Research Opportunity Announcement OTA-21-015K

RECOVER LONG COVID ANCILLARY STUDIES

1. PURPOSE

The National Institutes of Health invites applications for ancillary research studies that expand the Researching COVID to Enhance Recovery (RECOVER) Initiative's understanding of post-acute sequelae of SARS-CoV-2 infection (PASC, or Long COVID). This Research Opportunity Announcement (ROA) encourages research proposals that leverage RECOVER's established infrastructure, including its curated and well-characterized repository of biospecimens, comprehensive data resources, observational cohort studies (Adult, Pediatric and Autopsy) especially long-term follow-up studies, to investigate the pathobiological mechanisms underlying persistent symptoms and organ-specific deleterious effects of Long COVID. These studies, together with the complementary ancillary studies notice NOT-HL-25-027 and are expected to contribute to identifying, elucidating, and validating key pathophysiological mechanisms, prognostic biomarkers, and potential therapeutic targets for individuals affected by Long COVID.

2. BACKGROUND

The RECOVER Pathobiology Program has been instrumental in advancing our understanding of the long-term multifaceted consequences of SARS-CoV-2 infection. To date, three funding announcements were issued which supported more than 60 research projects including under NOT-OD-22-038-aimed at uncovering the pathobiological mechanisms involved in development and progression of Long COVID. As the NIH RECOVER initiative continues to evolve, there remains an urgent need to continue to leverage these resources to address RECOVER's Research Questions and exploit emerging opportunities under the RECOVER Ancillary Studies page and address the to investigate the pathobiological underpinnings and improve health outcomes of people suffering from Long COVID.

The research studies solicited under this ROA will address one or more of the following goals:

- Expand upon RECOVER's foundational clinical and translational research.
- Utilize established biospecimens, clinical data, imaging studies, and other relevant resources already curated under the RECOVER protocol.
- Propose observational or mechanistic approaches that complement—but do not duplicate—ongoing RECOVER Pathobiology efforts.
- Identify and validate biomarkers to assess risk, stratify patients, improve diagnosis of Long COVID, and monitor safety and efficacy of interventions for treatment of Long COVID.

- Identify and validate key contributing factors such as molecular, cellular, or other relevant signaling pathways as potential targets for therapeutic interventions.
- Address critical and emerging research gaps.
- Develop and validate bioassays that can inform and be utilized in clinical studies of Long COVID.

3. SCOPE AND ELIGIBILITY

This ROA is complementary to the ancillary studies solicitation notice NOT-HL-25-027 and is intended to support pathobiology studies that include at least one of the following:

- Propose studies whose goals are synergistic with the overarching aims of the RECOVER Program.
- Focus on long-term follow-up of individuals with Long COVID, including investigations on persistent symptoms and organ-specific deleterious effects that add scientifically supported clinical measurements or tests to the follow-up examinations or contacts of RECOVER Adult or Pediatric cohorts.
- Leverage existing RECOVER infrastructure, including biospecimen repositories, longitudinal clinical data (see RECOVER Ancillary Studies), and emerging innovative tools (e.g., Artificial Intelligence/Machine Learning (AI/ML)) to maximize and accelerate scientific discoveries.
- Utilize observational, mechanistic, or interventional study designs for long-term follow-up studies, as appropriate.

Investigators from academic, government, non-profit, and other eligible institutions are encouraged to apply. Investigators from previously funded RECOVER Pathobiology studies are eligible to apply, and collaborations that integrate multidisciplinary approaches are particularly welcomed.

4. SPECIAL AWARD TERMS

The complete terms and conditions of each sub-agreement issued under this ROA are subject to negotiation and will be contained in the Other Transactions Agreement entered between RECOVER Administrative and Coordinating Center (ACC), on behalf of the NIH, and the Awardee. This Special Award Terms section is provided for informational purposes only to provide prospective applicants with an understanding of key expectations and terms that may differ from traditional NIH award mechanisms.

Publications

Awardees are expected to adhere to the publication guidance inclusive of terminology referencing RECOVER from the RECOVER Presentations and Publications Oversight Committee (PPOC). All publications must reference the Other Transaction (OT) award number for the individual ROA award and include the following language in the acknowledgements and/or citation of funding section of all accepted publications

supported by this program: 1OT2HL156812-01 was supported by the NIH RECOVER Pathobiology Research Program.

Sharing of Data and Biospecimens

The NIH expects and supports the timely release and sharing of research data from RECOVER supported studies for use by other researchers to expedite the translation of research results into knowledge, products, and procedures to improve human health (NIH Scientific Data Sharing). The overarching goal of this ROA is to lead to rapid delineation of Long COVID pathobiology to foster progress in diagnostic, therapeutic, and preventive avenues for this condition. To achieve this goal, awardees must pledge to rapidly share data and biospecimens where it is not prohibited (i.e., Tribal data sovereignty) with the NIH RECOVER data and biospecimen repositories and ultimately with the broader research community. When scientifically appropriate and justified, applicants may propose additional collection and sharing of biospecimens that is not included in the main protocols of RECOVER.

Award recipients will work closely with RECOVER on data sharing activities to advance the science of Long COVID research across the country.

5. PROPOSAL FORMAT AND REQUIREMENTS

This ROA encourages collaborative research between different research groups within or outside of RECOVER teams. Applicants are encouraged to discuss their research plans with a representative from the RECOVER Pathobiology Program Scientist team, recoverpathbio@nih.gov, to ensure that the proposed research work is in alignment with the overall RECOVER program objectives.

The application should clearly and fully demonstrate the proposer's capabilities, knowledge, and experience, and should justify the budget proposed. The application should develop a plan to support analysis and reporting of the projected number of biospecimens based on participant selection criteria and sampling timepoints (see RECOVER Ancillary Studies). The actual number of biospecimens and timepoints used may be reduced or eliminated based on interim analyses, recruitment, or other considerations.

Proposals shall include the following required sections:

- Cover Page
- Project Summary
- Project Plan
- Appendix with required appendix items with budget justification

Each of these sections will be submitted electronically via the REDCap link provided below.

The Cover Page shall include:

A. The proposal title

B. The applicant's:

i) Legal entity name

ii) Address and contact information

iii) SAM UEI # and expiration date

iv) DUNS # and expiration date

v) EIN number

C. The name and contact information for the Principal Investigator(s) (maximum 3)

D. List of key personnel with titles and affiliations (maximum 10)

E. The name and contact information for the Awardee's Business Official, the person authorized to negotiate and bind the Awardee as a signatory to the Other Transaction agreement

F. The total cost proposed

The Project Summary (1 page maximum) shall include:

A. PI Name(s)

B. Institution(s)

C. Title of Project

D. Summary of Research Objectives, Aims, and Methods (not to exceed 500 words)

The Project Plan shall be limited to a maximum of 6 pages including figures and must contain:

- A clear statement of the study hypothesis, rationale, significance (e.g., why it is compelling and how it addresses emerging research challenges), and specific aims.
- Detailed methodology with emphasis on how RECOVER biospecimens, data, and resources will be integrated into the study design.
- A comprehensive description of the study design, including synergies with other ongoing studies and overall RECOVER program, cohort selection, longitudinal follow-up procedures, detection methodologies, statistical analysis, and outcome measures.
- Plans for ensuring adherence to human subject protection policies, data security protocols, and the maintenance of participant confidentiality.

- A feasibility assessment addressing potential challenges and proposed mitigative strategies.
- A timeline that aligns with long-term follow-up objectives and RECOVER milestones. Information regarding the structure of the Long-Term Follow-up Protocol can be found on the RECOVER Ancillary Studies webpage.

Specifically, the Project Plan must address the following five elements:

A. Technical Approach

The proposal must briefly describe how the work proposed will be accomplished. Proposers should provide a description of the precise analyses planned, along with any available information about sensitivity and specificity of technologies selected and indication of type and amount of biospecimens or data requested from RECOVER. Preliminary data on feasibility, limits of detection and sample pre-analytic considerations is expected. The applicant is expected to be fully familiar with these protocols. This section should also include a project plan with half-yearly measurable milestones and deliverables based on the listed objectives requested period of support.

B. Key Personnel Experience

Proposers must describe experience of key personnel supporting the planning and implementation of activities described in the ROA. Expertise in and support for the development, implementation, and execution of relevant analytic modalities, platforms, and methodologies on biospecimens, imaging procedures, and other examination components (e.g., ECGs, EEGs, etc.) collected within and outside of the RECOVER pediatric, adult, and autopsy protocols for proposed testing, as well as expertise in data analysis and management, statistical calculation, AI/ML, or bioinformatics should be included. Please provide biosketches describing key personnel in the appendix. Biosketches should conform to the most recent NIH template requirements and do not count towards the page limits.

C. Management/Staffing Plan

Proposals should detail how the proposer will provide the necessary project administration, organization, and staff to ensure quality control, compliance with ROA expectations, and necessary staffing adjustments. If relevant, proposers must discuss how existing funded project administration, organization, and staff will be leveraged for support of the RECOVER initiative.

D. Past Experience

Proposers should provide examples of prior project experience relevant to research areas described in this ROA. Each example should include the total funding awarded and dates of award, contact information for a sponsor able to serve as a reference, and a brief description of the project itself, including how the project was analogous to the needs identified in this ROA with respect to the

critical research area(s) being proposed. Applicants will need to demonstrate prior work with multi-center clinical research, consortia, or networks, if proposing a long-term follow-up proposal AND competency associated with the analyses being proposed.

E. Data Analysis, Management and Sharing Plan

Proposal should include a robust in-house plan for quality assurance for all proposed assays including data harmonization for batch effects, between differing assays and/or work performed as different research sites, if applicable. Proposals are strongly encouraged to include a strategy for the transfer and sharing of samples among other sites or laboratories involved in the application, as applicable. Detailed descriptions of the procedures for biospecimen selection and transfer to research site(s), including feasible and effective workflow to permit the sharing of samples released from the Long COVID Biorepository Core (BRC) for use in all aspects of the proposal, if a multi-site or multi-laboratory approach is selected. Proposals should provide statistical analysis and data management plans for raw data generated within the framework of the proposed research. Proposers should demonstrate the proposed statistician or statistical analysis team has the skill and experience to evaluate the hypotheses in the specific aims of the proposal. Utilization of biostatistics, data management, and/or bioinformatics core facilities at the hub site is permitted. Plans for data sharing should detail the types of data to be managed and shared, related tools, software and/or code needed to access or analyze the data and plans for data preservation and access as described in the Data Sharing requirements of this ROA. Data sharing plans should describe how data will be shared in accordance with NIH Scientific Data Sharing Policy and RECOVER Sharing Data for Broader Impact policies and processes.

Appendix Items

The technical plan may be supported with upload of the following required appendix items (not counting towards page limits):

A. An existing manual of operations from a prior or ongoing externally funded project serving as external core resource or cohort, if applicable

B. Key personnel biosketches

6. BUDGET AND PROJECT PERIOD

The Budget section must provide a realistic, fully justified project period, and the budget and cost must reflect the actual needs of the proposal for performing the work specified in the ROA. This section must also include a project timeline and measurable milestones. Proposed budgets should generally not exceed a maximum total direct cost of $500,000 per year and the total costs should not exceed $800,000 per year. Applicants applying to leverage data and biospecimens that are readily available in RECOVER should plan for a project period of up to 12 months. Applicants are highly

encouraged to submit their budgets using the SF424 R&R Budget Form. Multiyear budgets may be considered only if a long-term follow-up study is proposed. Requests for capital expenses for instruments or equipment are not permitted under this ROA. The budget and budget justification must be submitted via the REDCap link provided below.

7. SUBMISSION

Applications must be submitted electronically via the designated NHLBI internal submission system, REDCap by the stated deadlines on rolling basis with funding decisions made by NIH quarterly. The required application information must be entered by the PI or their designee on the form provided at the REDCap link below. A code will be provided for return access to the REDCap form. The completed proposal form must be submitted by an authorized business official via the REDCap. Applications nonresponsive to terms of this announcement will not be considered for review.

REDCap application submission page

8. REVIEW PROCESS

Applications will undergo a rigorous peer-review process on a rolling basis. To facilitate rapid research advances, NIH intends to provide funding support to awardees within 6 months from the submission date. The RECOVER Administrative Coordinating Center (ACC) will coordinate the review process. Applications received will be first assessed for completeness and responsiveness to this ROA by the ACC. The RECOVER Data and Biospecimens Cores including the RECOVER Biospecimen Access Committee (BAC), and Data Resource Center (DRC) will assess primary feasibility of data and samples requested in the applications. Applications meeting these requirements will be reviewed by subject matter experts for scientific merit. At the same time, the applications will be assessed by the RECOVER Ancillary Studies Oversight Committee (ASOC) for synergy with ongoing programs, alignment with RECOVER program objectives, utilization of existing data and biospecimen resources, feasibility of the proposed approach, and potential overlap with ongoing RECOVER efforts. In parallel, these applications will be additionally considered by Representatives from the National Community Engagement Group (NCEG) who will provide feedback on how well the proposed research addresses patient community's concerns. NIH RECOVER program staff will review the proposed budgets and budget justifications to ensure that the budget proposed is reasonable and the proposed project duration is justified. Applicants may be required to provide supplemental information or clarifications during the review process. NIH Program Scientists will consolidate all the above review assessments for the applications received to compile the list of recommended applications to the RECOVER Executive Committee (EC) for funding considerations. Final award decisions will be made by the RECOVER EC based on scientific priority and merit, potential impact on Long COVID research, availability of funds and requested budget, and programmatic balance on a quarterly basis.

Review Criteria

The review criteria described below will be considered in the review process:

- Budget and Project Period – NIH staff and various review components will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

- Overall Impact – Proposals will be assessed for how well they leverage the NIH RECOVER observational cohorts, associated resources, and potential synergies with ongoing studies to make rapid progress in understanding the mechanisms underpinning the manifestations of Long COVID, including the mechanisms responsible for the multi-organ/system dysfunction leading to the various symptoms of Long COVID.

Additionally, the reviewers will assess:

- How significant or compelling are the proposed hypotheses? Will the proposed studies address one or more emerging research challenges identified on the NIH RECOVER Ancillary Studies website. How might the proposed research increase understanding of the molecular pathways that underlie the long-term effects of SARS-CoV-2 infection, including its resolution?
- How are the applicants' hypotheses clinically relevant regarding the pathobiology of Long COVID, based on experience or expertise in pertinent biological pathways, systems, organs, or diseases?
- In what way does the proposed research have the potential to inform the diagnosis, prevention, mitigation, and/or treatment of Long COVID through elucidating the clinical pathogenetic mechanisms of Long COVID and the identification of associated clinical pathways?
- Is the proposed approach optimally designed to test the proposed hypotheses?
- In what way has the proposed research set forth appropriate methodology and feasible project timelines, milestones, and deliverables?
- In what way(s) do the applicants have expertise in understanding the clinical manifestations of Long COVID and similar post-infection disorders that may share clinical manifestations and mechanistic pathways with Long COVID?
- To what extent do the applicants have expertise and experience in cross-disciplinary clinical understanding of tissue/organ/system dysfunction caused by other forms of tissue/organ/system injury relevant to multisystem dysfunction in Long COVID?
- How well do the applicants propose to develop cross-disciplinary and collaborative research?
- How well do the applicants propose to rapidly share data and results with the broader research community, including, as appropriate, deposition into dbGaP or BioData Catalyst, and how will they rapidly submit results for publication?

9. CONTACT AND ADDITIONAL INFORMATION

For inquiries regarding the scope of this ROA, submission instructions, or further details about RECOVER's resources, please contact the RECOVER Program Coordination Office at RECOVERreviews@rti.org. Additional guidance, FAQs, and application resources are available on the research section of the RECOVER website.

Negotiation

NIH reserves the right to:

- Select for negotiation all, some, one, or none of the proposals received in response to this ROA.
- Segregate portions of resulting awards into components and their associated budget and/or milestones that differ from those that have been proposed.
- Accept proposals in their entirety or to select only portions of proposals for award.
- Fund projects in increments and/or with options for continued work at the end of one or more phases, which can consist of more than one milestone.
- Fund projects in increments with options to terminate activities e.g., based on evolving data/needs of the initiative.
- Request additional documentation (certifications, etc.).
- Remove proposers from award consideration should the parties fail to reach a finalized, fully executed agreement, or if the proposer fails to provide requested additional information in a timely manner.

Authority

This Research Opportunity Announcement (ROA) is issued with the goal of establishing an "other transactions" agreement or sub-agreement pursuant to 42 U.S.C. § 285b-3 and 42 U.S.C. § 282(n).

10. EFFECTIVE DATE

This Research Opportunity Announcement (ROA OTA-21-015K) is effective immediately. Proposals must be initiated upon award and adhere to NHLBI policy guidance for long-term and ancillary research studies.

By supporting innovative ancillary studies that utilize the RECOVER Program's comprehensive biospecimen and data resources, NIH seeks to advance our understanding of the long-term biological impacts of SARS-CoV-2 infection and accelerate the development of targeted interventions for Long COVID. We look forward to receiving high-quality proposals that contribute to mitigating the long-term consequences of COVID-19.

Issued by:

NHLBI Division of Cardiovascular Sciences
National Heart, Lung, and Blood Institute

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