specific type	At enrollment and every 3 months thereafter
Comorbidity	Seizure disorder	At enrollment and every 3 months thereafter
Comorbidity	Neuromuscular disease and specific type	At enrollment and every 3 months thereafter
Comorbidity	Movement disorder and specific type	At enrollment and every 3 months thereafter
Comorbidity	Cardiovascular disease and specific type	At enrollment and every 3 months thereafter
Comorbidity	Stroke or bleed and specific type	At enrollment and every 3 months thereafter
Comorbidity	Asthma	At enrollment and every 3 months thereafter
Comorbidity	Chronic obstructive pulmonary disease	At enrollment and every 3 months thereafter
Comorbidity	Other chronic lung disease	At enrollment and every 3 months thereafter
Comorbidity	Use of oxygen at home	At enrollment and every 3 months thereafter
Comorbidity	Anxiety, depression or PTSD	At enrollment and every 3 months thereafter
Comorbidity	Schizophrenia or bipolar disorder	At enrollment and every 3 months thereafter
Comorbidity	Other mental health disorder	At enrollment and every 3 months thereafter
Comorbidity	Chronic liver disease	At enrollment and every 3 months thereafter

Category	Element	Interval
Comorbidity	Sickle cell anemia	At enrollment and every 3 months thereafter
Comorbidity	Chronic pain syndrome or fibromyalgia	At enrollment and every 3 months thereafter
Comorbidity	Myalgic encephalomyelitis/chronic fatigue syndrome	At enrollment and every 3 months thereafter
Comorbidity	POTS or other form of dysautonomia or autonomic dysfunction and specific type	At enrollment and every 3 months thereafter
Comorbidity	Obesity	At enrollment and every 3 months thereafter
Comorbidity	Polycystic ovarian syndrome	At enrollment and every 3 months thereafter
Medications	Complete medication list	At enrollment and every 3 months thereafter
Symptoms	Overall health status	At enrollment and every 3 months thereafter
Symptoms	Social function	At enrollment and every 3 months thereafter
Symptoms	Physical function	At enrollment and every 3 months thereafter
Symptoms	Fatigue and fatigue details	At enrollment and every 3 months thereafter
Symptoms	Post-exertional malaise (e.g., feeling exhausted after walking)	At enrollment and every 3 months thereafter
Symptoms	Weakness in limbs	At enrollment and every 3 months thereafter
Symptoms	Fever, chills, sweats or flushing	At enrollment and every 3 months thereafter
Symptoms	Loss of or change in smell or taste	At enrollment and every 3 months thereafter
Symptoms	Pain in any part of body and site of pain	At enrollment and every 3 months thereafter
Symptoms	Headache details	At enrollment and every 3 months thereafter
Symptoms	Chest pain details	At enrollment and every 3 months thereafter
Symptoms	Shortness of breath or trouble breathing and details	At enrollment and every 3 months thereafter
Symptoms	Cough	At enrollment and every 3 months thereafter
Symptoms	Palpitations, racing heart, arrhythmia, skipped beats	At enrollment and every 3 months thereafter
Symptoms	Swelling of lower legs and details	At enrollment and every 3 months thereafter
Symptoms	Gastrointestinal symptoms and details	At enrollment and every 3 months thereafter
Symptoms	Bladder problems and details	At enrollment and every 3 months thereafter
Symptoms	Nerve problems and details	At enrollment and every 3 months thereafter

Category	Element	Interval
Symptoms	Problems with anxiety, depression, stress, or trauma-related symptoms like nightmares or grief	At enrollment and every 3 months thereafter
Symptoms	Depression screen and assessment	At enrollment and every 3 months thereafter
Symptoms	Suicidality screen and assessment	At enrollment and every 3 months thereafter
Symptoms	Anxiety screen and assessment	At enrollment and every 3 months thereafter
Symptoms	Stress	At enrollment and every 3 months thereafter
Symptoms	Problems thinking or concentrating and details	At enrollment and every 3 months thereafter
Symptoms	Problems with sleep and details	At enrollment and every 3 months thereafter
Symptoms	Faint, dizzy, "goofy," difficulty thinking soon after standing up from a sitting or lying position and details	At enrollment and every 3 months thereafter
Symptoms	Color changes in your skin, such as red, white or purple and details	At enrollment and every 3 months thereafter
Symptoms	Skin rash	At enrollment and every 3 months thereafter
Symptoms	Changes in sweating	At enrollment and every 3 months thereafter
Symptoms	Excessively dry eyes	At enrollment and every 3 months thereafter
Symptoms	Excessively dry mouth	At enrollment and every 3 months thereafter
Symptoms	Excessive thirst	At enrollment and every 3 months thereafter
Symptoms	Vision problems (blurry, light sensitivity, difficulty reading or focusing, floaters, flashing lights, "snow") and details	At enrollment and every 3 months thereafter
Symptoms	Problems with hearing (hearing loss, ringing in ears) and details	At enrollment and every 3 months thereafter
Symptoms	Hair loss	At enrollment and every 3 months thereafter
Symptoms	Problems with teeth or gums	At enrollment and every 3 months thereafter
Symptoms	Change in menstruation or menopause and details	At enrollment and every 3 months thereafter
Symptoms	Changes in desire for, comfort with or capacity for sex	At enrollment and every 3 months thereafter
Post-COVID utilization	Hospitalization since COVID or last assessment	At enrollment and every 3 months thereafter
Post-COVID utilization	Emergency department visit since COVID or last assessment	At enrollment and every 3 months thereafter
Clinical assessment	Height, weight, BMI	0, 6 months after infection then yearly

Category	Element	Interval
Clinical assessment	Waist circumference (cm)	0, 6 months after infection then yearly
Clinical assessment	Seated vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation)	0, 6 months after infection then yearly
Clinical assessment	30 second sit to stand	0, 6 months after infection then yearly
Clinical assessment	Active standing test	0, 6 months after infection then yearly
Clinical assessment	Wearable with continuous remote monitoring for ECG, RR, SpO2, sleep fragmentation, actigraphy	Every six months
Laboratory study	Comprehensive metabolic panel with cystatin-C	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	Complete blood count with differential	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	Lipid panel	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	Hemoglobin A1c	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	Coagulation panel	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	D-dimer	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	Troponin	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	NT-pro BNP	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	Thyroid panel	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	25-hydroxy vitamin D	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	Urinalysis	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	Urine microalbumin and creatinine	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	hsCRP	0, 3, 6 months after infection then yearly if abnormal
Laboratory study	SARS-CoV-2 spike and/or nucleocapsid antibody	On enrollment for uninfected controls
Laboratory study	SARS-CoV-2 NAAT	On enrollment for uninfected controls

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.

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

Category	Element
Clinical assessment	Home sleep test+
Clinical assessment	6 minute walk test+
Clinical assessment	Neurologic exam
Clinical assessment	Rehabilitation exam
Clinical assessment	ENT exam
Clinical assessment	Mini International Neuropsychiatric Interview (MINI)
Clinical assessment	Vision screen+
Clinical assessment	Smell Test+
Clinical assessment	NIH Toolbox oral reading recognition test age 3+ v2.0+
Clinical assessment	NIH Toolbox picture vocabulary test age 3+ v2.0+
Clinical assessment	NIH Toolbox auditory verbal learning test (Rey) 8+ v2.0+
Clinical assessment	NIH Flanker inhibitory control and attention test age 12+ v2.1+
Clinical assessment	NIH Toolbox pattern comparison processing speed test age 7+ v2.1+
Clinical assessment	NIH Toolbox picture sequence age 7+ v2.1+
Laboratory study	Anti-nuclear antibody+
Laboratory study	Anti-CCP+
Laboratory study	Rheumatoid factor+
Laboratory study	EBV+
Laboratory study	Anti dsDNA antibody+
Laboratory study	Ro antibody+
Laboratory study	La antibody+
Laboratory study	Smooth muscle antibody+
Laboratory study	RNP antibody+
Laboratory study	ACTH and cortisol+
Laboratory study	Hepatitis B and C testing+
Laboratory study	Cytokine panel (IL2 receptor; IL 1beta, 2, 4-6, 8, 10, 13, 17; interferon gamma, TNF alpha)+
Laboratory study	ICAM-1+
Laboratory study	Insulin c-peptide+
Laboratory study	Oral glucose tolerance test (time points 0, 30, 60, 120 min)
Laboratory study	Fecal WBC
Laboratory study	Fecal SARS-CoV-2 viral load (viral RNA and/or antigen) +
Radiology	Volumetric non contrast chest CT (with inspiratory/expiratory scans)
Radiology	Dual energy chest CT with contrast
Radiology	Resting transthoracic echocardiography with strain imaging
Radiology	Renal ultrasound
Radiology	Fibroscan
Procedure	Electrocardiogram
Procedure	Pulmonary function tests (no medication hold) with spirometry, resting SpO2 and single breath diffusion capacity

Pregnant Women:

Pregnant women and women within 3 months of delivery may **not** undergo the following Tier 2 procedures:

- Volumetric non contrast chest CT (with inspiratory/expiratory scans)
- Dual energy chest CT with contrast

Pregnant and post-partum women may undergo all other Tier 2 procedures.

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.

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

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

The following procedures may be performed under sedation:

- Bronchoscopy
- Right cardiac catheterization
- Upper endoscopy
- Colonoscopy with or without biopsy

The type of sedation used will be in accordance with institutional protocol.

Pregnant Women:

Pregnant women and women within 3 months of delivery may **not** undergo the following Tier 3 procedures:

- MRI brain with gadolinium
- Cardiac imaging with meta-iodobenzylguanidine (mIBG)
- Cardiac MRI with gadolinium contrast
- Gastric emptying study
- Skin biopsy
- Muscle biopsy
- Lumbar puncture
- Tilt table testing
- Full cardiopulmonary exercise testing
- Bronchoscopy
- Right heart catheterization
- Upper endoscopy
- Colonoscopy with or without biopsy

Women who are breastfeeding may not undergo the following Tier 3 procedures:

- Cardiac imaging with meta-iodobenzylguanidine (mIBG)
- Gastric emptying study

All clinical assessments and laboratory studies may be done in pregnant populations. The cardiovagal innervation testing and facility-based sleep study may also be done in pregnant individuals.