Research Opportunity Announcement
OTA-21-015A
Post-Acute Sequelae of SARS-CoV-2 Infection Initiative:
Clinical Science Core, Data Resource Core, and PASC Biorepository Core

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-21-015A focuses on the Clinical Science Core, the Data Resource Core, and the PASC Biorepository Core. Applicants may apply for one, two, or all three components as described in the Objectives section.

The NIH is also soliciting applications under a companion ROA OTA-21-015B that focuses on three research study areas: Clinical Recovery Cohort Studies, Autopsy Cohort Studies, and EHR- and Other Real-World Data-based Studies.

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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.

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, 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 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 Clinical Science Core, the Data Resource Core, and the Biorepository Core. The three research study areas (Clinical Recovery Cohort Studies, Autopsy Cohort Studies, and EHR- and

Other Real-World Data-based Studies) are the subject of a separate but related ROA that can be found at the following link: OTA-21-015B. 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.

Objectives

With this ROA, NIH is soliciting applications for three components to support the goals of the PASC Initiative and Investigator Consortium. These three components are the **Clinical Science Core** (CSC), the **Data Resource Core** (DRC), and the **PASC Biorepository Core** (PBC). These three components are presented in one ROA because they require close coordination and integration, each with the other; therefore, applicants must address specific processes and procedures for how they will achieve the required integration with the other components and for resolving any areas of disagreement. Applicants may apply for one, two, or all three components. If applying for more than one component, it should be noted that each component will be individually evaluated. The unprecedented scope and rapidly evolving nature of SARS-CoV-2 infection and uncertain public health impact of PASC requires a flexible, highly collaborative and integrative approach. Together and separately, each component must be adaptable, nimble, and innovative—able to adjust in scope, scale and direction to a changing pandemic landscape.

The **Clinical Science Core** will be established to coordinate the development and implementation of master protocols and to provide expertise in clinical protocol design, implementation, and execution of large clinical research studies. Activities to be performed under this award include, but are not limited to: the formation and support of collaborative investigator groups, including the PASC Investigator Consortium; facilitation of clinical protocol development and implementation; fostering the use of common data elements in all trials and across all cohorts; monitoring protocol conduct and quality control; collection and quality control of data sent to the DRC; support of ancillary and sub-study research; coordination of standardized mobile health measures and apps; monitoring and sharing with investigators evolving PASC literature and data; and support of phenotype characterization, diagnostic algorithm development, and results dissemination. The CSC will also be charged with promoting internal and external communication across all working groups and for public-facing digital channels (websites and social media), including an engagement capacity that solicits patient and stakeholder input and feedback. PASC Consortium studies will initially focus on a case-based cohort of SARS-CoV-2 recovery and PASC patients, but, in the future, will evolve to include new research protocols, including clinical trials. The CSC must, therefore, be flexible and able to adapt to an evolving PASC clinical and research landscape.

The **Data Resource Core** will provide the appropriate expertise in PASC-related data collection, harmonization, integration, and sharing as well as proven relationships and expertise with clinical consortiums and networks and capacity. Activities to be performed under this award include, but are not limited to: standardized collection of clinical data (i.e., incorporating common data elements and case report forms) as well as plans to incorporate less structured data (i.e., imaging reports, results of specialized tests) to maximize comparability across the program consortium and measurement modes (e.g., web, mobile app, in-person) for longitudinal research and evaluation of program impact; assist research projects with linking these data with stored biospecimens and data from other sources including but not limited to: publicly available databases (e.g., Census data, Area Deprivation Index, etc.), electronic health records (EHR), and others as needed; perform quality control, data curation, and analyses, and provide data informatics tools to monitor program consortium progress and performance; facilitate the necessary data harmonization and mapping to common data models (e.g., OMOP) and prepare necessary data across all sites for ingestion into the platforms that include, but may not be

limited to, the BioData Catalyst and N3C. The DRC will also provide statistical support to the CSC and Consortium, including input into protocol development, provision of analyses and analysis tools, and preparation of reports and publications. The DRC will incorporate and integrate data from Consortium studies via their individual Data Coordinating Centers, as needed.

The **PASC Biorepository Core** will establish and maintain a secure central repository for PASC Initiative biospecimens (e.g. blood, tissue, urine, stool, cerebrospinal fluid, and other biospecimens and their derivatives) generated from PASC studies. For PASC-related biospecimens maintained at Investigator sites or elsewhere, the PBC can also function as a "virtual" repository, tracking sample availability and location and incorporating information about the biospecimens, e.g. type of sample, volume, associated clinical data and any limitations on use.

The PBC will store and distribute quality biospecimens to the wider scientific community using standardized processes and procedures to maximize future scientific utility, facilitate access, and manage biospecimen and data requests and approval processes. Since the type, number, and volume of biospecimens are not currently known, the CSC-Biorepository must be flexible enough to accommodate expansion of scope to accommodate additional needs as the number of studies increases and if/when clinical trials are added. Once the needs of the PASC Initiative for biospecimens are fulfilled, it is anticipated that remaining biospecimens will be transferred and archived at an NIH central biorepository (to be identified).

Clinical Science Core

The NIH is soliciting proposals for a Clinical Science Core (CSC) to coordinate and support the development, implementation, and execution of PASC Initiative research programs, as well as to provide expertise on clinical study design, implementation, and oversight and on data management. The CSC will provide:

- Expertise in and support for development, implementation, and execution of PASC protocols.
    - Develop a plan for building an effective Consortium study team from the cohort investigator leads within a couple of weeks of the clinical study OT awards.
    - Work with the Consortium to identify:
        - A core set of PASCs common data elements (CDEs) and tools and to incorporate these into each study brought into the PASC Initiative and
        - Scientific questions to be addressed in adults and children.
    - Provide regular literature updates on sequelae of SARS/CoV2 infection.
    - Harmonize and coordinate clinical site and research activities to promote synergy and reproducibility and minimize overlap/redundancy within the Consortium .
    - In coordination with the DRC, collect and make available to investigators toolkits of rating scales, surveys, outcome assessments, and questionnaires for adult and pediatric participants using CDEs wherever possible and identify and implement the optimal mode of delivery (e.g., clinician evaluation, in-person, web, mobile app, telephone) for these tools.
    - Coordinate and provide expertise in the development of new and innovative PASC Core protocol(s), screening protocol(s), and sub-study protocols for both the case-based PASC cohort and the SARS-CoV-2 recovery cohort, including identification of applicable CDEs and definition of appropriate controls in adults and children, working with the Consortium in an iterative process.
    - Support the implementation of the protocols (in collaboration with the DRC), including the development of the manual of procedures (MOP), case report forms (CRFs), identification

and selection of surveys, questionnaires and CDEs, case-finding strategies, recruitment strategies to ensure inclusion of appropriate, inclusive, balanced and diverse participant populations to enhance the generalizability of research findings, retention strategies, use of mobile applications for data collection and participant/study tracking, consent processes that incorporate the use of e-consent, legally authorized representatives, and other alternative consent processes as appropriate, utilization and sharing of EHR data, as appropriate, and IRB submissions.
    - Training for clinical trial investigators and staff on the conduct of study tests and procedures. Collaborate with DRC in training investigators and staff on data management.
    - Develop evidence based case definitions and diagnostic algorithms with support from the DRC.
- Development and implementation of PASC protocol monitoring.
    - Development and tracking of study performance milestones, including recruitment, retention, subject follow-up, study progress, data quality and completeness.
    - Monitoring of recruitment to assure equitable and diverse enrollment and to balance recruitment across recovery and PASCs cohorts.
    - Development of safety monitoring procedures to document, track, and report adverse events.
    - Preparation of monitoring reports for the Consortium and for various oversight groups, such as Data and Safety Monitoring Boards (DSMBs) and the FDA, if applicable.
    - Work with the Consortium to develop and implement remediation plan(s) for any problems identified.
- Expertise in and support for the phenotyping of individuals to characterize the full multi-organ spectrum of SARS-CoV-2 infection in adults and children, including the acute and post-acute manifestations, at a clinical and biological level and across multiple medical specialties.
    - Work with investigators to collect a core set of assessments and biospecimens, in all PASC subjects across the consortium that address the broad spectrum of symptoms and potential organ dysfunction and other conditions of acute and post-acute SARS-CoV-2 infection.
    - Support for defining levels of depth of phenotyping (light, middle, deep).
    - Support for defining criteria for assigning participants to phenotype level.
    - Support for assigning participants to a depth of phenotype level, including algorithms to assign subjects to detailed investigations of specific organ dysfunction and other conditions.
    - Support for assigning participants to evaluation venues/centers.
    - Development of data, image, and biospecimen collection plans that enable a deeper understanding of the pathobiology, patient stratification, and identification of biomarkers.
- Fostering of communication within the Consortium and with external stakeholders.
    - Create and implement a web-based platform for Consortium communication, study management and performance tracking.
    - Communicate and provide technical assistance to researchers, clinicians, staff and PASC data collection sites.
    - Incorporate communications, outreach, and educational support/products for use by researchers and stakeholders in recruitment and outreach to appropriate patient populations and affected communities.
    - Coordinate efforts to message the value of future body donation for pathologic studies in the case of participant death.
- Integration with DRC and PASC Biorepository Core
    - Coordinate standardized biospecimen collection protocol with the PASC biorepository.

  - Develop a plan, in coordination with the DRC, for integration and linking of data from individuals across all data platforms and with their biospecimens in the PASC biorepository.
  - Work with the Administrative Coordinating Center and DRC to launch the Consortium .
  - Work with the Administrative Coordinating Center and DRC to assure compliance with applicable regulations and standards
  - Provide the Administrative Coordinating Center with reports on progress, milestone accomplishments, and identification of any challenges and proposed solutions
  - Review consent forms to ensure permission to share data and biospecimens for general research use.
  - Work with DRC to enable timely and efficient transfer of data, maintaining data fidelity.
  - Development of a plan for arbitration between the CSC and DRC for areas of disagreement.
- Determination of additional needs for development, implementation, successful conduct, and interpretation of the studies.
  - Identify infrastructure and resource needs for studies.
  - Evaluate, solicit, and select an image reading center, if needed.
- Logistical support for administration, execution, and results dissemination from SARS-CoV-2/PASC cohorts.
  - Provide logistical support, including scheduling, meeting, and communication platforms, for Consortium committees, working groups, external panels, patient groups, and oversight groups.
  - Coordinate functions of steering committee, external panels, and oversight groups and interactions with study investigators.
  - Execute and administer sub-agreements and contracts.
- Appointment of an overall Communication Coordinator to develop an overarching Communication Plan and coordinate efforts to inform interested stakeholders about the goals, objectives, activities, and progress of the consortium.
- Leadership of a Patient Engagement Working Group (e.g. a Community Advisory Board) to engage PASC patients, physicians and other stakeholders in shaping the research agenda initially and iteratively as research questions evolve, to work with investigators in disseminating information on the rationale and ethical basis for conducting the PASC studies, and to provide feedback from the community at large on the research. The Patient Engagement Working Group should be diverse and represent a broad range of patients and communities. Leveraging the principles of engagement, the working group will:
  - Identify key patient-centered factors to be included in each stage of PASC study development and conduct, including the development of common protocols and common data elements, for obtaining informed consent, and for collecting EHR data, mobile data and biospecimens.
  - Develop a plan for supporting engagement activities of studies in assembling and engaging research participants, patients, providers, and trusted community members and organizations in ways that serve to inform, educate, influence, and support the research, as well as advance the uptake of research findings.
  - Develop a plan for continued engagement with participants as the research progresses, including a patient-centered information system.
  - Develop a communication plan to disseminate proposed study operating procedures and results to the larger research and patient communities in collaboration with the Communication Coordinator.
  - Provide a mechanism for receiving and addressing queries from the public and patient and research communities.

- Work with the Administrative Coordinating Center in the development and posting of content on the public-facing external Web portal describing the PASC Initiative.

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Data Resource Core

The NIH is soliciting applications for a Data Resource Core (DRC) to provide data harmonization, integration, and sharing as well as statistical expertise and support for the Consortium.

- PASC Data Administrative Management and Tracking
  - Coordinate with the Clinical Sciences Core (CSC) to assist with implementing agreements, including DTAs, DUAs, ensure that appropriate participant patient consents are obtained for retrospective and prospective data and sample acquisition, transfer, and use of data and re-contact for follow-up.
  - Coordinate with the CSC and PBC to track and coordinate biospecimen storage, transfer, distribution, and archiving. The DRC will maintain links to the consortium data.
  - Monitor Electronic Health Record (EHR) integration plans for the recruitment sites and encourage (re)incorporation of study and diagnostic data back into EHR systems as feasible and appropriate.
  - Execute and administer sub-agreements in an expeditious and agile fashion and to be managed in accordance with milestone payment schedules and evolving circumstances that may require sub-agreement modifications.
  - Provide the Administrative Coordinating Center with reports on progress, milestone accomplishments, and identification of any challenges and proposed solutions.
- Expertise in data management and statistical analyses in support of clinical studies.
  - Provide data repository and management services for clinical, neuroimaging, physiological, biomarker, and -omics data including tracking, sharing, storage, curation, management, data quality controls, archiving, harmonization, integration, and export.
  - Work with the CSC to assure complete and accurate high quality data.
  - Coordinate standardized mobile health data collection protocol(s) with the PASC mobile data repository (to be identified).
  - Provide expertise in data systems to allow timely availability and/or transfer of data, management, quality control, and export as needed for analyses.
  - Provide statistical expertise and input for the preparation of protocols, study design, sample size calculations/power analysis and statistical analysis plans.
  - Work with the Consortium to develop case definitions, phenotype characterization, and diagnostic algorithms based upon collected data.
  - Provide statistical expertise for final data interpretation and publication.
  - Support the CSC and Consortium in their analyses to determine the incidence and prevalence of PASC in adults and children, identify predictors, understand the underlying biology, and support case definitions and algorithms.
- PASC Data Management, Harmonization, Integration, and Sharing
  - Work with the CSC and the Principal Investigators/leads of PASC Initiative studies to assemble and make available toolkits of rating scales, surveys, outcome assessments, and

questionnaires for adult and pediatric participants using common data elements (CDEs) wherever possible and to identify and implement the optimal mode of delivery (e.g., clinician evaluation, in-person, web, mobile app, telephone) for these tools.
    - Lead efforts for data harmonization, integration, curation, and sharing; track and coordinate data storage, transfer, and archiving; maintain data fidelity; and facilitate re-incorporation of study and diagnostic data back into EHR systems. For example, harmonizing formally-collected clinical data observations (from eCRFs and other sources) with other data sets such as the Trans-Omics for Precision Medicine TOPMed to facilitate cross-dataset analysis and allow for use of such data as controls.
    - Lead efforts for data harmonization and integration of mobile health data across the consortium, and coordinate strategies to return personal information based on mobile health data to participants when applicable.
    - Standardize clinical data collection with the CSC; facilitate transfer of data from the cohort studies to the DRC; harmonize data and map data to consistent data models across programs.
    - Obtain and manage participant data and maintain QA/QC of data.
    - Facilitate redaction and de-identification of data (e.g., removing PII/PHI) prior to submission to external databases and repositories, as appropriate.
    - When transferring data to external databases and repositories, ensure that data submissions are clearly linked to appropriate consent groups and that consent and associated Data Use Limitations are submitted and registered to each repository's controlled access authorization authority, e.g., dbGaP for BioData Catalyst (based on Institutional Certifications).
    - Ensure that provenance of data is maintained including managing de-identified participant IDs and capture of all data transformations and storage of untransformed data and data models.
    - Collaborate with the development and data management partners participating in N3C, BioData Catalyst, the Kids First Data Resource, and *All of Us* to ensure that data are ingested accurately, and in the manner most amenable to analysis using standard tools, that appropriate tooling is integrated and/or developed for analysis where necessary and made available for future use.
    - Prepare data for ingestion into the designated platforms as appropriate and according to platform specifications including submission of both raw untransformed data and transformed data and all associated transformations, data and meta-data models to enable full understanding of data provenance including deposition of transformations (tools, scripts, etc.), data and meta-data models in standard public repositories such as GitHub.
    - Ensure that consortium sites implement the Privacy Preserving Record Linkage "Hash tokens" consistent with the model being applied to N3C, C4R, *All of Us* and other repositories and programs.
- PASC Analytical Functions
    - In partnership with the CSC, within the designated platforms, facilitate tools, processes and workbenches for data analysis, including facilitation of data aggregation and meta-analyses for research within the Consortium .
    - Develop and adapt innovative tools for navigating and providing a portal for a cloud or other venue for data access and analysis (e.g. data workbench) by those outside the Consortium . The portal should include a dashboard of summary statistics, data and tools available and open access data such as synthetic data that is generated from the PASC project to maximize broad usability. Incentivize public interrogation and discovery.

- Ensure that Data Core managed systems obtain and maintain an Authority to Operate (ATO) compliant with applicable regulations and standards, including FISMA at the Moderate level and including cloud specific controls where appropriate. The Data Core will prepare all required Security Assessment and Authorization (SA&A) documentation based on NIST guidance and gain ATO approval from the appropriate Designated Authorizing Authority.
- Provide and maintain a schedule for submission of all data to public databases.
- Utilize and develop open source and well-documented software.
- Communicate and provide technical assistance to researchers, clinicians and PASC data collection sites.
- In partnership with the CSC, develop and manage the study website to serve as both an internal resource and public interface. Build focus area-specific domains to facilitate interactions.
- In collaboration with CSC and PASC Biorepository Core, develop and coordinate staff training for all data-related activities, use of CDES, use of CRFs and data collection tools such as use of a Laboratory information management system (LIMS) to allow for standardization of biological sample collection, interrogation and handling, etc. from receipt to storage/processing. Collaborate with CSC and PASC Biorepository Core in training investigators and staff on data management and data usage.
- Support collaboration across the program by coordinating data sharing, management and security, and data use and access, in coordination with, but not limited to, BioData Catalyst (dbGaP data access requests) and N3C (DUAs) procedures. Supervise and monitor these functions for fidelity.
- NIH encourages the use of data standards including common data elements, such as those available through the PhenX Toolkit (www.phenxtoolkit.org) and the NIH CDE repository (cde.nlm.nih.gov), terminologies and ontologies such as Mondo Disease Ontology (mondo.monarchinitiative.org), and Human Phenotype Ontology (hpo.jax.org),
- The Data Resource Coordinating Center is strongly encouraged to use OMOP models (https://www.ohdsi.org/data-standardization/the-common-data-model/) and Open mHealth schemas (https://www.openmhealth.org/documentation/#/schema-docs/schema-library) when applicable.
- Encourage adherence to federal health data standards including FHIR (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-122.html) and USCDI (https://www.healthit.gov/isa/sites/isa/files/2020-03/USCDI-Version1-2020-Final-Standard.pdf)- which includes three NLM supported vocabulary standards for codes (and names) for drugs, tests diagnoses, symptoms, some social determinants of health, some psychologic scores and all of the Medicare/Medicaid assessments.
- Communicate and provide technical assistance, as needed to encourage cross-program adherence to federal health data standards including FHIR (https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-122.html), USCDI (https://www.healthit.gov/isa/sites/isa/files/2020-03/USCDI-Version1-2020-Final-Standard.pdf), and HL7 FHIR Mobile Health Application Data Exchange Assessment Framework and Functional Requirements Implementation Guide (mHealth ADE FHIR IG; https://www.healthit.gov/sites/default/files/page/2021-01/AdvStandardsPrecisionMed_FinalReport.pdf), where applicable and within scope.

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required integration with the other components and for resolving any areas of disagreement. Applicants may apply for one, two, or all three components. If applying for more than one component, it should be noted that each component will be individually evaluated.

PASC Biorepository Core

The NIH is soliciting proposals for the PASC Biorepository Core (PBC). The PBC will:

- Establish a manual of procedures (MOP) and SOPs including, but not limited to, biospecimen preparation by submitters, shipping/batch shipments, specimen labeling/barcodes, specimen annotation, specimen preparation/processing on receipt, quality control, chain of custody, storage, inventory, tracking, and distribution.
- Receive, process, label, and store biospecimens, including autopsy specimens, using methods that preserve biospecimen integrity and scientific usefulness. Assure capacity for preserving biospecimens during events such as power failure.
- Harmonize biospecimen collection and receipt procedures.
- Provide training, leadership and guidance to investigators on biorepository processes for specimen collection, processing, and shipping. Distribute instructions and kits for sample collection, preparation, labelling and shipping to PASC investigators. Ensure adherence to procedures and standards.
- Link and integrate biospecimen information with clinical data from the same individual (in conjunction with CSC and DRC) while protecting the privacy and confidentiality of PASC research participants.
- Coordinate PBC activities and processes with PASC autopsy studies to the extent possible.
- Obtain applicable certifications and ensure compliance with applicable guidelines and standards for biorepositories such as
    - Collecting, Storing, Using, and Distributing Biospecimens. https://www.ncbi.nlm.nih.gov/books/NBK50729/
    - Biospecimen Collection, Processing, Storage, Retrieval, and Dissemination. 3/29/2016. Division of Cancer Treatment and Diagnosis, Cancer Diagnosis Program. National Cancer Institute. https://biospecimens.cancer.gov/bestpractices/to/bcpsrd.asp
    - CLIA or CLIA-equivalent certification
    - College of American Pathologist accreditation
    - GTR standards
- Provide QA/QC of biospecimens in coordination with CSC data QA/QC procedures and staff. Identify issues or problems needing remediation. Devise strategies to improve procedures and overcome difficulties.
- Provide inventory, monitoring, and regulatory reports to CSC leadership, as needed.
- Make biospecimens available.
    - Maintain an up-to-date inventory of biospecimens within the PBC and associated data that is accessible to researchers.
    - Facilitate access and maximize the scientific value of the PBC via utilization of CSC/PASC websites and resources to provide information on the PBC inventory and on how to request biospecimens.
    - Provide workspace to manage biospecimen and data requests.
    - Develop a process for review, adjudication and approval of biospecimen release/use requests.
    - Once approved, distribute quality biospecimens to requestors using standardized processes and procedures.

- Manage the PBC budget including costs of biospecimen intake, storage, management and distribution.
- Provide a mechanism for receiving and responding to PBC queries from researchers.
- At the end of the funding period and/or on instruction from NIH, deliver or ship to a repository specified by the NIH all biospecimens remaining together with the coded information needed to identify each sample by type and donor subject and to link to that participant's PASC data.

As noted in the Objectives, the Clinical Science Core, Date Resource Core, and Biorepository Core are presented in one ROA because they require close coordination and integration, each with the other; therefore, applicants must address specific processes and procedures for how they will achieve the required integration with the other components and for resolving any areas of disagreement. Applicants may apply for one, two, or all three components. If applying for more than one component, it should be noted that each component will be individually evaluated.

Special Award Terms

The complete terms and conditions of each OT Agreement or sub-agreement 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, the Clinical Science Core will be expected to issue sub-awards to entities identified and approved by the NIH under ROAs associated with the PASC initiative.

Negotiation

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 Coordinating Center 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.

Authority

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

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-Profit Organizations

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

Proposal Format and Requirements

The proposal should clearly and fully demonstrate the proposer's capabilities, knowledge, and experience and the budget proposed. Proposers shall provide a separate budget assuming an award term of four years to be funded on an annual basis. Proposals shall include a single Cover Page and for each Core being proposed a separate Project Plan and Budget. The Project Plan should be limited to a maximum of 12 pages for each Core for a maximum of 30 pages if applying to all 3 Cores.

The Cover Page should include:

A. The proposal title
B. The Awardee's
   i) Legal entity name
   ii) Address and contact information
   iii) SAM # and expiration date
   iv) DUN # and expiration date
   v) EIN number
C. The name and contact information for the Awardee's Principal Investigator (with NIH Commons Account information)
D. The name and contact information for the Awardee's Business Official, the person authorized to negotiate and bind the Awardee as a signatory to the Other Transaction agreement.
E. The total cost proposed

The Project Plan must address the following four elements:

A. Technical Approach

The proposal must describe how the work of the proposed Core(s) will be accomplished. The proposer must demonstrate its understanding of the PASC initiative and Core(s) being proposed by clearly showing a grasp of the range and the complexity of the work. This section should include a detailed project plan that includes milestones and deliverables for each phase of the Clinical Science Core, Data Resource Core, and/or PASC Biorepository Core implementation, with a particular focus on early steps needed to rapidly stand up the Core's key functions and capabilities. Proposers should demonstrate a conceptual understanding of the challenges specific to the tasks required in the ROA and suggestions for overcoming these. Applicants must address specific processes and

procedures for how they will achieve the required integration with the other components and for resolving any areas of disagreement.

B. Key Personnel Experience
Proposers must demonstrate experience of key personnel supporting the planning and implementation of activities described in the ROA. Please provide resumes describing key staff who will be assigned to manage performance and supervise the work for each task and subtask (as appropriate). These resumes will be reviewed to evaluate whether the individuals possess the required experience to perform the specific tasks. Resumes should be no more than three (3) pages in length and shall not count toward the page limits.

C. Management/Staffing Plan
Proposals should detail how the proposer will provide the necessary project administration, organization, and staff to ensure quality control, compliance with ROA expectations, and necessary staffing adjustments. In addition, proposers must demonstrate the ability to simultaneously manage multiple tasks within set time periods.

D. Past Experience
Proposers should provide at least 3 examples of prior project experience serving as an applicable Core (or in similar capacity) as described in this ROA. Each example should include the total funding awarded and dates of award, contact information for a sponsor able to serve as a reference, and a brief description of the project itself, including how the project was analogous to the needs identified in this ROA with respect to the Core(s) being proposed. Applicants will need to demonstrate prior work with clinical consortia or networks AND competency associated with the Core(s) being proposed.

The Budget must address the following:

The Budget section must provide a realistic, fully justified annual budget and cost proposal for performing the work specified in the ROA over a period of 4 years. Applicants must complete a SF424 budget. Budget information and any related administrative documentation shall not count toward the total proposal page limit.

The Budget should provide the overall expected cost 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 must be submitted via eRA ASSIST under OTA-21-015A and simultaneously emailed to NHLBI_OTA@mail.nih.gov not later than **March 16th, by 5 PM EDT**.

Inquiries can be submitted to NHLBI_OTA@mail.nih.gov. Financial and administrative questions should be addressed to Benjamin Sakovich, NHLBI Agreements Officer. Technical questions should reference in the subject line the OTA number and specific Core(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.