# Notice of Intent to Publish Research Opportunity Announcements (OTA-21-015) for the Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative

**Purpose**

This Notice is to alert the community that NIH plans to publish Research Opportunity Announcements (ROAs) as part of the Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) initiative. The solicited research will improve understanding of and develop strategies to prevent and treat post-acute manifestations of SARS-CoV-2 infection across the lifespan. The initial ROAs are expected to be published by mid-February 2021. Projects will be funded utilizing NIH's Other Transaction Authority (OTA), which offers flexibility and the ability to engage partners in collaborative innovation and problem solving. Initial awards are anticipated to be made in early March 2021.

This Notice is being provided for informational purposes to allow potential applicants additional time to develop responsive applications. NIH reserves the right to modify the scope and objectives as described in this Notice. Final scope, objectives, and requirements will be set forth in the published ROAs.

**Background**

Some COVID-19 survivors report experiencing symptoms beyond the usual recovery time from the infection. 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. Reported symptoms range from mild to incapacitating and can persist for months following acute disease. These symptoms and findings (i.e., post-acute sequelae) are reported in different organs and systems and can adversely affect overall quality of life. The magnitude of the public health impact of these sequelae is currently unknown but potentially profound, given the numbers of individuals across the age spectrum who have been and will be infected with SARS-CoV-2, the virus that causes COVID-19. It is a public health priority to understand and develop strategies to prevent and treat PASC.

**Research Initiative Details**

The goal of the PASC Initiative is to systematically advance our understanding of the recovery process after SARS-CoV-2 infection and to prevent and treat PASC. Toward these ends, the overall PASC Initiative is designed to address three fundamental scientific questions:

- What is the biologic basis of the heterogeneity in recovery from SARS-CoV-2 infection?
- For those patients who do not fully recover or develop new symptoms/sequelae, what is the incidence/prevalence, clinical spectrum, and underlying biology?
- What interventions might improve recovery after SARS-CoV-2 infection and prevent long-term disability due to PASC?

In implementing the PASC initiative, NIH will solicit research proposals to understand recovery after SARS-CoV-2 infection and PASC. The PASC initiative will leverage a variety of platforms, including large and long-standing longitudinal studies; large-scale EHR/health systems-based cohort studies; COVID-19 clinical trials/networks; and COVID-19 registries, observational and clinical studies. These will be augmented by utilization of mobile and digital health strategies for patient recruitment, data collection, and follow-up. Applicants will be encouraged to leverage multidisciplinary teams to generate the critical data necessary to rapidly enhance understanding of PASC, including its epidemiology, risk factors for illness severity and outcomes, natural history, and pathophysiology.

Exploratory clinical trials testing strategies to treat symptoms and prevent progression of SARS-CoV-2 infection to PASC are also an important part of this initiative and will be the subject of subsequent solicitations.

Together, these activities will constitute a rigorous and comprehensive research program on PASC across the spectrum of COVID-19 clinical presentation, across diverse populations, and throughout the lifespan, leading to findings and innovative treatment and preventive strategies that are applicable to all who are affected, including populations that bear a disproportionate burden of SARS-CoV-2 infection. NIH intends for projects funded under this program to be part of a coordinated Consortium that will collectively pursue the goal of understanding, treating, and preventing PASC by collaboratively developing common protocol elements; adopting common data elements; and sharing data, biospecimens, and knowledge within the Consortium and with the broader research community.

Toward these ends, NIH plans initially to publish three ROAs to solicit applications for:

**ROA #1**
**Clinical Research Studies** targeting three domains: (a) Clinical Case-Based Recovery Meta-Cohort, (b) Autopsy Studies, and (c) EHR-/Health Systems-Based Analyses. Applications for this ROA may encompass one or more of these three domains.

a. **Clinical Case-Based Recovery Meta-Cohort**
At the heart of the PASC Initiative is the SARS-CoV-2 Recovery Cohort, a collaborative meta-cohort that will leverage ongoing fit-for-purpose cohorts as well as new cohorts to facilitate the rapid launch of multi-disciplinary observational and mechanistic research on the incidence, risk factors, and mechanisms involved in PASC morbidity. This meta-cohort will bring together clinical cohorts of research participants across the lifespan with a history of SARS-CoV-2 infection, COVID-19, and/or PASC across the lifespan, of two main types:
    i. *Acute*. Cohort studies with well-characterized pre-infection and/or acute infection baseline data and established plans for continued follow-up from the acute infection to understand the natural history and underlying biology of the heterogeneous recovery after SARS-CoV-2 infection.
    ii. *Post-acute.* Cohort studies of the post-acute phase enrolling participants with SARS-CoV-2 infection, COVID-19, or PASC with appropriate comparison participants and conducting intensive investigation of relevant organ injury and other system dysfunction and continued longitudinal follow-up of health outcomes.

The studies funded will constitute a meta-cohort encompassing inclusive participation reflective of appropriate diversity and enrolling adults and children. For the purposes of studies of adults, NIH anticipates assembling from across all the contributing cohorts a total of at least 20,000 cases of SARS-CoV-2 infection/COVID-19 cases and at least 1,000 PASC cases. For the purposes of studies of children, we anticipate assembling from across the contributing cohorts a total of at least 10,000 cases of SARS-CoV-2 infection/COVID-19 cases and at least 500 PASC cases. Preference may be given to applicants capable of studying large numbers of cases and appropriate comparison participants; this will be further detailed in the ROA. Applicants proposing smaller samples will be expected to provide strong justification for their approach based on

other considerations, e.g., special population characteristics or deep pre-infection phenotyping, special investigations of specific organ dysfunction, etc.

b. **Autopsy Studies**: The goal of this effort is to provide in-depth histopathologic analysis of a broad range of organs and tissues in order to identify injury due to SARS-CoV-2 infection and/or its sequelae that lead to or contribute to PASC. Investigators will be expected to submit tissues to a biobank for distribution across the Consortium and more broadly with the research community.

c. **EHR-/Health Systems-Based Studies:** The goal of this effort is to advance the understanding and management of the post-acute effects of COVID-19 across the lifespan by: making innovative use of real world data such as electronic health records, health systems data, and other large data sets; by further expanding capabilities of existing data resources; leveraging health-systems based protocols to inform PASC clinical characterization through patient survey-based symptom reporting; and by working in an integrated fashion with other components of the coordinated NIH response to address PASC.

**ROA #2**

**Clinical Science Core,** for which applicants will be expected to:

- Foster collaboration across the Consortium; coordinate and provide logistical support (scheduling, meetings, communication platforms) for the PASC investigator consortium and all relevant working groups/committees, including platforms to solicit and incorporate patient viewpoints; facilitate use of toolkits of common data elements, surveys/questionnaires, and mobile health tools; incorporate use of various consent processes (e.g., e-consent) as applicable; interface with IRBs; and support the literature review in PASC.
- Provide expertise and statistical input on clinical study design, implementation, execution, and monitoring, including advising and coordinating the development and implementation of protocols/sub-study protocols; develop manual of procedures, case report forms, identification and selection of surveys and questionnaires, and recruitment strategies to promote inclusive participation; assure delivery of high-quality data, including mobile data, to the Data Resource Core; and develop monitoring procedures for study performance and safety.
- Support and provide expertise in clinical research study data management, data quality control, study monitoring, statistical analyses, sample size calculations, data reports for oversight and monitoring boards and regulatory entities, analysis expertise and support for phenotyping in adults and children, including the acute and post-acute manifestations, at a clinical and biological level.
- Provide framework/infrastructure and statistical expertise for results analysis, interpretation and dissemination, and development of final phenotype characterization and diagnostic algorithms.
- Coordinate receipt of the collection, analysis, deposition, and central management of patient biospecimens, transfer to the PASC biorepository (to be identified by NIH at a later date), and linkage of these biospecimens to clinical data in order to provide critical tools and resources for future PASC research.

**ROA #3**
**Data Resource Core,** for which applicants will be expected to:

- Facilitate the standardized collection of clinical data (i.e., usage of common data elements) and data harmonization, assist research projects with linking these data with other data, including but not limited to: publicly available sources (e.g., Census data, Area Deprivation Index, etc.), electronic health records (EHR) and others as needed, as well as perform quality control, data curation, and analyses, and provide data informatics tools.
- Maximize the value of the collective data sets and enable interoperability with other NIH COVID-19 research resources by supporting studies with a cloud-based data "workbench;" promoting adoption of common data elements and harmonized definitions of key variables; and facilitating seamless integration into existing large-scale well-curated genotypic and phenotypic data sets.
- Create a data coordination and analytics framework to compile and link data from extant clinical studies/networks, biosamples, imaging, EHR and related records data, mobile health data and other non-traditional data sources; and provide access to datasets for analysis by the research community.

Additional ROAs may be issued in the future as needed.

Researchers planning to apply are strongly encouraged to read all three of these interrelated research opportunities when they are published.

Inquiries

Please direct all inquiries to: NHLBI_OTA@mail.nih.gov