Research Opportunity Announcement

OTA-20-011A

Observational Studies of COVID-19 – A Cohort of Cohorts

Introduction

A wide variety of host and community-related factors – including age, sex/gender, race/ethnicity, socioeconomic status, lifetime exposures, and pre-existing disease – likely moderate the risks of and outcomes in COVID-19; this is evidenced by remarkable variations in the prevalence and severity of SARS-CoV-2 infection among different groups and the striking contributions of lung, cardiac, vascular, and hematologic dysfunction in COVID-19 morbidity and mortality. Given this, there is a critical need to systematically examine the characteristics of individuals who do and do not develop SARS-CoV-2 infection and serious sequelae of COVID-19. Such knowledge can identify risk factors, inform strategies for primary and secondary prevention, suggest prognostic and predictive biomarkers of infection and adverse outcomes, and illuminate pathophysiologic mechanisms that may be exploited with novel therapies. In addition, how infection and subsequent recovery from COVID-19 or the impact of its mitigation strategies influence risk of new or worsening heart, lung, blood, or sleep (HLBS) diseases, disorders, or health remains largely unknown.

Epidemiologic research often entails careful sampling of the population and detailed characterization of participants according to a stringent protocol. However, this type of sampling and data collection framework are likely not practicable 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 with sufficient numbers of exposed cases can be leveraged to provide invaluable resources that can be repurposed for research to understand the pathophysiology and complications associated with COVID-19.

The goal of this Research Opportunity Announcement (ROA) is to leverage the existing infrastructure, processes, data, and biospecimens from available cohorts or existing patient populations to establish a cohort of cohorts to rapidly launch assessments of the involvement of pulmonary, cardiovascular, and hematologic dysfunction in COVID-19 morbidity and mortality among diverse populations.

Because the incidence of severe COVID-19 resulting in hospitalization is relatively low, it may be necessary to assemble a sizable number of participants sufficient to accrue an adequate numbers of cases of severe COVID-19 to enable robust analysis of pre-exposure determinants of risk for adverse outcomes across groups defined by age, sex, race/ethnicity, and comorbid conditions. As a consequence, this program will prioritize cohorts, existing patient populations, and collaborations thereof, that are large and diverse, and those that can be readily combined with other populations recruited using similar design features and approaches, because no

single population will likely have sufficient size and diversity to address the goals of the program. Priority will be given to representative populations with relatively broad inclusion criteria that reduce the potential for selection bias, to populations with deep phenotyping conducted prior to the pandemic, and to studies with plans for continued longitudinal follow-up for HLBS and other outcomes.

Authority

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

Additional Information

- The NHLBI is soliciting letter of interests to develop a master protocol to establish a cohort of cohorts to study the involvement of pulmonary, cardiovascular, and hematologic dysfunction in COVID-19 morbidity and mortality among diverse populations to inform future efforts to combat the COVID-19 pandemic or minimize its consequences.
- Letters from groups with the following characteristics are strongly encouraged:
    - A strong track record of patient or participant follow-up and retention
    - Expertise in epidemiology and observational study design and conduct
    - Expertise in disease phenotyping related to HLBS diseases
    - Experience in using electronic health systems to identify and follow participants
    - Detailed plans for data and biospecimens collection
    - Identification of a large number of cases to facilitate inferences from multivariable and stratified statistical models
    - Plans for data harmonization that include creation or utilization of COVID-19 common data elements (CDEs)
    - Plans for rapid sharing of data and biospecimens for access and analysis by study and non-study investigators including deposition of data and biospecimens into an NHLBI approved repository
    - Strategies to rapidly ensure inclusion of appropriate patient or participant populations to enhance generalizability of research findings

Eligibility

Organizations

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)

Scope

The goal of this ROA is to leverage the existing infrastructure, processes, and data from available cohorts or disease populations to rapidly carry out observational research on the involvement of pulmonary, cardiovascular, hematologic, and sleep dysfunction or disorders in COVID-19 morbidity and mortality. The program is intended establish a cohort of cohorts to capture data and to collect and analyze biospecimens as appropriate to identify factors that are associated with the prevalence, severity, or outcomes due to SARS-CoV-2. 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 NHLBI-approved repository to facilitate access and analysis by study and non-study investigators. The ultimate master protocol should include the collection of data on cardiopulmonary comorbidities as needed as well as measures that would reflect the involvement of HLBS systems in COVID-19 or its sequelae. 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 prevalence rate of COVID-19 or of SARS-CoV-2 infection overall and according to pre-existing HLBS diseases.
- Determination of the prevalence rate of complications, including pneumonia, stroke, thrombosis, myocardial infarction, respiratory failure, coagulopathy, hospitalization, and/or death due to COVID-19 overall and according to pre-existing HLBS diseases.
- Identification of the presence of disparities in COVID-19 and its complications, including factors that may be responsible for these differences across populations.
- Multivariable analyses of factors suspected in COVID-19 severity, recovery, 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, clinical characteristics, presence of clinical or subclinical disease, genomic or other sequence data, inflammatory factors, markers of immune function, cardiopulmonary 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 COVID-19, presence of SARS-CoV-2 infection, or a positive serologic test is associated with new or worsening HLBS diseases, disorders, or health. Identify optimal approaches to distinguish between infection and immunization.
- Analyses to evaluate the association of HLBS disease treatments, including medications on COVID-19 and its complications.
- Determine whether trends exist in reports of stress, depression, substance abuse, health insurance coverage, housing instability, access to medical care, and other economic hardships experienced as a result of the COVID-19 pandemic and related mitigation strategies.
- Determine whether changes occur to health care utilization relevant to HLBS prevention or management as a result of the COVID-19 pandemic.
- Determine the impact of irregular sleep patterns and sleep deficiency on cohort immune responses to COVID-19 and related HLBS complications.

What is NOT eligible for funding under this ROA?

Examples include (but are not limited to) the following:

- Animal and *in vitro* research
- Clinical trials
- Community-directed research

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 NHLBI 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 NHLBI, successful multicenter Coordinating Center proposers will be expected to issue sub-awards to entities identified and approved by the NHLBI under this ROA.

Milestone Based Payment Schedule

NHLBI 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 NHLBI.

An "Operational Milestone" is an objective, measurable event that is indicative of project progress occurring as proposed in the application. NHLBI 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 NHLBI, adjustments may be made to the timeline for inclusion in the OT Agreement to ensure that funds are appropriately dispersed across Operational Milestones. If NHLBI determines, in its sole discretion, that an awardee has failed to satisfy one or more Operational Milestone(s), NHLBI 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 observational study initiative, (2) quality of the letters received, and (3) availability of funds. Agreements for all awards will be negotiated with eligible entities whose letters are determined to be the most meritorious and provide the best value to the NHLBI toward achieving the goal of HLB function and disease in the context of SARS-CoV-2 infection.

The NHLBI reserves the right to:

- select for negotiation all, some, one, or none of the letters 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 letters in their entirety or to select only portions of letters 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 NHLBI;
- fund proposers as sub-awardees of a separate Coordinating Center entity to be established by the NHLBI;
- 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 Process

Submission in response to this ROA requires submitting a Letter of Request.

NHLBI will review and determine whether the applicant should be invited to participate in a cohort of cohort's observational study. The NHLBI may request additional information be provided by the applicant to complete their eligibility. These requests will be sent to the applicant via email. Applicants are strongly encouraged to provide the requested information in a timely manner to prevent any potential delays in the review process. Letters that do not meet the initial Observational Study ROA program and eligibility criteria will be rejected.

The minimum required elements to be eligible for participating in the NHLBI cohorts of cohort's program include:

- An ongoing cohort study (population or HLBS diseases) with well characterized baseline data and established plans for continued follow-up.

In addition, for NHLBI to make an informed decision about whether to accept a proposed project, the Letter of Request should not exceed 3 pages and should include:

- The proposed project title
- Description of the existing cohort including how many subjects are readily available for enrollment in the study.
- The expected start date to launch the study (with the expectation of launching within 2-4 weeks of funding)
- The key personnel (the eRA Commons *userid* must be included for the PI or contact PI)
- The submitting organization or institution
- Demonstrated ability of the group or history of the investigators in conducting observational multi-center research
- Expertise of the investigative team in performing HLBS-relevant phenotyping of human subjects
- Capacity of the investigators and associated consortia of cohorts for enrollment and evaluation of adequate numbers of patients/participants
- Succinct summary of the 4-5 most compelling research question(s) to be addressed with a cohort of cohorts.
- 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 the diagnosis, consequences of infection or mitigation strategies, treatment and recovery, and/or prevention of COVID-19 and COVID-19 related conditions
- Efforts to standardize and collaborate with other studies including utilization, as appropriate, of COVID-19 CDEs, harmonized phenotypic measures, and leveraging multiple existing cohorts, or other relevant infrastructure and studies.
- Willingness to work collaboratively to develop a single master protocol for this project.
- Direct and total costs by year, and for the entire duration of the study – generally a one-paragraph description of major sources of costs in the study using one of the tables provided via the following link. Specify (1) any funding provided by other entities

(federal agencies, foundations, companies), and (2) any goods or services (and their value) provided by any of these parties, including assays, equipment, procedures, etc.

- 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.
- 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 NHLBI-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
- Letters that include centralized coordinating and data analysis functions should provide evidence of experience in extracting and harmonizing data across data management systems developed for different questions.

Budget

The Budget section of the letter must provide a realistic, fully justified budget and cost for performing the work over a specified period of performance needed to accomplish project objectives. In particular, the budget must include a proposed Operational Milestone-based payment schedule, including objective completion criteria and anticipated completion date for each Operational Milestone. 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 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 NHLBI. (see “Financial Contingency Plan” under Project Plan elements).

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

For best consideration, Letters of Request should be submitted via email by **Monday, July 27, 2020, by 5 PM EDT** 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 be addressed to the NHLBI Division that best aligns with the study: James Kiley, Division of Lung Diseases, David Goff, Division of Cardiovascular Sciences and Keith Hoots, Division of Blood Diseases and Resources.

A note about eRA Registration

NHLBI 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 letter 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/