Research Opportunity Announcement OTA-21-015J
RECOVER PASC PATHOBIOLOGY SUBSTUDIES

Frequently Asked Questions

Eligibility

Can you clarify whether one proposal may be submitted per site OR per hub?

Refer to Section 4 of the Research Opportunity Announcement (ROA) OTA-21-015J RECOVER PASC PATHOBIOLOGY SUBSTUDIES. Applications that are collaborative across multiple sites and hubs are encouraged. However, when the proposed research projects are not complementary, more than one application from a hub and its subcontracted sites will be considered.

How many applications to OTA-21-015J can one organization submit?

RECOVER cohort hubs or a hub's subcontracted enrolling site(s) are encouraged to submit a single application when possible. Research projects with complementary scientific goals should be submitted in a single application as a collaboration among various investigators and sites within the hub. Applications that are collaborative across multiple sites and hubs are also encouraged. However, when the proposed research projects are not complementary, more than one application from a hub and its subcontracted sites will be considered.

Can existing RECOVER CORES apply for this opportunity?

Yes, eligible entities for receipt of funding under this ROA must be either a RECOVER Consortium hub with a fully executed contract with the RECOVER Clinical Science Core (CSC) or a RECOVER enrolling site with a contract executed under an eligible RECOVER CSC hub.

Can existing RECOVER Clinical Trials apply for this opportunity?

Clinical trials applicants do not meet the eligibility criteria (see Section 3 of the Research Opportunity Announcement OTA-21-015J RECOVER PASC PATHOBIOLOGY SUBSTUDIES) for funding under this ROA.

Can you provide additional details about the comprehensive, longitudinal, multi-omics systems biology substudy that is under development to enable investigation of mechanisms of PASC and PASC subtypes across adults and children described in the ROA?

The RECOVER Systems Biology Working Group has a proposal currently undergoing review. To reduce duplicate proposals to this ROA, please see the study synopsis document and additional study design details.

The ROA strongly encourages several areas of research topics. How was this list derived, and are we limited to these bulleted research areas?

The list of research gaps and opportunities was derived in consultation with the RECOVER Observational Consortium Steering Committee (OCSC), Coordinating Committees, as well as through consultation with domain experts at the NIH. The announcement encourages proposals in these research areas. However, additional research areas can be proposed with a strong scientific rationale.

I am currently a RECOVER Investigator/part of a RECOVER study. Can I still apply to this ROA?

Refer to Section 3 of the ROA OTA-21-015J RECOVER PASC PATHOBIOLOGY SUBSTUDIES, eligible entities for receipt of funding under this ROA must be either a RECOVER Consortium hub with a fully executed contract with the RECOVER CSC or a RECOVER enrolling site with a contract executed under an eligible RECOVER CSC hub.

As a PI for a RECOVER Clinical Trial, would I be eligible to apply for the funding mechanism for this grant OTA-21-015J RECOVER PASC PATHOBIOLOGY SUBSTUDIES?

No, Clinical Trial applicants would not meet the eligibility criteria in the ROA. Eligible entities for receipt of funding under this ROA must be either a RECOVER Consortium hub with a fully executed contract with the RECOVER CSC or a RECOVER enrolling site with a contract executed under an eligible RECOVER CSC hub.

Are Principal Investigators (PIs) on the 45 ROA and NOSI projects eligible to apply for this opportunity, or are you required to be part of the RECOVER Consortium hub or at a RECOVER enrolling site?

The current 27 ROA awardees from Phase I are eligible to apply. The NOSI awardees are not eligible to apply directly unless at a RECOVER hub or site that has an existing Other Transactions (OT) agreement. Outside investigators are permitted to work with PIs within RECOVER, see lower tier agreements in the ROA announcement.

Is this ROA an R01-equivalent that might change my Early Stage Investigator (ESI) status?

The ROA is an OTA it should not affect ESI status.

If I am not part of a RECOVER group, am I ineligible to apply?

Only RECOVER hub sites with an active OT award can directly apply. Collaborations will be managed by lower tier agreement language in the funding announcement.

If I am at a site for a RECOVER EHR initiative, can I apply without needing to partner with another hub?

Yes.

Could institutions funded only for the RECOVER Electronic Health Records (EHR) initiative still submit for this?

Yes.

Can investigators at ABCD sites apply for the grant?

Yes.

Collaboration

I am interested in submitting a proposal but am not part of RECOVER. How do I connect with existing RECOVER PIs?

Please reach out to RECOVERPathBio@nih.gov and include a brief summary of your proposed research topic.

Should applicants propose to work with RECOVER hubs?

Yes. Eligible entities for receipt of funding under this ROA must be either a RECOVER Consortium hub with a fully executed contract with the RECOVER CSC or a RECOVER enrolling site with a contract executed under an eligible RECOVER CSC hub.

The funding opportunity at one point seems to require that an application have collaborators at ALL RECOVER sites. Is this correct?

No, we previously had language that was restrictive to indicate that we would accept one application from a hub or site. We've since removed that restriction, allowing hubs and sites to submit multiple applications, with the understanding that sometimes you may not be able to form a collaborative team based on the type of science that you're proposing. But we strongly encourage consolidating research teams so that we don't receive multiple applications in the same research area.

Does the Contact PI need to be a RECOVER Consortium member, or would a non-RECOVER PI working with a RECOVER PI suffice?

Both are allowable. Eligible entities for receipt of funding under this ROA must be either a RECOVER Consortium hub with a fully executed contract with the RECOVER CSC or a RECOVER enrolling site with a contract executed under an eligible RECOVER CSC hub.

Funding

Are these being funded as subcontracts from NYU-Langone?

The awards will be executed and managed by RECOVER CSC.

Do we need prior approval to submit proposals with budgets that are over $500,000 in direct costs?

No. As long as you can justify the budget scientifically, you can submit your application directly.

Is it $500–800K in total or per year?

Direct costs are not over $500K per year and total costs are not over $800K per year. This is the recommended budget, but the final budget may differ based on the project period and needs, with scientific justification.

General Questions

How many applications will be funded?

This will depend on the number of applications received and their review scoring. Research priority and gap areas will also be considered.

Is this a one-time application?

Yes.

If we have a question about Standard Operating Procedures (SOP) specifics (say on Cardiopulmonary exercise testing (CPETs) or CT scan protocols), who could we reach out to?

Please reach out to RECOVERPathBio@nih.gov with SOP related questions.

When is the due date of the application?

5pm EST, March 22, 2024

Will you consider applications focused on inflammation?

The ROA is not limited to any specific research area. However, proposals are strongly encouraged in the following high-priority topic areas identified by RECOVER, alone or in combination. This list may be updated as new research and needs emerge.

- Viral persistence/reactivation as a potential cause of some PASC subtypes
- Chronic immune dysfunction as a potential cause of some PASC subtypes
- Comparative studies of PASC with other post-viral and post-infectious syndromes
- Studies of vascular injury, thrombosis, and other related potential mechanisms of PASC (e.g., complement pathway dysfunction)
- Advanced imaging analysis, e.g., AI/ML, to define the long-term impact of COVID on organ structure/function and characterize PASC phenotypes
- Linking autopsy findings with pathobiological mechanisms of PASC to guide targeted interventions
- Effect of reinfection and/or emerging variants on the risk for PASC

- Intersectionality of social determinants of health, built environments and/or pre-existing conditions prior to acute infection and the risk for development or severity of PASC
- Remaining gaps in tissue-specific manifestations of PASC including molecular mechanism such as dysregulation or disruption of normal physiologic pathways (reduction in serotonin, mitochondrial or bioenergetic cellular functions), correlating abnormal MRI findings in the brain, heart and lung to pathologic mechanism associated with symptomology in PASC (shortness of breath, cognitive dysfunction, etc.)
- Studies that propose to validate published studies on potential mechanisms of PASC within the framework of the data and biospecimens collected within RECOVER cohorts.

The application requests our institution's Systems for Award Management (SAM) or Unique Entity ID (UEI) expiration date. Can you please clarify which date is needed?

SAM Registration expiration is the date that should be specified and can be found on the entity record in SAM.gov.

Is there a contact for general questions about the RECOVER?

We encourage you to go recoverCOVID.org for general information or contact us via RECOVERPathBio@nih.gov for specific questions.

Sample availability

Are the biologic samples intended to be only human, or can we propose an animal model to study as well?

The ROA is designed to leverage the RECOVER cohort data and samples; therefore, the budget should be focused on that. You would be permitted to do in vitro studies of cells or tissues obtained from RECOVER, but not permitted to utilize an animal model.

Are studies comparing PASC in non-human primate models and humans allowed?

This ROA is for mechanistic research leveraging RECOVER cohort samples. The RECOVER proposal doesn't have any language addressing the use of in vitro and animal models. We restricted that to the NIH administrative supplement program that closed about 2 years ago.

Could we leverage patients enrolled in other studies to do further assessments on blood and potentially perform exercise testing evaluation on?

For this opportunity, you could request to leverage additional data or biospecimens within the RECOVER cohorts as well.

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What type of resources are available from RECOVER for study (samples, data, etc.)?

Please refer to this table and the next question for types of resources available by request.

RECOVER Resources Considerations	
Samples and data requested	Stored data only Stored samples and data
Sample groups (clinical observational cohorts)	Adult Pregnancy Pediatric Autopsy
Infection status	Infected Uninfected
PASC status	PASC+ PASC -
Timepoints	Baseline 3 months 6 months 12 months 24 months 36 months
Other considerations	Number of samples Symptom descriptions

What types of biospecimen samples are available for request?

Please refer to the table below for general information. The formal request and justification for samples will be required in a separate form and submitted to the Ancillary Studies Oversight Committee (ASOC) for review.

Biospecimen Type	Adult	Autopsy	Pediatric
Plasma*	•		•
Serum	•	•	•
PBMC	•		•
PAXGene RNA Whole Blood	•		
Oragene OGR-600 Saliva	•		•
Urine	•		
Stool	•	•	
White Blood Cells	•		•
Red Blood Cells			•
Blood Spot		•	•
Nasal Cells	•		
Nasopharyngeal Cells	•		
Bronchial cells		•	

Biospecimen Type	Adult	Autopsy	Pediatric
Frozen Tissue		•	
FFPE Section		•	

**For Plasma, please specify the treatment type: EDTA, Sodium Citrate, Sodium Citrate-CPT, Doesn't matter*

Additional considerations for samples

- Sample size reduced to 14,880.
- 77% of survey visits completed.
- 70% of in person visits completed.
- Tier 2/Tier 3 tests are in the process of being scheduled/completed.

Do the adult samples collected include pregnant women?

There are some samples from a pregnant cohort.

Are red blood cells being collected/stored in the bank?

Not for the RECOVER adult cohort, but 1,035 samples have been collected to date for the RECOVER pediatric cohort.

What is the approximate volume and cell density of the PBMCs available from adults with PASC in the repository?

On average, an adult PBMC vial contains 5–6 million cells (we do not use a volume measurement); and an average of 8–10 million cells per collection.

Are cytokine assays available?

Cytokine assays are not part of the protocol currently in place.

Does the repository have the viral load of the participants available?

No, viral load measurements in stool were put on hold.

Is it possible to propose additional MRI scans, prospectively?

You are able to obtain a parallel IRB to collect additional new data as long as it is harmonized with what's being collected in RECOVER.

Are lung biopsy samples available from the autopsy cohort?

Please see the table below for a list of autopsy tissue samples.

What type of autopsy tissues can we access from the central repository?

Is there a limit to what we might request?

Please see the table below for a list of tissues that are sampled. For each, we have both Formalin-Fixed Paraffin-Embedded (FFPE) and snap frozen samples. All requests will be considered in relation to availability of the resources and priority of the questions being asked.

PBC Tissue Specimens	
Sural Nerve	Lung lesional tissue
Peroneal nerve	Spleen
Skin, calf including subcutis	Bone marrow (rib squeeze)
Muscle, gastrocnemius	Pancreas
Muscle, psoas	Liver, right lobe (central)
Duodenum	Mesenteric fat
Ileum	Kidney, right or left
Colon, right	Renal lesional
Colon, descending/sigmoid	Testis
Adrenal	Ovary
Aorta, ascending	Fallopian tube
Right ventricle, Posterior	Olfactory bulb
Left ventricle, lateral	Frontal cortex with leptomeninges
Left ventricle, basal	Basal ganglia
Right atrium/SVC (near SA node)	Thalamus
Left atrium	Hippocampus
Coronary artery, right	Occipital cortex
Coronary artery, left	Amygdala
Cardial lesional tissue	Pons
Hilar/mediastinal lymph nodes	Choroid plexus
Trachea	Medulla (area postrema)
Right upper lobe, with pleura	Cerebellum with dentae
Right Middle lobe	Dura with sinus
Right lower lobe	Spinal cord (thorax)
Left upper lobe, with pleura	Sympathetic chain with ganglia
Left lower lobe	Dorsal root ganglia

Can you please clarify if a proposal for this must include use of currently banked samples or if a proposal could fund analysis of samples obtained only at our institution that would still address questions pertaining to PASC pathobiology.

This ROA is intended to leverage RECOVER samples and data. While we have some studies in the first round ROAs analyzing cohort samples at their sites (i.e., parallel related data sets or specimens), if you do not plan to use RECOVER biospecimens or data, you would not be responsive to the ROA requirements.

Would you accept proposals that use non-RECOVER samples, while working with existing RECOVER samples for validation? We also have access to high quality samples from LMICs.

Yes, we do. Lower-tier agreements are permitted and will be considered with strong scientific justification. Funding for lower-tier agreements must be included in the applicant budget. These lower-tier agreements are intended to allow the Awardee to work with laboratories or investigators outside of the RECOVER Consortium to meet critical research needs or bring in expertise which may not be available at the site carrying the OT agreement. Lower-tier agreements will be managed by the awardees once approved with funding provided by the NIH. LMIC data could fit one of the high-priority areas to address risk factors related to social determinants of health, but the proposal should leverage the RECOVER cohorts in their primary goals.

What are biosafety levels required to acquire the samples?

Your institutional requirements for COVID-related research would likely apply.

Was the placenta collected?

These are not collected.

Are any of the participants in the cohorts or sub-studies screened for latent tuberculosis (TB) infection?

No, we do not currently have this data.

Are any kidney biopsy samples collected?

If kidney biopsy samples are being collected, it is only being done though a parallel IRB and not through RECOVER.

Are bronchoscopy samples currently available even though the protocol is still being determined?

No samples are currently available, but we anticipate there might be samples available in the second half of this year.

For the CPET testing described during the webinar, is there a standardized protocol being used for those data?

Yes, there is a standardized SOP for all Tier 2 and Tier 3 tests including CPET.

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Additional Questions about RECOVER biospecimen

Does the repository have a record of medications (if any) that the subjects were taking at the time of PBMC sample collection?

Yes, medications are collected by survey at enrollment and at each 3-month follow-up visit.

Does the repository contain subjects who are only smokers and do not consume alcohol?

We can assess if participants had more than 4 (for women) or 5 (for men) drinks containing alcohol in one day in the 12 months before infection and at 3-month follow-ups since the infection date. We categorized "Never" answers to these questions as a "Low or No Alcohol group," and answers were taken from the 12 months prior to infection period.

We can assess if participants smoked in the 12 months before infection (from less than monthly to daily; use of any tobacco product including e-cigs and vapes). We also collect smoking status every 3 months during follow-up since the infection date.

A non-smoker is defined as someone who answered "Never" on the same two questions from the same time period.

Does the repository have PBMCs from smoking and non-smoking control subjects available?

Yes.

Is this ROA primarily focused on investigators looking to use biospecimens? Could we utilize other data?

The ROA does permit use of data, not just biospecimens. However, this ROA is intended to leverage RECOVER samples and data. Although we have some studies in the first round ROAs analyzing cohort samples at their sites (i.e., parallel related data sets or specimens), if you do not plan to use RECOVER biospecimens or data, you would not be responsive to the ROA requirements.

Is there a time frame for data sharing of clinical/demographic data (or can that be requested)?

RECOVER data will be available to the public in waves as data freezes are completed.

Are the biologic samples intended to be only human, or can we propose an animal model to study as well?

The ROA is designed to leverage the RECOVER cohort data and samples; therefore, the budget should be focused on that. You would be permitted to do in vitro studies of cells or tissues obtained from RECOVER but not utilize an animal model.

Could we leverage patients enrolled in other studies to do further assessments on blood and potentially perform exercise testing evaluation on?

For this opportunity you could request to leverage additional data or biospecimens within the RECOVER cohorts as well. We encourage you to go recoverCOVID.org to get more information.

Are we allowed to contact participants for translational studies, or are we to only use existing samples?

You are expected to use the existing samples collected under RECOVER program. But if you have samples or cohorts outside of RECOVER, Lower-tier agreements are permitted and will be considered with strong scientific justification. Funding for lower-tier agreements must be included in the applicant budget. These lower-tier agreements are intended to allow the Awardee to work with laboratories or investigators outside of the RECOVER Consortium to meet critical research needs or bring in expertise which may not be available at the site carrying the OT agreement. Lower-tier agreements will be managed by the awardees once approved with funding provided by the NIH.

Is the addition of a new cohort (not using the RECOVER cohort) possible under the ROA?

Lower-tier agreements are permitted and will be considered with strong scientific justification. Funding for lower-tier agreements must be included in the applicant budget. These lower-tier agreements are intended to allow the Awardee to work with laboratories or investigators outside of the RECOVER Consortium in order to meet critical research needs or bring in expertise which may not be available at the site carrying the OT agreement. Lower-tier agreements will be managed by the awardees once approved with funding provided by the NIH. Pooling cohort data from other cohorts to ask research questions in parallel with RECOVER is permitted.

Could you provide information regarding which study sites collected data on long-term post-COVID taste and smell loss (either adults or children)?

Loss of smell/taste are assessed at every 3-month follow-up in RECOVER-Adult, and every 6-month follow-up on the RECOVER-Adult, Pediatric longitudinal cohort (Tier 2).

Do you have shared data of global pathological and gene expression data?

We have publications from RECOVER pathobiology program. Please contact us for more information or go to recoverCOVID.org for more information on publications. We will not have large-scale omics data available for secondary analysis at thi time. Within the existing ROA projects, some will have small-scale omics that will eventually be shared within the RECOVER gateway. However, this deposition has not happened for the first wave of research funded by the pathobiology program, because most of these are still within their research periods. The current second-wave ROA applications are due in March with an anticipated 1-year timeline, and it is difficult to determine what data would be available to groups to leverage in a new proposal.

Could I obtain detail on what survey questions are being asked of participants regarding their alcohol use?

Enrollment Questions

Question: In the 12 months before [COVID infection date], did you have five or more drinks* containing alcohol in 1 day?

Response: 1, Daily or Almost Daily|2, Weekly|3, Monthly|4, Less than Monthly|5, Never|-88, Prefer not to answer

Question: Since [COVID infection date], have you had four or more drinks containing alcohol in 1 day?

Response: 1, Daily or Almost Daily|2, Weekly|3, Monthly|4, Less than Monthly|5, Never|-88, Prefer not to answer

Follow-up questions (every 3 months)

Question: In [past 3 months], have you had five or more drinks containing alcohol in 1 day?

Response: 1, Daily or Almost Daily|2, Weekly|3, Monthly|4, Less than Monthly|5, Never|-88, Prefer not to answer

Question: In [past 3 months], have you had four or more drinks containing alcohol in 1 day?

Response: 1, Daily or Almost Daily|2, Weekly|3, Monthly|4, Less than Monthly|5, Never|-88, Prefer not to answer

**One standard drink is about 1 small glass of wine (5 oz), 1 beer (12 oz), or 1 single shot of liquor.*

Are Chest CT scans already read by a radiologist or are the films available for interpretation by external radiologists?

Clinical chest CTs are performed at the study sites. Data from the radiology report is extracted by study coordinators into a standardized REDCap form. A subset of chest CTs are send to the chest CT reading center for QC assessment with feedback to sites and for research reads.

What type of tests and assessment data is available?

Tier 2 Available Tests and Assessments	
Category	**Element**
Clinical assessment	Home sleep test+
Clinical assessment	6-minute walk test+
Clinical assessment	Neurologic exam

Tier 2 Available Tests and Assessments	
Category	**Element**
Clinical assessment	Rehabilitation exam
Clinical assessment	Mini International Neuropsychiatric Interview (MINI)+
Clinical assessment	Vision screen+
Clinical assessment	Smell test+
Clinical assessment	NIH Toolbox oral reading recognition test age 3+ v2.0+
Clinical assessment	NIH Toolbox picture vocabulary test age 3+ v2.0+
Clinical assessment	NIH Toolbox auditory verbal learning test (Rey) 8+ v2.0+
Clinical assessment	NIH Flanker inhibitory control and attention test age 12+ v2.1+
Clinical assessment	NIH Toolbox pattern comparison processing speed test age 7+ v2.1+
Clinical assessment	NIH Toolbox picture sequence age 7+ v2.1+
Laboratory study	ACTH and cortisol+
Laboratory study	Hepatitis B and C testing+
Laboratory study	Insulin c-peptide+
Laboratory study	Oral glucose tolerance test (time points 0, 30, 60, 120 min)
Radiology	Volumetric non contrast chest CT (with inspiratory/expiratory scans)
Radiology	Dual energy chest CT with contrast
Radiology	Resting transthoracic echocardiography with strain imaging
Radiology	Renal ultrasound
Radiology	Fibroscan
Procedure	Electrocardiogram
Procedure	Pre- and post-bronchodilator spirometry (no medication hold), resting SpO2 and single breath diffusion capacity

Tier 3 Available Tests and Assessments	
Category	**Element**
Clinical assessment	Audiometry
Clinical assessment	Complete neurocognitive testing+
Clinical assessment	Endopat testing
Laboratory study	Serum B12 with methylmalonic acid+
Radiology	MRI brain with and without gadolinium
Radiology	Cardiac MRI, with and without gadolinium contrast*
Procedure	Nerve conduction study*
Procedure	Electromyography*
Procedure	Facility-based sleep study
Procedure	Full cardiopulmonary exercise testing

Helpful Links

- RECOVER Study protocols can be found online at https://studies.recovercovid.org/about-us/about-studies/.
- The list of RECOVER publications is available online at https://recovercovid.org/publications.