Research Opportunity Announcement
OTA-21-015B
Post-Acute Sequelae of SARS-CoV-2 Infection Initiative:
SARS-CoV-2 Recovery Cohort Studies

The NIH is soliciting applications in support of the goals of the Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative and Investigator Consortium. This Research Opportunity Announcement (ROA) OTA-21-015B focuses on three research study areas: Clinical Recovery Cohort Studies, Autopsy Cohort Studies, and EHR- and Other Real-World Data-based Studies. Applicants may apply for one, two, or all three of these components as described in this ROA.

The NIH is also soliciting applications under a companion ROA OTA-21-015A that focuses on the Clinical Science Core, the Data Resource Core, and the PASC Biorepository Core.

Introduction

Recovery from SARS-CoV-2 infection is extremely variable with many recovering quickly while for other patients 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. It is a public health priority that we better understand and develop strategies to prevent and treat the post-acute sequelae of SARS-CoV-2 infection (PASC) and that these strategies enable rapid innovation, evolution, and adaptation as more is learned about PASC and its potential impact on public health.

TABLE OF CONTENTS
(hyperlinked)

The goal of the trans-NIH PASC Initiative is to rapidly improve understanding of recovery after SARS-CoV-2 infection and to prevent and treat PASC. Toward these ends, the Initiative is designed to address these fundamental scientific questions:

- What are the clinical spectrum of and biology underlying recovery from acute SARS-CoV-2 infection over time?
- For those patients who do not fully recover, what is the incidence/prevalence, natural history, clinical spectrum, and underlying biology of this condition? Are there distinct phenotypes of patients who have prolonged symptoms or other sequelae?
- Does SARS-CoV-2 infection initiate or promote the pathogenesis of conditions or findings that evolve over time to cause organ dysfunction or increase the risk of developing other disorders?

The Initiative is designed to be a collaborative and inclusive approach for rapidly advancing our

understanding of the recovery process and the epidemiology (including incidence/prevalence) and natural history (including duration) of PASC. Studies conducted will characterize: the clinical spectrum of recovery from SARS-CoV-2 infection, including the subset of patients who have symptoms of disease beyond the standard course; the individual, clinical, and contextual factors that contribute to the duration, types of symptoms, and severity of disease; phenotypes of patients who have prolonged symptoms or other sequelae; the impact of treatments for acute COVID-19 or for post-acute symptoms on the duration and severity of symptoms; and factors that impact the outcomes in patients infected by SARS-CoV-2.

At the heart of the Initiative is the rapid launch of the SARS-CoV-2 Recovery Cohort and SARS-CoV-2 Recovery Cohort Investigator Consortium.

The **SARS-CoV-2 Recovery Cohort** is a collaborative meta-cohort that will leverage ongoing fit-for-purpose cohorts as well as new cohort studies to chart the process of recovery in diverse adult and pediatric populations. This will include cohort studies of patients acutely infected with SARS-CoV-2 (acute cohort), as well as cohorts of persons suffering from post-acute symptoms (post-acute cohort), along with appropriate control participants. The PASC initiative will emphasize inclusive participation and leverage a variety of clinical platforms, including large-scale EHR/health systems-based cohort studies; large and long-standing longitudinal studies; COVID-19 clinical trials/networks; and COVID-19 clinics, registries, and observational studies. These will be augmented by utilization of mobile and digital health strategies for participant recruitment, data collection, and follow-up. These SARS-CoV-2 Recovery Cohort studies will characterize PASC symptoms and findings and their trajectory over time and across the lifespan. They will include investigator-initiated studies taking a variety of approaches to probe for evidence of tissue injury or organ system dysfunction or other conditions (e.g., immunologic, pulmonary, cardiac, neurologic, metabolic, and mental health). Some may focus on special populations including children, the elderly, new mothers, immunosuppressed patients, or those with relevant comorbidities. Diversity in study populations will be necessary to generalize findings to the U.S. population affected by SARS-CoV-2 infection; toward this end, the PASC initiative investigators are encouraged to collaborate where feasible with other relevant NIH initiatives (e.g., Rapid Acceleration of Diagnostics-Underserved Populations (RADx-UP), and Community Engagement Alliance Against COVID-19 Disparities (CEAL)).

Given the heterogeneity of symptoms and findings involving multiple tissues and systems, understanding PASC will require a multidisciplinary approach. Toward this end, all study investigators under this initiative will work together in a **SARS-CoV-2 Recovery Cohort Investigator Consortium** with the goal of immediately launching a multi-disciplinary collaboration to conduct rapid systematic screening and follow-up evaluations of SARS-CoV-2 infected individuals, to provide a resource for in-depth multi-disciplinary phenotyping, and to pool data and share biospecimens and data from across studies. After award, Consortium investigators will be convened to rapidly develop a streamlined set of common core protocol elements (specific hypotheses, design elements, screening evaluations, exams, lab tests, functional assessments, imaging, etc.) and to provide a collaborative for multi-disciplinary phenotyping. Consortium investigators may also propose site- or study-specific hypotheses that, due to specific expertise or technology constraints, may only be possible in subsets of the collaborative as sub-studies or ancillary studies. Successful applicants will be expected to participate in collaborative protocol development and implementation.

Importantly, the Initiative also will leverage **EHR- and other Real-World Data-based Approaches** to provide data and information on the incidence/prevalence of post-acute sequelae, PASC symptoms, imaging and lab test results to inform the definition of PASC; describe patient demographics; identify co-comorbidities; define health care utilization patterns; provide real world data for comparative effectiveness studies, as well as reducing time and scope of potential clinical trial design and implementation; and inform PASC clinical characterization through health systems-based patient surveys.

(See https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence for a description of real-world data.)

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

Also, critically important to understanding the pathology associated with PASC will be **Autopsy Cohort Studies** that will include in-depth histopathologic analysis of brain and other organs and tissues to identify tissue injury due to SARS-CoV-2 infection and/or its sequelae that lead or contribute to PASC.

Under this Initiative, all study investigators agree to appropriately share data and biospecimens and to consent participants for sharing and general research use of data, other medical information, and biospecimens.

Importantly, the goals of these clinical cohorts, autopsy studies, and EHR- and other Real World Data-based activities will be supported by three cores:

- A **Clinical Science Core** that will coordinate the investigator consortium; facilitate clinical protocol development, implementation, monitoring, and data analysis; foster the use of common data elements across groups; oversee collection and quality control of data and biospecimens; coordinate biospecimen management; promote multi-disciplinary collaboration; and foster community engagement.
- A **Data Resource Core** that will coordinate PASC data management, harmonization, integration, and sharing, and provide analytical tools and statistical support to the Clinical Science Core.
- A **PASC Biorepository Core** that will receive, manage, and make available a diverse range of biospecimens derived from PASC Consortium studies.

In addition, central coordination and oversight will be provided by an Administrative Coordinating Center.

Consortium investigators will be expected to develop, implement, and participate in a collaborative governance structure that includes community representatives and affected persons.

This initiative supports NIH's longstanding commitment to making the results and outputs of NIH-funded research available to the public through effective and efficient FAIR data sharing practices. Consortium investigators will make research data, and biospecimens available through the Clinical Science Core, Biorepository Core, and Data Resource Core at agreed upon milestones and upon completion of their study. Researchers will agree not to distribute controlled-access datasets and will acknowledge use of PASC datasets through citations in manuscripts and presentations.

This ROA focuses on the three research study areas:

- Clinical Recovery Cohort Studies;
- Autopsy-based Studies; and
- EHR-/Other Real-World Data-based Studies.

Of note, applicants are welcome to apply for one or more of the three major research components described below.

The Clinical Science Core, Data Resource Core, and Biorepository Core are the subjects of a separate but related ROA that can be found at the following link: OTA-21-015A. Applicants are strongly encouraged to review in detail this related ROA and to be familiar with its contents. Additional ROAs may be issued in the

future as needed.

Clinical Recovery Cohort Studies

There is a critical need to systematically examine the characteristics of individuals who do and do not develop post-acute sequelae of SARS-CoV-2 infection. Such research can identify risk factors, inform strategies for prevention, suggest prognostic and predictive biomarkers of adverse long-term outcomes, and illuminate pathophysiologic mechanisms that may be exploited with novel therapies. There is also a critical need to characterize the epidemiology, natural history, and clinical spectrum of post-acute sequelae of SARS-CoV-2 infection. In addition, how infection and subsequent recovery from SARS-CoV-2 infection or the impact of mitigation strategies influence risk of developing new or worsening chronic diseases and disorders, remains largely unknown.

Epidemiologic research requires appropriate sampling of the population and detailed characterization of participants according to a defined protocol. Mechanistic research also requires thoughtful consideration of patient selection for deep phenotyping studies into a subset of potentially affected organ systems. This type of sampling and data collection framework are challenging in the context of a public health emergency. In this unique context, existing clinical- or population-based cohorts or an assembled consortium of cohorts developed for other purposes might be repurposed usefully for recovery research and leveraged to provide invaluable resources in order to understand the pathophysiology and long-term complications of SARS-CoV-2 infection.

This ROA will support two types of clinical research efforts to rapidly leverage new and existing infrastructure, processes, data, and biospecimens from longitudinal studies of: a) individuals newly infected with SARS-CoV-2 to understand the heterogeneity in recovery processes and b) individuals previously infected with SARS-CoV-2 with either new or persistent symptoms and appropriate controls to understand the basis and natural history of these conditions. These studies will be combined to establish a Clinical Recovery Cohort of clinical cases of SARS-CoV-2 infection and PASC to rapidly launch assessments of the long-term outcomes among diverse populations across the lifespan.

Understanding the heterogeneity in recovery after SARS-CoV-2 infection

There are a variety of post-acute sequelae of SARS-CoV-2 infection that have been reported and perhaps others yet to be discovered. SARS-CoV-2 infection is known to affect a diversity or organ systems with a pattern of tissue injury that remains evolving. Longitudinal studies of persons infected with SARS-CoV2 that focus on the process by which post-infection recovery occurs is envisioned to lead to insights into factors associated with slow recovery and/or the development of persistent disability as well as the epidemiology, natural history, and clinical spectrum of post-acute sequelae of SARS-CoV-2 infection. In addition, such studies performed now could potentially lead to interventions that will enhance recovery or prevent permanent organ dysfunction/injury in the future. Studies that begin proximate to the acute infection and follow a cohort of patients over time might for instance collect data from the patients' acute infection including symptoms, severity, and duration of illness, viral dynamics, immunologic assessments, measures of organ dysfunction, past medical history, drug treatments, level of required medical care, laboratory and imaging abnormalities, genetic factors, environmental factors, etc. that may be associated with the nature of the recovery. Studies of recovery after acute infection should include a variety of investigator-initiated plans that concentrate on longitudinal change in symptoms and quality of life, psychological response to illness, as well as the immune response to the virus, viral dynamics, identification and characterization of specific types of organ injury and metabolic dysfunction. This may include a robust analysis of pre-infection determinants of risk for adverse outcomes across groups defined by age, sex/gender, race/ethnicity, and comorbid conditions.

It will be critical, that when combined, the studies initiated in this area of research address recovery in infected persons with different severity levels of the acute illness; ranging from those without symptoms, those treated as outpatients, those requiring hospitalization, and those requiring critical care. It should also reflect the demographics of the US population affected by the pandemic. Because the incidence of PASC is unknown, applicants proposing to study the heterogeneity of recovery will need to demonstrate that they can assemble and follow a sufficiently large number of participants with acute or subacute SARS-CoV-2 infection to accrue an adequate number of PASC cases to compare with those who recover more quickly. In addition, the NIH intends to fund a representative population focused on specific recovery issues among children, adolescents, and adults, including pregnant women and their offspring.

Understanding the biologic basis and burden of illness due to the post-acute sequelae of SARS-CoV-2
PASC cases are required in order to identify and characterize a comprehensive set of different symptom complexes in affected individuals and their effect on quality of life. Participants are to be followed over time to understand the natural history, clinical spectrum, and pathophysiology of PASC and its effect on well-being. In addition, such studies are encouraged to develop an algorithmic approach that will identify a pre-specified subset of participants for deep phenotyping studies that will characterize abnormalities in specific organ systems. These might include detailed investigator-initiated studies with appropriate comparison participants to explore one or more important scientific hypotheses relevant to PASC in areas such as: cardiac or pulmonary structure and function, autonomic and pain systems, immunologic responses, mental health, sleep disorders, microbiome and gastrointestinal system, metabolism, metabolic disorders, cognitive function, tolerance to physical and mental activity, etc.

Studies will be selected so that the research program as a whole provides a comprehensive assessment of the pathophysiology in PASC based on severity at presentation with SARS-CoV-2 infection or COVID-19 (i.e., those who required hospitalization, critical care, or management as outpatients). As noted above, NIH intends to fund a representative meta-cohort focused on specific recovery issues among children, adolescents, and adults, including pregnant women and their offspring. No single cohort will likely have sufficient size and diversity to address the goals of the initiative. As a consequence, this meta-cohort will prioritize studies that can be readily combined to produce a comprehensive characterization of PASC in the U.S., and include a broad spectrum of detailed studies that cover those organ systems likely to contribute to continued burden of illness due to PASC. Priority will be given to proposals with access to representative populations with relatively broad inclusion criteria that reduce the potential for selection bias, to cohorts with deep phenotyping conducted prior to the pandemic, and to cohorts with detailed data of the acute infection. All studies should be capable of continued longitudinal follow-up for long-term outcomes.

Several issues should be addressed when describing the proposed approach to defining the clinical spectrum of recovery following SARS-CoV-2 infection. First, there is significant uncertainty regarding the spectrum of adverse recovery patterns. The pre-disposing factors, temporal pattern of development, characteristic symptoms, signs, biological manifestations, and etiology are not yet sufficiently well known to enable a narrow and highly specific approach to data collection required to define the PASC condition. The PASC population may represent a heterogenous group of patients experiencing symptoms related to different biological mechanisms representing different sub-phenotypes of PASC. Hence, the scope of data collection relevant to phenotype and sub-phenotype definition and characterization should be described.

Second, based on current literature and clinician input, there appear to be partially overlapping groups of patients who present with a range symptoms suggestive of and evaluated for PASC including but not limited to individuals who are no longer having ongoing biological responses to the infection, and

have chronic complications, e.g., destruction of lung tissue, that results in long term symptoms, functional impairment, and morbidity; individuals with behavioral health challenges caused or worsened by their experience with the pandemic (e.g., social isolation, job loss, bereavement), whether they were diagnosed with acute SARS-CoV-2 infection or not; and individuals with a condition potentially related to an ongoing biological response to the virus. Hence, the approach to characterizing and distinguishing these overlapping groups should be described, insofar as practical.

Third, data availability and data collection/acquisition processes will differ across different types of studies, including, for example, studies with data extracted from electronic health records, studies with data collected in research clinic settings, and studies with data collected in community settings via innovative technology (e.g., mobile app). Hence, the definition of PASC and other variables and the approach to utilization of Common Data Elements (CDEs) should be described as appropriate to the proposed design.

Goals and Specific Objectives

The goal of this ROA is to leverage the new and existing infrastructure, processes, and data from available cohorts or disease populations to rapidly carry out observational and mechanistic research on the incidence, risk factors, and biologic abnormalities involved in PASC morbidity. The program is intended to establish a Clinical Recovery Cohort to capture data and to collect and analyze biospecimens (as appropriate) to identify factors that are associated with the development of PASC and other adverse long-term consequences of SARS-CoV-2 infection. The intent is to use common protocols, data elements, and biospecimen collection methods when possible and implement rapid sharing of data and biospecimens, including deposition of data and biospecimens into an NIH-approved repository (a PASC Biorepository Core) to facilitate access and analysis by study and non-study investigators. The core protocol should include the collection of data on comorbidities as well as measures that would reflect the involvement of various biological and organ systems in the development of PASC. The protocol should also demonstrate the flexibility to add new measures as scientific findings dictate and to support collaborations with outside investigators. This ROA is not intended to replace traditional NIH research funding mechanisms (e.g., R01, P01, U01).

Examples of research areas of interest include, but are not limited to:

- Estimation of the incidence of PASC, including potential sub-phenotypes, and other adverse long-term consequences of SARS-CoV-2 infection overall, by population sociodemographic characteristics, and according to pre-existing comorbidities.
- Identification of the presence of disparities in PASC, including potential sub-phenotypes, and other long-term consequences, including multilevel factors that may be responsible for these differences across populations.
- Multivariable analyses of factors suspected in PASC (including potential sub-phenotypes) occurrence, timing of onset, severity, recovery, trajectory, and its complications across the lifespan. Ideally, many of these factors should have been collected prior to infection or come from new assays of stored biospecimens. Examples of data include, but are not limited to, sociodemographic information, symptoms over time, health behaviors, psychosocial characteristics, sleep health, geospatial data, mobile sensor data, clinical characteristics, presence of metabolic abnormalities or clinical or subclinical disease, concomitant treatments including complementary health approaches, genomic or other sequence data, inflammatory factors, markers of immune function, imaging data, and other biomarkers.
- Assessment of the added value of sophisticated prediction models incorporating a wide variety of participant characteristics compared to more simplified models with basic demographic and clinical parameters.

- Determine whether the initial presentation and severity (asymptomatic, mild symptoms, hospitalization, ICU admission) of COVID-19 or a positive serologic or direct antigen test is associated with severity, pattern, timing of onset, metabolic dysfunction, or other characteristics of PASC, including potential sub-phenotypes, or other long-term consequences.
- Analyses to evaluate the association of concomitant treatments, including vaccinations, medications, and complementary health approaches for pre-existing chronic conditions and acute SARS-CoV-2 infection, on the development, severity, and characteristics of PASC and other long-term consequences.
- Detection of sub-clinical or occult abnormalities that may later manifest as or aggravate disease. This may involve comparison of deep phenotypic data (e.g., imaging studies) to equivalent measures obtained in the same participants prior to their infection with SARS-CoV-2.

Preferred and Minimum Applicant Capabilities

The NIH is soliciting applications from groups who seek to contribute to a large, collaborative Clinical Recovery Cohort from multiple existing cohorts and implement a core data-collection protocol to rapidly improve our understanding of and ability to diagnose, treat, and prevent PASC among diverse populations. Across the collaborative, NIH intends to assemble a population that encompasses the life span, including children (including MIS-C), adolescents, and adults, including pregnant women and their offspring.

Competitive applicant(s) will be able to demonstrate the following capabilities:

- Plans to propose and pursue high priority research hypotheses that could be addressed in the core protocol or ancillary studies. These plans should include hypotheses that would be investigated across the collaborative as part of the core protocol and could include site- or study-specific hypotheses, that may require specific expertise or technologies and can be addressed in subsets of the collaborative as sub-studies or ancillary studies. All successful applicants will be expected to participate in collaborative protocol development and implementation.
- A strong track record of managing and conducting collaborative multi-center clinical or observational research and proposed strategies for assuring effective collaborative program governance.
- Strategies for community and affected patient population engagement in initiative governance, design, and execution.
- A strong track record of patient or participant recruitment, follow-up, and retention, including strategies to ensure inclusion of appropriate and diverse patient or participant populations to enhance generalizability of research findings.
- Expertise in epidemiology, observational, and mechanistic clinical study design and conduct, including relevant phenotyping of human disease
- Expertise in health equity, underserved and marginalized populations, and social determinants of health will be seen as a strong positive feature
- Experience in using information technology (e.g., electronic health records systems, mobile devices) to identify and follow participants
- Capacity of the investigators and associated consortia of cohorts for enrollment and evaluation of adequate numbers of patients/participants with PASC.
- Identification of large numbers of cases to facilitate inferences from multivariable and stratified statistical models.
    - For the purposes of studies of adults, it may be necessary to assemble across the participating studies at least 20,000 cases of SARS-CoV-2 infection or COVID-19 or at

least 1,000 PASC cases; hence, preference may be given to applicants capable of contributing at least 1,000 cases of SARS-CoV-2 infection or COVID-19 or at least 200 PASC cases. An application may include a consortium of institutions or studies to achieve the numbers of cases needed. A suitable number of appropriate comparison participants should be included. Applicants proposing smaller samples should provide strong justification for their approach based on other considerations, e.g., special population characteristics, deep pre-infection phenotyping.

- For the purposes of studies of children, it may be necessary to assemble across the participating studies at least 20,000 cases of SARS-CoV-2 infection or COVID-19 or at least 500 PASC cases; hence, preference may be given to individual applicants capable of contributing at least 250 cases of SARS-CoV-2 infection or COVID-19 or at least 50 PASC cases in children. An application may include a consortium of institutions or studies to achieve the numbers of cases needed. A suitable number of appropriate comparison participants should be included. Smaller numbers of participants may be appropriate if a case-control study approach is proposed. Applicants proposing smaller samples should provide strong justification for their approach based on other considerations, e.g., special population characteristics, deep pre-infection phenotyping.

- Identification of suitable comparison participants who could include persons infected with SARS-CoV-2 who had a favorable recovery trajectory or persons who did not have SARS-CoV-2 infection or COVID-19. It is expected that comparison participants will be contemporary and will undergo the same procedures as cases insofar as appropriate.
- Established plans for data and biospecimens collection, including plans for data standardization and harmonization that include creation or utilization of COVID-19 and other appropriate CDEs, plans for rapid sharing of data and biospecimens for access and analysis by studyand non-study investigators including deposition of data and biospecimens into an NIH approved repository.

Applicants should address the minimum required elements to be eligible for participating in the Clinical Recovery Cohort program include:

- A rapidly accessible population of patients with SARS-CoV-2 infection, COVID-19 and/or PASC with appropriate comparison participants with the capacity to obtain continued longitudinal follow-up of health outcomes, or
- An ongoing cohort study or consortium of cohort studies with well characterized pre-infection baseline data and established plans for continued follow-up to identify SARS-CoV-2 infection or COVID-19 cases or PASC cases with appropriate comparison participants.
- To maximize comparisons across datasets or studies, ensure high quality biospecimens, and facilitate data integration and collaboration, researchers funded through this ROA are strongly encouraged to use the following standards and resources (where applicable):
    - Applicants are encouraged to conform to Findable, Accessible, Interoperable, and Reusable (FAIR) principles.
    - NIH encourages researchers to explore the use of the HL7 FHIR® (Fast Healthcare Interoperability Resources) standard to capture, integrate, and exchange clinical data for research purposes and to enhance capabilities to share research data (NOT-OD-19-122). The FHIR® standard may be particularly useful in facilitating the flow of data with EHR-based datasets, tools, and applications. NIH also encourages relevant studies to explore the use of HL7 FHIR Mobile Health Application Data Exchange Assessment Framework and Functional Requirements Implementation Guide9 (mHealth ADE FHIR IG).
    - NIH encourages clinical research programs and researchers to adopt and use the

standardized set of data classes, data elements, and associated vocabulary standards specified in the United States Core Data for Interoperability (USCDI) standards (NOT-OD-20-146), as they are applicable. Use of the USCDI can complement the FHIR® standard and enable researchers to leverage structured EHR data for research and enable discovery.

- NIH encourages the use of data standards including common data elements, such as those available through the PhenX Toolkit (www.phenxtoolkit.org), the NIH Public Health Emergency and Disaster Research Response (DR2) repository (https://dr2.nlm.nih.gov/), and the NIH CDE repository (cde.nlm.nih.gov), terminologies and ontologies such as Mondo Disease Ontology (mondo.monarchinitiative.org), Human Phenotype Ontology (hpo.jax.org), and common data models such as the Observational Medical Outcomes Partnership (OMOP; ohdsi.org).) and the NIH CDE repository (cde.nlm.nih.gov), terminologies and ontologies such as Mondo Disease Ontology (mondo.monarchinitiative.org), Human Phenotype Ontology (hpo.jax.org), and common data models such as the Observational Medical Outcomes Partnership (OMOP; ohdsi.org).
- Biospecimens collected should adhere to CAP (and in the absence of CAP guidance, OBBR (https://biospecimens.cancer.gov/resources/sops/default.asp, CLSI, or ISBER recommendations) for the collection, preparation and storage.

- Awardees will be required to identify representatives from within the patient population to be studied to serve on a PASC Initiative-wide Community Advisory Council, which will provide feedback to the PASC Consortium regarding the design and conduct of the PASC studies and on information from the studies to be conveyed back to patients and the public. These individuals should not be named in the application; however, commitment to this responsibility should be noted.

Applicants may submit proposals addressing only the Clinical Recovery Cohort component of this ROA, or addressing any combination of the three research study components of this ROA.

Acute and Post-acute SARS-CoV-2 Infection Autopsy Cohort Studies

To better understand the pathophysiology of SARS-CoV-2 infection and its lasting impact on the human body, the National Institutes of Health is seeking proposals for autopsy studies to comprehensively evaluate the pathophysiology of recovery from acute COVID-19 and PASC.

Goals and Specific Objectives

Applicants should propose autopsy cohort studies that will explore the pathology of SARS-CoV-2 infection in those that survived the acute illness. The studies should include recovering adult and pediatric patients who had confirmed SARS-CoV-2 infection. Patients should have recovered from SARS-CoV-2 infection (e.g., >30 days from onset in non-hospitalized, or >30 days from discharge in hospitalized patients), and those patients who meet clinical criteria of PASC (e.g., persistently symptomatic >30 days from onset of infection). As described in the Introduction, awardees will participate in an Investigator Consortium for comprehensive evaluation of PASC and are expected to develop a common set of core measures and descriptors as part of their pathology protocols, share pathology tissues, data, and methodology with Consortium members.

Each site is expected to perform comprehensive autopsies on the patients, and should propose specific research questions to address the pathophysiology of potential long-term effects of SARS-CoV-2 infection on human health. One specific aim should be addressable with tissue obtained from autopsies performed only at the applicant's site. A second specific aim should be designed to use tissues potentially available from other pathology investigators/autopsy sites within the Consortium.

Preferred and Minimum Applicant Capabilities

Applicant must address the following minimum required elements to be eligible for award:

- Applicants must provide data that substantiate the site's expertise and ability to perform a sufficient number of the autopsies to conduct the proposed studies.
- Sites may focus on adult and/or pediatric patients. Inclusion of PASC as well as both MIS-C and MIS-A cases is highly desirable. To reduce bias and enhance reproducibility, specific research questions concerning MIS-C and MIS-A cases should be answered using tissue from multiple sites within the Consortium rather than using material obtained from a single site.
- A minimum of 10% of subjects should be in the subacute phase (d15-60 post-infection) to enable reference of the earliest stages of tissue injury/repair.
- The majority of subjects should consist of those diagnosed with PASC together with appropriate controls, i.e., those who were previously infected but who recovered to their pre-morbid functional baseline.
- Autopsies must be performed within a post-mortem interval under 24 hours. Applicants should describe plan for timely transportation of patients dying outside the hospital, or other plans to minimize the post-mortem interval (e.g., access to an in-hospital hospice).
- As noted above, autopsies should be comprehensive pathologic examinations and collection of tissue should include oversampling of all organs routinely evaluated at autopsy and including those that demonstrated dysfunction during the acute phase of SARS-CoV-2 infection in that individual.
- Each autopsy must accrue 75% of the tissues specified for the research protocol, dependent on the autopsy (full, restricted to body (no head) and CNS only). Applicants are not to propose limited autopsies, but may focus their research interest on specific organ systems.
- Investigators must have access to sufficiently detailed information regarding pre-mortem medical history to inform tissue sampling and subsequent analyses of autopsy data, including past medical history, interventions during COVID-19, demographics, post-COVID-19 care (as appropriate).
- Tissue handling SOPS that meet CAP/CDC guidance for biospecimens and COVID-19 biospecimens must be utilized.
- As part of their participation in the Consortium, study investigators must develop and fully adopt recommendations for the collection of control tissues (e.g., suggested metrics, age, sex, BMI, as well as appropriate comparator tissues from COVID-19 full recovery, SARS-CoV-2 infection naive, influenza-associated death).
- All tissue must be collected prospectively or be derived from autopsies documented to have been performed in accordance with the agreed upon research plan and SOPs.
- Applicants must have the capacity to collect and freeze tissue in accordance with appropriate biohazard considerations at time of autopsy.
- Applicants must demonstrate a commitment and capacity to submit tissues to a virtual or physical biobank for distribution across the Consortium and more broadly with the research community, including tissues, medical history, whole slide imaging of tissues, and relevant diagnostic information. It is anticipated each site will retain diagnostic autopsy tissue but will make available/submit to a centralized biobank (the PASC Biorepository Core) all research tissue not consumed by local protocol (not to exceed 20% of all tissue collected/patient).
- All sites must meet CAP Biobanking requirements for the storage of research tissue under this protocol.
- Examination of the CNS should be included in the protocol and must be pursued when consented.
- Post mortem brains should be sectioned appropriately to preserve key structures, including but not limited to those relevant to autonomic dysregulation in PASC (e.g. hypothalamus, area postrema).

- When feasible, inclusion of post-mortem MRI is highly desirable but it should be noted that this is not a requirement.
- Applicants must have the capacity to perform quantitative PCR assessment of viral load in tissue as well as histomorpholocalization of virus in tissue.
- Ancillary studies will be allowed to perform high impact intensive investigation (imaging, single-cell analysis, transcriptomics, electron microscopy, etc.).
- Sites must have the capacity to share EHR, clinical data, pathology data and whole slide imaging with the Data Resource Core.
- Sites must agree to share appropriately anonymized EHR and other clinical data.
- Funding for equipment is restricted to that required to perform the autopsies (including PPE), and for storage of the tissue and does not include purchase of equipment for the research question (e.g., advanced staining and imaging systems).
- To maximize comparisons across datasets or studies, ensure high quality biospecimens, and facilitate data integration and collaboration, researchers funded through this ROA are strongly encouraged to use the following standards and resources (where applicable):
    - Applicants are encouraged to conform to Findable, Accessible, Interoperable, and Reusable (FAIR) principles.
    - NIH encourages researchers to explore the use of the HL7 FHIR® (Fast Healthcare Interoperability Resources) standard to capture, integrate, and exchange clinical data for research purposes and to enhance capabilities to share research data (NOT-OD-19-122). The FHIR® standard may be particularly useful in facilitating the flow of data with EHR-based datasets, tools, and applications. NIH also encourages relevant studies to explore the use of HL7 FHIR Mobile Health Application Data Exchange Assessment Framework and Functional Requirements Implementation Guide9 (mHealth ADE FHIR IG).
    - NIH encourages clinical research programs and researchers to adopt and use the standardized set of data classes, data elements, and associated vocabulary standards specified in the United States Core Data for Interoperability (USCDI) standards (NOT-OD-20-146), as they are applicable. Use of the USCDI can complement the FHIR® standard and enable researchers to leverage structured EHR data for research and enable discovery.
    - NIH encourages the use of data standards including common data elements, such as those available through the PhenX Toolkit (www.phenxtoolkit.org), the NIH Public Health Emergency and Disaster Research Response (DR2) repository (https://dr2.nlm.nih.gov/), and the NIH CDE repository (cde.nlm.nih.gov), terminologies and ontologies such as Mondo Disease Ontology (mondo.monarchinitiative.org), Human Phenotype Ontology (hpo.jax.org), and common data models such as the Observational Medical Outcomes Partnership (OMOP; ohdsi.org).) and the NIH CDE repository (cde.nlm.nih.gov), terminologies and ontologies such as Mondo Disease Ontology (mondo.monarchinitiative.org), Human Phenotype Ontology (hpo.jax.org), and common data models such as the Observational Medical Outcomes Partnership (OMOP; ohdsi.org).
    - Biospecimens collected should adhere to CAP (and in the absence of CAP guidance, OBBR (https://biospecimens.cancer.gov/resources/sops/default.asp, CLSI, or ISBER recommendations) for the collection, preparation and storage.

Applicants may submit proposals addressing only the Autopsy Studies component of this ROA, or addressing any combination of the three research study components of this ROA.

EHR- and Other Real-World Data-Based Studies

The first North American cases of what is now known as COVID-19, the illness caused by infection with the

SARS-CoV-2 novel coronavirus, were diagnosed in January 2020. Since that time, much has been learned about the virus and the spectrum of illness it causes. From relatively early on in the pandemic, survivors of SARS-CoV-2 infection reported that they were experiencing a variety of symptoms and challenges that persisted well beyond the acute phase of their illness and that were not present before they were infected with SARS-CoV-2. From the multisystem inflammatory syndrome in children (MIS-C) to adults experiencing the signs and symptoms of what is often described as "long COVID" to a range of other signs and symptoms, real-world data (RWD, see https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence for a description of RWD) from many different sources (e.g., electronic health records (EHRs), digital devices and applications, and environmental data sources) point to a need for increased understanding of what happens after the acute SARS-CoV-2 infection. For example, one of the key outstanding questions is understanding the ways in which the post-acute sequelae of SARS-CoV-2 infection are similar to, and/or distinct from, other post-infectious and post-acute illness syndromes. Moreover, understanding some very basic features of the post-acute sequelae of SARS-CoV-2 infection including incidence and prevalence, spectrum of illness, and the many different clinical manifestations, risk factors, protective factors, disproportionately affected populations, etc. calls for the use of RWD, as there are no experimental models or pre-existing definitions from which to begin research efforts.

Goals and Specific Objectives

This Research Opportunity Announcement is intended to solicit applications that propose to advance the understanding and management of the post-acute sequelae of SARS-CoV-2 infection in both children (including MIS-C) and adults (including pregnant women), by making innovative use of RWD such as EHRs, health systems data, digital health data, and other large datasets; by further expanding the capabilities of existing data resources toward these ends; and by working in an integrated fashion with other components of the coordinated NIH response to address the post-acute sequelae of SARS-CoV-2. Separate applications for pediatric and adult cohorts are permissible.

This solicitation is for applications that propose to use RWD, particularly large, aggregated data resources, to address pressing scientific and clinical questions and needs relevant to the post-acute sequelae of SARS-CoV-2 infections (PASC) across the lifespan. Such population studies could be based in healthcare systems, previously established large cohorts for study of other conditions, private or public health databases, or other similar resources. Applicants could propose means to establish incidence and prevalence of those suffering from post-COVID-19 conditions, risk factors for developing specific post-acute sequelae of SARS-CoV-2 infection , or the influence of prior SARS-CoV-2 infection on developing illness in the future. Studies might employ methods to analyze RWD such as EHRs and to augment existing RWD by employing tools such as patient surveys, standardized patient-reported outcomes tools, and digital health data (e.g., data collected from wearables). The goal of such studies is to efficiently detect effects of SARS-CoV-2 infection on the risk of developing common conditions appropriate to the age group under study, including but not limited to heart failure, dementia, chronic kidney disease, atherosclerosis, thrombotic disorders, diabetes mellitus, depression, anxiety, post-traumatic stress disorder, dysautonomias, neurocognitive impairment, exercise intolerance, decline in school or employment/job performance, as well as new/emerging conditions (e.g., SARS-CoV-2 infection-linked loss of smell/taste or SARS-CoV-2 infection-linked alopecia) and more rare conditions such as autoimmune or immune disorders. Such large studies of tens of thousands of persons infected with the virus would also be expected to cover the diversity of the US population. They could also be engaged to recruit persons for studies based on presence of acute COVID-19 illness, that include people followed longitudinally for development of post-SARS-COV-2 infection sequelae, or based on the presence or absence of a defined post-SARS-CoV-2 infection condition.

Preferred and Minimum Applicant Capabilities
Competitive applications will address the following objectives:

- Use RWD (such as EHR, digital health, environmental, and administrative data) to develop post-acute SARS-CoV-2 infection phenotype definitions that map both to computable phenotype definitions and to definitions deployable for cohort discovery, cohort creation, and for inclusion/exclusion criteria in clinical trials.
- Implement secure, privacy-preserving strategies in collaboration with other Consortium components to augment and to integrate existing RWD resources through linkages to other data resources and data types (e.g., mobile health data, multi-omics data, imaging data, environmental data).
- Identify and address health disparities across the lifespan, as well as geospatial elements, that are germane to the post-acute sequelae of SARS-CoV-2 infection and that are discernible in RWD.
- Create, deploy, and validate workflows for using large RWD resources to enhance PASC clinical research and practice through evaluation of comparative effectiveness questions and through innovative approaches to contact/re-contact individuals for optimal matching of participants to prospective observational and interventional studies.
- Help to standardize the landscape of PASC data science research through establishment and promotion of best practices for the application of artificial intelligence, machine learning, and natural language processing to EHR/RWD resources; and use of modern real-world interoperability resources such as FHIR.
- Help to democratize the landscape of PASC research through extension of training and outreach efforts to engage talented data scientists in underserved communities.
- Develop clinical decision support tools, implementation tools, and other work products that use RWD to enhance the effectiveness and efficiency of the care for people with post-acute sequelae of SARS-CoV-2 infection.

Although a wide variety of approaches are possible for addressing the above objectives, applicants must address the following points in their project plan:

Capacity for post-acute SARS-C0V-2 infection research within data resources

- A description of the number of individuals with and without SARS-CoV-2 infection including those with COVID-19, an estimate of the number of individuals with and without post-acute sequelae of SARS-COV-2 infection, an estimate of numbers of adults and/or children, an estimated sex and gender breakdown, and an estimate of racial/ethnic representation. Applications with robust numbers will be evaluated as more competitive. Separate applications for pediatric and adult cohorts are permissible.
- Estimated rate of ongoing accrual of SARS-CoV-2 infected (including those with COVID-19) and post-acute SARS-CoV-2-infected individuals as well as, if known, estimated rate of accrual of vaccinated individuals
- Capacity for shortest achievable data refresh rate (e.g., 1-2 weeks)

Ability to package RWD and augment data resources

- Applicants should describe how and where they will be sharing data resulting from this project including deposition of data and biospecimens into an NIH-approved and designated repository to facilitate access and analysis by study and non-study investigators. Data sharing of relevant pathology and radiology images is highly desired. The description of data sharing plans should address pathology and radiology reports, which may be housed in LIS/PACS systems.
- For applicants proposing to use EHR-based approaches, applicants describe their intention to transfer data to the National COVID Cohort Collaborative (N3C) or another secure NIH-approved

repository. The N3C is a centralized national data resource for the research community to study COVID-19 EHR RWD as the pandemic continues to evolve. Specifically, the N3C will enable the rapid collection and analysis of clinical, laboratory and diagnostic data from hospitals and health care plans. For submitting to N3C, applicants can find relevant instructions and forms here: Data Transfer: https://ncats.nih.gov/n3c/resources/data-contribution#:~:text=NCATS%20Data%20Transfer%20Agreement,%40mail.nih.gov%20, and Data Use: https://ncats.nih.gov/n3c/resources/data-access.

- Applicants should describe their standardized collection of RWD or use an already established query, such as https://github.com/National-COVID-Cohort-Collaborative/Phenotype_Data_Acquisition/wiki/Latest-Phenotype) to maximize comparability across the program Consortium for longitudinal research and evaluation program impact; perform quality control, data curation, and analyses; facilitate the necessary data harmonization, and prepare necessary data from the site(s) for ingestion into the N3C or other platform that will house the EHR data. Note to applicants to familiarize themselves with the Data Core ROA.
- Description of plans to develop and implement novel consent and contact/re-contact approaches that could be deployed across post-acute sequelae of SARS-CoV-2 infection studies
- Description of plans to enhance data resource capabilities through approaches such as privacy-preserving linkages across multiple data resources, use of mobile health data, use of publicly available data.

Expertise of the project team

- Expertise in multiple clinical domains relevant to post-acute sequelae of SARS-CoV-2, and other infectious diseases (e.g., immunology, pulmonology, cardiology, neurology, nephrology, endocrinology), with representation of adult and pediatric expertise as appropriate to the proposal.
- Expertise in informatics, health IT, coding, AI/ML.
- Expertise in modern data standards, information and data models, interoperability standards, privacy and ethics standards.
- Expertise in health equity, underserved and marginalized populations, and social determinants of health will be seen as a strong positive feature
- Ability to engage with expert consultants in key areas (e.g., regulatory expertise) as needed.

Expected data-facing and community-facing activities

- Description of plans for development and validation of workflows to address questions of incidence/prevalence of PASC phenotypes, identification of risk factors for developing PASC phenotypes, comparative effectiveness of different strategies for managing acute SARS-CoV-2 infection and post-acute sequelae that are captured within RWD, causal inference studies using RWD, and other analytical approaches using RWD.
- Description of plans to make workflows available to the community of investigators in an expedient fashion.
- Identification of opportunities for training and outreach efforts to the broader community of scientists and plans for how such opportunities will be utilized and built upon.
- Detailed description of how planned data analysis, training, and outreach efforts will be leveraged to address health inequities and to target underserved communities.
- Description of how the above efforts will be translated toward the development and dissemination of clinical decision support tools, training tools, implementation tools, and other work products the empower RWD to enhance the effectiveness and efficiency of the care of people with PASC.

Project management, integration, and Consortium participation

- Commit to working with the Consortium as a whole to make protocols, procedures, best practices, workflows, analysis pipelines, and other work products available to communities outside the Consortium as quickly as possible. This will include, but is not limited to:
    - Commit to rapidly developing and implementing core protocol elements in conjunction with the Clinical Sciences Core, Data Resource Core, and other clinical studies
    - Commit to rapidly developing, implementing, promoting, and curating common data elements within the Consortium and across other research efforts
    - Commit to working with the Consortium Data Resource Core to map RWD onto Consortium CDEs and information and data models
    - Commit to working with the Consortium Clinical Sciences Core to discover and validate multiple PASC phenotypes and sub-phenotypes
    - Commit to working with observational and interventional studies within the Consortium to utilize RWD to maximize optimal and efficient matching of interested participants to available studies
    - Applicants must describe a plan for how they will coordinate with the Data Resource Core, the Administrative Core, and the Clinical Sciences Core to ensure that RWD resources and RWD work products and activities are harmonized across the Consortium by way of the 3 organizing cores.
- To maximize comparisons across datasets or studies and facilitate data integration and collaboration, researchers funded through this ROA are strongly encouraged to use the following standards and resources (where applicable):
    - Applicants are encouraged to conform to Findable, Accessible, Interoperable, and Reusable (FAIR) principles.
    - NIH encourages researchers to explore the use of the HL7 FHIR® (Fast Healthcare Interoperability Resources) standard to capture, integrate, and exchange clinical data for research purposes and to enhance capabilities to share research data (NOT-OD-19-122). The FHIR® standard may be particularly useful in facilitating the flow of data with EHR-based datasets, tools, and applications. NIH also encourages relevant studies to explore the use of HL7 FHIR Mobile Health Application Data Exchange Assessment Framework and Functional Requirements Implementation Guide9 (mHealth ADE FHIR IG).
    - NIH encourages clinical research programs and researchers to adopt and use the standardized set of data classes, data elements, and associated vocabulary standards specified in the United States Core Data for Interoperability (USCDI) standards (NOT-OD-20-146), as they are applicable. Use of the USCDI can complement the FHIR® standard and enable researchers to leverage structured EHR data for research and enable discovery.
    - NIH encourages the use of data standards including common data elements, such as those available through the PhenX Toolkit (www.phenxtoolkit.org), the NIH Public Health Emergency and Disaster Research Response (DR2) repository (https://dr2.nlm.nih.gov/), and the NIH CDE repository (cde.nlm.nih.gov), terminologies and ontologies such as Mondo Disease Ontology (mondo.monarchinitiative.org), Human Phenotype Ontology (hpo.jax.org), and common data models such as the Observational Medical Outcomes Partnership (OMOP; ohdsi.org).) and the NIH CDE repository (cde.nlm.nih.gov), terminologies and ontologies such as Mondo Disease Ontology (mondo.monarchinitiative.org), Human Phenotype Ontology (hpo.jax.org), and common data models such as the Observational Medical Outcomes Partnership (OMOP; ohdsi.org).

Applicants may submit proposals addressing only the EHR- and Other Real-World Data component of this

ROA, or addressing any combination of the three research study components of this ROA.

Authority
This ROA is issued with the goal of establishing an "Other Transactions" (OT) agreement or sub-agreement pursuant to 42 U.S.C. § 285b-3 and 42 U.S.C. § 282(n).

Eligibility
The following entities are eligible to apply 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-*

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

Foreign (non-US based) Institutions
- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education
- Non-profit institutions
- For-profit institutions

Special Award Terms
The complete terms and conditions of each OT or sub-OT award issued under this ROA are subject to negotiation and will be contained in the Agreement entered between the NIH and the Awardee. This Special Award Terms section is provided for informational purposes only in order to provide prospective applicants with an understanding of key expectations and terms that may differ from traditional NIH award mechanisms.

Lower Tier Agreements
With mutual consent of the Awardee and the NIH, successful awardees may be expected to issue sub-awards to entities identified and approved by the NIH under this and other PASC related ROAs.

Milestone Based Payment Schedule
NIH funds issued under the OT or sub-OT Agreement will be disbursed based upon achievement of specific Operational Milestones, as proposed by the Awardee in its application and subsequently approved by NIH.

An "Operational Milestone" is an objective, measurable event that is indicative of project progress occurring as proposed in the application. NIH establishes Operational Milestones in the OT Agreement based upon information provided in the application. Except for the first payment issued upon the execution of the OT Agreement, payments will be obligated and disbursed upon completion of specific Operational Milestones.

With mutual consent of the Awardee and the NIH, adjustments may be made to the timeline for inclusion in the OT Agreement to ensure that funds are appropriately dispersed across Operational Milestones. If NIH determines, in its sole discretion, that an awardee has failed to satisfy one or more Operational Milestone(s), NIH may terminate the OT Agreement.

Award Criteria and Selection Information

Awardees will be selected through an objective review process. Multiple awards are anticipated. The level of funding for awards made under this ROA has not been predetermined but will depend on (1) the objectives proposed by the applicant and how well they fit with the overall goals of the initiative, (2) quality of the applications received, and (3) availability of funds. Agreements and sub-agreements for all awards will be negotiated with eligible entities whose applications are determined to be the most meritorious and provide the best value to the NIH toward achieving the goal of rapidly improving our understanding of and ability to treat and prevent the post-acute sequelae of SARS-CoV-2 infection across the lifespan.

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 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 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 proposers as sub-awardees of a separate Data Resource Core and Clinical Science Core entity to be established by the NIH;
- request additional documentation (certifications, etc.); and
- remove proposers from award consideration should the parties fail to reach a finalized, fully executed agreement, or the proposer fails to provide requested additional information in a timely manner.

Proposal Format and Requirements

Proposals are being accepted for one or more of the three major research components described in this ROA. To facilitate preparation of applications a single proposal may be submitted. The following common proposal elements should be included for each major research component for which funding is requested under this ROA:

- A detailed technical project plan (max of 10 pages) for addressing proposed research questions as well as accomplishing the goals and objectives of the PASC initiative as described in this ROA:
    - The proposed project title
    - Succinct summary of the 4-5 most compelling research question(s) to be addressed
    - Plan for collaboration and integration with the Clinical Science Core, the Data Resource Core, and the other components of the PASC Consortium.
    - The expected start date to launch the study (with the expectation of launching

within 2- 4 weeks of funding)

- Detailed Budget and Justification (please see budget section for more details)
- Operational Milestone-based Payment Schedule (please see budget section for more details)
- The key personnel
- The submitting organization or institution
- A description of any anticipated agreements with third-parties relevant to the proposed project, including details about any provisions or restrictions related to intellectual property, publication, data and specimen sharing, and dissemination of results.
- Any existing sources of funding supporting the proposed research

Specific to the Clinical Recovery Cohort component, the following elements should be included:

- Description of the existing cohort or patient population including how many participants are readily available for enrollment in the study, including specific data for participants with SARS-CoV-2 infection, COVID-19, PASC, and comparison participants.
- Brief description of the rationale for and importance of the research question(s), particularly from a public health perspective, describing what the study will contribute to advancing our understanding of and ability to treat and prevent PASC and other long-term consequences of SARS-CoV-2 infection.
- A detailed description of the data proposed for collection, including the particular measurements to be performed. Discuss whether proposed measures are validated in relevant populations, the level of staff training required to perform the tests, whether measures require physical interaction with the research participants, and the feasibility of the measures in the context of COVID-19.
- Efforts to standardize and collaborate with other studies including utilization, as appropriate, of COVID-19 CDEs, harmonized phenotypic measures, a mobile app, and leveraging multiple existing cohorts, or other relevant infrastructure and studies.
- Estimates of the numbers of research participants required within each group to allow statistically meaningful analyses. These numbers may exceed those proposed for enrollment by the applicant for research questions that would be addressed by a common, core protocol.
- Given the context of the current COVID-19 public health emergency:
    - Plan for expedited data and biospecimen sharing through: usage of COVID-19 CDEs; plans for the use and sharing of data, as applicable; plans, including timelines, for making data and biospecimens available rapidly through NIH-designated repositories; and sharing data and biospecimens, as available, with public health agencies.
    - Plan for rapidly disseminating the results for clinical or public health practice, including a brief description of the intended audience, approaches designed to reach that audience, and a timeline.

Specific to the Autopsy Cohort Studies component, the following elements should be included:

- Applicants should provide an SOP for their comprehensive autopsy plan. Only those autopsies performed in accordance with the final agreed upon research plan and SOPs will be funded by this ROA and count toward autopsy cohort accrual numbers.

Budget

The Budget section of the application must provide a realistic, fully justified budget and cost for performing the work. Proposers shall provide a separate budget assuming an award term of one year, renewable annually for up to a total funding period of four (4) years, contingent upon satisfactory performance assessed at least annually. Budgets that are broken down by annual activities and

associated costs for up to 4 years will provide the greatest clarity for assessing proposals. Separate budgets must be provided for each research component proposed.

In particular, the budget must include a proposed Operational Milestone-based Payment Schedule. Each milestone will include a description of the work to be completed, objective completion criteria, anticipated completion date , and the associated percentage of overall total cost budget that would be released upon successful completion. In particular, the Operational Milestone-based Payment Schedule should include a timeline for protocol launch, cohort participant accrual and evaluation, as well as data (and if applicable biospecimens) acquisition and deposition into PASC designated repositories. The proposed milestone schedule may need to be harmonized with other consortium studies in coordination with the Data Resource Core and Clinical Science Core. Except for the first payment issued upon the execution of the OT agreement or sub-agreement, payments will be disbursed upon completion of these specific Operational Milestones subject to the availability of funds. Costs resulting from a delay or failure to meet an Operational Milestone will be the sole responsibility of the Awardee. Successful applicants will therefore have thoughtfully accounted for foreseeable project risks and developed contingency plans that do not involve the need for additional funding from NIH. NIH prefers applicants use an SF424 template to complete their budget but this is not required. For non-traditional applicants defined as those applicants who are not registered in eRA Commons, NIH will accept a budget that provides the annual overall expected cost covering the entire duration of the study for each of the following categories:

- Personnel
- Equipment
- Travel
- Subawards/subcontracts/consultants
- Other direct costs
- Total cost (with indirect costs included)
- Proposed Cost Share contribution

Submission and Contact Information

Proposals should be submitted by the proposing entity's business official via eRA ASSIST not later than **March 23rd by 5 PM EDT.** If applicants are not registered in eRA or experience difficulty with submission please contact NHLBI_OTA@mail.nih.gov for assistance. Inquiries can also be submitted to NHLBI_OTA@mail.nih.gov. Financial and administrative questions should be addressed to Benjamin Sakovich, NHLBI Agreements Officer. Questions about the scientific scope of the studies should reference in the subject line the OTA number and specific research study component(s) in question to help route the inquiry as appropriate.

Applicants are encouraged to register for the Technical Assistance Workshop to learn more about this important research opportunity.

A note about eRA Registration

NIH uses the eRA Commons system to administer OT awards. If you are selected to participate you may need to submit additional information in eRA ASSIST, you will need to be registered in eRA Commons, which can take some time to complete – as many as several weeks in some cases. Therefore, if you are considering submitting a proposal and are not yet registered in eRA, it is highly recommended that you begin the process of registering your organization, Program Director/Principal Investigator (PD/PI) and Signing Official (SO) in eRA Commons as soon as possible to avoid possible award processing delays. To register, please follow the instructions via this website: https://public.era.nih.gov/commons/public/registration/registrationInstructions.jsp.

1. Complete the online Institution Registration Form and click Submit.
2. The NIH database will send you an email with the link to confirm your email address.
3. Once your email address is verified, the NIH will review your request and let you know of the result via email.
4. If your request is denied, you will get an email notifying you of the reason.
5. If your request is approved, you will get an email with your Commons User ID and temporary password.
6. Log into Commons with the temporary password and the system will prompt you to change temporary password to a permanent one. Your SO will be prompted to electronically sign your registration request. (Please review your registration information carefully.)
7. Once your SO has electronically signed the request, your organization will be active in Commons and you may create and maintain additional accounts for your institution staff.

To complete the registration above, you may need to register for the following if you haven't done so already:

- Dun & Bradstreet Number (DUNS) - https://fedgov.dnb.com/webform/
- Employer Identification Number (EIN)- https://www.irs.gov/businesses/small-businesses-self-employed/apply-for-an-employer-identification-number-ein-online
- Small Business Administration (SBA) - https://www.sbir.gov/registration
- System for Award Management (SAM) - https://www.sam.gov/SAM/