



American  
Heart  
Association.

## Mechanisms Underlying Cardiovascular Consequences Associated with COVID-19 and Long COVID

### Request for Applications:

#### Key Dates

RFA Published Online	December 10, 2021
ProposalCentral open for this mechanism	December 17, 2021
Application Deadline	February 1, 2022 by 3 PM Central
Peer Review	February – early March 2022
Notification of Applicants	By March 15, 2022
Award Start Date	April 1, 2022

#### Purpose

The American Heart Association (AHA) announces a Request for Applications (RFA) to study mechanisms that underly cardiovascular and cerebrovascular effects of COVID-19 and/or Long COVID.

The COVID-19 (Coronavirus Disease 2019) pandemic has had a devastating global impact, resulting in over 5,000,000 deaths. In the United States alone, nearly 800,000 individuals have died from COVID-19. Like other diseases associated with the coronavirus family such as SARS (Severe Acute Respiratory Syndrome), COVID-19 is a disease of the respiratory system. COVID-19 often results in an extensive array of clinical symptoms, however, and those most likely to succumb to COVID-19 often have a number of co-morbidities, including hypertension and cardiovascular disease.

In response to the coronavirus pandemic, the international scientific enterprise has acted rapidly. This has resulted in advances in understanding of the biological effects of coronavirus, and in significant advances in combating its effects. For example, vaccines developed for COVID-19 are extremely efficacious, resulting in a substantial decrease in infection and death. Recent data from the Center for Disease Control and Prevention (CDC) indicate unvaccinated individuals are 6.1 times more likely to get COVID-19, and they are 11.3 times more likely to die from it (<https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status>).

Also promising are development of therapeutics that appear to be effective in minimizing hospitalizations and death from COVID. A number of monoclonal antibodies have received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) for treating mild or moderate COVID in those who are at high risk for serious complications. In addition, the antiviral drug remdesivir has been approved by the FDA to treat those hospitalized with COVID. As of November 2021, the FDA is considering approval of two oral antiviral agents for EUA. Initial results show these agents can significantly reduce hospitalization or death in high-risk patients compared to placebo.

Despite the advances in vaccination and treatment, the likelihood that COVID-19 remains a prominent health challenge is high. Indeed, there is a developing consensus that COVID-19 will not be eliminated. A number of factors underly this expectation, including the possible emergence of novel strains that may be resistant to vaccines, uneven vaccination rates globally, and lack of broad availability of effective treatments. This point has been driven home recently with the emergence of the novel omicron variant. This variant has dozens of mutations, some of which could result in reduced efficacy of currently available vaccines. This variant has spread rapidly through communities in South Africa, where it is believed to have emerged.

It thus remains critically important to understand the mechanism through which COVID-19 acts. Cardiovascular complications of COVID-19 include venous thrombosis, myocarditis, arrhythmias, heart failure, and myocardial infarction (Tomidokoro and Hiroi, *J Cardiol*, <https://doi.org/10.1016/j.jjcc.2021.09.010>, 2021). Whereas our understanding of the biology of coronavirus has grown, including its effects on the heart and vasculature, major gaps remain in understanding mechanism(s) underlying these consequences of COVID-19.

It became apparent relatively early in the pandemic that a subset (estimated at 10-30%) of those who contract COVID-19 will suffer from its effects well beyond the expected time course of 2-3 weeks. This phenomenon has been termed, among other names, Long COVID, post-COVID, Long-haul COVID, Chronic COVID syndrome. The description of the condition, including the duration symptoms may persist, has varied (Yong, *Infect. Dis.* 53: 737, 2021 and references therein). The CDC describes this condition as “a wide range of new, returning or ongoing health problems people can experience four or more weeks after first being infected with the virus that causes COVID-19. Even people who did not have COVID-19 symptoms in the days or weeks after they were infected can have post-COVID conditions. These conditions can present as different types and combinations of health problems for different lengths of time.”

<https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html>

Whereas in some cases Long COVID symptoms may be an extension of those present during active COVID-19, recent meta-analyses suggest a more extensive array of symptoms during Long COVID, possibly upwards of 100 (Hayes et al., *Frontiers in Med*, 2021; Lopez-Leon et al., *Sci Reports*, 2021). In addition, whereas a precise definition of Long COVID remains elusive, it is apparent that some of the most frequently reported symptoms have clear or likely cardiovascular-related aspects; these include fatigue, chest pain, and shortness of breath (Hayes et al., *Frontiers in Med*, 2021; Lopez-Leon et al., *Sci. Reports*, 11: 16144, 2021; Sudre et al., *Nature Med*, 27:626, 2021). Effects of Long COVID on the central nervous system are also common, including both psychological effects such as anxiety and depression, as well as cognitive effects such as confusion and deficits of memory and concentration.

The cause(s) of Long COVID are also not understood; due to the array of symptoms observed, several pathologies and/or dysfunctions are likely to be involved. A number of studies have reported evidence of long-term damage to tissues, including the heart and brain. Results from other studies suggest a persistent pathologic inflammatory state may contribute to Long COVID (Yong, *Infect. Dis.* 53: 737, 2021). In general, however, understanding of the factors underlying Long COVID remains poor.

COVID-19 has differentially impacted racial and ethnic groups. Whereas the disparities across populations have decreased somewhat since the early stages of the pandemic, significant racial and ethnic disparities remain. For instance, recent data from the CDC shows that rates of hospitalization and death remain at

least two-fold higher for American Indian and Alaska Natives, Black individuals, and Hispanic or Latino persons (<https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html>). The disparities are also apparent in Long COVID.

## Science Focus Areas of Interest

To better understand both COVID-19 and Long COVID, the American Heart Association (AHA) invites research proposals that will contribute to understanding the mechanism(s) underlying cardiac, vascular and cerebrovascular effects of these conditions, as well as mechanisms that contribute to differential susceptibility to Long COVID. Proposals are sought that will utilize contemporary and innovative approaches to assess tissue damage and/or dysfunction of the heart and vasculature/cerebrovascular, and/or potential associated dysregulation of various signaling pathways and systems. Proposals directed toward leveraging basic mechanistic discoveries, including identification of biomarkers, to develop therapeutic approaches for cardiovascular consequences of COVID are also of interest. Due to the heterogeneity of Long COVID, important insights into key mechanistic underpinnings and potential treatment strategies are most likely to be achieved in participant populations with well-characterized phenotypes.

**Because of the racial and ethnic disparities associated with COVID-19 and Long COVID noted above, proposals should have a strong focus on inclusion of demographically diverse subject populations.** Applicants proposing studies engaging individuals who have active Long COVID are encouraged to consider utilization of a patient-centered approach in designing, conducting and disseminating their studies (<https://www.pcori.org/research-results/2021/using-body-mapping-develop-patient-centered-research-agenda-about-long-covid>).

## Important Notes

- NOTE: All applicants MUST incorporate the naming of *at least* two full-time pre- or postdoctoral trainees during the three-year award term. Additionally, *at least one* other early-career faculty member (up to and including assistant professor) must be included in a substantive manner during the award period.
- Applications must be received before 3 p.m. Central Time on the deadline date. Early submission is encouraged, as the system closes at 3 p.m. Central Time and will not accept submissions after that time.
- Potential applicants should review the Features of All AHA Awards on the [AHA Application Information](#) page for answers to commonly asked questions about eligibility and award details. NOTE: scroll down to see “Features of AHA Awards.”
- All proposals must be submitted electronically via [ProposalCentral](#). The system will open several weeks prior to the application deadline. You can, however, begin to create your documents at any time; please refer to the [AHA Application Instructions \(PDF\)](#).
- Applicants must be [AHA Professional Members](#) at the time of application. This must be completed online. Join or begin the membership process well before the deadline.

- AHA strongly supports diversity and inclusion and encourages applications from women, underrepresented racial and ethnic groups in the sciences, military veterans, people with disabilities, members of the LGBTQ community, and those who have experienced varied and non-traditional career trajectories.

## Relevant Policies and Requirements

### Institutional Eligibility / Location of Work:

AHA awards are limited to U.S.-based non-profit institutions, including medical, osteopathic and dental schools, veterinary schools, schools of public health, pharmacy schools, nursing schools, universities and colleges, public and voluntary hospitals and others that can demonstrate the ability to conduct the proposed research. Applications will not be accepted for work with funding to be administered through any federal institution or work to be performed by a federal employee, except for Veterans Administrations employees.

### Eligibility of Project PIs:

- Must hold a doctoral-level degree.
- Must hold a faculty-rank position of any level. This award is not intended for trainees.

### Required Assurances:

- For all applications selected for funding, all institutional assurances (e.g., IACUC, IRB) must be submitted to AHA prior to release of funds.

**Interim Assessment:** Awardees must report progress on a minimum annual basis. Progress assessment may take the form of a required written report in addition to video conferencing, phone calls, and/or face-to-face visits. Reporting will be focused on achievement of stated milestones as indicated in the project timeline. AHA reserves the right to request additional updates, site visits, or reporting.

**Public Access:** The AHA's public access policy requires that all journal articles resulting from AHA funding be made freely available in PubMed Central (PMC) and attributed to a specific AHA award within 12 months of publication. It is the responsibility of the awardee to ensure journal articles are deposited into PMC.

**Open Data:** Any factual data that is needed for independent verification of research results must be made freely and publicly available in an AHA-approved repository within 12 months of the end of the funding period (and any no-cost extension). Moreover, the COVID-19 pandemic has led to an unprecedented demand for data. To accelerate science, an emphasis has been placed on having COVID-19 related data available in easy-to-use formats that are machine-readable and non-proprietary. Both using and creating open data align with the AHA's strategic goals.

**Other Data Sharing:** Awardees may also be required to deposit all data collected through this funding mechanism to the AHA's Precision Medicine Platform (below). Supporting information needed to verify results, such as data dictionaries and codebooks, should also be deposited to adhere to the FAIR (Findable, Accessible, Interoperable and Reusable) Guiding Principles of Data Stewardship.

**Preregistration:** AHA requires clinical trials to preregister using ClinicalTrials.gov.

For more information on the above policies, see AHA's [Open Science Policy](#) webpage.

**Use of AHA's Precision Medicine Platform:** Applicants are encouraged to utilize **AHA's Precision Medicine Platform (PMP)**, powered by Amazon Web Services.

- The PMP supports cloud computing in a secure and private workspace and enables investigators to collaborate and analyze data securely. Funded projects may be eligible to receive Amazon Web Services computational credits to offset the cost of using the platform. Grantees requesting a workspace are asked to pay a nominal annual license fee, which may be charged to the AHA award or invoiced to the grantee directly. Please refer to this [FAQs \(PDF\)](#) document for more details.
- Data analysis is enabled in secure workspaces by a friendly web user interface that allows researchers to code in various languages, including R and Python and use statistical software including but not limited to SAS and R studio. The most up-to-date machine learning and artificial intelligence software available from Amazon Web Services is also included. For a full list of the analytical tools available, please see [precision.heart.org/workspace/about](https://precision.heart.org/workspace/about). Researchers are also able to upload their own tools.
- To learn more about the Precision Medicine Platform and how it can enable your research, please access the following videos. The first ([Learn more about the platform – video 1](#)) provides a high-level overview, while the second ([Explore the capabilities of the platform – video 2](#)) provides more detail about accessing data and analytical tools, data storage, and sharing of data.
- The Platform is HIPPA and FedRAMP compliant.

## **Award Amount and Duration**

Grant amounts will be a minimum of \$500,000 and a maximum of \$1,000,000 over a three-year funding period, including up to 10 percent institutional indirect costs. The AHA anticipates funding up to \$10 million in awards.

### **Submission requires the following:**

- Applicant/PI NIH Biosketch (5 pages) and Biosketch of Co-Investigator(s), if applicable
- Budget Request and Justification (2 pages)
  - Provide a total budget request between \$500,000 and \$1,000,000 across the three-year period, inclusive of the 10 percent institutional indirect costs.
  - A line-item detailed budget is not required but a [Budget Justification \(DOC\)](#) narrative must be included.
- [Research Project Environment \(DOC\)](#) (2 pages)
- Research Plan (up to 6 pages), inclusive of the following:
  - Specific Aims
    - Provide a clear, concise summary of the aims of the work proposed and its relationship to your long-term goals. State the hypothesis to be tested.
  - Background and Significance
    - Sketch the background leading to this application. Summarize important results outlined by others in the same field, critically evaluating existing knowledge. Identify gaps that this project is intended to fill.
    - State concisely the importance and relevance of the research to cardiovascular and/or cerebrovascular function or disease, or to related fundamental problems. Also, it is incumbent upon the applicant to make a clear link between the project and the mission of the AHA. The significance section will be assessed in terms of potential

impact on the AHA mission; this will be factored into the overall priority score as noted in the peer review criteria.

- Preliminary Studies (if applicable)
  - Describe concisely previous work related to the proposed research by the applicant that will help to establish the experience and competence of the investigator to pursue the proposed project. Include pilot studies showing the work is feasible. (If none, so state.)
- Research Design and Methods
  - Description of proposed tests, methods or procedures should be explicit, sufficiently detailed, and well defined to allow adequate evaluation of the approach to the problem. Describe
  - Discuss any new methodology and its advantage over existing methodologies.
  - Clearly describe overall design of the study, with careful consideration to statistical aspects of the approach, the adequacy of controls, and number of observations, as well as how results will be analyzed. Include details of any collaborative arrangements that have been made.
  - Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims
- Literature Cited (2 pages)
- Summary for Non-scientists/Lay Summary
  - The lay summary is not a document to be uploaded, rather it is entered through form fields in ProposalCentral. It is listed here so that the applicant is aware this is required.

## Peer Review

Peer review for this program will be conducted using a [distributed peer review approach](#) (Merrifield and Saari, *Astronomy and Geophysics*, 50, 4.2, 2009). This is also known as the [Mechanism Design Proposal Review Process](#).

Distributed peer review relies on the principles of a traditional peer review panel: academic integrity, rigor, transparency, and a desire to advance the best science. As opposed to traditional peer review, distributed peer review capitalizes on the expertise of the applicant pool and incentivizes timely review in fairness to all applicants. Additionally, this peer review mechanism exposes applicants to new ideas and could foster new potential collaborations.

**All applicants who submit a proposal will be required to serve as a peer reviewer within this program and will be assigned 6-9 proposals for review.** By agreeing to the program terms at the time of proposal submission, the principal investigator is concurrently agreeing to serve as a peer reviewer within this program and meet all peer review expectations and requirements.

Principal investigators will declare conflicts of interest and will only be assigned proposals for which they do not have an institutional or individual conflict; PIs (reviewers) are bound by all other requirements associated with peer review. PIs will be provided ~30 days to complete review and scoring of the proposals to which they are assigned.

**Only peer reviewers who complete their assigned reviews and record their scores in a timely fashion will**

**in turn have their own proposal evaluated** for advancement. Principal investigators who have not completed their reviews nor submitted their scores by the stated deadline will have their proposals withdrawn and returned as not in compliance with the program announcement, and they will not receive scores should any have been completed for their proposal.

Peer review will require submission of scores using ProposalCentral; there will be no peer review panel discussions or meetings. All other [AHA Peer Review processes](#) apply.

Contacting AHA peer reviewers concerning your application is deemed a form of scientific misconduct and will result in the removal of your application from funding consideration and institutional notification of ethical concerns.

### **Peer Review Scoring Criteria**

To judge the merit of the application, reviewers will score proposals according to the following criteria. Reviewers will not be asked to provide written feedback.

1. **Approach:** Are the conceptual framework, design, methods and analyses adequately developed, well integrated, well-reasoned and appropriate to the aims of the proposal? Does the applicant acknowledge potential problem areas and consider alternative tactics?
2. **Significance:** If the aims of the application are achieved, will knowledge or clinical practice be significantly impacted? Will there be an effect on the concepts, methods, and technologies that drive this field?
3. **Investigator and Environment:** Is the investigator appropriately trained and well suited to carry out this work, even if relatively new to COVID-19 or Long COVID research? Does the investigative team bring complementary, appropriately qualified, and integrated expertise to the proposal (if applicable)? Does the proposal benefit from specific features of the environment, or subject populations, or employ useful collaborative arrangements?
4. **Innovation:** Is this a highly innovative, high impact proposal that could lead to significant advances in addressing COVID-19 or Long COVID?
5. **Impact:** Applications for research funding will be assessed for their potential impact on the AHA Mission, and on the applicant's ability to effectively describe the proposal and its potential outcomes to non-scientists. This potential impact assessment will be based primarily on the Summary for Non-scientists. This assessment will be factored into the Impact peer review criterion, which will account for 5-10% of the overall priority score.

### **Questions**

Please direct inquiries regarding any aspect of this RFA to [strategicawards@heart.org](mailto:strategicawards@heart.org)

### **American Heart Association and the Global COVID-19 Pandemic**

Visit [AHAjournals.org/Coronavirus](https://AHAjournals.org/Coronavirus) for the AHA president's statement, related journal articles, and other resources. Included on the site is a Circulation series of video interviews on best practices and insights from healthcare providers on the front lines, across the U.S. and around the world.