Title: RECOVER-Adult Cohort Cycle 2: A Long-Term Follow Up Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults

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

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Revision history

Version Number	Version Date	Summary of Revisions Made
1.0	2/13/2026	Original release
2.0	4/08/2026	Section 8.2: Removed note on no exclusions related to blood volume collection. Section 9.1: Added waiver of authorization to allow records review for recruitment activities. Section 10.1: Removed 18-month visit for Wide Range Achievement Test-4 or Word Accentuation Test. Section 10.6: Changed same day to within 48 hours for clinician contact for positive suicidality screens. Section 11: Edited for clarity and to align with study requirements. Section 15.4: Clarified use for biospecimens collected in this study and added consent opt-in to future genetic research. Section 15.7: Deleted statement regarding biospecimens not undergoing genotyping, whole genome/exome sequencing, or other genomic analyses, to avoid restricting potential future ancillary studies. Section 15.8: Added future research of stored data and biospecimens may include whole genome and genetic testing and its associated risks. Section 15.8.1: Added new section heading and future research areas, added steps taken to ensure samples from those who did not consent to future research involving genetic/whole genome research, are not used for this research. Clarifications and minor updates made throughout document.

List of Abbreviations

AE	Adverse Event
BMI	Body mass index
CFR	Code of Federal Regulations
CFS	Chronic Fatigue Syndrome
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSC	Clinical Science Core
DRC	Data Resource Core
DHHS	Department of Health and Human Services
ED	Emergency Department
EDC	Electronic Data Capture
EHR	Electronic Health Record
FISMA	Federal Information Security Modernization Act of 2002
HIPAA	Health Insurance Portability and Accountability Act of 1996
IACC	Infection–associated chronic conditions
ICF	Informed Consent Form
i2b2	Implementing Informatics from Bench to Bedside
IRB	Institutional Review Board
LC	Long Covid
LCRI	Long COVID Research Index
ME	Myalgic Encephalomyelitis
MOP	Manual of Operations and Procedures
N	Number (typically refers to participants)
NASEM	National Academies of Sciences, Engineering, and Medicine
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OSMB	Observational Study Monitoring Board
PASC	Post-Acute Sequelae of COVID-19
PBC	PASC Biorepository Core
PHI	Personal Health Information
PI	Principal Investigator
QoL	Quality of Life
REDCap	Research Electronic Data Capture
REDCap Central	Research Electronic Data Capture Central dataset
SAE	Serious Adverse Event
US	United States

Table of Contents

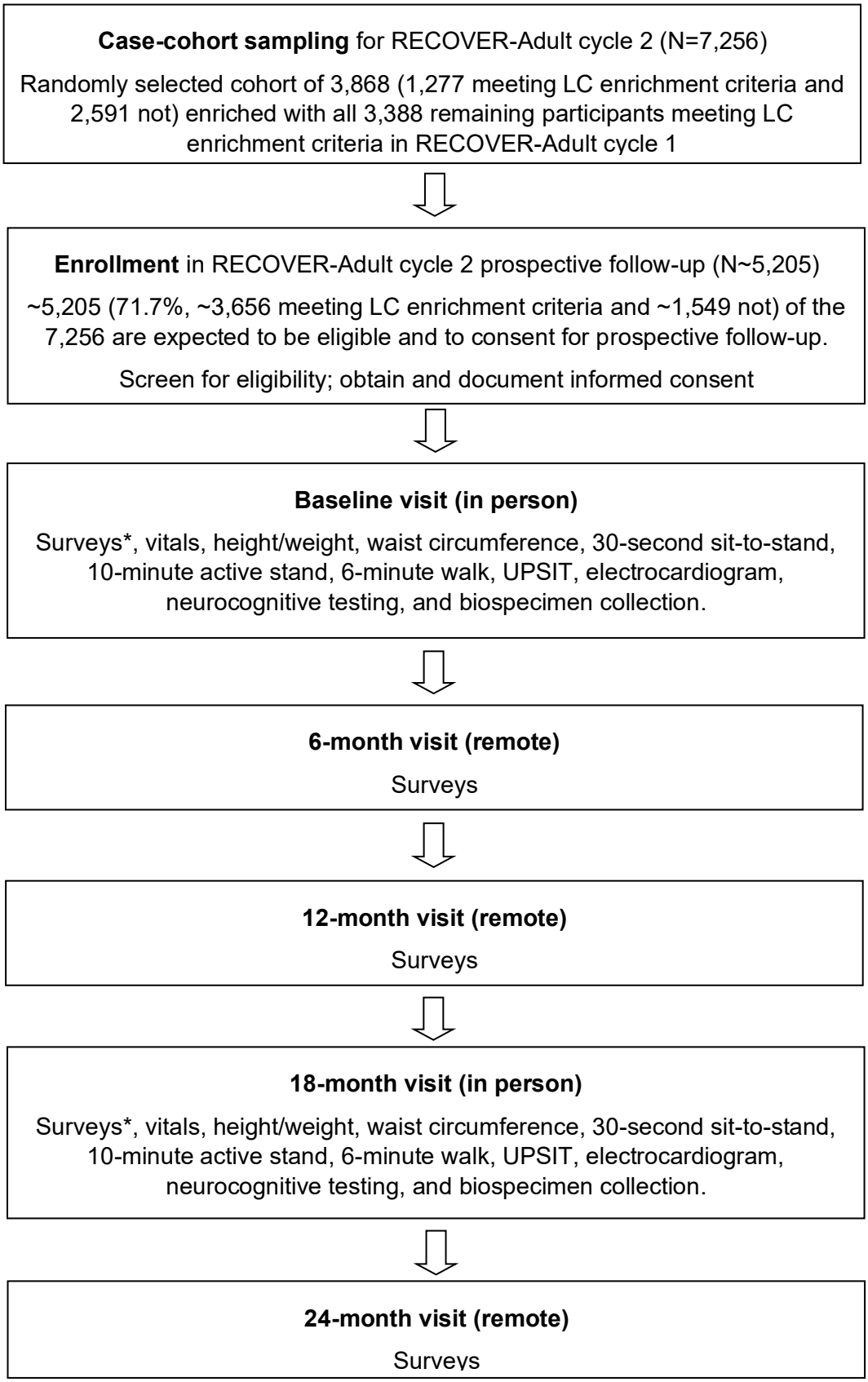
1 Protocol Summary

Title	RECOVER-Adult Cycle 2: A Long-Term Follow Up 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	Long COVID (LC) affects an estimated 5-10% of individuals with SARS-CoV-2 causing a persistent physical, cognitive, and functional impairment with potentially severe socioeconomic consequences. While RECOVER-Adult cycle 1 established the largest, most comprehensive U.S. adult LC cohort (14,730 participants), key questions remain about long-term disease trajectories, biological mechanisms, and late-emerging complications. RECOVER-Adult cycle 2 will follow selected participants for two years each, focusing on neurocognitive, cardiopulmonary and infection-associated chronic conditions (IACC) such as Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and autonomic dysfunction. Using a case-cohort design, the study will investigate disease persistence versus resolution, biological mechanisms, and onset of new chronic illnesses, generating critical insights to guide prevention, treatment, and public health policy.
Objectives	To define the long-term clinical trajectories, biological mechanisms, and late-onset complications of Long COVID, focusing on high-burden sub-phenotypes (neurocognitive, cardiopulmonary, IACC) and to identify prevention and intervention targets that inform clinical trial development and health policy. The specific aims are: **Specific Aim 1:** Determine long-term trajectories of a) neurocognitive, b) cardiopulmonary, and c) IACC (ME/CFS, autonomic dysfunction) sub-phenotypes among individuals with a history of SARS-CoV-2 infection. **Specific Aim 2:** 2.1) Investigate associations of clinical and demographic factors with risk of long-term persistent versus remitting symptoms among individuals with a history of LC and a) neurocognitive, b) cardiopulmonary and c) IACC sub-phenotypes. 2.2) Provide preliminary data for candidate interventions in clinical trials through observational investigations of candidate treatments. **Specific Aim 3:** Evaluate associations between new onset chronic conditions and LC with a) neurocognitive, b) cardiopulmonary and c) IACC sub-phenotypes.

Methodology	RECOVER-Adult cycle 2 will be conducted using a case-cohort design constructed by randomly selecting 20.3% of RECOVER-Adult cycle 1 participants and then augmenting the sample with all remaining participants meeting one or more of three Long COVID enrichment criteria at three or more visits during RECOVER-Adult cycle 1 (excluding visits within three months of an infection). The three Long COVID enrichment criteria include: 1) RECOVER-Adult 2024 Long COVID Research Index (LCRI) 11 or greater, as defined by Geng et al, 2024; or 2) At least 1 RECOVER-Adult LCRI symptom and either a) response of "poor" on the Patient-Reported Outcomes Measurement Information System (PROMIS)-10 quality of life (QoL) question, or b) "bother scale" is "quite a bit" or "very much" for corresponding LCRI symptom; or 3) At least 1 National Academies of Sciences, Engineering, and Medicine (NASEM) common symptom and either a) poor QoL, or b) "bother scale" is "quite a bit" or "very much" for corresponding NASEM symptom.
Endpoint	Primary Endpoints (defined over RECOVER cycles 1 and 2): • LCRI ≥ 11 with and without presence of specific neurocognitive, cardiopulmonary and IACC symptoms • Long COVID remission • New onset conditions, including but not limited to dementia, coronary artery disease, diabetes, renal disease, cancer, and ME/CFS. Secondary Endpoints: • Quality of life and overall physical health.
Study Duration	Four years (May 2026 – April 2030)
Participant Follow-up	Approximately two years per participant
Population	Subset of adults previously enrolled in RECOVER-Adult cycle 1, who did not withdraw consent to use their data, and are located proximate to a cycle 2 enrolling site.
Number of participants	To identify participants for RECOVER-Adult cycle 2, we have drawn a randomly selected cohort of 3,868 (of whom 1,277 met LC enrichment criteria and 2,591 did not), and have augmented it with all remaining participants meeting the LC enrichment criteria (3,388). Among these, 6,121 (84%) did not end participation in cycle 1 prematurely, and will be the target population for prospective follow-up in RECOVER-Adult cycle 2. Among these, approximately N=5,205 (85%) are expected to meet eligibility requirements and consent to be enrolled in RECOVER-Adult cycle 2 prospective follow-up (anticipated ~3,656 meeting LC enrichment criteria and ~1,549 not).

Statistical Analysis	Aim 1. Finite mixture models for longitudinal data using the Expectation-Maximization algorithm will be used to identify distinct longitudinal profiles using the LCRI as a Poisson-distributed continuous outcome variable. Adjustment via inverse probability of sampling weights will be applied to account for the case-cohort design. Aim 2. Using well-defined landmark cohorts, we will apply multivariable Cox proportional hazards models in the discrete-time survival framework to evaluate clinical and demographic predictors of persistence and remission, among individuals with a history of LC. Aim 3. The average treatment effect (ATE), an additive contrast of potential outcomes, will be used to quantify differences in new onset conditions driven by LC status. Inverse probability weighted and targeted minimum loss estimators will be applied to address selection bias due to confounding of the exposure-outcome relationship. Inverse probability of sampling weights and censoring weights will also be used to account for the case-cohort sampling and to correct for differential loss to follow-up, respectively.

2 Schematic of Study Design



*The survey component of the baseline and 18-month visits may be performed remotely if preferred by participant.

3 Key Roles

Principal Investigators Clinical Science Core	**RECOVER Contact Principal Investigator:** 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 **Protocol Principal Investigator:** Leora Horwitz, MD, MHS Professor, Departments of Population Health and Medicine Director, Center for Healthcare Innovation and Delivery Science Director, Division of Healthcare Delivery Science NYU Grossman School of Medicine 550 1st Avenue, Suite 1803 New York, NY 10016 646-501-2685
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4 Introduction, Background Information and Scientific Rationale

4.1 Background Information and Relevant Literature

Approximately 5-10% of people with SARS-CoV-2 infection go on to develop Long COVID (LC) and experience persistent physical and mental symptoms, along with functional limitations. As we are only five years since the first known infection, the natural history and disease trajectory of LC remain uncertain. The basic biology of LC is not yet understood. Delayed onset of serious chronic complications such as neurodegenerative disease, major adverse cardiovascular events (MACE), autoimmune disorders, or cancer may yet emerge. LC symptoms can affect work performance or ability to maintain employment, but questions about quality of life, work capacity and socioeconomic impacts on affected individuals remain largely unanswered. Given the scale of the pandemic, the economic impact of LC in terms of income loss, disability and health care utilization is likely to be in the trillions of US dollars. A comprehensive understanding of natural history, biologic underpinnings, and chronic complications is essential for creating effective policies and interventions, as demonstrated in the response to other epidemics such as HIV.

The Researching COVID to Enhance Recovery (RECOVER) adult cohort (RECOVER-Adult) is the largest and most methodologically robust study of LC in adults, with >14,700 enrolled participants across the US. It has established a robust infrastructure, including a curated dataset, a priceless specimen bank including pre- and peri-infection samples, highly motivated participants, an engaged group of patient/caregiver/community representatives, and dedicated scientific teams. This cohort, along with its ancillary studies, is significantly advancing our understanding of LC, including its clinical features and subtypes, mechanisms, and biomarkers, while also supporting multiple ongoing treatment trials. As a result of these observations, we now have increased confidence that biological abnormalities play a crucial role in the symptoms of LC. Leveraging the extensive advancements from the first cycle of RECOVER-Adult, the second cycle of RECOVER-Adult will focus on three highly prevalent and high impact domains: neurocognitive, cardiopulmonary, and infection-associated chronic conditions (IACC) – (myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and autonomic dysfunction) – to enhance our knowledge of long-term trajectories, investigate the biology of and potential interventions for disease persistence beyond the initial five years of illness, and assess the late-onset development of chronic complications. The first cycle of RECOVER-Adult systematically assessed a wide range of symptoms, collected biospecimens and tests for deep phenotyping, and ensured comprehensive, repeated, and prospective capture of data to rigorously assess pathophysiology, temporal relationships and associations between exposures and outcomes. We thus propose to continue observing a subset of the RECOVER-Adult cohort over the next four years using a case-cohort design, which optimizes analytic efficiency and scientific flexibility. Our rigorous design will help delineate long-term trajectories, identify targets for prevention and therapeutic intervention in patients with high disease burden, yield concepts for clinical trials, generate a pool of potential clinical trial participants, inform public health strategies, and mitigate the long-term impact of LC. Recognizing that LC is a new and evolving condition with many unknown aspects, we propose a pragmatic four-year study that will both support the primary aims and provide a foundation for future ancillary studies that explore a wide range of additional and critical research questions.

4.2 Rationale and Study Significance

LC is a novel, evolving condition with potential lifelong consequences; however, its natural history, pathobiology, and long-term complications remain unclear. Given the high prevalence and economic impact of LC, understanding trajectories and mechanisms is essential for developing effective treatments, informing public health interventions, and reducing long term societal burden. Leveraging the RECOVER-Adult Cohort Cycle 1 infrastructure maximizes scientific return and accelerates discovery, while providing a solid foundation for future clinical trials and ancillary studies.

5 Potential Risks and Benefits

5.1 Known Potential Risks

This study includes patient-reported questionnaires, data extraction from electronic health records (EHR) and claims data, basic clinical examinations, and biological sample collection. We describe the risks of each in turn.

Risks of survey completion: While we anticipate no risk greater than that found in everyday life from survey completion, completing questionnaires about the COVID-19 experience could cause participants to become upset or frustrated. In addition, survey completion may be tiring or cognitively difficult for people with LC. To minimize risk, staff will be trained to let participants know that they can stop the survey at any point and return to continuing it when ready.

Loss of confidentiality for the participants' answers is another potential risk. Loss of confidentiality could result in damage to a participant's financial standing, employability, insurability, or reputation. See **Section 15.6** for details of data security by which risk of inadvertent data release is minimized.

Risks of in-person visit: Coming for an in-person visit may make symptoms worse in people with post-exertional malaise or women who are pregnant, either during or after the visit. To minimize risk, staff will be trained to let participants know that they can stop the assessments at any time and return to them when ready. In addition, rest periods are built into the in-person visit schedule, symptoms are regularly assessed, extra rest can be added when needed and stop rules for assessments are detailed in each SOP where relevant (e.g., dizziness, chest pain, palpitations, or obstetric discomfort).

Basic clinical examinations: (e.g., vital signs, height and weight, waist circumference, 30-second sit to stand test, UPSIT smell test): These pose no appreciable additional risk.

Active stand and 6-minute walk tests: Some participants may get tired, lightheaded or short of breath or have palpitations during these tests.

Electrocardiogram: Electrode placement and/or shaving on the chest may cause discomfort such as redness or itching for some people.

Cognitive tests: The tests of memory, attention, and thinking may be frustrating or stressful for some people. Participants may stop the questions at any time and resume when ready.

Phlebotomy: Having blood taken poses minimal risks like lightheadedness, feeling faint, or syncope (passing out) on standing. Syncope after blood draw may result in injury. Redness, pain, bruising, bleeding, or (rarely) infection may occur at the site of a puncture during blood collection.

Risk of incidental findings: Assessments may provide results that indicate a clinically significant or medically actionable condition might be present. Institutions should follow local state and institutional policies on sharing any incidental findings.

5.2 Known Potential Benefits

There are no known potential benefits to this study to participants, but there is a potential benefit to public health. Healthcare providers may have a better understanding of how to meet the needs of individuals with LC more effectively.

6 Objectives and Purpose

The purpose of this study is to characterize the trajectory of LC over time and identify clinical and demographic risk factors in adults in the United States.

6.1 Primary Objective

The specific aims of this study are to:

Specific Aim 1: Determine long-term trajectories of a) neurocognitive, b) cardiopulmonary, and c) IACC (ME/CFS, autonomic dysfunction) sub-phenotypes among individuals with a history of SARS-CoV-2 infection.

Hypothesis: Distinct trajectories will be identified based on integrated longitudinal data spanning up to seven years of follow-up for each sub-phenotype.

Specific Aim 2: 2.1) Investigate associations of clinical and demographic factors with risk of long-term persistent versus remitting symptoms among individuals with a history of LC and a) neurocognitive, b) cardiopulmonary and c) IACC sub-phenotypes. 2.2) Provide preliminary data for candidate interventions in clinical trials through investigations of candidate treatments.

Hypothesis: Participant level clinical and demographic factors will predict persistence.

Specific Aim 3: Evaluate associations between new onset chronic conditions and LC with a) neurocognitive, b) cardiopulmonary and c) IACC sub-phenotypes.

Hypothesis: New onset neurodegenerative disease, cardiometabolic disease, and autoimmune disease will have higher incidence in each respective LC sub-phenotype group compared to participants with no history of LC.

7 Study Design and Endpoints

RECOVER-Adult cycle 2 is a longitudinal cohort study leveraging the existing RECOVER-Adult cycle 1 cohort to investigate the long-term clinical course, mechanisms, and outcomes of LC. It will be conducted using a case-cohort design with a proposed sample size of N=7,256 of whom ~N=5,205 (3,656 participants meeting the LC enrichment criteria) will be prospectively followed. The RECOVER-Adult cycle 2 case-cohort will be constructed by randomly selecting 20.3% of eligible RECOVER-Adult participants (**Figure 1**, Step 1) and then augmenting the sample with all remaining participants meeting the LC enrichment criteria (**Figure 1**, Step 2). Eligible participants in the Cycle 2 sample will be enrolled in the cycle 2 cohort and prospectively followed (**Figure 1**, Step 3). Randomization for this study will be conducted using the statistical software R. This software enables the generation of reproducible and unbiased random allocation sequences, ensuring rigorous and transparent random selection procedures across study sites.

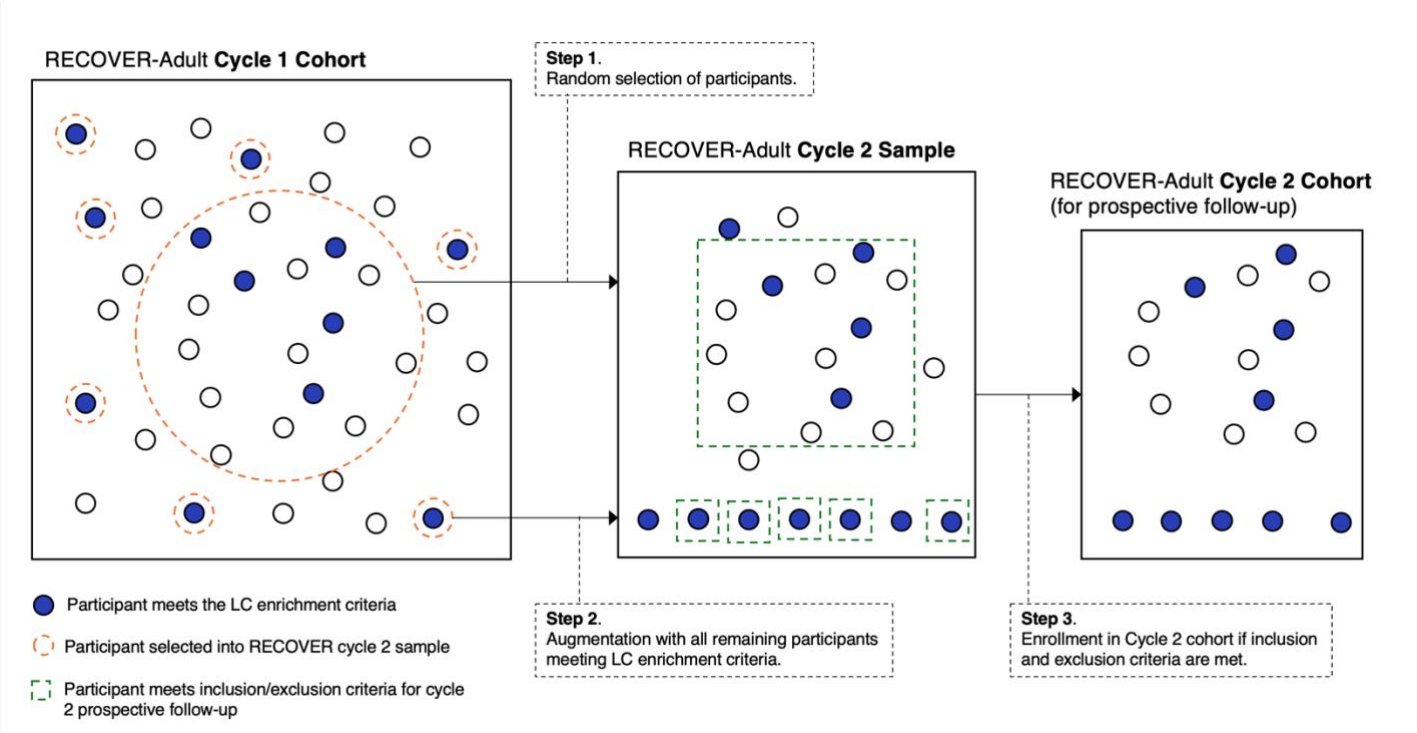

Figure 1: Study design and participant selection

The LC enrichment criteria include any of the following three specifications at three or more visits during RECOVER-Adult cycle 1 (excluding visits within three months of an infection):

1) RECOVER-Adult 2024 LCRI 11 or greater, as defined by Geng et al, 2024;[1] or

2) At least 1 RECOVER-Adult LCRI symptom and either a) poor quality of life (QoL) as defined by a response of “poor” on the PROMIS-10 QoL question or b) “bother scale” is “quite a bit” or “very much” for corresponding LCRI symptom; or
3) At least 1 NASEM common symptom and either a) poor QoL, or b) “bother scale” is “quite a bit” or “very much” for corresponding NASEM symptom.

The LC enrichment criteria incorporate the LCRI and the NASEM criteria. They include participants with persistent symptoms, with symptoms that have waxed and waned over time, with late onset symptoms, and with improved symptoms. This design also ensures that a large proportion of participants meeting RECOVER-adapted criteria for SARS-CoV-2-associated ME/CFS are represented.

The RECOVER-Adult cycle 2 case-cohort sample size (N=7,256) is given by $N * [\alpha + (1 - \alpha) * \beta]$, where N=14,481 is the cycle 1 sample size after excluding participants who did not start the protocol, withdrew consent to use data, or, if originally enrolled at a site not participating in cycle 2, are not within 50 miles of a participating cycle 2 site; α=0.2670 is the sampling fraction; and β=0.3193 is the proportion of participants meeting the LC enrichment criteria.

The RECOVER-Adult cycle 2 prospective follow-up subset is expected to include N=5,205 participants – 3,656 (70.2%) who meet the LC enrichment criteria and 1,549 (29.8%) who do not. We base these estimates on the cycle 1 study withdrawal rates, which were 7.8% and 29.7% in the cases and non-cases, respectively. An additional ~15% in each group are expected to not meet inclusion criteria or not agree to participate in prospective follow-up.

Primary Endpoints:

- Long COVID Research Index (LCRI) ≥ 11 with and without presence of specific neurocognitive, cardiopulmonary and IACC symptoms
- Long COVID remission (vs. persistence) among participants with LC
- New onset conditions, including but not limited to dementia, coronary artery disease, diabetes, renal disease, cancer, and ME/CFS

Secondary Endpoints:

Quality of life and overall physical health

8 Study Enrollment and Withdrawal

8.1 Inclusion Criteria

The case-cohort design requires sampling from amongst all participants in RECOVER cycle 1, regardless of whether they are still active in the study for continued follow-up, as long as they have not elected to withdraw consent and have all their data removed from data analysis and biospecimens discarded.

To be eligible for the RECOVER cycle 2 prospectively followed cohort, participants must:

1) Be selected into the RECOVER cycle 2 sample (see **Section 7**), and
2) Not have ended participation in cycle 1 prematurely (i.e., not withdrawn, lost to follow-up), and
3) Be able to enroll at a participating RECOVER-Adult cycle 2 site (see **Section 8.6**).

8.2 Exclusion Criteria

The following exclusions apply for the RECOVER-Adult cycle 2 prospectively followed cohort:

1) Individuals who have a known or documented hemoglobin lower than 8.5 g/dL,
2) Individuals who have not yet reached the age of majority,
3) Individuals who are unable to provide consent,

4) Individuals who are unwilling to consent to biospecimen collection or are unwilling to participate in the complete protocol, including all assessments and the cycle 2 visit schedule,
5) Individuals in hospice care,
6) Individuals with a serious medical condition which would prevent in-person participation,
7) Individuals participating in the study NIH RECOVER-Pediatric: Understanding the long-term impact of COVID on children and families, unless enrolled only as caregiver, or
8) Long-term incarcerated individuals

Note that participation in other observational or intervention studies while participating in RECOVER is not an exclusion criterion. Individuals participating as caregivers in the RECOVER-Pediatric cohort are eligible for inclusion in this protocol if they enrolled in RECOVER-Adult Cycle 1.

8.3 Vulnerable Populations

8.3.1 Pregnant Women

There is no restriction on enrollment for women who are pregnant at the time of enrollment or study visit. All study activities may be completed by pregnant women. Pregnancy status will be assessed by self-report at each visit; no pregnancy testing is performed. Additional safeguards and risk minimization efforts are described in Section 5.1. Additionally, any concerning obstetric symptoms will trigger onsite evaluation and referral to obstetric care per local policy.

8.3.2 Prisoners

The study will not enroll prisoners per 45 CFR 46.306. If an enrolled participant becomes a prisoner, all study procedures will pause, and the site will notify the IRB. Continued participation while incarcerated, if proposed, would require Subpart C review, including a prisoner representative; otherwise, only pre-incarceration data will be retained. Participants may resume participation in the study when no longer incarcerated.

8.3.3 Students and Employees

Students and employees of RECOVER-affiliated institutions recruited as research participants 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. Consent will be obtained by staff outside the participant's supervisory/academic chain. Participation/non-participation will not affect employment or academic status. 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. Compensation will be identical to non-employee/student participants.

Students or employees will not be specifically targeted for participation in this protocol but will also not be excluded based on these protected statuses. All prospectively enrolled students or employees will be told of the specific privacy and confidentiality risks compromised before signing consent. This information may include sensitive topics included in the RECOVER protocol including comorbidities, mental health, sexual behavior, and/or drug/alcohol use.

8.3.4 Participants without capacity

Participants who are unable to provide consent, either at the start of the study or at any point thereafter, may not participate in the study. If, due to poor performance on cognitive testing or other concerns, the study investigator feels the participant may no longer have capacity to continue to provide consent, a standard

clinical capacity evaluation will be performed to assess whether the participant still understands the risks and benefits of the study, and requirements for participation. If not, the participant will be withdrawn.

8.4 Strategies for Recruitment, Minimizing Attrition and Engagement

8.4.1 Strategies for Recruitment

Participation in this study is restricted to those already enrolled in the RECOVER-Adult cycle 1 cohort. Participants in RECOVER-Adult cycle 1 who meet overall eligibility requirements and eligibility requirements for the prospective follow-up component for cycle 2 will be identified by the Data Resource Core (DRC). A list of participant IDs will then be provided to each site by the DRC to be used for recruitment. Site staff will evaluate whether candidate participants meet inclusion and exclusion criteria and will reach out to eligible participants using IRB-approved recruitment language or material either by text, email, patient portal (e.g. MyChart), letter or telephone to recruit into this study. Any recruitment information sent by email will utilize a secure encrypted email platform.

Additional information sent to or available to participants prior to enrollment may include videos, slide presentations, pamphlets, or website information that provides a general overview of the study and/or more details about the informed consent form. Participants may view these materials prior to consent. All materials intended for participant recruitment will be provided to the IRB for review and approval before use in the study.

8.4.2 Strategies for Minimizing Visit Attrition

Study-specific efforts to minimize visit attrition could include: 1) reminders for in-person visits and surveys; 2) flexibility in rescheduling missed visits; and 3) maintaining contact information (e.g., updating at each visit, obtaining alternate contacts). Study-specific retention materials such as reminder letters directly related to activities performed in the study will be submitted to the IRB for review and approval prior to use, ensuring compliance with ethical guidelines.

8.4.3 Strategies for Participant Engagement

Non-study-specific engagement activities focus on fostering participant engagement without directly referencing study-related activities. Examples include distributing general newsletters with updates on study progress, milestones, health tips (e.g., meditation, diet, exercise), and published scientific findings; sending post-visit thank-you notes, or follow-up calls to express appreciation; and sharing special occasion cards (e.g., birthdays, holidays, end-of-year). These materials are voluntary, non-coercive, and free from recruitment or promotional language to maintain neutrality and ethical standards. Newsletters and cards sent to participants will be reviewed for health literacy to ensure comprehension among participants of varying literacy levels. These materials do not include language related to retention, recruitment, or any calls to action for these purposes and will therefore not be submitted to the IRB. The CSC principal investigator (or designee) will review the materials for compliance prior to use.

8.5 Duration of Study Participation

Each participant will be enrolled between May 1, 2026, and April 30, 2027, and followed for approximately 2 years.

8.6 Total Number of Participants and Sites

Approximately 5,205 participants will be enrolled in this study at up to 72 participating sites. In order to participate in RECOVER-Adult cycle 2, sites must:

1) Agree to rely on the NYU sIRB, unless explicitly exempted by NIH, and
2) Be able to conduct every component of the study, including all components of the in-person assessment, and
3) Be able to conduct local processing of all biospecimen collections except peripheral blood mononuclear (PBMC) collection. Site may still participate if local processing of PBMC is not feasible, in which case the PBMCs will not be collected.

8.7 Loss to Follow-up

Participants 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 **Section 8.4**). For each missed visit, the site should attempt to contact the participant through at least three different methods at various times. Contact methods include email, text, 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 **Section 8.8**); 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.

8.8 Subject Termination and Withdrawal

Participants are free to stop participating in the study at any time upon request. Once the participants stop participating, no more information will be collected. Participants may also withdraw consent from participation and ask for their data not to be used in future analyses. The participant 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 not be used in future analyses and unused biospecimens (if collected) be destroyed. This would flag collected data to not be used in future analyses, and destruction of any unused biospecimens. However, data that have already been distributed will not be removed. Participants will be informed about this during the consenting process. Participants may not re-enroll in the study once they have withdrawn their consent, and removal of data from future analyses cannot be reversed, nor destroyed biospecimens restored.

Participants may be terminated from the study by study investigators for lack of adherence to protocol requirements or inappropriate conduct with study staff. An investigator may also terminate participation in the study if the participant's medical condition changes such that continued participation in the study would not be in the best interest of the participant, or the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

8.9 Premature Termination or Suspension of the Study or Study Site

This study or a study site 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, CSC, 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 with protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study or study site may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the NIH, CSC, and/or IRB.

9 Study Schedule

9.1 Screening

Participants will be identified as potentially eligible for the study by the DRC, following the criteria outlined in **Section 8**. Upon receipt of the list of candidate participants, sites will verify that the participant did not end

participation in cycle 1 prematurely, and that the participant does not meet any exclusion criteria. If not, site will proceed with outreach as described in **Section 8.4.1** and with consent, as described in **Section 15.3.** Once enrolled, participants will be scheduled for the baseline (time 0) study visit. An IRB-approved waiver of authorization will be implemented at participating sites to allow study teams to review potentially eligible participant's medical records to verify eligibility criteria.

9.2 Study visits

The RECOVER-Adult cycle 2 study schedule (**Table 1**) includes both participant surveys and in-person assessments at defined intervals from the time of enrollment. The cadence balances the need for robust longitudinal data collection with the goal of minimizing participant burden.

Key features of the schedule include:

- Remote surveys completed at home every 6 months from enrollment up until approximately 24 months after enrollment
- In person assessments at baseline visit and the 18-month visit
- Recruitment window from May 2026 – April 2027
- Site close-out from May 2029 – October 2029
- Core close-out period from November 2029 – May 2030

The rationale between the visit intervals is that the 6-month survey cadence provides sufficient data collection for scientific studies, without extensive participant burden. Additionally, the one-year recruitment windows provide flexibility for sites to spread out the enrollment and 18-month in-person visits. The 18-month in-person visit will be sufficiently far from index infection to capture changes in cognitive function while providing enough data in calendar time to contribute to requests for further cohort extensions. Activities performed at each study visit are detailed in **Table 1**.

Table 1: Study schedule

	Months from enrollment Calendar time window				
	Enrollment and baseline visit May 2026-Apr 2027	**6m visit** Nov 2026-Oct 2027	**12m visit** May 2027-Apr 2028	**18m visit** Nov 2027-Oct 2028	**24m visit** May 2028-Apr 2029
Enrollment	✓				
Survey	✓	✓	✓	✓	✓
In-person procedures	✓			✓	
Biospecimen collection	✓			✓	

10 Study Procedures/Evaluations

10.1 Procedures

The following minimal risk procedures were selected to evaluate long-term outcomes in neurocognitive, cardiopulmonary, and ME/CFS related sub-phenotypes. All of the procedures are minimal risk, and the scientific justification for each is described in **Table 2**.

Table 2: **Procedures performed at in-person visits**

Procedure	**Frequency**	**Rationale**	**Returned to participants**

Vitals, height, weight, waist circumference	Baseline and 18 months	Assess cardiovascular, pulmonary and metabolic health	Yes
30-second sit-to-stand	Baseline and 18 months	Assess lower body strength, endurance, and fall risk	Yes
6-minute walk test	Baseline and 18 months	Assess endurance and exercise tolerance	Yes
10-minute Active Stand Test	Baseline and 18 months	Assess orthostatic intolerance and POTS	Yes
University of Pennsylvania Smell Identification Test (UPSIT)	Baseline and 18 months	Assess olfactory function	Yes
Electrocardiogram	Baseline and 18 months	Assess cardiac function	Yes
Montreal Cognitive Assessment	Baseline and 18 months	Assess general cognition	No
Flanker inhibitory control and attention test [in NIH Toolbox v3.0]	Baseline and 18 months	Assess executive functions of attention control and impulse control	No
WAIS-IV Digit Span	Baseline and 18 months	Assess attention and working memory	No
Rey-15	Baseline and 18 months	Assess performance validity	No
Rey auditory verbal learning test	Baseline and 18 months	Assess delayed recall/retention	No
Craft Story 21 Recall	Baseline and 18 months	Assess delayed recall/retention	No
Category Fluency ('Animals')	Baseline and 18 months	Assess language fluency and speed of processing	No
Phonemic Fluency ('L')	Baseline and 18 months	Assess language fluency and speed of processing	No
Trail Making Tests Part A and B	Baseline and 18 months	Assess processing speed and executive functioning	No
Pattern comparison processing speed test [in NIH Toolbox v3.0]	Baseline and 18 months	Assess processing speed for visual information	No
Benson Complex Figure Copy	Baseline and 18 months	Assess visuospatial capacity	No
Picture Vocabulary Test [in NIH Toolbox v3.0]	Baseline and 18 months	Assess premorbid ability	No
Wide Range Achievement Test-4 or Word Accentuation Test	Baseline only	Assess premorbid ability	No

Neurocognitive testing results will not be returned to participants because they are selected for research purposes and do not constitute a comprehensive clinical neuropsychological evaluation. Isolated test scores could be misleading or distressing if misinterpreted by participants without full clinical context.

10.2 Site Certification and Quality Control for Cognitive Assessments

Neurocognitive testing training and certification is preparatory to research and does not constitute human subjects research. Certification procedures, including submission of a video, are not required for sites with

C-level trained clinicians administering assessments. The certification process will follow an SOP and site staff must complete this process prior to administering cognitive assessments for the RECOVER protocol.

In addition, to maintain high quality neurocognitive exams, at predefined intervals a random sampling of 20% of research studies will be reviewed by the neurocognitive team. Site staff will be asked to upload de-identified, selected exams to NYULH REDCap for review. For tests that are scored by staff (i.e., those not in the NIH Toolbox), if the variability in scoring is greater than 5% for a particular test across the whole cohort, the study would move to 100% double scoring of that test. Furthermore, if the variability in scoring is greater than 5% across tests for a particular site, that site will be subject to 100% double scoring of all staff-scored tests, and site staff will need to meet with the neurocognitive team to review their exam and undergo additional training as needed.

10.3 Laboratory tests

No laboratory tests are collected in the main study.

10.4 Biospecimens

10.4.1 Specimen Collection Procedures

Blood biospecimens will be collected from participants on this protocol. The PASC Biorepository Core (PBC) located at the Mayo Clinic (Rochester, MN) will create all kits for specimen collection. Details of collection and processing are described in the Biospecimen Manual of Procedures (MOP). Briefly, all biospecimens must be processed locally at participating sites. At the start of the study, sites will advise the biorepository whether they are able to support local processing of PBMCs as directed in the MOP. Sites that are able to support local processing of PBMCs will do so utilizing the PBMC Blood Kit. Sites that are unable to support local processing of PBMCs will utilize the Non-PBMC Blood Kit. In all cases, samples are processed locally: some sites will generate PBMCs while others will not. The generated sample volume will be different depending on whether PBMCs are generated or not, per **Table 3** below. To prevent the PBMC kit from requiring too much blood, volumes of some non-PBMC samples will be reduced relative to those in the non-PBMC kit.

To support collection and processing, each site will be provided with one RECOVER biospecimen kit for each in-person study visit:

- One blood kit (kit type determined at start of study by PBMC processing capabilities):
    - Collected and processed on site
        - Kit 1: PBMC Blood kit (Total blood volume: 70.9 mL); OR
        - Kit 2: Non-PBMC Blood kit (Total blood volume: 62.8 mL)

Table 3: Components of blood kits

Collection Tube	Volume Per Tube	PBMC Blood Kit			Non-PBMC Blood Kit		
		# of Tubes	Sample Shipped	Expected Total Volume	# of Tubes	Sample Shipped	Expected Total Volume
2.7mL Sodium Citrate	2.7mL	2	Plasma	5.4mL	4	Plasma	10.8mL
8mL Sodium Citrate CPT	8mL	4	Plasma and PBMC	32mL			
8.5mL SST	8.5mL	2	Serum	17mL	3	Serum	25.5mL
4mL EDTA	4mL	1	Whole Blood	4mL	1	Whole Blood	4mL
10mL EDTA	10mL	1	Plasma and WBC	10mL	2	Plasma and WBC	20mL
2.5mL PAXgene	2.5mL	1	Collection Tube	2.5mL	1	Collection Tube	2.5mL

Total		**11**		**70.9mL**	**11**		**62.8mL**

10.4.2 Biospecimen Preparation, Handling and Storage

Following biospecimen collection and processing, samples will be retained locally in frozen (-80C) storage until the next scheduled shipment to the biospecimen repository. All samples will ultimately be shipped to the Mayo clinic for storage, following standard procedures. Biorepository specimens will be stored using de-identified matrix tube IDs. The mapping of the participant ID to the matrix tube IDs will be maintained in REDCap based on data entry by the enrollment sites. The biospecimens will be stored indefinitely, or until the sample is used up or a participant requests destruction in writing. Stored de-identified biospecimens may be used for future research as approved by the NIH and RECOVER scientific leadership (see **Section 15.8**).

10.4.3 Specimen Shipment

Biospecimens will be shipped using supplies provided by the PBC overnight via FedEx to the Mayo Biorepository in Rochester, Minnesota. Frozen specimens collected at sites will be batched and shipped Monday – Wednesday weekly or monthly on dry ice.

10.5 Questionnaires

Participants will complete a battery of questionnaires through REDCap at every study visit (thus, at enrollment and every 6 months thereafter). Topics covered by the questionnaires are shown in **Table 4.**

Table 4: Questionnaire measures

Category	Element
Demographics	Name and contact information
Demographics	Alternate contacts
Demographics	Marital status
Social determinants	Homelessness
Social determinants	Description of living place
Social determinants	Financial insecurity
Social determinants	Employment
Social determinants	Health insurance
Social determinants	Medical discrimination
Social determinants	Alcohol and substance use
COVID prevention	Steps taken to minimize SARS-CoV-2 exposure
Long COVID	Treatment for Long COVID
Disability	Disability benefit and accommodation status
Pregnancy	Pregnancy status
Pregnancy	Pregnancy outcomes
Vaccination	Vaccination status and vaccine details
Comorbidity	Immunocompromised condition and specific types
Comorbidity	Rheumatologic, autoimmune or connective tissue disease and specific types
Comorbidity	Diabetes and specific type

Category	Element
Comorbidity	Gastrointestinal, liver, or kidney disease and specific type
Comorbidity	Active cancer or cancer treatment and specific type
Comorbidity	Dementia or cognitive impairment and specific type
Comorbidity	Central nervous system infection, inflammatory disease or demyelinating disease type
Comorbidity	Seizure disorder
Comorbidity	Neuromuscular disease and specific type
Comorbidity	Movement disorder and specific type
Comorbidity	Cardiovascular disease and specific type
Comorbidity	Stroke or bleed and specific type
Comorbidity	Asthma
Comorbidity	Chronic obstructive pulmonary disease
Comorbidity	Other chronic lung disease
Comorbidity	Use of oxygen at home
Comorbidity	Anxiety, depression or PTSD
Comorbidity	Schizophrenia or bipolar disorder
Comorbidity	Other mental health disorder
Comorbidity	Sickle cell anemia
Comorbidity	Chronic pain syndrome or fibromyalgia
Comorbidity	Myalgic encephalomyelitis/chronic fatigue syndrome
Comorbidity	POTS or other form of dysautonomia or autonomic dysfunction and specific type
Comorbidity	Obesity
Comorbidity	Gynecologic problems
Comorbidity	Thyroid problems
Comorbidity	Blood or blood clotting problems
Comorbidity	Transplant and type
Comorbidity	Headache problems
Comorbidity	Sleep problems
Comorbidity	Allergy problems
Comorbidity	Infections
Comorbidity	Other health problems
Medications	Complete medication list
Symptoms	Overall health status
Symptoms	Social function
Symptoms	Physical function
Symptoms	Fatigue and fatigue details
Symptoms	Post-exertional malaise (e.g., feeling exhausted after walking) and details
Symptoms	Weakness in limbs and details
Symptoms	Fever, chills, sweats or flushing and details
Symptoms	Loss of or change in smell or taste and details
Symptoms	Pain in any part of body and site of pain
Symptoms	Headache and details

Category	Element
Symptoms	Chest pain and details
Symptoms	Shortness of breath or trouble breathing and details
Symptoms	Cough and details
Symptoms	Palpitations, racing heart, arrhythmia, skipped beats and details
Symptoms	Swelling of lower legs and details
Symptoms	Gastrointestinal symptoms and details
Symptoms	Bladder problems and details
Symptoms	Nerve problems and details
Symptoms	Depression screen
Symptoms	Suicidality screen
Symptoms	Anxiety screen
Symptoms	Stress
Symptoms	Problems thinking or concentrating and details
Symptoms	Problems with sleep and details
Symptoms	Faint, dizzy, "goofy," difficulty thinking soon after standing up and details
Symptoms	Color changes in skin, such as red, white or purple and details
Symptoms	Skin rash and details
Symptoms	Changes in sweating and details
Symptoms	Excessively dry eyes and details
Symptoms	Excessively dry mouth and details
Symptoms	Excessive thirst and details
Symptoms	Vision problems and details
Symptoms	Problems with hearing and details
Symptoms	Hair loss and details
Symptoms	Problems with teeth or gums and details
Symptoms	Change in menstruation or menopause and details
Symptoms	Changes in desire for, comfort with or capacity for sex and details
Symptoms	Post-exertional malaise 2 weeks before and after the in-person visit

See for **Table 5** for PHI elements that will be collected in REDCap as part of these questionnaires. Sites will also retain PHI elements locally in a HIPAA-compliant manner for purposes of follow up and data retrieval.

Table 5. 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	Electronic mail addresses
8	Dates of diagnoses or other events

10.6 Reporting of Clinically Actionable Findings

Tests performed by certified clinical laboratories or the electrocardiogram reading center that are analytically valid and either clinically significant or medically actionable will be reviewed by the Principal Investigator or other designated licensed medical professional at each site. If the Principal Investigator or licensed designee determines that the result is clinically significant or medically actionable, the participant will be contacted 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 or other physician, if appropriate. The results of incidental findings will be shared with participants consistent with state and local regulation. Any additional testing ordered by the primary care physician will be paid for by the participant or their insurance company.

Positive suicidality screens will trigger clinician contact within 48 hours, risk assessment, safety planning, and referral (ED or mobile crisis) as indicated.

11 Safety and Adverse Events

In this low-risk, non-interventional study, adverse events (AEs) will be limited to events reasonably related to study procedures (phlebotomy; functional tests; surveys), with relatedness adjudicated by the site PI or licensed designee; non-related medical events will not be collected as AEs.

By focusing exclusively on study-related events, this approach enhances efficiency, reduces unnecessary reporting of unrelated medical events, and ensures data collection remains relevant. Serious adverse events (SAEs) and unanticipated problems involving risks to participants or others will continue to be reported per IRB policies and federal regulations, consistent with guidance from the U.S. Office for Human Research Protections (OHRP). This refined definition supports meaningful data collection while maintaining participant safety and compliance with ethical standards.

11.1 Definitions

11.1.1 Unanticipated Problems Involving Risk to Participants 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**
- **is serious; suggests that the research caused harm to participants or others or places participants or others at greater risk of harm** (including physical, psychological, economic, or social harm) **than was previously known or recognized**

11.1.2 Adverse Event

For this study an ***adverse event*** (AE) is defined as any symptom, sign, illness or experience directly related to study procedures that develops or worsens in severity during the course of the study.

Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal,
- is associated with a serious adverse event,
- is associated with clinical signs or symptoms, or
- is considered by the investigator to be of clinical significance.

11.1.3 Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** (SAE) is any AE that:

- is fatal,
- is life-threatening,

- requires or prolongs hospital stay,
- results in persistent or significant disability or incapacity,
- results in a congenital anomaly or birth defect, or
- is an important medical event.

Important medical events are those that may not be immediately life-threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, syncope after blood draw resulting in traumatic head injury would be considered serious.

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

11.1.4 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 as a consequence of study activities.

11.2 Follow-up of Adverse Events

All unresolved adverse events related to study participation should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study for a period of up to six months following the subject's last visit. The investigator should notify the study sponsor of any death or serious and unexpected adverse event occurring within six months after a subject has discontinued or terminated study participation that may reasonably be related to this study.

11.3 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events related to study activities by specific questioning and, as appropriate, by examination. Information on all related adverse events should be recorded immediately in the source document, and also in the appropriate adverse event case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events related to study activities during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that study participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome.

11.4 Reporting of Unanticipated Problems and Other Reportable Events

This section describes the NYULH IRB reporting requirements for unanticipated problems and other reportable events, though investigators at participating sites are responsible for meeting the specific requirements of their IRB of record if not NYU.

Unanticipated Problems
Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to participants or others. Unanticipated problems are:

- unexpected, AND
- related or possibly related to study participation, AND
- serious; caused harm to participants or others, or placed participants or others at a greater risk of harm than was previously known or recognized.

Unanticipated problems represent rare and unforeseen events that pose increased risks to participants or others involved in the research. These events are unexpected in nature, and their occurrence typically

necessitates modifications to critical study documents, including the study protocol and informed consent, to address new risks and ensure participant safety. Documenting and addressing unanticipated problems are essential for maintaining ethical standards and regulatory compliance throughout the study.

Other Reportable Events
Other Reportable Events refers to any new information, unanticipated events or unintentional mistakes that may impact the conduct of an IRB-approved study or the safety and welfare of participants in the study. These could include complaints, protocol deviations/violations, breaches of confidentiality, non-compliance, audits, or other reports, but if the event **does not affect the conduct of the research or the participants' safety and/or welfare, it does not qualify for immediate reporting to the NYULH IRB**. The site Principal Investigator should assess whether an event meets the criteria for immediate reporting.

When to Report Events

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

- Any change in the IRB-approved study protocol that was taken without prior IRB review to eliminate immediate hazard to participants. The event requires immediate intervention to prevent serious harm to participants or others
- Death of a participant, if it is unexpected and related to a study procedure

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

Related 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.

11.5 Reporting Process

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

12 Study Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at their site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a data and safety-monitoring plan (see **Section 12.1**). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

12.1 Monitoring Board

Oversight of data and safety is provided by the RECOVER Observational Safety Monitoring Board (OSMB) appointed by the National Heart, Lung, and Blood Institute (NHLBI). A charter of the OSMB is provided to the sIRB. The OSMB will meet at least annually 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 RECOVER-Adult cycle 2 study does not involve any interventions, an early stopping rule for efficacy or futility is not indicated.

13 Statistical Considerations

13.1 Study Hypotheses

Specific Aim 1 Hypothesis: Distinct trajectories will be identified based on integrated longitudinal data spanning up to seven years of follow-up for each sub-phenotype.

Specific Aim 2 Hypothesis: Participant level clinical and demographic factors will predict persistence.

Specific Aim 3 Hypothesis: New onset neurodegenerative disease, cardiometabolic disease, and autoimmune disease will have higher incidence in each respective LC sub-phenotype group compared to participants with no history of LC.

13.2 Sample Size Determination

Detectable risk differences for remission based on a two-sample test of proportions are given in **Table 6** for the overall expected number with LC and the numbers within sub-phenotype group representing 20% and 30% of all participants with LC, assuming two-sided type-1 error of 0.05 and 80% power. For example, if there are 731 participants with a LC sub-phenotype, 30% are exposed (e.g., to a given putative risk factor), and the rate of the outcome (e.g., remission) is 20% in the exposed group, then there is 80% power to detect a risk difference of 0.084 (8.4%) at a significance level of 0.05 (assuming exposure is associated with a higher rate of remission). Remission rates of 20-50% among exposed are consistent with preliminary data.

Table 6: Detectable differences in risk of remission between exposure groups among LC sub-phenotype cases

Number with LC	Sub-phenotype proportion	Number with LC sub-phenotype	Proportion exposed	Prop with outcome among exposed	Detectable risk difference
3656	0.20	731	0.3	0.20	0.084
3656	0.20	731	0.3	0.50	0.112
3656	0.20	731	0.5	0.20	0.076
3656	0.20	731	0.5	0.50	0.103
3656	0.30	1097	0.3	0.20	0.069
3656	0.30	1097	0.3	0.50	0.092
3656	0.30	1097	0.5	0.20	0.063
3656	0.30	1097	0.5	0.50	0.084

Detectable risk differences for new onset conditions based on a two-sample test of proportion are given in **Table 7** for the overall expected number with LC and the numbers within sub-phenotype group representing 20% and 30% of all participants with LC, assuming a two-sided type-1 error of 0.05 and 80% power. For example, if there are 731 exposed (LC sub-phenotype) and 1549 unexposed (non-LC), and the rate of the outcome (new onset condition) is 20% in the exposed group, then there is 80% power to detect a risk difference of 0.048 (48%) at an alpha level of 0.05 (where being exposed is associated with a higher rate of the outcome).

Table 7: Detectable differences in risk of new onset conditions between participants with LC-sub-phenotype and participants without LC

Effective sample size	Number with LC	Sub-phenotype proportion	Number with LC sub-phenotype	Number without LC	Prop with outcome among those with LC sub-phenotype	Detectable Risk Difference
5205	3656	0.20	731	1549	0.20	0.048
5205	3656	0.20	731	1549	0.50	0.063
5205	3656	0.20	731	1549	0.80	0.052
5205	3656	0.30	1097	1549	0.20	0.042
5205	3656	0.30	1097	1549	0.50	0.055
5205	3656	0.30	1097	1549	0.80	0.046

13.3 Statistical Methods

Statistical methods for aim 1. Finite mixture models for longitudinal data using the Expectation-Maximization (EM) algorithm will be used to identify distinct longitudinal profiles using the LCRI as a Poisson-distributed continuous outcome variable.[2] Profiles will be generated overall and stratified by history of LC and each of the three sub-phenotypes. Additional summaries of demographic and clinical characteristics, including numbers of reinfections and vaccine doses, will be summarized by profile. Risk factor analyses will account for the large number of potential confounding variables. This aim is considered hypothesis generating. Primary analysis will include all RECOVER-Adult cycle 2 participants. Recognizing that trajectory prevalence estimates will be biased due to the case-cohort sampling design, further adjustment via inverse probability of sampling weights will be performed. As this cohort is augmented for participants with LC, it is expected to improve efficiency for identifying distinct profiles among those with LC. We anticipate this aim will yield distinct profiles across the three sub-phenotypes, as well as novel sub-phenotypes.

Statistical methods for aim 2. Characterizing time to improvement among individuals with LC is complicated by the diverse timescales over which individuals develop and resolve LC symptoms, and in some cases develop new symptomologies. As a result, analyses require definition of a common timescale over which to evaluate improvement, such as time to improvement among everyone who has LC at a pre-specified number of months after infection. This example corresponds to a so-called 'landmarking' approach that chooses clinically relevant landmark timepoints following index infection (e.g., 6 months, 18 months, etc.). For each landmark time, we will restrict to individuals with persistent LC at that time and perform an analysis of time until subsequent improvement.[3] The result will be several landmark-specific analyses, characterizing time to improvement in cohorts defined by the presence of LC at different clinically relevant landmark times.[4] In this way, we can examine trajectories of remission, and how they vary among individuals with persistent LC at later times since infection. Definitions of improvement will be flexible and include measures that capture durability as well as early signs of resolution. Analysis will use tools for discrete-time survival analysis to acknowledge that data collection occurs at fixed interval follow-up visits.[5] For each landmark model, we will estimate cumulative probability of remission using a discrete-time Kaplan-Meier estimator. Analyses will be completed overall and for each LC sub-phenotype. We will additionally evaluate associations between individual characteristics and time to remission using discrete-time Cox proportional hazards modeling. Focused consideration in this aim will be given to identifying promising pharmaceutical and non-pharmaceutical interventions for consideration in future RECOVER clinical trials.

Statistical methods for aim 3. For this aim, a unified analytic strategy will be used to account for differential sampling, informative missingness and imbalance in exposures (in this case, LC status). The average treatment effect (ATE), an additive contrast of potential outcomes, will be used to quantify differences in new onset conditions driven by LC status. Under standard assumptions,[6,7] the ATE is non-parametrically identified as a functional of the underlying data-generating distribution: the covariate adjusted mean difference of the outcome across exposure conditions. This forms the basis of the inverse probability weighted (IPW) and targeted minimum loss (TML) estimators we will employ. To adjust for the selection bias induced by the case-cohort sampling scheme, the IPW and TML estimators can be adjusted to incorporate inverse probability of sampling weights,[8-10] while correcting for differential loss to follow-up can be achieved by additionally incorporating inverse probability of censoring weights under the assumption of exchangeability of the censoring mechanism and potential outcomes. We will consider the TML estimator as an alternative strategy as it makes use of the efficient influence function (EIF), which characterizes the best possible asymptotic variance in the non-parametric model. The EIF will be modified to incorporate inverse probability of censoring weights and to account for selection bias due to case-cohort design.[11-14]

14 Source Documents and Access to Source Data/Documents

Source data is 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, participants' 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. In this study, REDCap is considered the source document when there is no other source report available (e.g., self-report survey responses entered by the participant directly into REDCap through secure link, data collected by study staff at site during an in-person visit such as vitals, clinical assessments). Data that are first captured and reported through other platforms (e.g., NIH Toolbox app, EKG report, etc.) will have other data formats as source document. Clinical data will be entered directly from those source documents.

The electronic study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. 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.

In the event that a site cannot use the electronic CRF, the equivalent paper CRF must be used and data later transferred to the eCRF. If using the paper version, if a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A." All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

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/Ethics Committee, NIH, the CSC, the DRC, 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., protocol-specific laboratories).

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

15 Ethics/Protections of Human Participants

15.1 Ethical Standards

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants in Research codified in 45 CFR Part 46.

15.2 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 participants need to be re-consented.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion of risks and possible benefits of participation will be provided to the participants and, if desired, their families in lay terms 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 participants must 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.

Participants will have the opportunity to carefully review the IRB-approved written consent form and ask questions prior to signing. The investigator or suitable designee will ensure that all the required elements of informed consent are discussed and will address all questions about the study. Comprehension of the study procedures and risks will be confirmed with standardized questions to the subject. Participants will have the opportunity to discuss the study with their physician, family or friends or think about it prior to agreeing to participate. Participants will be provided with 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. All prospective participants will be provided key information that summarizes essential study information for quick reference.

When the enrollment visit is completed in person, informed consent will be obtained and documented in writing before participation in study procedures can begin. When the enrollment visit is completed remotely (e.g., by telephone or video conference), either electronic or paper consent may be used. For sites using eConsent, their 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. For remote consenting, participants will be sent the link to the consent form via encrypted email, and participants will be given the phone number of a study team member to call after they have reviewed the consent. The study team members will follow the consenting procedure described above. 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.

If a subject cannot provide an electronic signature during a remote visit, they must 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.

For all participants, a copy of the signed informed consent document will be stored in the subject's research record along with documentation of the consent process, including the name of the individual obtaining consent. Any alteration to the standard consent process (e.g., use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented. Documentation of consent will also be recorded electronically in the central REDCap system.

15.4 Consent and Other Informational Documents Provided to Participants

Participants will receive the consent form and key study information, which describe in detail the study, study procedures, and risks. Written documentation of informed consent is required prior to starting the study. In addition to the required regulatory elements, the consent document will include:

- consent for participation in all study activities;
- consent for sharing identifiable data with the secure REDCap Central database;
- consent to obtain and link data from electronic health records, regional health information exchanges, claims data and the National Death Index;
- consent for sharing of identifiable and de-identified data and specimens through RECOVER databases and specimen repositories (in addition to other NIH-designated repositories);
- consent for contact for ancillary and other studies;
- consent for collection of biospecimens to be stored for future research;
- consent to opt-in to future genetic research (see **Section 15.8**).

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

15.5 Posting to ClinicalTrials.gov

The proposed study is posted on clinicaltrials.gov.

15.6 Participant and Data Confidentiality

Information about study participants 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 participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of research subject to revoke their authorization for use of their PHI.

If a participant 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 participants 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. The measures to protect confidentiality are as follows:

15.6.1 Storage of Study Materials and Data

Site investigators will take all reasonable measures to protect the confidentiality of the study participants through the measures used in all RECOVER studies, including storage of study materials in locked, secure locations accessible only to study investigators, and use of secure password-protected computer access and encrypted transmission of patient information.

At the DRC, all software that manages PHI in use as part of the study is hosted on a secure, FISMA-moderate Azure cloud environment at Mass General Brigham. This environment hosts i2b2, which enables data harmonization; REDCap Central; and all statistical analysis tools. It leverages 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).

15.6.2 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 in addition to the clinical information relating to participants. 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 sponsor, the CSC, 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 participants in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored in the central study database and 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 a minimum of six years or longer as dictated by local institutional regulations.

To help us protect the privacy of participants in the RECOVER cohort study, a Certificate of Confidentiality was 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 Office for Human Research Protections (OHRP). 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.

15.7 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, related conditions, potential biomarkers, and therapeutic targets.
- Storage: Access to stored samples will be limited with policies and procedures requiring multiple reviews prior to the release of any samples for analysis. Only approved investigators will have access to the samples and data.
- Tracking: Data will be tracked using i2b2 at the DRC. Each specimen will be labeled and tracked with a record ID and kit ID that aligns with REDCap.
- Disposition at the completion of the study: All stored samples will be sent to the PBC. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

15.8 Secondary Use of Stored Data and Biospecimens

Consent for future use of stored data and biospecimens is required for enrollment.

This protocol does not include large-scale genomic or genetic sequencing research and therefore is not subject to the NIH Genomic Data Sharing (GDS) Policy. However, future research using stored data and biospecimens from this cohort may include whole genome sequencing (WGS), genetic, or epigenetic analyses. The research consent form will therefore ask participants to opt-in to future genetic research. Consent to future genetic analyses is not required for study enrollment. Participant consent choices will be tracked individually in REDCap and for participants who do not consent to future WGS or genetic analyses, their samples and data will be labeled as such by the DRC and the PBC and will not be released to researchers for genetic research, even once de-identified.

The reasonably foreseeable risks of future genetic testing are primarily informational rather than physical. Because genetic data is highly sensitive and may be inherently identifiable, there is a risk of loss of privacy or breach of confidentiality despite the use of data security safeguards. Unauthorized access or inadvertent disclosure could result in social, psychological, or economic harms, including stigma or discrimination. No additional physical risks are anticipated, as all research will be conducted using previously collected data and biospecimens.

Reasonably foreseeable risks related to future genetic analyses using stored data and biospecimens are described in the informed consent form provided to participants prior to enrollment in this study.

15.8.1 Storage and Maintenance of Stored Data and Biospecimens

Data collected for this study will be analyzed and stored at the DRC. For future research use by RECOVER or other investigators, data will be stored in registries housed by NHLBI BioData Catalyst® (BDC). BDC is a cloud-based ecosystem that houses NHLBI repositories and provides the necessary analytics platform for analysis. Data will be available in three forms: 1) identified line-level, in a private data repository (RECOVER Data Gateway; RDG) maintained by BDC and accessible only to RECOVER Consortium investigators upon approval by a RECOVER PI and the RECOVER publications committee following established policies and procedures; 2) fully de-identified line-level, in a data repository at BDC accessible upon request to the public, for which access is managed by the Database of Genotypes and Phenotypes (dbGaP); and 3) publicly-available, grouped, anonymized data for exploration and cohort-building through BDC using the Patient-centered Information Commons: Standardized Unification of Research Elements (BDC-PIC-SURE)

tool. No permissions are required to access PIC-SURE because it is fully anonymized count data. See **Section 16.1** for details of data handling. Researchers may use data in any of the three available repositories to study mechanisms and clinical manifestations of SARS-CoV-2 infection, related conditions, potential biomarkers, and therapeutic targets, as well as unrelated conditions. The data will be retained indefinitely. Permission to transmit data to the repository is required and will be included in the informed consent.

Biospecimens collected for this study will be stored at the PBC. After the study is completed, de-identified, archived specimens will remain at the biorepository, under the supervision of the PBC PI for use by other researchers including those outside of the study as determined by the policies and procedures of the RECOVER ancillary studies oversight committee and upon approval by the biospecimen availability committee. Researchers may use these specimens to study mechanisms and clinical manifestations of SARS-CoV-2 infection, related conditions, potential biomarkers, and therapeutic targets, as well as unrelated conditions. The specimens will be retained indefinitely or until used up by future analyses. Permission to transmit data to the PBC is required and will be included in the informed consent. Verification of consent for future genomic research is required for samples to be used in future research intending to perform whole genome sequencing. The DRC will flag all participants who did not consent for genetic research if future genomic research consent is not given. This flag alerts users of the lack of genomics consent and prevents selection for future research where whole genome sequencing could be used.

During the study, site staff and the DRC will have access to the linking code that connects the participant ID to the participant's identity. Upon study completion, the DRC will maintain the linking code for a period of up to 5 years. An individual participant can choose to withdraw consent to have their data and biological biospecimens stored for future research by contacting the site PI. Withdrawal of consent for biosample storage is possible only within 5 years after the study is completed, as all samples will be fully anonymized after that time. Participants may request destruction of unused biospecimens and exclusion of identifiable data from future use by contacting the site PI. Once data and specimens are de-identified and shared, withdrawal and destruction are no longer possible.

There is no anticipated potential commercial use or application that may result from stored and shared data and biospecimens.

Table 8: Summary table of secondary use of stored data

Data repository	Management oversight	Access	Identifiers
Recover Data Gateway (RDG)	NHLBI via BioData Catalyst	Only to RECOVER Consortium investigators	Dates, 9-digit zip code, free text entered by participants
Public data access at BDC	NHLBI via BioData Catalyst	General public, upon request to dbGaP	None. Fully de-identified; no free text; dates shifted.
BDC-PIC-SURE	NHLBI via BioData Catalyst	General public, no permission required	None. Grouped, anonymized data only, for counts.
PASC Biorepository	PASC Biorepository Core at Mayo Clinic	Only to investigators approved by the RECOVER Ancillary Studies Committee and upon approval by the Biospecimens Committee	Dates. Can be linked to any of the other datasets with relevant approvals via participant ID.

16 Data Handling and Record Keeping

16.1 Data Collection and Management Responsibilities

16.1.1 Data Collection

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. See **Section 14** for details of data collection and recording requirements. All study data will be obtained from study participants (e.g., questionnaires), results from clinical assessments conducted per study, and relevant data from the EHR as necessary. RECOVER-Adult Cohort Cycle 2 will also incorporate relevant RECOVER-Adult Cycle 1 cohort data to support longitudinal analyses.

Data are collected in several different datasets

- REDCap is the electronic data capture (EDC) system for this study. This secure HIPAA compliant electronic data capture system will enable study coordinators to record participant data and participants to directly answer surveys. REDCap 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.
- Biospecimen data are managed in a Laboratory Information Management System (LIMS) at the PBC.
- The electrocardiogram reading center will read ECGs separately and send data into the DRC environment for harmonization with other study data. The staff at these participating institutions may access some identifiers that have been already collected, such as participant ID, sex, age (or an indication they are over 90 years old), and demographic information that is necessary to perform these reads.
- During the study local sites will collect and retain participant identifiers to facilitate participant reimbursement, contact and retention. All locally held data will be held in HIPAA-compliant locations.

16.1.2 Data Management

The REDCap data are housed at the DRC. Biospecimen and ECG data will be securely transferred to the DRC, where they will be harmonized with REDCap and additional data types as needed, such as Census data. All RECOVER tools for capturing and harmonizing data reside in highly secure, FISMA-moderate compliant cloud environments (see **Section 15.6.1**).

The DRC will transfer data at regular intervals to BDC to manage for investigator-initiated research. Research on RECOVER data may take place on private, identified data (RDG at BDC); on public, de-identified line-level data (at BDC); or on public, de-identified grouped data (BDC PIC-SURE). All of these datasets are managed by NHLBI through BDC. See **Section 15.8** for details of these different types of data and access controls for each. The private, identified data at RDG may contain participant identifiers (e.g., participant ID, date of birth, visit dates, 5-digit zip code, or other data that is entered by participants or study staff into free text fields). The BDC Data Management Core is responsible for fully de-identifying these data to create the de-identified line level dataset at BDC and the grouped cohort tool (BDC PIC-SURE), both of which are available to the public. Access to the public, de-identified dataset is managed by NHLBI through dbGaP (see **Section 15.8**).

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

16.2 Study Records Retention

Study documents will be retained for a minimum of 6 years after close-out. 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.

16.3 Protocol Deviations

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

All deviations associated with change in risk to participants or that compromise the scientific integrity of the study must be addressed in study source documents, reported to RECOVER program scientific directors at

NIH, the Clinical Science Core Principal Investigators at NYU Langone Health, the RECOVER DRC Principal Investigators at Massachusetts General Hospital, the IRB of record, and the RECOVER OSMB. Protocol deviations that do not impact risk or scientific integrity must be reported on a note to file or in the appropriate field in REDCap. Sites that do not rely on the NYU sIRB should report protocol deviations according to their local IRB guidelines. The site PI/study staff is responsible for knowing and adhering to IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

16.4 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 result from NIH funds to the digital archive PubMed Central upon acceptance for publication. This study will also comply with the NIH Data Sharing Policies https://grants.nih.gov/policy-and-compliance/policy-topics/sharing-policies and the NHLBI Supplement to the NIH Policy for Data Management and Sharing (effective May 25, 2023) (https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-policy-for-data-sharing.

17 Study Finances

17.1 Funding Source

This study is financed through an award 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).

17.2 Costs to the Subject

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

17.3 Subject Reimbursements or Payments

Sites will offer participants a nominal reimbursement for participation in the remote interval assessments (amounts to be determined by each enrolling site). The payment amount criteria will be determined locally by the sites based on a combination of the complexity of the study; inconvenience to the participant; discomfort associated with the assessment; degree of risk, time, effort, and commitment needed from participants; engagement of vulnerable populations; and geographical location of the site. The recommended subject reimbursements are listed in **Table 9**.

Table 9 Recommended subject reimbursement by type of study visit

Visit type	Participant reimbursement per visit
Baseline and 18-month in-person visits	$180
6-month, 12-month and 24-month remote survey visits	$40
Travel reimbursement	As per receipts received

18 Study Administration

18.1 Study Leadership and Oversight

The scientific direction of the protocol is determined by the Adult Coordinating Committee, which is comprised of Hub and Core PIs. Scientific leadership for the study is also provided by the RECOVER Clinical Science Core (CSC) at the NYU Grossman School of Medicine and the Data Resource Core (DRC) at Mass General Brigham. The CSC additionally provides operational oversight of sites participating in the study ensuring compliance with federal regulations, including ethical review, safety monitoring, and data reporting. The DRC leads statistical analyses, data management and data storage. Biospecimen storage is

at the RECOVER biorepository at Mayo Clinic. The activity of the RECOVER cohorts is overseen by the Observational Cohorts Steering Committee, composed of the Core PIs, NIH Scientific Program leads, and Chairs of RECOVER Coordinating Committees; and an Executive Committee composed of NIH Institute leadership and Centers for Disease Control leadership. The Steering Committee and Executive Committee will meet at least twice yearly.

To ensure participant safety and study integrity across sites, a management plan oversees unanticipated problems, interim results, and protocol modifications. All sites will be trained to promptly report unanticipated problems to the CSC and sIRB using standardized procedures. The OSMB will review these reports and interim analyses per its charter. Proposed protocol changes will be submitted to the IRB for approval before implementation. Written communications and training ensure consistent application. Regular CSC-site communication supports timely updates on safety, interim findings, and protocol changes.

19 Conflict of Interest Policy

All recipient institutions and investigators in the RECOVER 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 RECOVER 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.

20 References

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