RECOVER
Researching COVID to Enhance Recovery

Manual of Operations and Procedures (MOP)
for

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

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

Study ID: s21-01226

Protocol Version: Version 1.2

Revision History

Revision number	Date	Summary of Revisions
1.1	12/24/2021	Minor typographical errors corrected throughout Section V.E: Clarified that PI need not be a physician Section X.A.1.b: Clarified process for accessing Huron documents Section XI.B.1: Indicated where to find the pre-activation checklist (attestation form) Section XI.C: Noted that subsites must have a contract with their hub prior to activation, and that a copy should be sent to the CSC Section XI.D.2: Clarified how to complete REDCap training Section XI.D.3: Clarified how to complete Biorepository training Section XI.D.4: Clarified how to access RISE training platform Section XI.E: Added to provide details on the activation (green light) letter Section XII.C: Clarified that 1:1 matching will not be performed Section XII.F.2.iii: Defined “community transmission” Section XII.G.3: Clarified that WHO probable criterion d is not applicable to the adult protocol Section XII.G.4: Clarified that WHO confirmed criterion b is modified to include positive antibody test Section XII.G.5: Clarified criteria for adult without SARS-CoV-2 infection Section XII.I: Placeholder; text will be added to clarify handling of changes in infection status and new on-study infections Section XIV: Removed reference to electrocardiogram in baseline visit Section XV.A: Clarified that laboratory tests are drawn at month 3 Section XV.A.3: Clarified details of urinalysis and urine microalbumin Section XV.D: Moved list of all central lab assessments to this new section for clarity
1.2	12/30/2021	Minor typographical errors corrected throughout; deleted extra page before Table of Contents Sections renumbered after VIII. Regulatory and Administrative Procedures Section XVII.A: Added windows for Tiers 2 and 3 assessments to be completed.

I. Table of Contents

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II. Abbreviations

Table 1: Abbreviations

COI	Conflict of Interest
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CSC	Clinical Science Core
DRC	Date Resource Core
EDC	Electronic Data Capture
FWA	Federalwide Assurance
ICF	Informed Consent Form
IMV	Interim Monitoring Visit
IRB	Institutional Review Board
LTFU	Lost to Follow-up
MOP	Manual of Operations and Procedures
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
NYULH	NYU Langone Health
OSMB	Observational Safety Monitoring Board
OTA	Other Transactional Agreement
PASC	Post-Acute Sequelae of COVID-19
PBC	PASC Biorepository Core
QA	Quality Assurance
QC	Quality Control
RECOVER	REsearching COVid to Enhance Recovery
sIRB	Single IRB

III. Introduction to the Manual of Operations and Procedures

A. Purpose

The purpose of the Manual of Operations and Procedures (MOP) is to facilitate consistency in protocol implementation and data collection across study participants and study sites. Any process in the MOP should be followed with the same degree of vigor as those documented in the protocol. Use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that study participant safety and scientific integrity are closely monitored.

This MOP is to be used as a reference document for policies and procedures related to the study **NIH RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults** (short title: Understanding the Long-term Impact of COVID-19 in Adults; referred to hereafter as "the study").

All study staff participating in the conduct of the study, "Understanding the Long-term Impact of COVID-19 in Adults" at study sites will have ready access to the MOP and be familiar with its contents. The current version of the MOP and archived or draft versions are posted on MS Teams, in the General and MOP channels, respectively**.** It is recommended that study sites refer only to the MOP on the MS Teams general channel to ensure adherence to the current version of the MOP. Once the study website goes online, a current version of the MOP will be also be posted on the website.

B. Updating and Version Control

The MOP is a dynamic document that will be updated throughout the conduct of the study to reflect any protocol or consent amendments, as well as the refinement of the case report forms (CRFs) and study procedures. As sections/chapters are revised, the MOP version information and date on the cover page and Table of Contents will be updated; the Revision History table will list the chapters that have changed and will include a general summary of those changes. The version date and version number in the page footer will be updated to reflect the new version on those chapters that have been modified for ease of identification.

As the study progresses, the Clinical Science Core (CSC) will be responsible for documenting any recommended and approved changes to the MOP. When finalized, the revised MOP will be posted to MS Teams, and a message will be posted to Teams to indicate that the MOP has been updated and is available. If required, study coordinators and investigators at the study sites will be trained on the changes.

Study staff at the study sites can log into MS Teams to access the complete MOP or specific sections.

IV. Study Protocol Summary

The protocol NIH RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults can be found in the MS Teams Adult general channel. A protocol summary is below.

Title	NIH RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults
Short Title	Understanding the Long-term Impact of COVID-19 in adults
Brief Summary	This is a combined retrospective and prospective, longitudinal, observational meta-cohort of individuals who will enter the cohort with and without SARS-CoV-2 infection and at varying stages before and after infection. Individuals with and without SARS-CoV-2 infection and with or without PASC symptoms will be followed to identify risk factors and occurrence of PASC. This study will be conducted in the United States and participants will be recruited through inpatient, outpatient, and community-based settings. Study data including age, demographics, social determinants of health, medical history, vaccination history, details of acute SARS-CoV-2 infection, overall health and physical function, and PASC symptom screen will be reported by participants or collected from the electronic health record using a case report form at specified intervals. Biologic specimens will be collected at specified intervals, with some tests performed in local clinical laboratories and others performed by centralized research centers or banked in the Biospecimen Repository. Advanced clinical examinations and radiologic examinations will be performed at local study sites with cross-site standardization.
Objectives	Characterize the incidence and prevalence of sequelae of SARS-CoV-2 infection. Characterize the spectrum of clinical symptoms, subclinical organ dysfunction, natural history, and distinct phenotypes identified as sequelae of SARS-CoV-2 infection. Define the biological mechanisms underlying pathogenesis of the sequelae of SARS-CoV-2 infection.
Methodology	Ambidirectional longitudinal meta-cohort study (combined retrospective and prospective) with nested case-control studies.
Endpoint	Primary Endpoints: Presence of candidate PASC symptoms over time (incidence and prevalence). Secondary Endpoints: Biological and recovery trajectories from SARS-CoV-2 infection; organ injury; incident clinical disease.
Study Duration	Four years
Participant Duration	Up to four years

Population	Infected: Individuals at least 18 years of age meet WHO criteria for suspected, probable or confirmed SARS-CoV-2 infection on or after March 1, 2020. Uninfected: Individuals at least 18 years of age who have never met any of the WHO criteria for suspected, probable or confirmed SARS-CoV-2 infection.
Number of participants	15,000 total participants with SARS-CoV-2 infection and 2,680 total participants without SARS-CoV-2 infection.
Statistical Analysis	A flexible study design is proposed to allow modifications to PASC case definition, tiered phenotyping assessments, comparator groups, and/or statistical plan after its initiation to optimize public health impact without undermining validity and integrity of study findings. Modifications in study design may be based on analyses of structured cohort data, unstructured cohort EHR data, and other cohort EHR data.

V. Study Organization

A. Clinical Science Core (CSC)

The PASC CSC will provide seamless integration of all clinical, project management and data management activities to support the effective, efficient conduct of PASC RECOVER for all cohorts at the hub sites and sub-sites. Statistical collaboration and leadership for study design, protocol development and ongoing safety monitoring of the trial is completely integrated with the clinical and data management support. The CSC will provide:

- comprehensive support and oversight of the hub sites and subsites for day-to-day operations, including all aspects of study implementation, training, and regulatory reporting
- oversight and management of the scientific protocol, MOP and IRB regulatory documents
- the preparation and dissemination of study results through presentations, publications and data sharing consistent with National Institutes of Health (NIH) policies and standards.

The CSC is the primary day-to-day contact for hub sites. The CSC staff will develop and implement educational and training plans, communication modalities, conference calls, newsletters, a website, and social networking media. The CSC staff will collaborate with the hub sites to assure their understanding of the protocol, successful identification of eligible participants for screening and enrollment, and accurate operationalization/implementation of the protocol. Management of the subsites lies primarily with the hub; however, staff at the CSC are available to lend support.

The CSC has developed and will maintain this MOP, which provides extensive details about operations for every aspect of the study. The CSC will train site staff, monitor study progress and compliance, and assist the Principal Investigators (PIs) in reporting study progress for submission to the Institutional Review Board (IRB), NIH and OSMB.

The responsibilities of the CSC include, but are not limited to:

- Development and maintenance of study materials including, the MOP and study forms
- Development of the data flow and data management procedures including data entry, error identification and correction.
- Site monitoring and reporting
- Communications with study sites, scheduling of meetings and training sessions, responding to and documenting ad hoc communications
- Monitoring to ensure adherence to the protocol and procedures
- Quality control procedures
- Reports (e.g. enrollment, adverse events, participant status, site performance, quality control)

The CSC will be responsible for monitoring the conduct of the study at the hub and sub sites to confirm that the protocol is being conducted as specified, that the data reported are accurate and complete and that the human research requirements are appropriately followed. Contact information for members of the study team will be maintained on the study webpage. Contacts for key study items, as well as roles and responsibilities for key personnel or groups, are outlined below.

1. CSC Key Contacts

Table 2: CSC contact information

General Email Accounts		
General inquiries, protocol inquiries, regulatory matters, IRB inquiries		RECOVER_CSC@nyulangone.org
Budget and contracting		RECOVERsubawards@nyulangone.org
Finance		RECOVER_Finance@nyulangone.org
Multiple Principal Investigators		
Stuart Katz, MD	MPI, Pediatric Cohort	stuart.katz@nyulangone.org
Leora Horwitz, MD	MPI, Adult Cohort	leora.horwitz@nyulangone.org
Andrea Troxel, ScD	MPI, Autopsy and EHR Cohorts	andrea.troxel@nyulangone.org
Key Faculty Leads		
Lorna Thorpe, PhD	Faculty Co-Lead, EHR Cohort	lorna.thorpe@nyulangone.org
Jasmin Divers, PhD	Faculty Co-Lead, EHR Cohort	jasmin.divers@nyulangone.org
JohnRoss Rizzo, MD	Faculty Lead, Mobile Health	johnross.rizzo@nyulangone.org
CSC Administration		
Carol Chang	Project Director	carol.chang@nyulangone.org
Mary Thomas	Senior Program Coordinator	mary.thomas@nyulangone.org
Lei Lei	Senior Project Manager	lei.lei@nyulangone.org
Priscilla Sangurima	Administrative Coordinator	priscilla.sangurima@nyulangone.org
Yvette Burgos	Administrative Coordinator	yvette.Burgos@nyulangone.org
Sarah Laury	Data Research Associate	Sarah.laury@nyulangone.org
CSC Clinical Operations and Project Management		
Caitlin Sanford	Project Director	Caitlin.sanford@nyulangone.org
MeeLee Tom	Senior Research Project Manager (Adult Cohort, Site Activation and Monitoring)	meelee.tom@nyulangone.org
Holly Anger	Senior Research Project Manager (Pediatric/Autopsy Cohorts)	holly.anger@nyulangone.org
Gabrielle Maranga	Research Project Manager (Adult Cohort)	gabrielle.maranga@nyulangone.org

Stephanie Montenegro	Research Project Manager (Adult Cohort)	stephanie.montenegro@nyulangone.org
Anika Mitchell	Research Project Manager (Pediatric Cohort)	anika.mitchell@nyulangone.org
Elliott Bueler	Research Project Manager (Pediatric Cohort)	Elliott.Bueler@nyulangone.org
Phoebe Del Boccio	Research Project Manager (Autopsy Cohort)	phoebe.delboccio@nyulangone.org
Precious Akinbo	Clinical Research Associate (Autopsy Cohorts)	precious.akinbo@nyulangone.org
Nadia Malik	Clinical Research Associate CRA (Pediatric Cohort)	nadia.malik@nyulangone.org
Daniel Nwanonyiri	Clinical Research Associate CRA (Adult Cohort)	daniel.nwanonyiri@nyulangone.org
Susanna Zavlunova	Project Manager (Safety Monitoring)	susanna.zavlunova@nyulangone.org
CSC Statistics and Data Management		
Joa (Qiuyun) Yao	Data Analyst	qiuyun.yao@nyulangone.org
CSC Financial Management		
Shelley (Mengxue) Qu	Grants Manager	mengxue.Qu@nyulangone.org
Crystal Wong	Financial Coordinator	crystal.wong@nyulangone.org
Wenfei Tang	Financial Coordinator	wenfei.tang@nyulangone.org
CSC Other Transitional Agreements (OTA)		
Tony Carna	Senior Director, Sponsored Programs Administration	RECOVERSubawards@nyulangone.org
Rebeca Franco	Director, Grants Administration	RECOVERSubawards@nyulangone.org
Samantha Ebel	Associate Director, Contracts	RECOVERSubawards@nyulangone.org
Priya Rao	Contracts Manager	RECOVERSubawards@nyulangone.org
Sandra Fink	Contracts Manager	RECOVERSubawards@nyulangone.org
Emmanuelle Mercier	Contracts Manager	RECOVERSubawards@nyulangone.org
Jenn Glass	Sr. Contracts Specialist	RECOVERSubawards@nyulangone.org
CSC Communications		
Susanne Tranguch	Associate Dean, Research Training & Communications	susanne.tranguch@nyulangone.org
Ramona	Project Manager (Communications)	ramona.almenana@nyulangone.org

Almeñana		
CSC Community Engagement and Recruitment		
Stephanie Albert	Assistant Professor, Population Health	stephanie.albert@nyulangone.org
Natasha Williams	Assistant Professor, Population Health	natasha.williams@nyulangone.org
Jasmine Briscoe	Research Coordinator (Community Engagement and Recruitment)	jasmine.briscoe@nyulangone.org
Victoria Guerra	Research Nurse (Community Engagement and Recruitment)	victoria.guerra@nyulangone.org

2. Who to Contact

The first point of contact should be the RECOVER email address (RECOVER_CSC@nyulangone.org), and the inquiry will be routed to the appropriate staff member. However, you can also contact the CSC personnel directly for questions about key study items.

- Site activation process questions: Research Project Managers and Senior Research Projects Managers for each cohort
- Protocol questions: Research Project Managers and Senior Research Projects Managers for each cohort
- Enrollment eligibility and randomization questions: Research Project Managers and Senior Research Projects Managers for each cohort
- Consent form and IRB questions: Research Project Managers and Senior Research Projects Managers for each cohort
- Contract questions: CSC OTA Team
- Site monitoring questions: MeeLee Tom and cohort CRA
- Finance questions: Shelley Qu
- Recruitment questions: Research Project Managers and Senior Research Projects Managers for each cohort, and Community Engagement team

B. Data Resource Core (DRC)

The DRC manages the process of ingesting and managing REDCap Central data from the primary clinic sites into REDCap Central. Each site collects identifiable data in a secure REDCap form. The DRC is responsible for data management of the REDCap data.

1. DRC Key Contacts

Table 3: DRC Key Contacts

General Email Account	
General inquiries, REDCap Access or other related issues	MGB-RECOVER-DRC@partners.org
Multiple Principal Investigators	

Andrea Faulkes		afoulkes@mgh.harvard.edu
Shawn Murphy		snmurphy@partners.org
Elizabeth Karlson		ekarlson@bwh.harvard.edu
Section Leads		
Natalie Boutin	Sample Management Program Management	nboutin@partners.org
Vivian Gainer	I2b2 Data Management	vgainer@partners.org
Dustin Rabideau	REDCap Central Management	drabideau@mgh.harvard.edu
Lynn Simpson	REDCap Central i2b2 Data Hub Integration	
Tanayott Thaweethai	Biostatistics	tthaweethai@mgh.harvard.edu
Caryn Boehm	Administrative Assistant	

C. PASC Biorepository Core (PBC)

1. PBC Key Contacts

Table 4: PBC Key Contacts

General Email Account		
General inquiries, supplies, reorders		recoverPBC@mayo.edu
Multiple Principal Investigators		
Mine Çiçek, Ph.D.	MPI/ Contact PI	Cicek.mine@mayo.edu
Stephen Thibodeau, Ph.D.	MPI/Co-Investigator	sthibodeau@mayo.edu
Thomas Flotte, M.D.	MPI /Autopsy Focus	flotte.thomas@mayo.edu
Section Leads		
Jordan Weyer	Program Manager/Main Contact	weyer.jordan@mayo.edu
Heba Abseh, M.Ed.	Education Specialist/SOP & Training SME	abseh.heba@mayo.edu

D. Administrative Coordinating Center (ACC)

1. ACC Key Contacts

Table 5: ACC Key Contacts

Key Contacts		
Nedra Whitehead, PhD	Principal Investigator	nwhitehead@rti.org

Lisa Newman, MSPH	Project Director	lnewman@rti.org
JoNita Cox	Project Manager	jcox@rti.org
Tonya Farris	Committee and Oversight Support	tfarris@rti.org
Sarah Hatcher	Committee and Oversight Support	shatcher@RTI.org
Alex Bornkessel	Communication	abornkessel@RTI.org

E. Participating Sites

Each participating site will be led by a Principal Investigator (PI), in partnership with co-investigators. Each site will have at least one Clinical Research Coordinator (CRC) who will execute study-related activities under the supervision of the site PI. Each site PI, co-investigator and CRC will be required to undergo protocol training prior to enrolling study participants. They will also be trained in the use of the REDCap Central electronic data capture (EDC) system for completion of CRFs. Each PI is responsible for the accuracy and timely entry of the data and is required to verify and sign-off on the CRFs at the end of study.

Principal Investigator (PI)

The PI should be qualified by education and training and experience to assume responsibility for the proper conduct of PASC RECOVER, should meet all the qualifications specified by NIH and the CSC, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation. It is not a requirement the PI be a licensed physician; however, if the PI is not a licensed physician, the study team should include at least one co-investigator who is a licensed physician and can assess any adverse events or serious adverse events that occur in any study participants at the site. The PI is responsible for the overall conduct of the study at his/her hub-site/sub-site. PI responsibilities include, but are not limited to:

- Providing the overall administrative, scientific, and fiscal responsibility for the study.
- Ensuring that there are adequate resources available during the course of the trial. This includes:
    - the potential to recruit the required number of suitable study participants within the agreed recruitment period.
    - having sufficient time to properly conduct and complete the study within the agreed study period.
    - having an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
    - Ensuring that all personnel working on the trial are adequately informed about the PASC protocol, the study medication and their study-related duties.
- Conducting the study in compliance with the protocol and in accordance with the CSC's procedures developed for study conduct.
    - No deviation from, or changes of the protocol should be implemented without agreement and prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants.
- Ensuring the initial Institutional Review Board (IRB) approval of the protocol and informed consent is obtained prior to protocol implementation/initiation of study.

- Ensuring IRB continuing review of the protocol and informed consent are obtained annually, and that there is no lapse in IRB approval of the protocol.
- Supervising and ensuring informed consent is obtained from the study participant prior to the implementation of any study-specific procedures.
- Maintaining adequate study records and assuring study participant confidentiality.
- Ensuring accurate and timely entry of data.

Clinical Research Coordinator (CRC)

The CRC will be responsible for the day-to-day operation of the study, coordinating all activities of the PI and co-investigator(s), and ensuring that study data are collected and submitted in an accurate and timely manner. The CRC provides continuity from participant recruitment through enrollment, follow-up and study closeout. The CRC must have an in-depth knowledge and understanding of all aspects of the protocol. Other duties include, but are not limited to:

- initiating recruitment and conducting pre-screening interviews.
- serving as a liaison between the site and the CSC
- assisting the PI and co-investigators with any protocol-related tasks during a study participant's visit.
- submission of data collected during a study visit to the Data Resource Core (DRC) via the REDCap Central system, preferably within 1-3 days of the visit, and at most within 14 days.
- any other protocol-related duties as assigned by the PI.

1. Participating Hub Sites

Table 6: Hub Sites

Adult Cohort

Site	Site Contact PI	Site Contact PI E mail
Columbia University	Robert Barr	rgb9@cumc.columbia.edu
University of California-San Francisco	Steven Deeks	Steven.Deeks@ucsf.edu
ISB	James Heath	jim.heath@isbscience.org
West Virginia University	Sally Hodder	slhodder@hsc.wvu.edu
University of Alabama at Birmingham	Jeanne Marrazzo	jmarrazzo@uabmc.edu
University of Arizona	Janko Nikolich	nikolich@arizona.edu
Emory	Igho Ofotokun	iofotok@emory.edu
BWH	Bruce Levy	blevy@bwh.harvard.edu
Mount Sinai	Alexander Charney	alexander.charney@icahn.mssm.edu
Howard University	Hassan Brim	hbrim@Howard.edu
UIC	Jerry Krishnan	jakris@uic.edu
Stanford University	Upinder Singh	usingh@stanford.edu
Case Western Reserve University	Grace McComsey	Grace.McComsey@UHhospitals.org
University of Utah	Rachel Hess	rachel.hess@hsc.utah.edu
UTHSCSA	Thomas Patterson	PATTERSON@uthscsa.edu

Pediatric Cohort

Site	Site PI	Site PI E mail
UC San Diego/ABCD	Terry Jernigan	tjernigan@ucsd.edu
Healthcore/NERI	Julie Miller	JMiller@healthcore.com
Columbia University	Melissa Stockwell	mss2112@cumc.columbia.edu
UC San Diego	Kelan Tantisira	ktantisira@health.ucsd.edu
Arkansas Children's Research Institute	Jessica Snowden	JSnowden@uams.edu
Children's Hospital Los Angeles (USC)	David Warburton	dwarburton@chla.usc.edu
Rutgers University	Lawrence Kleinman	Larry.Kleinman@Rutgers.edu
LEGACI (Rhode Island)	Sean Deoni	sdeoni@mac.com

Pregnancy Cohort

Site	Site PI	Site PI E mail
Utah	Torri Metz	Torri.Metz@hsc.utah.edu
UCSF	Vanessa Jacoby	Vanessa.Jacoby@ucsf.edu

Autopsy Cohort

Site	Site PI	Site PI E mail
University New Mexico	Lauren Decker	ldecker@salud.unm.edu
Mayo Clinic	Robert Reichard	Reichard.robert@mayo.edu
CV Path	Aloke Finn	AFinn@CVPath.org
Duke University	Chris Woods	chris.woods@duke.edu
John Hopkins University	Kelly Gebo	kgebo@jhmi.edu
BWH	Robert Padera	rpadera@bwh.harvard.edu
Mount Sinai	Carlos Cordon-Cardo	carlos.cordon-cardo@MSSM.EDU

EHR

Network	Site PI	Site PI E mail
PCORnet	Rainu Kaushal	rak2007@med.cornell.edu
PEDSnet	Chris Forrest	FORRESTC@chop.edu
N3C	Melissa Haendel	melissa.haendel@cuanschutz.edu

VI. Governance and Committees

A. NHLBI

The RECOVER effort is funded by OTA with NIH scientific leadership (multi-institute involvement). The National Heart, Lung, and Blood Institute (NHLBI) is the study sponsor. It provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood disorders and enhance the health of all individuals so that they can live longer and more fulfilling lives.

B. Executive Committee

The Executive Committee will be composed of NIH Senior Oversight Committee members, other NIH personnel, external experts, the community advisory board patient co-chair, and ex officio members from the RECOVER Cores, FDA, CDC, CMS, PCORI and the chair of the steering committee. This committee will assess progress of RECOVER activities, make recommendations to NIH regarding strategy and programmatic plans, and decide on budget questions.

C. Steering Committee

The Steering Committee will be composed of an external expert, RECOVER Cores leadership, site Principal Investigators, and patient/caregiver representatives. This committee will review recommendations from the RECOVER Core Operations Group and working groups, address operational challenges and solutions identified by the working group, and make recommendations to the executive committee regarding programmatic plans, issues/challenges/opportunities, and budget concerns.

D. RECOVER Core Operations Group

The RECOVER Core Operations Group will be composed of CSC, DRC, and PBC leadership. This committee will provide programmatic guidance, provide ongoing strategic and operational oversight, and evaluate working group issues for referral to the Steering Committee.

E. Study Group Committees

Study Group Committees will address specific aspects of RECOVER studies as described below and make recommendations as needed to the RECOVER Cores Committee.

1. Study Committee Membership

Committee membership will include RECOVER Cores faculty (CSC, DRC, PBC, and others), Cohort site investigators (one from each site), and patient/caregiver representatives.

2. Study Committee Governance

All study committees will have a Chair and Co-Chair selected by the Cores Committee. In most groups, the Chair and Co-Chair positions will be filled by the site investigators. Chairs and Co-Chairs will serve a term of one year. Study committee Chair/Co-Chairs may create sub-committees as needed.

Study Committees Chair/Co-Chair s will make recommendations that will be reviewed by the RECOVER Cores Committee, RECOVER Steering Committee, and RECOVER Executive Committee. Executive Committee approval will be required before implementation of Study Committee recommendations.

3. Scope of Work by Committee

- Ancillary Study Committee. Will review proposals for use of RECOVER data and/or biospecimens not initially funded by the RECOVER initiative. Applications will be submitted on a standardized form with description of plans for external funding. Applications will be reviewed and triaged by the ancillary study committee. Limited datasets (number of participants, numbers of biospecimens) may be released to support external applications.
- Study Design Committee. Will review RECOVER data (EHR and prospective cohort data) and external sources of data to make recommendations for modifications of the RECOVER protocols and need for centralized reading centers and core laboratories to be funded under the RECOVER Initiative.
- Publications Committee. Will create a charter to establish policies and procedures for use of RECOVER data for publications and presentations, and qualifications for authorship. The publications committee will establish the core RECOVER publications (design papers, first data papers, major findings papers) and create writing groups for each of these publications. The publications committee will also review requests for use of RECOVER data for manuscripts from internal and external sources and make recommendations for prioritization of these requests.
- Patient engagement committee. Will establish policies and procedures for patient/caregiver representative participation in the overall RECOVER governance structure, lead collaborations with the RECOVER national patient engagement committee, work with cohort site investigators to support local patient engagement activities, and direct development of educational and recruitment materials.
- Adjudication Committee. Will review both study-related adverse events and outcome measures of PASC diagnosis and adverse events according to pre-specified definitions. The results of the adjudication process will be reviewed by the RECOVER Cores committee and transmitted to OSMB and other committees.
- Operations Committee. Will review reports generated by the DRC to oversee fidelity to protocol specifications for biospecimen collection, data management, and quality control.

F. OSMB

A safety monitoring board is composed of independent senior researchers with experience in adult and pediatric medicine, epidemiology, biostatistics and study design, bioethics; and patient representatives. This committee will review data quality and participant safety data and issue reports to the NIH.

VII. Communications with the CSC

A. Microsoft Teams (MS Teams) Overview

MS Teams will be the main form of communication between the CSC and study sites. MS Teams is a collaboration app that helps a group of users have conversations and share documents. MS Teams will serve as an open forum for the discussion of the protocol, recruitment, retention, data collection, and other relevant issues, as well as to share successful strategies and processes. Study site staff can have conversations and collaborate with other study sites in MS Teams. CSC Project Managers can also use MS Teams to share documents with all the study sites participating in a cohort.

A video which reviews MS Teams functionality and features will be available in MS Teams and on our online training platform, RISE platform. Please refer to section XI.D.4 (Training and Certification through RISE).

1. Accessing MS Teams

CSC will first invite contact PI of each hub site to MS Teams. If contact PI would like to add any colleague or site staff, they can follow instructions on MS Teams to submit such request to CSC. Once added, study site staff will receive an email from MS Teams with a link to open the channel and will be directed to the page below.

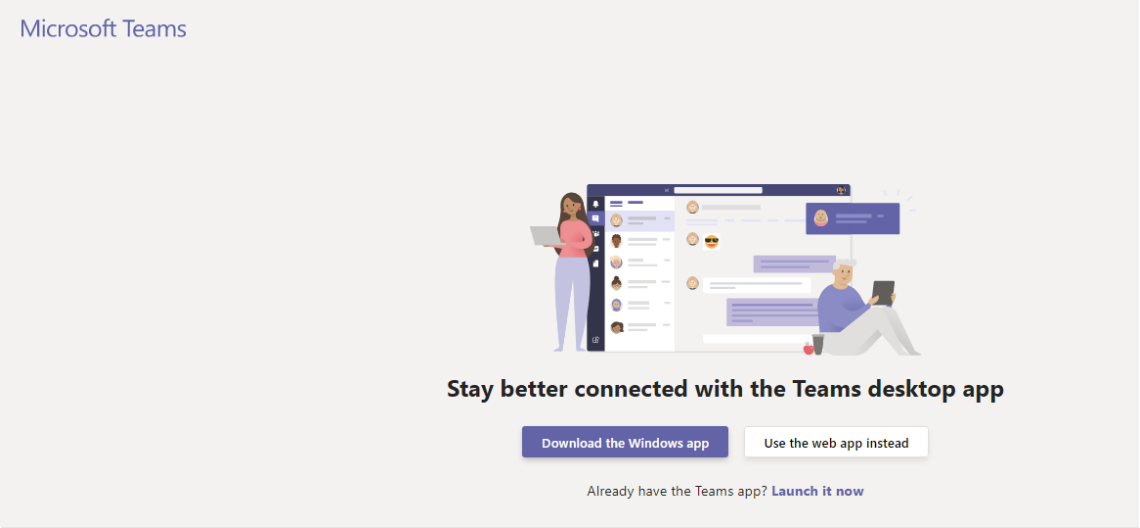


Figure 1 Introductory screen for MS Teams

Users can choose to download the app or use the web app instead. The MS Teams app can be downloaded at https://www.microsoft.com/en-us/microsoft-teams/download-app.

2. MS Teams General Principles

- We will be using Teams to facilitate discussions and workflow pertaining to the RECOVER initiative.
- To uphold confidentiality, it is imperative that PHI is not shared or mentioned in Teams—please do not share PHI in any of the teams, channels, or chats.

- We will be minimizing the number of teams and channels that can be created to streamline communications and prevent excessive notifications.
- Teams can only be created by authorized users within CSC.
- Channels can only be created by the team's Owner.

3. Channels in the Adult Team

Request to add a colleague: This channel is where you can request to add colleagues from your institution to your team or channel(s) within your team. To make a request, simply click on the Request to add a colleague channel under you team, select "New conversation," and enter the following information about the colleague(s) you wish to add:

- Their full name
- Their email address
- The channel(s) in your team that you want them to have access to

When you're done, click the "Send" button. (This button is the paper airplane icon located at the bottom right corner of your screen.) A CSC staff member will respond to your request in the form of a Reply, which will contain status updates about your request and, if necessary, ask you for clarification. If you have any follow-up questions or comments about a particular request you've made, please put them as a Reply to your initial request and not a "New conversation."

General: The General channel is where you can share your thoughts, comments, or queries that don't quite fit within the specified topics of your team's other channels. It's also where announcements that impact everyone throughout your team will be posted. **We will post current, official versions of all key study documents to this channel (including IRB protocol, consents, recruitment materials, MOP, training materials and more).** Please be advised that everything you share on the General channel will be seen by the rest of your colleagues across the entire team. So, if your thoughts are specific to your hub site, you might want to use your hub site channel (which is named after your hub site) instead of the General channel.

Any files posted to the General channel must not be removed, edited or otherwise changed. These files represent final documents that are not to be altered.

Coordinators Channel: This channel is for coordinators to share best practices, tips, checklists, and to ask questions of their colleagues.

Hub's private channel: This is a private channel between your hub site and CSC. This space is for discussion and questions specific to your hub site. Only the contact PI and colleagues requested by contact PI have access to this channel.

Literature Channel: This channel is a forum for people to post new studies or key literature as it is released.

MOP Channel: The MOP channel houses all discussions about the Manual of Procedures. This is where you can talk about what will go into the MOPs, share additions or changes you would like to see made to them, and ask questions about the current MOP or any of the MOP drafts. MOP drafts will be put into the Files tab of the MOP channel, where you can work on edits to or make comments on the documents with your colleagues in the channel. Please note that anything uploaded to the MOP channel's Files tab will ONLY be viewable by those who have access to that MOP channel. Final versions of the MOP will be placed within the General channel's Files tab, so that everyone within the Team can see it.

PI Channel: This channel is restricted to Hub PIs, CSC, DRC, biorepository and NIH staff, and will serve as a forum to post PI meeting minutes and materials, and to engage in discussions related to study organization and administration.

Press Release and Public Messaging Channel:

This channel is how press releases and other public messaging will be approved. Post here, any and all, media products to this channel in advance of their release and tag @Tranguch, Susanne and @Almenana, Ramona, CSC Communication team, in your post. The language must be consistent with NIH-developed talking points in the document **RECOVER Messaging (10.21**), posted to Files in this channel. Posting a draft on this channel will serve as notice to NIH that the draft is ready for review. Sites will upload their drafts in folder ***1. NEW—For Review.*** The CSC will then alert NIH to review the draft and move it to folder ***2. Under Review with NIH*** once NIH confirms receipt and works on their review. NIH will either approve or implement changes to the document and upload the draft into its appropriate folder, to folder: ***3. Changes Needed—***for Sites to revise their draft with NIH's tracked changes as edits, *or* folder ***4. Approved***—if the draft is approved with no revisions, the Site may proceed with this version as their press release if their contract is fully executed. The CSC will relay the draft's approval or edits needed to the Site on Teams and notify them to retrieve their document. If the document requires revision, the Site will implement the changes, per NIH's edits, and will upload the final version in folder ***5. Final Release.*** Hubs and Sub-sites are free to make their announcement only once:

- The Site has executed their contract, and
- CSC has the approved draft or acknowledged receipt of the final press release copy on Teams

Study Design Channel: The purpose of this channel is to provide a space for discussions about study design questions such as participant definitions, recruitment protocols, and questions/tests/procedures for consideration for addition/removal. Draft copies of protocols and CRFs may be posted here but final versions of those documents will be on the **General channel** files for everyone in the Team to access.

Training Channel: The Training channel is a place of recourse for protocol-related training, MOP-related training, and other PASC study specific learning requirements for you and your team. In this channel, you may find important training resources such as links to quiz websites or training videos. Training materials and relevant literature will be uploaded to the Files tab of the Training channel for you and your team to see.

B. Using MS Teams for Communications

At least one person from each Hub and subsite must be designated to check the RECOVER Adult Team at least daily. That person from each Hub should indicate that they have read daily updates and other important announcements posted by the CSC, DRC or NIH. Such posts will have an indication "please indicate receipt." A thumbs up, or other emoji, on the post Indicates the person has read a post; there is no need to reply to the post.

When posting a new message to a channel, you have the option to tag individuals or groups if you want to be extra sure they see your message. A message that has been tagged will have an icon at the top right of the message that indicates who has been tagged. See Figure 2 for a guide to the icons.

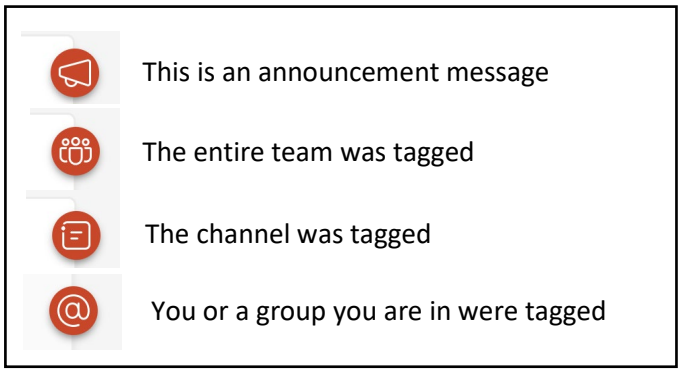


Figure 2 Guide to MS Team icons

Individuals who have set their notifications to be alerted if they are tagged will then be alerted. Note that individuals who have not set their notifications to be alerted if tagged may not receive a separate message but will still see the icon indicating that they are tagged in the message when they look at the Team.

- @name notifies the person with that name that there is a new message directed to them
- @channelname notifies everyone in the channel that there is a new message (caution, there are >500 people in the main public channels)
- @Site PI notifies the PIs and NIH/DRC/CSC staff that there is a new message
- @CSC notifies CSC PIs and staff that there is a new message
- @DRC notifies DRC PIs and staff that there is a new message
- @PBC notifies PBC PIs and staff that there is a new message
- @NIH notifies NIH staff that there is a new message
- @RECOVER Adult Cohort notifies every person in the team that there is a new message (caution, there are >500 people in the team)

See https://support.microsoft.com/en-us/office/using-tags-in-teams-667bd56f-32b8-4118-9a0b-56807c96d91e for additional guidance about how to use tags in Teams.

When replying to a post, the initial poster should be tagged with @name to ensure they are alerted about the response.

Teams can be set to send you email if you have not read a post on a Team or a particular channel in Team or a message you are tagged in after a customizable timeframe. Follow the instructions here to customize notifications:

1. Click profile icon in the upper right corner in MS Teams, then choose “Manage account”

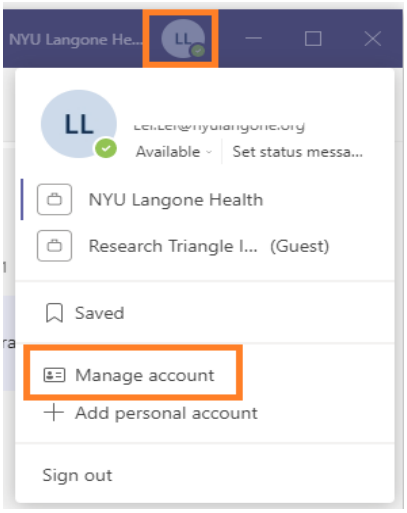


Figure 3 Manage account screen in MS Teams

2. Choose “Notification”, and then choose your preferred email frequency. You can also choose to get notifications for all activity, mentions & replies or build your own custom settings.

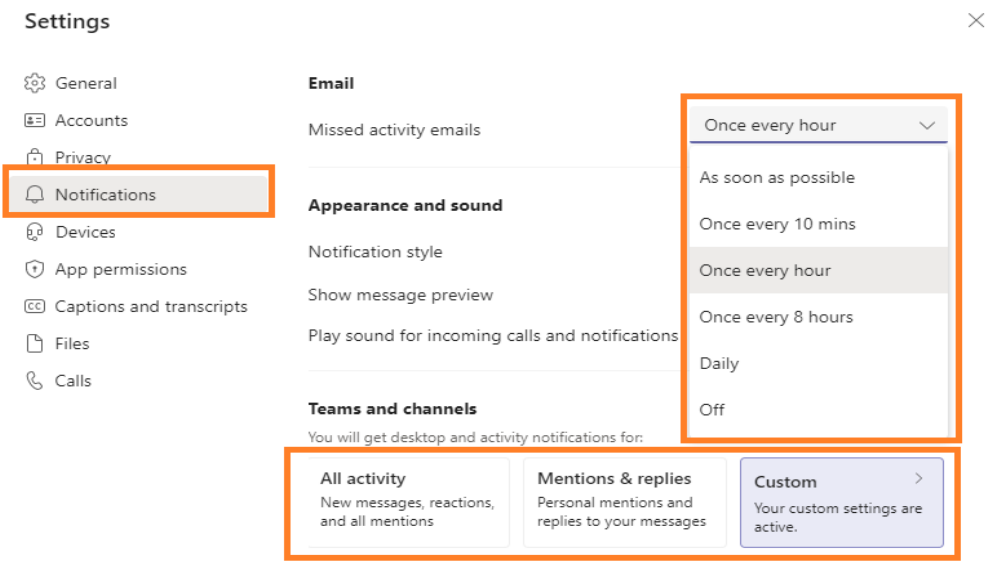


Figure 4 Notification screen in MS Teams

C. Video Conferencing

MS Teams can be used for video conferencing with one or more of your colleagues.

D. Email

Although MS Teams is the main form of communication, emails can also be used. Study site should have received the contact information of their appointed Research Project Manager in the site welcome letter. If a study site does not have this contact, please email recover_CSC@nyulangone.org.

Encrypted email should be used to send PHI or study participant information (for monitoring purposes).

VIII. Regulatory and Administrative Procedures

A. Regulations and Regulatory Bodies

Clinical research involving human participants must comply with current human participants' regulations. The **NIH RECOVER: A Multi-site Observational Study of Post-Acute Sequelae of SARS-CoV-2 Infection in Adults** is funded through the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health NIH) and is thus participant to the regulations of the Department of Health and Human Services (DHHS).

1. Applicable Regulations and Guidelines

Table 7: Applicable regulations

Reference	Title
45 CFR Part 46	Federal Policy for Protection of Human Participants ("Common Rule")
NIH	NIH Grants Policy Statement (April 2021)

CFR: Code of Federal Regulations
NIH: National Institutes of Health
Click on the reference to access the regulation or guideline. The NIH Grant Policy Statement can be accessed online at: https://grants.nih.gov/grants/policy/nihgps/nihgps.pdf.

B. Federal wide Assurance

All institutions engaged in the conduct of research involving human participants that is federally funded will have in place a Federal wide Assurance (FWA) with the DHHS Office for Human Research Protections (OHRP). This assurance documents the institution's commitment to abiding by the regulations on the protection of human participants engaged in research, 45 CFR 46, known as the Common Rule.

Hub sites should forward documentation of the current FWA number to the PASC CSC. It is the responsibility of a hub site to assure each enrolling site in their network has a FWA number.

C. Revised Common Rule (45 CFR Part 46 (2018))

The Federal Policy for the Protection of Human Participants is known as the "Common Rule" because it has been adopted by a number of federal departments and agencies. The basic policy provides requirements such as the composition and function of the IRB, criteria for IRB approval, informed consent requirements, and definitions. In addition to the basic policy, HHS also has additional protections for pregnant women, human fetuses and neonates, prisoners, and children, adopted by fewer federal agencies or departments.

HHS and other federal departments and agencies issued final revisions to the Common Rule in 2017; the final rule, also known as the 2018 Requirements, was published in the Federal Register on January 19, 2017, and was amended to delay the effective and compliance dates on January 22, 2018, and June 19, 2018. The revised Common Rule became effective on January 21, 2019.

The revised Common Rule can be found on the HHS website.

D. Conflict of Interest

Since PASC RECOVER is federally funded, investigators are participant to Department of Health and Human Services (DHHS) regulations on the disclosure, evaluation, and management of financial conflicts of interest (FCOI). A conflict of interest in research is any interest, commitment, or relationship in or with an outside entity that might compromise the integrity of how scientific research is designed or conducted, whether real or perceived.

In accordance with the Other Transitional Agreement, hub sites will follow their institution's FCOI policy. The policy must comply with the requirements of PHS and NIH. Investigators will report any FCOI to NYULH's Administrative Representative. Any FCOI that is identified shall, when applicable, subsequently be reported to the NIH.

All enrolling subsites will follow their institution's FCOI policy, which must comply with the requirements of PHS and NIH. Investigators will report any FCOI to their hub site. Any FCOI that is identified shall, when applicable, subsequently be reported to the NIH.

A list of outside entities, or vendors will be provided once available.

IX. Protection of Human Subjects

An Institutional Review Board (IRB) is a group of individuals that has been formally designated to review and monitor biomedical research involving human participants. An IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research participants.

The purpose of IRB review is to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights and welfare of humans participating as participants in the research. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures) to ensure protection of the rights and welfare of human participants of research.

A. Single IRB (sIRB) Review of the Protocol

In accordance with NIH policy and the revised Common Rule (45 CFR 46.114(b)), multi-site or cooperative research involving human participants funded by the NIH and carried out in the United States is required to use a single IRB (sIRB) for the review of the protocol. The goal of this policy is to enhance and streamline the IRB review process in the context of multi-site research so that research can proceed as effectively and expeditiously as possible.[1] Using a sIRB can improve the quality and efficacy in the oversight of multi-center studies and reduce the workload on study staff at the centers with respect to interactions with the IRB.

On October 8, 2020, the DHHS Office for Human Research Protections (OHRP) issued an exception to the sIRB review requirements for certain HHS conducted or supported Cooperative Research Activities participant to the 2018 Requirements during the COVID-19 Public Health Emergency. This exception states an exception to the requirement to use a sIRB is appropriate for cooperative research "ongoing or initially reviewed by the IRB during the Coronavirus Disease 2019 (COVID-19) public health emergency, as declared by the Secretary of Health and Human Services," "where reliance on a single IRB would not be practical," and "for which the HHS division supporting or conducting the research approves of the use of this exception." PASC RECOVER received a waiver from the requirement to use a single IRB for review and oversight of the study.

1. NYU Langone Health sIRB

The NYU Langone Health (NYULH) IRB External Review Unit is the sIRB for the study. The NYULH sIRB utilizes the SMART IRB platform and Huron Exchange. Hub sites indicating they will be using the services of the NYULH sIRB will receive a reliance packet with steps required to rely on the NYULH sIRB. The following will be included in the reliance packet:

- Addendum to SMART IRB agreement – execution of the document indicates the site's agreement to rely on NYULH sIRB
- Huron Exchange guidance document
- PASC NYU site questionnaire – gathers institutional profile to facilitate the submission
- Current IRB approved PASC protocol and informed consent forms (ICF) and/or assent forms

The hub site is responsible for:

[1] NIH notice Number: NOT-OD-17-076

- identifying all subsites and subsite investigators;
- distributing all documents in the reliance packet to their subsites;
- updating the NYULH sIRB on site and subsite status;
- ensuring all subsites complete all materials accurately and in a timely manner;
- ensuring subsites register and complete all steps in the Huron Exchange.

a) SMART IRB

SMART IRB is a platform that offers a master IRB reliance agreement (the SMART IRB Agreement) and a web-based system that provides a central process for participating institutions and their investigators to request, track, and document study-specific reliance arrangements. Investigators and their study teams, together with institutional and HRPP/IRB offices, use the SMART IRB platform to initiate sIRB review of a study.

Institutions will be required to sign a master reliance agreement when they join SMART IRB. The NYULH sIRB also requires institutions to sign an addendum to the SMART IRB agreement.

b) Huron Exchange

The Huron exchange is a cloud-based document sharing portal to connect sIRBs and participating sites for multi-site research studies. Sites can use Huron to view and download study materials, make revisions and re-upload for IRB review and approval. It allows sites to upload study materials, including site-specific ICFs and key information sheets, recruitment materials and the site PI's curriculum vitae (CV) to the NYULH sIRB portal for review and approval.

IRB approved documents are downloaded for use through the Huron Exchange. Further information about signing up for the Huron Exchange will be provided by the sIRB representative at the NYULH sIRB.

c) Steps to Rely on the NYULH sIRB

- All enrolling sites are required to complete the local context questionnaire. Hub sites are responsible for submitting questionnaires for their enrolling subsites to the NYULH sIRB.
- Provide local site PI's CV
- Enrolling sites will be required to complete the master SMART IRB reliance agreement and the addendum to the SMART IRB agreement.
- After the reliance is in place, sites will have to register for the Huron Exchange.
    - If the site is not previously registered on the Huron Exchange, an authorized representative (ex: reliance coordinator, site IRB representative, or authorized individual responsible for adding new personnel to the Huron Exchange) will complete a one-time registration and create an institutional profile for the Huron Exchange. The authorized representative will receive an email confirmation when the Huron team has confirmed the registration, usually 24 to 48 hours.
    - The authorized representative can create accounts for users (e.g., PI, research coordinator, regulatory coordinator) at the institution. Registered users will receive an email notification to verify their email address and will receive another email once they have successfully signed into the exchange.
    - Users will accept the invitation to the exchange. After acceptance, the user can download, edit and submit documents for the study.

d) Initial IRB approval

Once a site has completed all steps to rely on the NYULH sIRB, a user can download the ICF and key information sheet templates from the Huron exchange, insert any local context into the template and then upload the site-specific ICF for review and approval.

The only revisions allowed to the template ICF are local context as follows:

- Site contact information
- HIPAA authorization language
- Participant injury language
- Participant stipend language
- Certificate of confidentiality language

Sites also have the option of adding their institutional logo to the first page of the ICF and information sheet.

Once the documents have been reviewed and approved by the NYULH sIRB, users will receive an email notification to log into the Huron Exchange and download the approved documents.

e) Modifications

Study wide modifications, such as protocol amendment or documents to be used across all sites, will be submitted by the staff at the PASC CSC and will not require submission at the site level. Once a modification is approved by the sIRB, it is approved for implementation at all sites. However, if a protocol amendment requires a revision of the ICF/assent form and key information sheet, users at the site will have to submit their revised documents for review and approval. Users will be notified of the approval through the Huron Exchange.

Any site-specific modifications, such as site-specific recruitment material, can be submitted through the Huron Exchange.

f) Continuing Review

Staff at the PASC CSC will submit the continuing review application for all sites – there is no need for site personnel to submit an application. However, site users can submit site-specific information, such as enrollment numbers, through the Huron Exchange. Once continuing approval is granted, users will be notified through the Huron Exchange.

g) Reportable New Information (RNI)

Reportable new information (RNI) is defined as events that are unanticipated and may cause risk of harm to the participant or others. RNI include:

- Unanticipated drug or device reactions
- A protocol deviation that caused harm to a participant or that was intended to eliminate apparent or immediate harm to the participant.
- Incarceration of an enrolled participant when the study was not approved to include prisoners
- An unresolved participant complaint that indicates a potential increase in risk or an unexpected risk
- New information that presents a change to the risks or potential benefits.

Staff at the PASC CSC will report RNI on behalf of the site. Each site is responsible for notifying PASC CSC staff of RNI immediately upon knowledge of the information so it can be reported within the required timeframe of 10 business days.

2. Using another sIRB

Because PASC RECOVER received a waiver from the single IRB policy, hub sites that are part of another sIRB network or have their own sIRB can use that sIRB for ethical review of the protocol for **all enrolling sites within the hub**. Exceptions to this are any Veteran Administration subsite and Tribal Nation subsites. The hub site is responsible for initial submission of the protocol, and any modifications and other submissions, in accordance with the sIRB policy.

Materials to be submitted will be provided by the PASC CSC through MS Teams or email. Prior to initial submission, site personnel should send any changes to the ICFs for review. Changes to the ICF should be limited to the required local context.

The hub site is responsible for sending any approval letters and approved documents to the PSC CSC for all enrolling sites within the hub.

B. HIPAA Privacy Rule

Among other provisions, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) implements data security and privacy safeguards for a wide variety of healthcare-related activities. For certain organizations, defined as covered entities, information gathered during the conduct of clinical research is covered under HIPAA. In terms of human participant's protections, the requirements, rights, and obligations provided for by HIPAA must be disclosed to and acknowledged by clinical research participants.

All study sites are covered by HIPAA, and thus the study participants must be informed of their privacy rights under HIPAA.

The informed consent form template approved by the NYULH sIRB includes the HIPAA authorization language; however, site-specific HIPAA language may be used.

Additional details on the HIPAA Privacy Rule for research are at the HHS website.

X. Study Activation

A. Overview of Study Activation

The CSC has a responsibility to ensure that mechanisms and procedures are in place to protect the safety of participants in this NIH-supported clinical research study. Therefore, prior to a site receiving approval to start study participant enrollment, regulatory, IRB, contract and training, and requirements must be met. Hub sites will be sent a welcome packet with instructions and materials for site activation. It is the responsibility of the hub site to instruct all enrolling sites within the hub of study activation requirements.

1. Regulatory Requirements/Essential Documents

- Protocol signature page signed and dated by the site PI
- Institutional Review Board (IRB) approval letter
- Approved informed consent form (ICF)
- Curriculum vitae for site PI, co-investigator(s) and coordinators
- Federal Wide Assurance number

2. Contract Requirement

- Hub sites will be required to have an executed Other Transactional Agreement (OTA)
- Enrolling sites under the hub site will be required to have a signed agreement with the hub site

3. Training Requirements

- Protocol training and certification
- REDCap Electronic Data Capture (EDC)
- Biorepository procedures
- Human Participants Protection (HSP)

4. Virtual Site Initial Visit

- Required for the site PI and research coordinator(s)

When all requirements for study activation are satisfied, an activation letter stating that the site may begin study participant enrollment will be sent to the site PI and study coordinator.

B. Essential Documents

Essential documents are those documents that individually and collectively permit evaluation of both the conduct of clinical research and the quality of the data produced. Essential documents may relate to the general conduct of the study at the site, or to individual study participants at the site.

Essential documents should be stored electronically and should be accessible to all members of the study team.

1. Required Documents

Essential documents can be submitted to the CSC via MS Teams or email. Original copies of all documents should be kept at the site and a copy sent to the CSC.

The following essential documents must be retained at the site, must be accurately maintained, and may be verified during study monitoring visits:

Table 8: Required documents

	Document	Filed at CSC[1]	Filed at Site[1]
Site documents	• Signed OTA between the NYULH and the site[1]	✓	✓
	• IRB-approved protocol and protocol amendments[1]	✓	✓
	• Current version of IRB-approved informed consent forms[1]	✓	✓
	• Any other IRB-approved written information provided to the study participants[1]	✓	✓
	• IRB documentation, approvals and correspondence, including: [1]	✓	✓
	○ Copies of all IRB submissions[1]	✓	✓
	○ Documentation of initial approval of protocol and ICF[1]	✓	✓
	○ Documentation of continuing review[1]	✓	✓
	○ IRB approvals or acknowledgements of any recruitment materials, study participant newsletters, OSMB correspondence[1]	✓	✓
	○ IRB member roster[1]	✓	✓
	• Documentation of FWA number[1]	✓	✓
	• Any study communication from the CSC		
	• Delegation of duties log[1]	✓	✓
	• Screening logs		✓
	• Study participant identification number list		✓
	• Enrollment log		✓
	• Serious adverse event (SAE) log	✓	
	• Protocol deviation log	✓	
	• Monitoring correspondence ○ Initiation ○ Interim monitoring ○ Close-out	✓	✓
	• Curriculum vitaes, resumes or biosketches[1]	✓	
	• Medical Licenses, as applicable[1]	✓	
	• Financial disclosure forms[2]	✓	✓
	• Documentation of and Protection Human Participants training	✓	✓
	• Documentation of protocol training and certification[1]	✓	✓
Study participant documents	• Signed informed consent forms		✓
	• Source documents, including but not limited to:		✓

	Document	Filed at CSC[1]	Filed at Site[1]
	○ Clinic/ office charts ○ CRF worksheets ○ Hospital records ○ Lab reports		

[1]Required prior to study activation for the PI and coordinator

[2]Sites should follow their institutional policy for FCOI disclosure

Hub sites should submit all documents from their site to the CSC. However, only IRB related documents from all their enrolling sites are required to be submitted to the CSC. In addition, hub sites will be required to submit a signed attestation form for each of their enrolling sites to the PASC CSC, indicating they have collected all the required study activation documents. This attestation form is entitled "Pre-Activation Checklist" and is posted to each hub site's private channel files tab.

2. Source Data and Source Documents

Source data is defined as all information in original records and copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or copies).

Source documents must meet certain fundamental qualities, collectively known as ALCOA-C:

- **A**ttributable: Data should be traceable to a person, data and study participant visit.
- **L**egible: Written data should be clearly understood; electronic data should be recorded on a durable medium.
- **C**ontemporaneous: Data should be recorded at the time of trial conduct.
- **O**riginal: The source should be the first place where the data is documented
- **A**ccurate: The information collected should describe an honest, accurate and thorough representation of the conduct of the study.
- **C**omplete: The source data should include all necessary information

3. Electronic Case Report Forms (eCRF)

Data collected during the study will be submitted into the REDCap Central electronic data capture (EDC), administered through the Data Resource Core (DRC). Paper copies of the CRFs will be available on MS Teams and on the study website once that is developed.

C. Contract Requirements

Hub sites must sign an Other Transactional Agreement (OTA) with NYULH. Representatives from the NYULH business or contracts office will provide a template OTA. Any questions related to the OTA can be sent to RECOVERSubawards@nyulangone.org.

Enrolling subsites are required to have a signed agreement with the hub site. The hub site should forward a copy of the sub agreement to the NYULH contract office at RECOVERSubawards@nyulangone.org.

D. Training Requirements

1. Protocol Training

All study staff will receive training and certification on the protocol prior to participating in the conduct of the protocol, to include:

- Study objectives
- Study design
- Inclusion/exclusion criteria
- Screening and recruitment of study participants
- Study participant visit schedule
- Tiers 1, 2 and 3 assessments
- Biorepository procedures
- Safety monitoring
- Protocol deviations/protocol compliance

Study staff will receive training in the following areas of clinical operations as applicable:

- Investigator responsibilities
- Research coordinator functions
- Informed consent procedures
- Study visits and procedures
- Completion of electronic CRFs (eCRFs) in REDCap
- Monitoring visits
- Communication
- Essential document collection and storage
- IRB reporting requirements
- Audits and inspections for monitoring
- Query process for eCRF completion

Investigators and research coordinators will receive training at the Site Initiation Visit (SIV). This can be a live WebEx or through a recorded session. Those attending a recorded session can also join live Question and Answer sessions the CSC will be hosting. All investigator and research coordinators will be required to complete an online quiz.

2. REDCap Central Electronic Data Capture Training

The Research Electronic Data Capture (REDCap) Central system administered through the DRC will be used for sites to submit data for the study. Data can be entered by the Clinical Research Coordinator (CRC) and other study team members delegated the task of data entry, and by directly by the study participant, in the case of surveys. Study team members who will be entering data, or signing off on submitted data will be required to complete training on the REDCap Central system. Training can be completed by attending a live SIV via WebEx or review of a recorded session through the RISE platform.

a) Access to REDCap Central

Access to REDCap Central will be granted after a study team member has submitted all their start up documents and completed all required training.

Startup documents include current CV, License (as applicable), protocol training, human subjects protection training and REDCap Central training.

After all requirements all complete, the Research Project Manager assigned to the site will provide the DRC with a list of study team members, including name, site name, site number, role and email address. The DRC will create a user account and send an email from recover-admin@hms.harvard.edu, with the user name, temporary password and link to the REDCap website. The user should log onto the website and change the password.

User names and passwords are unique to the individual and should not be shared with anyone.

3. Biorepository Training

The PASC Biorepository Core (PBC) will train the delegated study team members at a participating site on all relevant biorepository procedures (refer to the DRC manual, posted in their channel on MS Teams). Training can be completed by attending a live SIV via WebEx or review of a recorded session through the RISE platform. The study team members will also be required to complete a brief quiz on the RISE platform. Once trained and certified, the staff at the PBC will identify a training coordinator at a hub enrolling site to training staff at each on the hub's enrolling sites. These study team members will also be required to complete the online quiz.

Staff at the PBC will be available to respond to any questions.

4. Training and Certification through RISE

RISE is an online platform to provide training. Study team members, regardless of whether or not they attended the SIV, will be required to complete training on the platform and take a brief quiz to assess knowledge of the protocol and procedures. To gain access to RISE, one person at a site should complete the spreadsheet posted to MS Teams and repost the completed spreadsheet to your hub channel. Staff at the CSC will monitor the channels and create accounts for the requested users. Once created, users will receive an email from notification-no-reply@rise.com with the user name. RISE can be accessed at https://nyu-langone-health.rise.com/login.

5. Human Subjects Protection Training

All investigators and staff involved in the conduct, oversight or management of clinical trials are required to have training in Good Clinical Practice and Human Subjects Protection. Investigators and study staff cannot participate in the conduct of the study prior to completing the required training. This training needs to be completed every 3 years. Acceptable forms of training include:

- Human Subjects Protection through a training program offered through your local IRB. This is usually through the Collaborative Institutional Training Initiative (CITI Program) (www.citiprogram.org), but if sites have a different training program, that training is acceptable.
- Several NIH institutes offer free training, including NIDA (https://gcp.nidatraining.org/) and NIAID (https://learningcenter.niaid.nih.gov/).

E. Activation Letter

Following completion of all study activation requirements, the site will receive an activation ("green light") letter indicating they are approved to begin screening and enrollment activities.

- For hub sites, the letter will come from the CSC.
- For enrolling subsites, the letter will come from the hub site. Once the attestation form for enrolling subsites has been reviewed and approved by the hub project manager at the CSC, the PM will communicate with the hub site team and approve them to send out the "green light" to the sub enrolling site.
- Hub sites should use the letter template (RECOVER Final Approval Letter Subsite Template) posted to the General channel of teams to create activation letters for their subsites and should send a copy to their CSC project manager.

XI. Recruitment and Screening

A. General recruitment principles

Recruitment of people with and without SARS-CoV-2 infection will be stratified to ensure adequate representation by sex and race/ethnicity as described in section 6.2 of the protocol. For patients with SARS-CoV-2 infection recruited during or after acute infection, priority will be placed on recruiting participants from lists of SARS-CoV-2 infected patients to ensure that (a) potential participants were identified prior to study enrollment to minimize bias associated with self-referral, and (b) enrollment response rates can be generated from known denominators. If lists are large, recruitment can be phased using random sampling and adequate "working of recruitment lists" to maximize generalizability. Attempts will be made to include a diversity of sites of care (e.g., not only from a post-COVID clinic or only from patients cared for in academic medical centers) and severity of illness (i.e., not only from hospitalized participants). Post-COVID (long COVID, PASC) clinic recruitment could result in ascertainment bias.

The target sample size for each category of participant for the full RECOVER study is shown in Table 9. The target sample size for sites with the standard recruitment objective of 909 subjects is shown in Table 10. Sites may use the target percentages of total enrollment to inform their own recruitment strategies.

Table 9: RECOVER adult cohort overall target sample size

	Classification based on index date	Target N		Total
		Hospitalized	Non-Hospitalized	
Acute Infected, N (% of total)	Enrollment date < 30 days after infection	1,950 (11%)	5,850 (33%)	7,800 (44%)
Acute non-infected, N (% of total)	Enrollment date < 30 days after negative test	300 (2%)	900 (5%)	1,200 (7%)
Post-acute infected, N (% of total)	Enrollment date ≥ 30 days after infection	1,800 (10%)	5,400 (31%)	7,200 (41%)
Post-acute non-infected, N (% of total)	Enrollment date ≥ 30 days after negative test	370 (2%)	1,110 (6%)	1,480 (8%)
Total		4,420 (25%)	13,260 (75%)	17,680

Table 10: Target enrollment for a hub with standard 909 enrollment target

	Classification based on index date	Target N		Total
		Hospitalized	Non-Hospitalized	
Acute Infected, N (% of total)	Enrollment date < 30 days after infection	139 (15%)	418 (46%)	557 (61%)
Acute non-infected, N (% of total)	Enrollment date < 30 days after negative test	21 (2%)	64 (7%)	86 (9%)

Post acute infected, N (% of total)	Enrollment date ≥ 30			
Post acute non infected, N (% of total)	Enrollment date ≥ 30 days after negative test	11 (1%)	34 (4%)	45 (5%)
Total		227 (25%)	682 (75%)	909

B. Recruitment methods

Generic IRB approval recruitment materials are included in Appendix 1. The materials can be customized with site contact information without further IRB approval. If sites want to use other recruitment and materials, they will have to be submitted to the IRB for approval. Social media platforms, websites, conventional mass media (radio and print publications), flyers or other advertising may also be used for recruitment purposes. All recruitment materials or text for any of these platforms will be submitted to the IRB for approval prior to use.

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

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

Potential candidates can be identified through the following methods:

- Self-referral
  - Potential participants may hear about the study through the main RECOVERCovid website, a site-specific website, or through posters, emails, news releases or other site-specific publicity. These materials will include a telephone number, web link or email through which interested participants can contact study staff to volunteer for the study. When contacted, a member of the study team will answer the participant's phone call or email and explain the study. If the participant expresses an interest and meets the inclusion criteria (Section XII.G), study staff will schedule a screening appointment. Note that potential participants who take initiative to contact study staff without any direct outreach and from an unknown denominator population are considered self referral participants; their total number may not exceed 15% of enrollees.
- Community recruitment from a known list of potential participants:
  - A member of the study team will reach out to a potential participant on the list through a phone call or a secure email and explain the study. If the participant expresses an interest and meets the inclusion criteria (Section XII.G),, study staff will schedule a screening appointment.
  - If the participant leaves a message, study personnel will call them back and explain the study. If the participant expresses an interest and meets the inclusion criteria (Section XII.G), study staff will schedule a screening appointment.
- Health system-based recruitment from a list of known tested subjects:
  - If the participant has provided prior consent to be contacted for research at their study site institution, the site study team may create a query in the local EHR system to identify potential

participants based on study entry criteria (age, and history of prior diagnosis or testing related to COVID-19).
    - The treating physician of such patients will be given a list, advertisement, letters or oral script to use when contacting potential participants
    - The treating physician and site PI will send a letter to all potential participants
    - If the treating physician agrees, the study team will directly contact potential participants on behalf of the physician by letter, phone, email, or an electronic medical record patient portal.
    - Alternatively, if a patient is hospitalized for acute COVID-19, study staff may contact the treating physician as soon as possible to see if they are willing to enroll their patient if the patient is interested. If the patient agrees to be contacted, the research coordinator may contact the patient or request that the patient come in for an appointment after hospital discharge.
- Public health-based recruitment
    - Institutions may partner with local health departments to obtain complete case lists of people with positive tests in a geographic area.
    - A secure email will be sent to potential participants to solicit interest in the study, with instructions for contact of the study team if interested to participate. This email will be provided to the IRB for review and approval before use in the study.
    - Once contacted by the potential participant, the study PI or designated study staff members will provide additional IRB-approved information to the patient and may schedule a study visit.
    - The EHR query or public health department query may be repeated for the duration of the 4-year study. All query responses will be deleted at the end of the study.

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

C. Special considerations for recruitment of uninfected controls

Patients without SARS-CoV-2 infection (“uninfected controls”), will be randomly sampled and recruited from similar communities, demographics, and sites of care as those being recruited into the SARS-CoV-2 positive cohort following the same process as in Recruitment methods.

Recruitment will be stratified to match the SARS-CoV-2 positive group in terms of racial/ethnic diversity, index time point, and proportion of participants not hospitalized, hospitalized but not in the intensive care unit, and those hospitalized in the intensive care unit. Individual 1:1 matching with infected subjects will not be performed.

D. Special considerations for recruitment of post-acute participants

For patients enrolled after acute infection, preference should be given to those who have data and/or biospecimens collected before or during the acute phase available to the investigators, though efforts should still be made in such cases to recruit an unbiased sample of such participants (for instance, by oversampling this group for underrepresented minority participants or those in communities not already well-represented in the cohort).

E. Recruitment of special populations

Sites should attempt to recruit from special populations, defined as those individuals meeting at least one of the following conditions:

- Non-hospitalized subjects with acute COVID-19 (<4 weeks since time of symptoms or positive testing)
- Subjects meeting study entry criteria who reside in a rural area as defined by the Health Resources and Services Administration
    - To find HRSA qualifying rural areas, go to https://data.hrsa.gov/tools/rural-health
- Subjects meeting study entry criteria who reside in a medically underserved area as defined by the Health Resources and Services Administration
    - Medically underserved areas/populations are areas or populations designated the by Health Resources and Services Administration as having too few primary care providers, high infant mortality, high poverty or a high elderly population.
    - To find HRSA qualifying medically underserved areas, go to https://data.hrsa.gov/tools/shortage-area/by-address
- Subjects meeting entry criteria who speak a primary language other than English
    - To qualify for this designation, all study activities must be conducted in the non-English language.

F. Screening

Recruited participants will make an appointment for screening to determine whether they satisfy eligibility based on inclusion/exclusion criteria. Assignment to enrollment type (e.g., acute infection, post-acute infection, acute control or post-acute control) will be determined by COVID-19 status and COVID-19 PCR and antibody test result at screening test.

Screening Phase:

- The study coordinator will meet with prospective participants to explain the study.
- The study coordinator will begin the process of determining whether the participant meets the eligibility criteria.
- The study coordinator will inquire about the participant's ability to complete the study:
    - Does the participant intend to relocate during the study?

Study coordinator will collect contact information, including contact information for one family member and one neighbor.

1. Screening Log

Each site must maintain a screening log. The screening log may be maintained on paper and/or electronic format. The screening log is part of the reporting requirements for data and safety monitoring.

A screening log records all individuals who have been evaluated for study eligibility. The log will include the individual's name or initials; age; gender; race and ethnicity using the same top level categories as in the REDCap demographics form; denominator population using the same categories as in the REDCap enrollment form; screening date; and eligibility status (e.g., eligible for study participation and date enrolled; ineligible for study participation and reason; refused consent and reason). A template screening log is included in Appendix 2.

G. Inclusion and Exclusion Criteria

Study eligibility is determined by the following sets of specific inclusion and exclusion criteria outlined below. Potential participants must meet **all** entry criteria and not meet any of the exclusion criteria.

1. Inclusion Criteria

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

2. WHO Criteria for SARS-CoV-2 Infection: Adults with suspected SARS-CoV-2 infection

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

a) Participants who meet the following clinical criteria plus one of the epidemiological criteria:
   1. **Clinical criteria**: Acute onset of fever and cough OR acute onset of any three of more of the following signs or symptoms: fever, cough, general weakness /fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status.

   2. Epidemiological criteria:

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

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

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

      * for purposes of this protocol, we define “community transmission” as any county with at least substantial community transmission according to the CDC definition (50 or more cases per 100,000 in past 7 days). Historical data about community transmission levels can be found here: https://data.cdc.gov/Public-Health-Surveillance/United-States-COVID-19-County-Level-of-Community-T/nra9-vzzn. Caution: this is a very large file

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

3. WHO Criteria for SARS-CoV-2 Infection: Adults with probable SARS-CoV-2 infection

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

a) A patient who meets clinical criteria for suspected SARS-CoV-2 AND is a contact of a probable or confirmed case or linked to a COVID-19 cluster;
b) A suspect case with chest imaging showing findings suggestive of COVID-19 disease;
c) A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause;
d) *Death, not otherwise explained, in an adult with respiratory distress preceding death AND was a contact of a probable or confirmed case or linked to a COVID-19 cluster* (Note, this criterion is not applicable to the RECOVER adult protocol, which requires the subject to be alive)

4. WHO Criteria for SARS-CoV-2 Infection: Adults with confirmed SARS-CoV-2 infection

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

a) Any person with a positive Nucleic Acid Amplification Test (NAAT);
b) Any person with a positive SARS-CoV-2 Antigen-RDT OR positive SARS-CoV-2 antibody test* AND meeting either the probable case definition or suspected criteria A or B;
c) An asymptomatic person with a positive SARS-CoV-2 Antigen-RDT who is a contact of a probable or confirmed case

*This protocol modifies the WHO criterion b to add detectable SARS-CoV-2 antibody as a qualifying test, as described in XII.F

5. Criteria for adult with no SARS-CoV-2 infection

An adult with no SARS-CoV-2 infection:

a) Does not meet WHO criteria for a suspected, probable, or confirmed case of SARS-CoV-2 infection, AND
b) Has a documented negative SARS-CoV-2 PCR test from a respiratory specimen in the past, if being enrolled as a post-acute control (see XII.H), AND
c) Has a documented negative SARS-CoV-2 PCR test from a respiratory specimen at the time of enrollment/screening, AND
d) Has a negative SARS-CoV-2 nucleocapsid protein antibody and spike protein antibody test (spike only if not vaccinated) at the time of enrollment, AND
e) Lives in the same communities or recruited from the same sources as those in the SARS-CoV-2 infected cohort

Note: uninfected individuals may participate independent of their vaccination status

6. Exclusion Criteria

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

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

H. Determining enrollment and index dates

Acute infected cases

Study enrollment date is < 30 days after infection date (first positive SARS-CoV-2 test result date or if test not available, date of COVID symptom onset)

Index date = first positive SARS-CoV-2 test result date or, if test not available, date of COVID symptom onset

Acute uninfected controls

Study enrollment date is < 30 days after negative SARS CoV-2 test result date. Subject had a documented negative SARS-CoV-2 test result, AND no prior history of positive SARS-CoV-2 test result, AND no current SARS-CoV-2 symptoms, AND negative SARS-CoV-2 test was not performed because of COVID-like symptoms, AND PCR and antibody tests on enrollment return negative

Index date = a qualifying negative SARS-CoV-2 test result date

Post-acute infected cases

Study enrollment date is ≥ 30 days after infection date (first positive SARS-CoV-2 test result date or if test not available, date of COVID symptom onset)

Index date = first positive SARS-CoV-2 test result date or, if test not available, date of COVID symptom onset

Post-acute uninfected controls

Study enrollment date is ≥ 30 days after negative SARS-CoV-2 test result. Subject had a documented negative SARS-CoV-2 test result, AND no prior history of positive SARS-CoV-2 test result, AND no current SARS-CoV-2 symptoms, AND negative SARS-CoV-2 test was not performed because of COVID-like symptoms, AND PCR and antibody tests on enrollment return negative.

Index date = a qualifying negative SARS-CoV-2 test result date

I. Handling of Changes in Infection Status and New On-Study Infections

1. Change in Infection Status on Enrollment

TBD

2. New Infection in Uninfected Control Subject

TBD

3. New Infection in Previously-Infected Subject after Enrollment

TBD

J. Vulnerable Populations

1. Pregnant Women

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

2. Prisoners

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

XII. Informed Consent

In accordance with 21 CFR 50 Subpart B and ICH GCP E6 (R2), no investigator may involve any study participant in human research unless the investigator has obtained legally effective written informed consent of the study participant. The informed consent process must consist of three components to make it ethically valid:

1. Information: the extent and nature of information provided should be such that a reasonable person should be able to make an informed decision about whether or not to participate.
2. Comprehension: the individual obtaining informed consent is responsible for ascertaining that the potential study participant is able to make an informed decision.
3. Voluntariness: agreement to participate is only valid it is given freely (i.e. free of coercion or undue influence.

Informed consent can be obtained at the time of enrollment or at a prior visit.

A. Informed Consent Process

Informed consent is a process, not just a signature on a form. It not only involves reading, understanding and signing the ICF document, but also a discussion of the details of study participation with a qualified, knowledgeable member of the study team. The potential study participant should be given sufficient opportunity and information to consider whether to participate. Informed consent should be conducted in a private setting where the potential study participant can feel comfortable asking questions, and with enough time conducive to good decision making.

The site PI is responsible for the informed consent process. The current IRB-approved version of the informed consent form must be used. The PI or another investigator will obtain the consent, or may delegate the task to a study coordinator. The person(s) obtaining consent should be knowledgeable about the study and should be able to answer any questions the study participants have. Potential study participants may be given the IRB-approved ICF to review before the screening visit. This will enable ample time for potential study participants to review the ICF and consult with family members and others.

The person(s) obtaining informed consent will provide the following information to the study participant in a language that is clear and understandable:

- the study involves research and the purpose of the research
- participation is voluntary
- the expected duration of the study (approximately 4 years)
- description of the procedures
- possible risks of participation
- possible benefits of participation
- statement about pregnancy
- statement about confidentiality
    - permission to disclose health information in connection with the study
    - will not be able to participate if they do not authorize disclosure
    - what information is disclosed
    - who the information is disclosed to
    - how long authorization will be in effect

  - withdrawal of authorization
- statement about study related injuries
- statement that refusal to participate will not affect benefits
- contact person to answer questions about the research and the study participant's rights
- circumstances under which the study participation may be terminated
- what the costs are to the study participant
- statement that the study participant will be informed of any new significant findings which may affect the participant's willingness to participate
- approximate number of participants to be enrolled
- the study is observational

An informed consent checklist is provided in Appendix 3. Sites that are using a similar checklist may use theirs.

The following script can be used to assess the patients understanding of the information presented during the informed consent process. This is also available as a separate document in Appendix 4.

ASSESSMENT OF UNDERSTANDING OF CONSENT FORM INFORMATION

Instructions: Please check for understanding of the consent form by asking the participant the following questions AFTER you have gone through the consent process with them but BEFORE they sign the consent form.

Part I. (Yes/no questions)
Suggested opening statement: "*It's my job to explain things clearly. To make sure I did a good job, I'd like to hear your understanding of the research study*."

1. **"Do you feel that you have to be in the study?"**
   - If participant says NO - then say - "That is correct, as I said earlier, it is up to you to decide if you want to be in the study, and if you want to sign the consent form."
   - If participant says YES - then say - "Actually, it is up to you to decide if you want to be in the study. You do not have to sign this form if you do not feel comfortable being in the study."

   Ask question again - if participants are able to correct their understanding then go to question 2. If they are confused and cannot correct – **then they are not eligible**.

2. **"If you decide to be in this project, do you think you will need to stay in it until the end even if you want to stop?"**
   - If participant says NO - then say - "That is correct, as I had mentioned, you can stop being in the study at any time."
   - If participant says YES - then say - "Actually, you can stop being in the study at any time."

   Ask question again - if participants are able to correct their understanding then go on to question 3. If they are confused and cannot correct – **then they are not eligible**.

3. **"If you decide to be part of this study do you think you have to answer every question or do every part of the study?"**

- If participant says NO - then say - "That's right, you can skip any question you do not want to answer, and you can decide not to do any part of the study."
- If participant says YES - then say - "Actually, you can skip any question you do not want to answer, and you can decide not to do any part of the study."

Ask question again - if participants are able to correct their understanding then go on to question 4. If they are confused and cannot correct – **then they are not eligible**.

PART II. (Teach back)

Instructions: If participants are correct for the first 3 questions, let them have a copy of the consent form in front of them as you ask the following questions. Remember that the purpose of this exercise is to check understanding, not memory. Listen for simple parroting; probe further if a potential participant uses technical terms.

Goal of the Research and Protocol

1. ″**Tell me in your own words why we are doing this study and what will happen if you agree to be in this study."**

Response for main informed consent form CORRECT if they mention all of the following concepts:

- Reason for doing the study is: understanding COVID or long COVID / understanding why some people who got COVID are still sick many months after being infected / understanding how COVID affects the body, and
- What will happen in the study: Must mention all of the following concepts:
  - Periodic surveys
  - Blood tests
  - Simple office examinations
  - Sending samples to a central place for storage
  - For some people, radiology tests and more intensive office exams

Response for Tier 3 informed consent form CORRECT if they mention all of the following concepts:

- Reason for this part of the study is: to better understand what is going on in the body for people who have symptoms, or to compare what is going on in the body for people who do not have symptoms to those who do
- What will happen in the study: must be able to describe what tests the participant is being asked to do

Response is INCORRECT if they say

- Reason for being in the study is to help them get treated for COVID / cured
- What will happen leaves out key aspects of the study

  If incorrect - clarify reason and point to/ discuss information on planned activities. Then say: "Can you try again and tell me in your own words [why we are doing this study] and/or [what will happen if you agree to be in this study]?"

Benefits

2. **"What do you expect to get by taking part in this research?"**

Response CORRECT if they mention:

- Results of the study will be important in helping patients, caregivers, and parents understand how COVID affects the body long-term.
- People will get paid for their time to do surveys and tests, as well as have costs related to travel paid for.

Response INCORRECT if they say:

- They think their health will get better
  If incorrect - say - “Being in the study will not help you or your family get treated or cured for long COVID. Results of the study will be important in helping patients, caregivers, and parents understand how COVID affects the body long-term. Can you try again and tell me in your own words what you expect to get by taking part in this research study?”

Risks

3. **"What risks would you be taking if you decided to be a part of this study?**"

Response for main informed consent form CORRECT if they mention all of the following concepts:

- Loss of private information
- Minor discomfort from blood tests and examinations
- Radiation from CT scan (in some people)

Response for Tier 3 informed consent form CORRECT if they mention the key risks listed in the consent form for the specific procedure(s) they are being asked to undergo.

Response INCORRECT if they say:

There are no risks, or incorrect risks are mentioned.

If incorrect - say - “Take a look at this section of the consent form to see the risks.” Point and summarize. Then say “Can you try again and tell me in your own words what risks you would be taking if you decided to be a part of this study.”

1. Electronic Consent (e-Consent)

Electronic informed consent (e-Consent) refers to using electronic methods to obtain and document informed consent. e-Consent Methods and materials may include, but are not limited to, electronic devices, digital media (e.g., websites, video) and electronic communication services. e-Consenting can apply to either the process of consenting, the documentation of consent, or both.

E-consent can occur in-person or remotely:

- In-person e-Consenting uses an electronic device such as a tablet or computer when participants are onsite with study personnel present in the same location. This could either be at the investigator's office, the hospital or the participant home.
- Remote e-Consenting takes place when the investigator, or other study team member obtaining consent, is in a different location from the study participant, so some or all elements of the consent process may not be witnessed.

The device, system, or platform used to obtain informed consent must allow enough time for completion, the ability to navigate forwards and backwards, and the option to stop and resume at a later time. Electronic methods of communication should allow the participant to contact the researcher again at any point in the process in order to ask additional questions.

The IRB must review all forms (electronic and paper) and other informational materials, including any videos and Web-based presentations, which the participant will receive and view during e-Consenting. The e-Consent document must have the same content as the IRB-approved ICF. The IRB will also review any optional questions or methods used to gauge participant comprehension of key study elements. During its review, the IRB will review the proposed e-Consent process to determine the usability of the e-Consent materials. If the program uses hyperlinks to convey study-related information, the IRB will review the online materials in order to ensure that the study-related information is accurate and appropriate.

Examples of Methods of e-Consenting

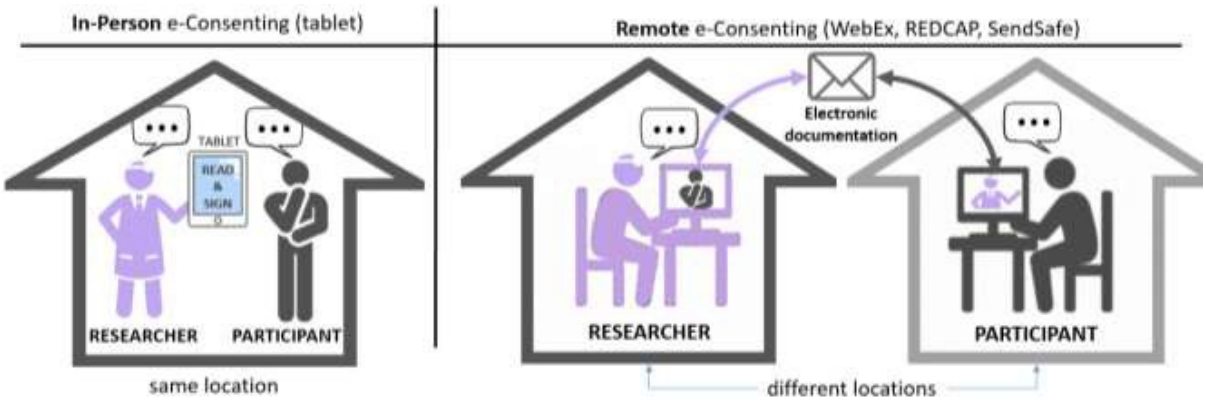
- The participant meets study personnel on-site or at home for a discussion. Comprehensive materials and the ability to sign may be provided through a device such as a tablet.
- The participant is screened remotely by study personnel through a WebEx conference before they receive link that allows them to read comprehensive materials and sign remotely on a personal computer.
- The participant is screened remotely through a telephone call before they receive an encrypted email containing consent materials. They may print the document at home, sign it, scan it, and return it to the study personnel through encrypted email.

In-person e-Consenting versus Remote e-Consenting

While e-consenting is allowed face-to-face using a tablet or other electronic device, NYU Langone Health will also allow the consent process to take place remotely (e.g., at the participant's home or another convenient venue). In this case, the participant reviews the consent document in the absence of study personnel. The e-Consent materials may be provided for both on-site and remote access. In some cases of remote e- consenting, it may be required that the electronic system has a method in place to ensure that the person electronically signing the informed consent is the participant who will be participating in the research study or is the participant's legally acceptable representative.

Researchers should have methods in place to ensure that the e-Consent process provides the opportunity to consider whether to participate and to ask questions about the study before they sign the consent, as well as at any time during the participant's involvement in the research study. This may be accomplished by a discussion between study personnel and the participant, whether it is in-person, a telephone call, or a video conference. When video conferencing is used during the e-Consent process, study personnel should conduct the e-Consent discussion in a private location. **Services such as Skype, FaceTime or Zoom are not HIPAA compliant and are prohibited. WebEx or Redcap can be used.** Additionally, the signed documentation of consent from the participant, whether a scanned paper document returned electronically or a digital form with electronic signature, must be obtained.

Figure 5: In-person versus remote e-Consenting



B. Documentation of the Informed Consent Process

Prior to any study related procedures being performed, the ICF should be signed and personally dated by the study participant, and by the person obtaining the consent. The study participant should be given a copy of the signed and dated ICF.

In addition to the signed ICF, the informed consent process should be documented in the study binder or progress notes of medical records. This documentation should include:

- name of the study
- name of the person obtaining consent
- a statement that the study participant was capable of understanding the information
- a statement that the study was explained fully, and the study participant was given ample opportunity to ask questions
- a statement that no study-related procedures were completed prior to obtaining informed consent
- a statement that a copy of the signed ICF was provided to the study participant.

To facilitate documentation of the informed consent process, a checklist is provided (Appendix 3). It should be completed and placed in the medical record or study record (ex: study binder or study file).

Finally, the consent tracking form(s) in REDCap Central should be completed, indicating the main and local site version number of the consent used, the date consent was obtained, and the specific responses to each of the individual opt in sections of the consent form. See DRC MoO for details.

C. Re-consenting for Protocol Changes

If a consent document is revised due to changes in study procedures, study participants who were enrolled prior to the change, but are affected by the change, will be informed of the changes and will be asked to sign the revised ICF or a key information sheet. If a consent document is revised due to changes in the risks or safety of the study, all active study participants must sign the revised consent.

XIII. Visit Schedule

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

Home Visits

Some study testing or procedures may be conducted through home visits to alleviate travel burden for participants. These home study visits will be conducted by members of the clinical research study staff and will follow COVID safety protocols for the duration of the visit. As only research staff will be performing these visits, responses and specimens collected will be strictly confidential. These study visits will be strictly for data and/or specimen collection and all research tests and procedures which may be performed through home visits are indicated in Appendices 3 and 4 of the protocol.

Table 11: Schedule of Visits

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

XIV. Description of assessments

The RECOVER adult study includes three different levels of test: Tiers 1, 2, and 3. All participants should complete Tier 1 assessments at the specified intervals. Some participants whose tier 1 tests results return as abnormal may be assigned to tier 2 and/or tier 3 tests. Some participants who do not have symptoms will be randomly assigned to complete tiers 2 or 3 tests as controls for participants with symptoms.

A. Tier 1 Assessments

Tier 1 assessments are conducted on enrollment and then according to the schedule of assessments (Table 11). Symptom surveys are repeated every 3 months. Office-based assessments are conducted at month 0,6,12,24,36,48 (and then every 12 months within the study period) after index date. Laboratory tests are conducted at month 0,3,6,12,24,36,48 (and then every 12 months within the study period) after index date IF the prior test was abnormal. Once normal, Tier 1 laboratory tests do not need to be repeated.

1. Tier 1 symptom survey

2. Tier 1 office-based assessments

- Weight and height measurement
- Waist circumference
- Seated vital signs (pulse, blood pressure, oxygen saturation)
- Active standing test (supine blood pressure and pulse after 5 minutes supine, standing blood pressure and pulse at 1 min, 3 min, 5 min, 10 min)
- 30 Second sit to stand

3. Tier 1 laboratory tests

- Complete blood count with differential (WBC, RBC, hematocrit, platelets, differential)
- Comprehensive metabolic panel (glucose, Na, K, Cl, HCO3, BUN, Cr, glucose, calcium, ALT, AST, alkaline phosphatase, protein, albumin)*
- Cystatin C
- D-dimer
- Lipid panel (HDL, LDL, triglycerides)*
- Hemoglobin A1c
- TSH and free T4
- Troponin (high sensitivity Troponin preferred)
- High sensitivity CRP
- NT-pro BNP
- 25-hydroxy vitamin D
- Coagulation panel (PT/INR/PTT)
- Urinalysis with reflex microscopy
- Spot urine microalbumin and creatinine (not 24 hour)
- *if possible, labs should be drawn fasting to obtain reliable fasting glucose and triglycerides; there is a space to indicate fasting status on the REDCap result form

B. Tier 2 Assessments

Tier 2 tests will be administered starting 3 months post-index date once participant meets criteria. Participants continuing to meet criteria for Tier 2 evaluation may have the study repeated, but not more than once a year. Note that hepatitis C antibody can only be performed once.

1. Tier 2 office-based or home-based assessments

- Home Polysomnography
- 6 minute walk test
- Vision test (Snellen chart)
- ENT examination
- UPSIT Smell test
- NIH Toolbox for cognition
    - NIH Toolbox oral reading recognition test
    - NIH Toolbox picture vocabulary test
    - NIH Toolbox auditory verbal learning test
    - NIH Toolbox Flanker inhibitory control and attention test
    - NIH Toolbox pattern comparison processing speed test
    - NIH Toolbox picture sequence memory test
- Neurologic examination for neuropathy
- Rehabilitation examination for physical function (PT/OT)
- Mini International Neuropsychiatric Interview (MINI)

2. Tier 2 laboratory studies

- Hepatitis B surface antigen, hepatitis C antibody (once only)
- Oral glucose tolerance test (time points 0, 60, 120 min)
- ACTH and cortisol

3. Tier 2 radiology studies

- Dual energy chest CT with contrast*
    - OR, if not available, volumetric non contrast chest CT (with inspiratory/expiratory scans)*
- Fibroscan
- Renal ultrasound
- Echocardiogram with strain imaging

*CT scan may not be performed in pregnant women and requires an antecedent pregnancy test in women of childbearing age

4. Tier 2 procedures

- Electrocardiogram (ECG)
- Complete pulmonary function testing (spirometry, diffusion capacity, lung volumes)

C. Tier 3 Assessments

Tier 3 assessments may be conducted only once during the course of the study, when the participant meets criteria, but not sooner than 3 months after index date.

1. Tier 3 office-based assessments

- Complete audiometry
- *Endopat testing (on hold)*
- Full neurocognitive testing
  - Digit span forward/backward
  - Trailmaking A
  - Trailmaking B
  - Hooper Visual Organization Test
  - MOCA/blind MOCA
  - Multilingual naming test
  - Phonemic test
  - Benson complex figure copy
  - CERAD word list
  - Craft Story 21 Recall
- Full eye examination

2. Tier 3 laboratory tests

- Serum B12 with methylmalonic acid
- Supine and upright plasma catecholamine testing (concurrently with tilt table testing)

3. Tier 3 radiology studies

- Gastric emptying study*
- Cardiac MIBG*
- Cardiac MRI*
- MRI brain with and without gadolinium*

*asterisked imaging may not be performed on pregnant participants and require an antecedent pregnancy test in women of childbearing age

4. Tier 3 procedures

- Nerve conduction study
- Electromyography
- Skin biopsy*
- Muscle biopsy*
- Lumbar puncture*
- Facility-based sleep study
- Tilt table testing*
- Cardiovagal innervation testing
- Full cardiopulmonary exercise testing
- Bronchoscopy*
- Right heart catheterization*
- Upper endoscopy*
- Colonoscopy with or without biopsy*

*asterisked procedures may not be performed on pregnant participants and require an antecedent pregnancy test in women of childbearing age

D. Central lab assessments

The following studies will be performed by a central laboratory using specimens kept at the biorespository and should NOT be run on site by local labs:

1. Tier 1 central lab assessments

- Anti-CCP
- Rheumatoid factor
- ANA
- EBV DNA PCR

2. Tier 2 central lab assessments

- Antibody testing (Anti dsDNA, Ro, La, Smooth muscle, RNP)
- Cytokine panel (IL2 receptor; IL 1beta, 2, 4-6, 8, 10, 13, 17; interferon gamma, TNF alpha)
- ICAM-1
- Insulin c-peptide
- Fecal WBC
- Fecal SARS-CoV-2 viral load (viral RNA and/or antigen)

3. Tier 3 central lab assessments

- CPK, aldolase, myositis panel
- Serum protein immunofixation electrophoresis
- Anti-Mullerian hormone
- Neurofilament light chain
- Total Tau (single molecule array SIMOA)

XV. Handling of existing data

A. Time window for acceptable use of clinical data

To optimize participant safety and minimize burden, studies that a participant qualifies for must not be repeated if they were done within a qualifying time period.

- For subjects who are within 30 days of index date (e.g. baseline visit for acute uninfected or acute infected participants), the qualifying time period is any time **on or after** index date.
- For subjects who are between 30 days of index date and 18 months of index date, the qualifying time period is any time within the **prior 30 days**.
- For subjects who are at least 18 months from index date, the qualifying time period is any time within the **prior 90 days**.

B. Selecting data if there are multiple qualifying results

If multiple labs exist (as may happen for acute enrollees), use the result (or panel of results) that include the most abnormal value. For example:

- For basic metabolic panel, take the panel of results that includes the highest creatinine value
- For complete blood count
    - take the panel of results that includes the lowest white count (if baseline visit for an acute COVID participant), else
    - take the panel of results that includes the lowest hemoglobin; if all hemoglobin normal but there is an abnormal platelet count, take the panel with most abnormal platelet count; if all hemoglobin and platelet normal but there is an abnormal white blood cell count, take the panel with most abnormal white count
- For liver function tests, take the panel of results that includes the highest ALT; if all ALT normal but there is an abnormal bilirubin, take the panel with the highest total bilirubin

XVI. Visit 1

Once a participant is enrolled in the study and signs the informed consent, the baseline visit (visit 1) will occur as soon as possible. The baseline/visit 1 is conducted to acquire participants' basic information and current state of physical, emotional, and mental health. Each participant will provide information that may be used to determine health status pre and post COVID-19 infection.

Optimally, visit 1 activities will happen on the same day, but may occur over multiple days:

- If a participant visits a study site, then all events may occur at the visit.
- Participants may complete the assessments electronically and site may mail biospecimens to the biorepository core if requirements are made for home clinical assessment and biospecimen collection.
- Some participants may complete the informed consent and questionnaires electronically and visit a study site for clinical assessment and biospecimen collection at a later date.

A. Coordinator-completed forms

If the participant has an existing health record at the study site and/or the study site has access to claims data or data from other health systems, project coordinator will complete the following REDCap instruments based on those data, ideally in advance of the visit:

- Comorbidities
- COVID treatment
- Medications
- Identity
- Visit

The Visit instrument will indicate that this is a baseline event. Completion of the Visit instrument prior to giving the participant access to any instruments is essential in order to insert the correct question stem into the questionnaires.

Ideally prior to the first visit, the study coordinator will also review the chart for laboratory, radiology or procedure results completed within 30 days of the study visit (but not before index date, in the case of an acute enrollment visit) that would otherwise be due at the visit.

Refer to the DRC MoO for instructions about how to complete forms in REDCap.

B. Participant-completed forms

The following baseline questionnaires will be administered to the participant:

- Demographics
- PASC symptoms
- Vaccine status
- Disability

- Baseline social determinants
- Pregnancy (if relevant)

The study coordinator will then review the study coordinator-completed forms (comorbidities, medications, COVID treatment) with the participant to revise and correct any information as needed.

Refer to the DRC MoO for instructions about how to assist participants in completing surveys in REDCap.

C. Activities to perform with the participant

The coordinator will give the participant the wearable device, with appropriate instruction [when available, currently on hold]

The Tier 1 office assessment will be completed.

Blood will be drawn for Tier 1 blood tests. If possible, labs should be drawn fasting to obtain reliable fasting glucose and triglycerides; there is a space to indicate whether fasting or not on the REDCap result form

A COVID-19 PCR test and antibody test will be administered if the participant is being enrolled as an uninfected control. If the participant has been vaccinated, the nucleocapsid antibody will be sent. If the participant has not been vaccinated, the spike and nucleocapsid antibody tests will be sent.

Biospecimens will be collected

- Nasal swab - Nasopharyngeal
- Blood[1]
  - 4 x 8 ml CPT tubes – for peripheral blood mononuclear cell (PBMC) collection
  - 2 x 8.5 ml SST tubes – for serum collection
  - 1 x 2.5 ml PAXgene tube – for mRNA
- Urine
- Saliva
- Stool
- If relevant, retrieval of samples that may have been banked if patient was hospitalized for acute COVID.

I. [1] Blood specimens will be replaced by serum collected via Mitra, TAP or other similar product for patients who cannot undergo phlebotomy.

Refer to the biorepository MOP each procedure and Biospecimen and lab assessment protocol.

XVII. Follow-up Visits

A. Visit windows

Participants will be asked to complete an interim survey at every three month time point since infection (e.g, 3 months after infection, 6 months after infection, 9 months after infection) through the first quarter of the fourth year of the study. For acutely enrolled participants, the first interim survey will take place at 3 months after infection. For post-acute enrolled participants, the baseline visit will be assigned to the nearest 3 month interval either before or after, and the first interim survey will take place at the next scheduled 3 month interval after that. For example, a post-acute participant enrolled at 20 months after infection would have the baseline visit assigned to the 21 month interval. The first interim survey would take place at 24 months after infection, 4 months after enrollment. A post-acute participant enrolled at 7 months after infection would have the baseline visit assigned to the 6 month interval. The first interim survey would take place at 9 months after infection, 2 months after enrollment.

At the time of each follow-up visit, the next follow-up survey should be added to a participant study calendar for release to the patient at the appropriate time. The goal for scheduled follow-up surveys or an in person follow-up visit is the targeted date ± 1 week (targeted window). If a follow-up visit cannot be scheduled within the targeted window, then it must be scheduled within an acceptable window of ± two weeks from the targeted date. All routine protocol procedures (i.e. Tier 1) should be completed on the day of the visit. However, if this is not possible another visit should be scheduled *within the acceptable window* to complete any missed procedures. Any triggered clinical assessments (i.e. Tiers 2 and 3) must be completed within four weeks from when the assessment was triggered; however it is preferable to have them completed within two from when it was triggered.

If a study participant misses a study visit during the targeted or acceptable window, study procedures should be completed at the next routine office visit, if possible.

To minimize the occurrence of missed visits, the study staff should send a reminder, either by telephone, regular mail, email or text, approximately one week before the scheduled visit. A courtesy phone call or text reminder one or two days before is encouraged.

A study visit scheduler will be provided to facilitate the scheduling of follow-up visits within window (Appendix 5). When the date of the Enrollment Visit (Visit 1) is entered into scheduler, the open and close dates for the targeted windows and for the acceptable windows will be calculated. Once the visit windows are calculated, a print out of the study visit scheduler should be placed in the study participant's record so that it can be easily accessed when scheduling a visit.

B. Interim Surveys

A current symptom inventory will be collected at 3-month intervals, with further physical examination, blood/specimen and radiologic testing conducted in a subset per protocol (MOP – Clinical Assessments).

If the participant has an existing health record at the study site and/or the study site has access to claims data or data from other health systems, project coordinator will complete the following REDCap instruments based on those data, in advance of the scheduled survey date:

- Comorbidities update
- Medication update

At this time the study coordinator will also review the chart for laboratory, radiology or procedure results completed within the eligible time period that would otherwise be due at the visit. These will be entered into REDCap as clinical results and those tests will not be performed at the study visit.

The study coordinator will complete the Identity and Visit instruments. Completion of the Visit instrument prior to giving the participant access to any instruments is essential in order to insert the correct question stem into the questionnaires.

The following instruments will be administered to the participant, either in person or remotely:

- PASC symptoms
- Vaccine follow up
- Social determinants follow up
- Alcohol/tobacco
- Pregnancy follow up (if relevant)
- The participant will be asked to review the comorbidities and medications update for accuracy

C. All subsequent interim surveys

For all subsequent interim surveys, occurring at 3 month intervals, the following procedure will be followed:

At this time the study coordinator will also review the chart for laboratory, radiology or procedure results completed within the eligible period that would otherwise be due at the visit. These will be entered into REDCap as clinical results and those tests will not be performed at the study visit.

The study coordinator will complete the Identity and Visit instruments. Completion of the Visit instrument prior to giving the participant access to any instruments is essential in order to insert the correct question stem into the questionnaires.

The following instruments will be administered to the participant:

- PASC symptoms
- Vaccine follow up
- Social determinants follow up
- Alcohol/tobacco
- Pregnancy follow up (if relevant)
- The participant will be asked to review the comorbidities and medications update for accuracy

XVIII. Biorepository Procedures

Please refer to the PBC MOP.

XIX. Managing Study Progress and Promoting Study Compliance

A. Retention strategies

Retention of study participants is always a challenge, particularly in longitudinal studies. It is important for participants to not feel pushed to adhere with study requirements should they refuse; it is better to maintain contact with participants, even infrequent contact, than to have them withdraw completely from the study. If a participant voices hesitation about continuing in the trial, it is important for study staff to talk about why they do not want to continue in the study and work with them to address their concerns. Engaging subjects in topics unrelated to ISCHEMIA can also help maintain contact. Maintaining even minimal contact with participants during periods when motivation is low makes it easier to re-engage them in the study.

Some retention strategies are described in the following sections.

1. Facilitate Access to the Office

a) Maps and Signs

For visits that are conducted at the site, the study offices should be easy to find. Detailed information such as elevator location, floor, and room numbers are needed to guide study participants to the specific area/locations for each study visit.

b) Transportation

Convenience and cost of transportation are two factors that will affect study retention, particularly among lower income participants, and those who reside or work in areas in which public transportation is not well developed. Many communities have volunteer transportation services for senior citizens, which can be utilized at low or no cost to the study. The marketing and social services departments at your institution are potential resources for information on transportation issues.

2. Maximize Availability of Staff

a) Appointment Hours

Study participants should be considered high priority. As volunteers, study visits should be scheduled at times convenient for the participants, and they should be seen promptly. The hours that staff is available for visits should be as flexible as possible to accommodate study participants' schedules.

b) Availability Outside Business Hours

Study participants should be able to talk with staff at times other than study visits. Each participant should be given a study card with staff contact information. These cards will require IRB approval before use.

c) Staff Willingness to Spend Time with Study Participants

The perception that study staff is willing to make extra efforts to accommodate study participants' needs enhances retention. This begins at the front door with friendly reception by staff and continues through the duration of the volunteers' participation in the study. Pleasant, kind, helpful, and attentive staff will facilitate bonding and retention.

Some tips on maintaining the participant's interest in the study include:

- complimenting the participant on their important contribution to the success of the trial.
- providing participants with brief update on study progress.
- conveying confidence of the success of the study.
- listening and addressing concerns that may be affecting their adherence.
- looking after patient health beyond study procedures.
- making monthly phone calls, or contact by other means, in addition to reminders of study visits.

d) Facilitating Appointments

There are some strategies staff should follow to ensure study participants keep appointments, including:

- providing an appointment card.
- sending reminders of upcoming visits.

e) Keeping Study Participants Engaged

Engaging study participants in topics unrelated to the study can also help maintain contact. Maintaining even minimal contact with study participants during periods when motivation is low makes it easier to re-engage them in the study.

Establish a personal connection with the study participant:

- Remember their birthday with a simple wish, or a birthday card.
- Wish them a good weekend or happy holiday, as appropriate.
- Thank them for coming in for their visit.

B. Study Participants Who Cannot be Contacted, Lost to Follow-up or Withdraw

1. Unable to Contact

Every means possible should be made to locate and contact the participant including:

- sending email and mobile text messages.
- contacting spouses or alternate contacts listed on the Contact Form (see Appendix 6).
- contacting referring physicians or other health professionals.
- review electronic health records or public records to determine vital status.
- mailing a return-receipt letter to the study participant requesting that they contact the study team.

All attempts at contact should be documented in the study participant's medical records and/or study files.

2. Lost to Follow-up (LTFU)

Lost-to-follow up participants compromises the scientific integrity of the study. Every attempt should be made to locate study participants using the methods described above.

The status of "Lost to Follow-up" should only be used at the time of study closeout, if the study team is unable to contact a study at the time of study closeout.

C. Study Participants Who Move to a Different Location

If a study participant moves to a different location, efforts should be made to retain him/her in the study.

If the study participant moves to a region in close proximity to another site, it may be possible to transfer the participant to that site. Upon learning of the study participant's intent to move, obtain information about where they are moving to and whether they would be willing to continue the study at a different site. Participating sites can be found on the study website. Additional information about transferring study participants to another site will follow.

If the study participant moves to a region without access to a study site, she/he can remain in the study if information can be obtained by another method other than through a completed study visit. Certain study assessments can be completed outside of a study site.

D. Death of a Participant

Upon learning of a participant death, the following information (if available) should be collected and submitted in REDCap as soon as possible:

- Date of death
- Cause of death
- Site of death

E. Participant Withdrawal of Consent

Study participants are free to withdraw their consent at any time. Study staff should engage the participant in conversation to discern the reason they are withdrawing their consent and addresses any concerns they may have about the study.

Instructions for capturing information about withdrawals are provided in the DRC MOP.

XX. Safety Assessment and Adverse Events

A. Definitions

Adverse Event (AE)

An **adverse event** is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study (excluding endpoints determined to be due to SARS-CoV-2 infection. Intercurrent injuries should be regarded as AEs. Abnormal results of research procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event (SAE)

AEs are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

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

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

Preexisting Condition

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

General Physical Examination Findings

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

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the

investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a participant that has participated in this study.

B. Recording of Adverse Events in REDCap Central

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

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

C. Reporting of Adverse Events

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

- Upper respiratory infection
- Fever
- Flu-like symptoms
- Pneumonitis
- Respiratory failure
- Psychosis and delirium
- Multi-system inflammatory syndrome
- Multisystem organ failure
- Arterial thromboembolic events including stroke and myocardial infarction
- Venous thromboembolic events including deep vein thrombosis, CNS venous thrombosis, and pulmonary embolism
- Myocarditis
- Cholelithiasis and cholecystitis
- Acute kidney failure
- Autonomic dysfunction
- Headache
- Hair loss
- Tooth loss
- Tinnitus
- Loss of smell and taste

- Fatigue
- Malaise
- Muscle pain and weakness
- Bone pain
- Generalized pain
- Anxiety
- Depression
- Neurological symptoms (loss of concentration, loss of memory)
- Palpitations
- Shortness of breath
- Cough
- Poor appetite
- Nausea, vomiting, diarrhea, abdominal pain
- Glucose intolerance
- Skin Rash
- Thirst
- Raynaud's phenomenon
- COVID (chilblain-like) toes

Investigators will conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to participants or others

For Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study center
- Participant number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

D. Notifying the IRB

Unanticipated problems posing risks to participants or others should be reported to the reviewing IRB. The following describes the NYULH IRB reporting requirements, though investigators at participating sites are responsible for meeting any additional local requirements and/or those of the relevant sIRB.

1. Sites Utilizing the NYULH sIRB

A Reportable New Information (RNI) form must be submitted to the NYULH IRB through the Huron Exchange for any events qualifying for prompt reporting. After review, an acknowledgement of the RNI will be available through the Huron Exchange.

The following events qualify for prompt reporting.

Report Promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly, but no later than 5 working days from the time the investigator becomes aware of the event:

- Unanticipated problems including adverse events that are unexpected and related
  - Unexpected**:** An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - Related to the research procedures**:** An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.
  - Harmful: either caused harm to participants or others, or placed them at increased risk

Other Reportable events:

The following events also require prompt reporting to the IRB, ***no later than 5 working days***:

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

2. Sites Utilizing a sIRB Other Than NYULH

Participating hub sites and subsites utilizing a sIRB other the NYULH must follow the reporting policies of that sIRB. A copy of the submission and any acknowledgement should be forwarded to the PASC CSC.

XXI. Protocol Deviations

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

Protocol deviations are deviations from the study protocol that:

- Increase the risk to a participant
- Decrease the benefit to a participant
- Affect participants' rights, safety, and/or welfare
- Affect the integrity of the resultant data

Protocol deviations include, but are not limited to the following:

- Enrollment of an ineligible patient
- Informed consent not obtained prior to performing any study related procedures
- Protocol specified procedures not completed as required
- Breach of participant confidentiality
- Non-compliance with study randomization procedures (for example, dispensing wrong bottle number to study participant)

Protocol deviations may be:

- Anticipated or planned (require prior approval)
- Implemented in order to eliminate an immediate hazard to participants
- Unanticipated

It is the responsibility of the site to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation. All deviations associated with change in risk to participants or compromise of scientific integrity of the study must be addressed in study source documents, reported to RECOVER program scientific directors at NIH, the CSC, and the RECOVER PASC DRC at Massachusetts General Hospital. Protocol deviations that do not impact risk or scientific integrity must be recorded on the protocol deviation reporting form and reported to the Observational Safety Monitoring Board (OSMB) at 6-month intervals. Protocol deviations must be reported to the reviewing IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

A. Notifying CSC/DRC

The PASC CSC is to be notified of all protocol deviations, whether or not they are reportable to the IRB. Protocol deviations will be reported as follows:

- Anticipated protocol deviations must receive approval of the PASC CSC prior to the implementation of any such deviation, except where deviation to the protocol is necessary to eliminate an immediate hazard(s) to participants.
- Protocol deviations implemented to eliminate an immediate hazard(s) to participants will be reported to the PASC CSC soon after the deviation occurs.

- Unanticipated protocol deviations need be reported as soon as possible after the deviation occurs.
- Protocol deviations will be reported on the Protocol Deviation Reporting Form (Appendix 7) and submitted to the CSC. However, when deviations are reportable to the IRB, sites are permitted to submit IRB correspondence to the CSC in lieu of the Protocol Deviation Reporting Form. If the CSC requires additional information, the site will be notified.
- Upon PASC CSC review, a signed copy of the Protocol Deviation Reporting Form will be returned to the site. The PASC CSC will follow-up on any corrective action necessary for the protocol deviation in question or to prevent similar deviations.
- At each site, all protocol deviations will be recorded on a log, either the Protocol Deviation Log provided (Appendix 8), or a site template, if preferred. The deviation log is to be stored in the site Trial Master File (TMF) and submitted annually to IRB with progress reports as part of continuing review.

B. Notifying the IRB

1. Sites Utilizing the NYULH sIRB

The following protocol deviations qualify for prompt report (within 5 days of knowledge of the deviation):

- one or more participants were placed at increased risk of harm
- the event has the potential to occur again
- the deviation was necessary to protect a participant from immediate harm

Protocol deviations that do not qualify for prompt reporting will be submitted at the time of continuing review.

2. Sites Utilizing a sIRB Other Than NYULH

Participating hub sites and subsites utilizing a sIRB other the NYULH must follow the reporting policies of that sIRB. A copy of the submission and any acknowledgement should be forwarded to the PASC CSC.

XXII. Site Monitoring

The purposes of monitoring are to verify that:

- the rights and well-being of human participants are protected;
- the reported trial data are accurate, complete and verifiable from source documents;
- the conduct of the trial is in compliance with the currently approved protocol/amendments, with ICH GCP E6 (R2), and with the applicable regulatory requirements (HHS 45 CFR 46).

A. Risk-based Monitoring Approach

The PASC has adopted a risk-based approach to clinical monitoring, focusing on risks to the most critical data elements and processes necessary to achieve the study objectives. The following monitoring techniques will be utilized:

- Centralized monitoring
- Remote monitoring

Centralized, remote and on-site monitoring will be performed by Clinical Research Associates (CRA). The CRAs are trained on the protocol, informed consent process, any processes in the MOP, any written information to be provided to the study participants. They will follow the PASC RECOVER Clinical Monitoring Plan (CMP) and standard operating procedures (SOPs) for monitoring.

Additional monitoring and trial oversight activities will be performed by the DRC.

The Senior Research Project Manager for Site Monitoring will determine the frequency of monitoring visits. The CRA will communicate with the site's study team via MS Teams and emails to conduct interim monitoring, with appropriate attention to data privacy and security.

B. Routine Remote Interim Monitoring

When a site is identified for routine remote interim monitoring, the CRA will communicate with the site PI and CRC via MS Teams or email. The CRA will provide a list of study participants selected for remote monitoring and a request to send the study records. All source documents should be redacted and not contain any patient identifiers, except for the study participant number. If institutional policy allows, granting remote access of the participant's electronic medical records (EMR) to the CRA can facilitate monitoring.

The CRA will perform the monitoring activities, communicating with site staff as necessary. Within two weeks after the monitoring activities are completed, the site PI and staff will receive a report of the monitoring session detailing the findings. As applicable, a list of open action items will be included. A target gate of resolution will be given. Most open action items are to be completed within two weeks, however there may be some action items that cannot be resolved until the study participant's next follow-up visit. The site staff should notify the CRA when an action item is completed so that the CRA can verify and close out the item.

C. Monitoring Activities

Monitoring activities/assessments include but are not limited to activities outlined in the table below.

Protocol Compliance	Confirm that the site is conducting the study in accordance with the protocol, MOP, and applicable regulations and guidelines. Discuss any PDs with investigator(s) and request action as appropriate. In the event of a protocol amendment, verify that no study participant was included/treated as per the protocol prior to IRB approval of the amendment. Verify that appropriate study participants are enrolled.
Enrollment and Retention	Check that enrollment and retention rates are aligned with study expectations. Review screening log and identify common reasons for enrollment failures and discuss with study staff strategic planning to reach recruitment goals. Ensure study participant status information is updated at each visit, and that data are collected, as required, for enrollment failures. Discuss retention rates, different levels of study participant compliance with protocol, and provide any necessary re-training as it relates to study participants lost to follow-up or who withdrew consent. Verify the site is using IRB approved advertising materials.
Source Documentation Verification / eCRF data verification	Verify that data entered into eCRFs is accurate and complete. Conduct review on approximately 10% of other data elements, focusing on selected key variables collected during enrollment and follow-up visits).
Informed Consent Form(s) Verification	Verify that the appropriate IRB has approved the informed consent document. Assure that the study participant has signed and dated the most current IRB approved ICFs as necessary throughout the study. Verify that the ICFs were signed and dated by the study participant prior to any study procedure. Verify that additional signature lines requested by the IRB are signed and dated according to IRB requirements, e.g. witness lines, PI or co-investigator signatures.
eCRF Data Review	Review selected data entered (or expected to be entered) in the eCRFs.
Data Quality and Completeness - Review of data issues	Review for incomplete data, status of open queries, responses to queries, and timeliness of data entry.

XXIII. Site Payments

A. Payment Protocol

Payments will be made based on schedules presented in the Other Transitional Agreement (OTA) executed between NYU Grossman School of Medicine and the subawardees.

- Study-specific budgets are developed by NYU in collaboration with the NIH, protocol MPIs, other team members, and site representatives, and are reviewed and approved by NYU.
- The Hub institution and the subsites shall execute required milestones of the contract for payment.

B. Payment Procedures

Each study research Subawardee will have the following responsibilities:

- Activating enrollment sites as described in the contract
- Review and sign the executed contract
- Review and sign the reliance agreement with the single IRB/Review or sign the MOU to determine roles between the institute and NYU
- Adhere to the study protocol – including study start-up, training, management, and closeout
- Serve as a clinical resource for sites and monitors
- Execution of enrolling site contracts and payments
- Participation in preparation of publications

C. Payment Schedule

Study start up and fixed payments

Hub Management Fee

A one-time Hub Management fee is payable to each Subawardee institution as soon as the institute reviews and signs the executed contract and reviews and signs the reliance agreement with the single IRB/Review or sign the MOU to determine roles between the institute and NYU Langone Health.

Site enrolling payment

Subawardees shall also be paid enrolling site payments once the institute achieves following milestones: preparation of all regulatory documents including site-specific IRB and informed consent forms, completion of all required trainings and financial disclosure etc, review and execute the clinical research agreement with enrolling site. This payment shall vary yearly upon completion of all services and milestones required from the institute. Subawardees shall only be entitled to retain the Fee in full in the event they meet Hub Expectations related to Enrollment Site's targets.

Site activation payment

This one-time amount shall become payable to the Subawardee when the Subawardee and all of its Enrollment Sites have been approved to begin enrollment as determined by NYU.

Annual payment(s) shall be made to the Hub within forty-five (45) days of completion of applicable milestone(s) and/or requirements.

Study Reimbursement

Upon recruitment of patients into Tiers 1, 2 or 3, payments will be made to each institute per participant enrolled.

Institutes may compensate enrolled participants for test(s) completed up to a maximum of Corresponding SOP for each procedure and must be adhered to in order to receive payments.

XXIV. Study Completion and Close-out Procedures *(Reserved)*

A. Virtual close-out visit

B. Closing out with the IRB

C. Terminating the OTA

D. Communications with the participant

E. Records Retention