



Research Opportunity Announcement
OTA-21-015H
RECOVER Clinical Trials

Introduction

This Research Opportunity Announcement (ROA) solicits applications proposing clinical trials in those over 18 years old in the prevention and/or treatment of Post-Acute Sequelae of SARS-CoV-2 infection (PASC) as part of the [NIH RECOVER initiative](#).

Background

Recovery from SARS-CoV-2 infection is extremely variable with many patients recovering quickly while for others there are important post-acute sequelae. Reported symptoms among persons who have been infected with SARS-CoV-2 range from mild to incapacitating, may persist after recovery from acute disease, may involve multiple organs and systems, and can adversely affect overall quality of life. In some cases, new symptoms and findings are reported that appear linked to the timing of acute infection but emerge subsequently and evolve over time. The magnitude of the public health impact of these sequelae is currently unknown but potentially large given the numbers of individuals across the age spectrum who have been and will be infected with SARS-CoV-2. The NIH RECOVER initiative was developed to improve our understanding of and develop strategies to prevent and treat the post-acute sequelae of SARS-CoV-2 infection (PASC). These strategies should enable rapid innovation, evolution, and adaptation as more is learned about PASC and its potential impact on public health. Initial trials will focus on interventions that have shown promise in other recovery contexts and on current hypotheses regarding pathogenesis. Examples of current prevailing hypotheses as to the etiologies of PASC include persistent SARS CoV2 virus or viral particles, reactivated dormant viruses, virus-induced inflammatory or auto-immune syndrome, and host tissue injury, among others.

NIH previously solicited for a RECOVER Clinical Trials Data Coordinating Center (CT-DCC). The RECOVER CT-DCC will provide overall project coordination, administration, comprehensive data management, final protocol development, site selection, operational support for the trials including regulatory submissions, study materials and training, safety monitoring, biostatistical support, and rapid results dissemination for the RECOVER trials in collaboration with proposing entities. It is anticipated that awards pursuant to this ROA will be issued as sub-agreements under the CT-DCC.

Authority

Awards will be funded through an “Other Transactions” (OT) sub-agreement pursuant to 42 U.S.C. § 285b-3 and 42 U.S.C. § 282(n).

Objectives

This ROA is to solicit applications proposing clinical trials protocols to be finalized and executed rapidly in collaboration with the RECOVER CT-DCC for the identification of safe and effective treatments and preventive strategies for PASC in those over 18 years of age. A future ROA is anticipated for the solicitation of trials on safe and effective treatments in children.

With the uncertain etiology or etiologies and the multiple clinical manifestations underlying PASC, NIH

is seeking proposals for clinical trials testing a range of interventions and using diverse methods to address symptoms/symptom clusters and underlying mechanisms of pathobiology. Trials appropriate in response to this ROA include Phase IIb trials as well as efficacy and effectiveness trials (Phase III) that provide adequate statistical power to support informed clinical decision making and, as appropriate, sub-group analyses; pragmatic trials; trials with Bayesian designs and adaptive platform protocols that could be modified to add and drop interventions as indicated. Trials that allow seamless transition from phase II to phase III would also be in scope. Acceptable interventions could include, but are not limited to, registration and non-registration pharmacologic (e.g., anti-virals, immunomodulators, other drugs and biologics), non-pharmacologic (e.g., complementary and integrative approaches), devices (e.g., stimulators, neuromodulators), as well as behavioral health and lifestyle intervention strategies (e.g., cognitive behavioral therapy, neurocognitive and cardiopulmonary rehabilitation). Interventions may include those that leverage treatments for which there is already an evidence base for addressing other relevant conditions.

All trials are expected to include a global measure of functional status, which can be shared across trials and should include, but not be limited to, patient-centered outcomes. In addition to measures of general well-being, measures of specific signs and/or symptoms and biomarkers of underlying pathobiology are appropriate. NIH strongly encourages the use of NIH COVID-19 common data elements (CDEs). The CT-DCC is charged with working collaboratively to maintain a trial CDE library for RECOVER trials.

While applicants are expected to submit trial protocols, the proposed trial may not be conducted as submitted. Protocols will undergo review and modifications may be necessary to meet the priorities of the program. Further, successful applicants may be asked to work collaboratively with other awardees to develop a new protocol that incorporates multiple intervention strategies including some evaluated and prioritized by NIH. The final protocol will be developed in collaboration with the RECOVER CT-DCC.

An important component of the RECOVER Initiative is the active engagement and contribution of people suffering with PASC and their caregivers in the development of the research program. Applicants should provide documentation/description of processes and ways in which the proposed protocol incorporated patient and other stakeholders input and a plan for the ongoing inclusion of patients and caregivers in the development and conduct of the protocol and selection of interventions and outcomes.

The RECOVER CT-DCC will provide administrative, logistical, screen and select the clinical recruitment sites with the necessary expertise (e.g., neurocognitive, cardiopulmonary, mental health) and population for trial execution, data management, and statistical support for the RECOVER Clinical Trials, as described above. The CT-DCC will also be responsible for working with the RECOVER Data Resource Core (DRC) for data flow, integration and harmonization with the RECOVER observational cohort data. Awardees will work collaboratively with the CT-DCC for the development and conduct of the trial. As RECOVER is an existing program with multiple components, applicants must agree to work collaboratively with other RECOVER components.

As our understanding of underlying mechanisms of PASC improves, additional candidate interventions may be evaluated through consultative processes engaging researchers and patients and prioritized and selected by NIH for testing in clinical trials.

Given the urgent public health needs of finding effective treatment for the large number of people affected by PASC, NIH puts high priority on obtaining rapid results and expedited data sharing through: usage of COVID-19 CDEs; plans, including timelines, for making data and specimens available rapidly through NIH-designated repositories; and sharing data and results, as available, with public health agencies and the public to inform clinical and/or public health practice.

Proposals

Applications should include the following:

- The proposed project title;
- Important note, in the project title please include which domain your project falls into from the following choices:
 - drug immunomodulator anti-inflammatory
 - drug anti-viral
 - drug other
 - cognitive behavioral
 - rehabilitation
 - complementary alternative medicine
 - devices
 - modulators dysautonomia/pots
 - other
- Project Summary: Description of the project.
- The eRA Commons *userid* must be included for the PI or contact PI
- The number of the Research Opportunity Announcement to which you are responding (OTA-21-015H);
- The expected start date to launch activities outlined in this announcement (time from award);
- Identification of lead investigators, other key investigators, and contracts and the roles of each.
 - All Key Personnel who are major scientific contributors to the study must provide an NIH Biosketch whether or not they are budgeted.
 - Description of and justification for other personnel.
 - Justification for contracts (e.g., drug packagers, drug distribution).
 - Team Organization Chart: Team structure, leadership and communications plan.
 - Description of ability of PI(s) to commit a significant effort to support the conduct and execution of the award.
 - The experience of all Key Personnel must be carefully documented and roles and responsibilities must be well-defined, including their experience in the conduct of multi-center clinical trials, collaboration, meeting milestones and timelines, and expertise in the content area of the proposed clinical trial.
 - Describe efforts to standardize and collaborate with other studies including utilization, as appropriate, of COVID-19 and RECOVER CDEs.
 - The application must ensure that a multidisciplinary team of appropriate personnel (clinical trialist(s), clinician(s), Project Manager(s), study coordinator(s), etc.) is proposed at the contributing institution(s) to facilitate the rapid implementation of all aspects of the clinical trial, including recruitment and follow-up of participants, and design/implementation of the trial protocol.
- Description of the protocol, including, but not limited to:
 - A detailed description and rationale for the research hypothesis(es), background, and pilot data, if available.

- Detailed description of the intervention with justification for its selection and including dosing and route of administration for drugs and exposure and parameters of utilization for devices. Provide safety profile as appropriate, availability of drug or device, and feasibility of implementation in various settings.
- For drug/device trials, provide a discussion of regulatory requirements and regulatory status and, if not already approved, what regulatory pathway will be sought, and details on how the drug/device will be obtained and any special considerations for distribution. Time to obtain should be incorporated into the timeline for trial start up.
- The rationale for the specific trial design chosen, including justification for why the proposed study population is the most appropriate group to answer the research question(s)
- Evidence supporting that: 1) equipoise exists between the arms of the trial and 2) the intervention(s) or control arm(s) tested are not known to be inferior to the range of practice (or usual care) in their community, and described in relevant standards of care.
- Inclusion and exclusion criteria, including criteria for identifying the chosen study population(s).
- Include information regarding the number and diversity of participants, trial design, and types of interventions studied.
- Comparator group(s), including rationale/evidence basis for selection.
- Primary and secondary endpoints selection, including analysis and justification.
- Justification for all assessments including clinical, laboratory, physiological, behavioral, patient-centered, or other outcomes addressing the primary and secondary research questions; a description of the use of patient reported outcomes as well as non-traditional data collection approaches (e.g., telephone, mobile devices, or web-based systems).
- A description and justification of the laboratory evaluations (as appropriate).
- Plans to implement and monitor Good Clinical Practices (GCP) and Good Laboratory Practices (GLP), as appropriate, should be provided.
- A discussion of major anticipated challenges in implementing and conducting the study and how they will be addressed.
- Monitoring plan, including safety mitigation and monitoring, and adverse event identification, monitoring and reporting.
- Statistical analysis plan, including:
 - A discussion of event rates.
 - Effect size estimate, including description of the evidence base used for the estimate.
 - Estimated needed sample size.
 - Contingency plans if the effect size or event rate is underestimated.
 - Planned approach to statistical analysis including interim futility analyses. The final statistical analysis plan will be developed collaboratively by the CT-DCC.
- Plans for recruitment and retention, including:
 - Recruitment and enrollment plan including an estimate of the number and type of enrolling sites needed to execute the protocol.
 - Plan for diverse enrollment, including evidence base for past success in enrolling diverse participants from populations underrepresented in biomedical research. Include information about experience in and strategic approaches for recruiting diverse research participants into clinical trials.
 - Plans for consent, including use of innovative approaches to consent (e.g., e-consent).
 - Participant follow-up procedures, including plans for data collection in compliance with NIH policies and requirements (<https://grants.nih.gov/policy/clinical-trials/reporting/index.htm>).

- Strategies to address potential participant co-enrollment in other trials and/or the observational cohort study.
- Statement of support for participation in Consortium working groups and compliance with RECOVER governance and policies
- Plans to leverage as applicable the RECOVER Mobile Health Platform and Electronic Health Record resources to implement trials as appropriate (e.g., patient recruitment, implementation of “low touch” trials, e-consent, remote data collection, patient engagement).
- Trial timeline: The plan should describe trial milestones. Each trial milestone should include objective completion criteria, showing each milestone in a Gantt chart-like format.
- Additional administrative information about the applicant and institution or organization (name, address, entity and Principal Investigator NIH Commons Registration information), including SAM information and DUN and Bradstreet number, human subject research assurance approvals as appropriate.
- Project Plan uploaded as searchable PDF format in a font size of 11 or 12 point and font type of Arial or Times New Roman. Margins must be 1-inch wide (top, bottom, left, and right). The project plan must not exceed 50 pages in length. Biosketches must not exceed 4 pages in length and are not counted in the page limit. Also excluded from the page limitation are cover sheets, letters from collaborators and consultants, and representation and certification documents.
- Resources and Environment: Resources available to the project and environment in which the activities will be performed.
- The Awardee must obtain Federal Wide Assurance (FWA) from the DHHS Office for Human Research Protections (OHRP) (<https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/fwas/fwa-protection-of-human-subject/index.html>), and comply with 45 CFR 46 (<https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html>), and, as applicable, any relevant FDA regulations (e.g., 21 CFR 11, 50, 54, 56, 312, and 812) (<https://www.fda.gov/medical-devices/medical-device-databases/code-federal-regulations-title-21-food-and-drugs>) governing the protection of human subjects and the conduct, management, and oversight of clinical trials. The Awardee will need to provide to the Administrative Officer evidence of an active FWA prior to the commencement of any human subject research activities contemplated under this Agreement. Further, Awardee must comply with all applicable laws and regulations relating to the privacy and confidentiality of human subjects.
- References

Eligibility

The following entities are eligible to receive an award under this ROA:

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

Nonprofits Other Than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Foreign Institutions

- Non-domestic (non-U.S.) Entities (Foreign Institutions) are not eligible to apply

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- Non-domestic (non-U.S.) components of U.S. Organizations are eligible to apply
- Foreign components, as defined in the NIH Grants Policy Statement, are allowed

Budget

The Budget section of the application must provide a realistic, fully justified budget and cost proposal for performing the work over a specified period of performance needed to accomplish project objectives. Budget should reflect the proposed total costs, accounting for cost share amounts offered by the applicant. (If proposing F&A, include a negotiated federal rate approval.) It is recommended to use the R&R form but not required.

Provide the overall expected cost for each of the following categories:

- Personnel (Study Chair, Co-Investigators, Project Manager)
- Proposed patient capitation
- Patient compensation costs
- Patient engagement costs
- Site start-up costs
- Case report form design
- Informed consent development
- Drug costs including labeling, packaging, and distribution if applicable
- Device costs including distribution, if applicable
- Equipment
- Subawards/subcontracts/consultants
- Other direct costs
- Total cost (with indirect costs included)
- Proposed Cost Share contribution if applicable

Award Criteria and Selection Information

Awardees will be selected by NIH through an objective review process. The number and size of awards have not been predetermined and will depend on the range of proposed functions, the quality of the applications received, and availability of funds. Given the urgency of finding safe and effective treatment and preventive strategies for PASC, it is imperative that trials be designed to provide robust evidence in as rapid a timeframe as possible. Awards will be negotiated with eligible entities whose proposals are determined to be the most meritorious and provide the best value to the NIH toward achieving the goals of the RECOVER Initiative and in accordance with the NIH priorities.

The 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 proposals 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 proposals of two or more applicant entities as part of a reorganized, consolidated consortium operating under an article of collaboration, teaming arrangement, or other means acceptable to the NIH;
- Fund applicants as sub-awardees of a separate Data Coordinating Center entity to be named by the NIH;

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- Request additional documentation (certifications, etc.); and
- Remove applicants from award consideration should the parties fail to reach a finalized, fully executed agreement, or the applicant fails to provide requested additional information in the timeframe indicated.

Applications will be assessed using the following criteria:

Investigator Team Expertise and Experience,

- Have the investigators demonstrated an ongoing record of accomplishments that have advanced their field(s)?
- Do the investigators demonstrate significant experience with coordinating collaborative research? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise and skills relevant to the conditions that make up the Post-Acute Sequelae of COVID-19 infection, including what is termed “Long Covid”? Are their leadership approach, governance, plans for conflict resolution, and organizational structure appropriate for the trial proposed? Does the applicant have experience overseeing selection and management of subawards, if needed?
- Do the PDs/PIs and key personnel have the experience and capability in clinical trials, regulatory support and trial design? Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project?
- Is the organizational structure appropriate?
- With regard to the proposed leadership for the project, do the PD/PI(s) and key personnel have the expertise, experience, and ability to organize, manage and implement the proposed clinical trial and meet milestones and timelines?
- Does the applicant demonstrate experience enrolling different populations (e.g., adults (including pregnant individuals); testing pharmacologic and non-pharmacologic interventions?
- Is there diversity among the investigator team?
- Is there evidence of patients and caregivers engagement in the protocol development and a plan for on-going input?
- How well-defined are the roles and responsibilities of the leadership?
- How strong is the project management expertise represented among the key personnel?
- How adequate are the descriptions of roles/responsibilities of the Project Manager(s) and other key personnel?
- Does the proposed PI(s) indicate ability to commit a significant effort to support the conduct and execution of the award?

Approach

- Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project?
- Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?
- Are potential problems, alternative strategies, and benchmarks for success presented?
- Are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, age, and ethnicity justified in terms of the scientific goals and research strategy proposed?
- Is the study design justified and appropriate to address primary and secondary

outcomes/variables/endpoints that will be clear, informative and relevant to the hypothesis being tested?

- Is the scientific rationale/premise of the study based on available research?
- Given the methods used to assign participants and deliver interventions, is the study design adequately powered to answer the research question(s), test the proposed hypothesis/hypotheses, and provide interpretable results?
- Is the trial appropriately designed to conduct the research efficiently?
- Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?
- Are potential ethical issues adequately addressed? Is the process for obtaining informed consent or assent appropriate?
- Is the eligible population available? Are the plans for recruitment outreach, enrollment, retention, handling dropouts, missed visits, and losses to follow-up appropriate to ensure robust data collection? Are the planned recruitment timelines feasible and is the plan to monitor accrual adequate?
- Does the applicant show engagement of relevant stakeholders in affected communities and their providers in study design, implementation, and analysis and present a plan for on-going input?
- Has the need for randomization (or not), masking (if appropriate), controls, and inclusion/exclusion criteria been addressed? Are differences addressed, if applicable, in the intervention effect due to sex/gender, age, and race/ethnicity?
- Are the applicants' plans to standardize, assure quality of, and monitor adherence to, the trial protocol and data collection in collaboration with the CT-DCC appropriate?
- Is there a plan to obtain required study agent(s)?
- Are the endpoints clearly defined and how appropriately is the intervention characterized?
- Are adverse events appropriately captured and monitored?
- How strong is the discussion of event rates and are these realistic?
- Does the application propose to use existing available resources, as applicable?
- Does the application adequately address Good Clinical Practices (GCP) and Good Laboratory Practices (GLP), if applicable?

Additional Criteria

- How strong is the description of risk assessment and risk management procedures?
- How well are contingencies addressed, including, if applicable, contracts and sub-contracts processing?
- How strong are the strategies proposed to address potential implications of participant co-enrollment in the RECOVER observational cohort study and other clinical trials?
- Are the institutional support, equipment and other physical resources available to the investigators adequate for the trial proposed?
- Will the results of the study have potential applicability to clinical practice?

Submission and Contact Information

For best consideration, applications should be emailed by **May 19, 2022** to NHLBI_OT@mail.nih.gov by an authorized business official of your institution. Financial, administrative, and technical programmatic questions should be addressed to the OT inbox (above). Please reference **OTA-21-015H** in the title of your inquiry.

A technical assistance webinar is tentatively scheduled for May 6th, 2022. Additional information

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and a registration link will be posted on the NIH RECOVER website
(<https://recovercovid.org/funding>)