Strategically Focused Research Network (SFRN) on Inflammation in Cardiac and Neurovascular Disease

Key Dates

RFP Posted:	Tuesday, August 29, 2023
Required Pre-proposal Deadline:	Tuesday, November 28, 2023
Proposal Deadline:	Tuesday, January 23, 2024
AHA 2-Phase Peer Review:	February and March 2024
Notification of Awards:	March 2024
Award Start Date:	April 1, 2024

Applicant Requirements and Background

AHA Membership Requirement

Any individual applying as a Center Director or a Project Principal Investigator (PI) must be an AHA Professional Member before submitting a full proposal. (Membership is not required to submit a pre-proposal.) Join or renew when preparing an application in ProposalCentral, online, or by phone at 301-223-2307 or 800-787-8984. Membership processing may take 3-5 days; do not wait until the application deadline to renew or join.

Required Pre-Proposal

Each Center Director is required to send a pre-proposal to provide the following (DATE HAS PASSED):

- Name and institution of the Center Director and each Project PI
- Center title, and title and performance site of each proposed project

If required, the mechanism through which partnering requirements are being met. See "Additional Expectations and Opportunities" and "Institutional Eligibility/Location of Work" sections.

As part of the required Pre-Proposal, if the submitting institution or a partnering institution is not a research-intensive institution of higher learning, the lead for that institution must upload a letter from a Senior Institutional Official (e.g., president, provost, dean, etc.) indicating they meet the definition of a non-research-intensive institution as stated in the "Additional Expectations and Opportunities" section.

AHA staff will review for compliance. A non-complying institution will not be permitted to submit a full proposal. This administrative review is part of the Pre-Proposal process, which is required and, though rare, may prevent an applicant from moving forward. Even though the Pre-Proposal is required, each Center and Project applicants should begin planning and designing their applications *before* the Pre-Proposal deadline to maximize the amount of time available to develop their full proposal.

Purpose
The American Heart Association (AHA) announces this Request for Proposals for the Strategically Focused Research Network (SFRN) on Inflammation in Cardiac and Neurovascular Disease.

THE ROLE OF INFLAMMATION IN CARDIAC AND NEUROVASCULAR DISEASE

Throughout the body, inflammation plays a crucial role in maintaining tissue homeostasis and initiating appropriate immune responses against pathogens or injury. However, dysregulation of inflammatory processes can lead to detrimental effects, contributing to the development and progression of many disease states, such as autoimmune conditions, cancer, diabetes, kidney disease and liver disease.[1]

The heart and nervous system are also subject to disease with dysregulation of the inflammatory system. Inflammatory myocarditis, characterized by inflammation of the myocardium, is more likely to occur in males compared to females.[2] It is most commonly triggered by viral infection; triggering viruses include adenoviruses, enteroviruses, parvoviruses and coronaviruses (including SARS-CoV-2), among others.[3] Less commonly, myocarditis is caused by bacterial or fungal infection or autoimmune diseases. Of more recent note, it was discovered during the COVID-19 pandemic that vaccines developed against SARS-CoV-2, particularly those using mRNA technology, elicited myocarditis in a subset of vaccine recipients.[4] The highest incidence (approximately 50 / 100,000) was found in men under 40.

Myocarditis can be subclassified based on a number of characteristics. The most prominent symptoms are chest pain and dyspnea,[5] and in many cases, myocarditis may resolve on its own. One notable exception is fulminant myocarditis, a rare and severe form of myocarditis that is responsible for a high proportion of cardiac-related deaths in young individuals.[6] Acute myocarditis is defined as that for which symptoms are of recent onset, generally within a month or so. Inflammatory processes associated with myocarditis, such as infiltration of immune cells, release of pro-inflammatory cytokines, and oxidative stress, can lead to myocyte damage, fibrosis, and impaired contractility.[3,7-8] Myocarditis that is associated with cardiac dysfunction and remodeling of the ventricle is referred to as inflammatory cardiomyopathy, a condition that is typically irreversible. It may result in arrhythmias, ventricular dysfunction or heart failure and requires lifelong therapy and/or heart transplant.

Within the nervous system, inflammation has been implicated in an array of pathologies, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.[9-10] Inflammation also plays a prominent role in stroke.[11-13] A robust neuroinflammatory response is initiated following an ischemic event. Sex differences are also observed with stroke, with the risk being higher for females than males.[14] The primary cause of this neuroinflammation is the activation of immune cells in the brain, including microglia and astrocytes. These cells are responsible for defending the brain against pathogens and injuries. However, under certain conditions, they can become overactivated and release inflammatory molecules. Neuroinflammation can have both beneficial and detrimental effects. In acute situations, neuroinflammation helps clear pathogens, promote tissue repair, and support the restoration of normal brain function. However, chronic or excessive neuroinflammation can damage neurons, impair synaptic communication, break down the blood-brain barrier, and disrupt the delicate balance of the brain's environment.[11]

CARDIOTOXICITY

Cardiotoxicity describes a condition wherein a decrease in cardiac function results from administration of drugs or other agents. Currently, the term is largely identified with changes in cardiovascular function resulting from treatment with a number of cancer therapies. Whereas a decrease in left ventricular ejection fraction is the cardiac parameter most closely aligned with cardiotoxicity, additional cardiac effects (e.g., left ventricular systolic dysfunction, angina, and acute coronary syndrome) may also be characterized as cardiotoxicity.[15]
There are several potential mechanisms underlying cardiotoxicity of chemotherapeutic agents, including inflammation. For example, use of chemotherapeutics of the anthracycline class, widely prescribed because of their efficacy against both solid and hematologic tumors, is associated with a high incidence of cardiotoxicity.[16] Despite this effect of anthracyclines being described decades ago, the mechanism(s) underlying cardiotoxicity are not fully elucidated. Studies in more recent years do suggest, however, that at least part of the cardiotoxic actions of anthracyclines are related to inflammation.[17] In addition, pre-clinical studies assessing effects of anti-inflammatory agents against anthracycline-induced cardiotoxicity have shown favorable results.[18-19] Targeting inflammation thus holds promise for preventing or mitigating cardiotoxic effects of this class of chemotherapeutic.

More contemporary cancer treatments also elicit adverse cardiac effects. Immune checkpoint inhibitors (ICIs), a new and promising class of anti-cancer drugs, may elicit a severe form of myocarditis.[20] Whereas the incidence is relatively low, the mortality rate is high, due in part to the fact that many individuals present with a fulminant-like form of myocarditis. The mechanism underlying ICI-induced myocarditis remains unclear. The promise of this new class of cancer treatment will not be fully realized unless the mechanism is identified, which will facilitate therapeutic strategies to prevent or mitigate this severe adverse effect.

While our understanding of the role inflammation plays in cardiac and brain dysfunction has grown considerably in recent years, several hindrances remain that preclude improved recognition and treatment of these conditions. For instance, significant gaps remain in understanding of the downstream signaling events and potential crosstalk; development of new animal and in vitro models would support these needs. In addition, notable opportunities for optimization of diagnostic capabilities exist, such as identification and assessment of biomarkers with improved specificity and development of improved imaging techniques. Clinical trials designed to assess outcomes more specifically for distinct types and/or stages of inflammatory conditions are also needed.

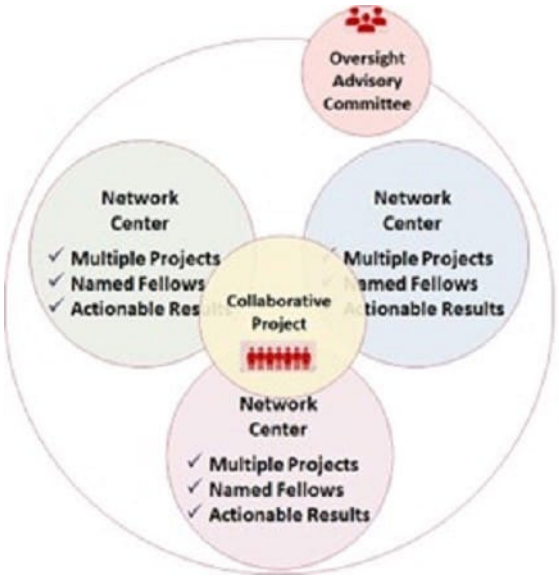
Network Overview and Structure

GENERAL OVERVIEW

This SFRN on Inflammation in Cardiac and Neurovascular Disease will consist of at least three centers, each of which will propose novel research studies to address this issue. Funded centers will be expected to collaborate on solving the core issues underlying this problem, including via development of a common network-wide collaborative project (see below).

NETWORK CENTERS

Each center application will include three (3) research projects, one of which must be categorized as a basic science study, with a second having a clinical/translational component. Applicants may choose the science discipline (basis, clinical/translational, or population health) for their third project.



Projects may all be from a single institution, or they may be from multiple institutions. A Project Principal Investigator (PI) will lead each research project, and must have the necessary research team, required infrastructure and ability to conduct the stated research. One overall Center Director will also be a key component of each center. Each Center's Director will facilitate activities within their center and work closely with the other Network Center Directors to facilitate activities across the Network, including end-of-network deliverables.

OVERSIGHT ADVISORY COMMITTEE

To facilitate the success of this SFRN, an Oversight Advisory Committee (OAC) will be established. The OAC will be comprised of volunteers who are subject matter experts in the focus areas.

REPRESENTATIVE APPROACHES RESPONSIVE TO THIS RFA

The intent of this initiative is to support a collaborative network of researchers whose collective efforts will lead to enhanced understanding of the role of inflammation in the myocardium, cardiotoxicity, and/or neurovascular disease. Potential areas of investigation are listed here; this list is not exhaustive and is not meant to direct applicants to a particular area of study:

1. Mechanistic assessment: Whereas much is known about the molecules activated with cardiac and neural inflammation, the intricate interactions between these molecules and the downstream signaling cascades are not well understood. Elucidating the signaling pathways, cellular interactions, and immune responses involved will provide a foundation for the development of targeted therapies.

2. Novel models: Several animal models exist for inflammation-driven cardiac and neural pathologies; these models have significant limitations, however. Models that better mimic conditions observed in humans are needed for improved understanding of mechanism and assessment of potential therapeutic approaches.

3. Therapeutic targets: The development of anti-inflammatory therapies has shown some promise for improving outcomes in cardiac- and stroke-related conditions driven by inflammation; additional clinical trials are needed to further assess this approach. Future research should focus on identifying and testing specific inflammatory pathways and molecules that can be therapeutically targeted to modulate the inflammatory response and improve outcomes.

4. Improved detection and diagnostics: Improvements in viral detection methods are needed to improve accuracy of diagnosis of myocarditis/inflammatory cardiomyopathy. There is also a need to discover novel biomarkers that can differentiate between various causes of myocardial injury and more accurately reflect disease severity.

5. Enhanced imaging techniques: Current imaging techniques for inflammation-driven pathology for both cardiac and neural tissues provide important information, but the ability to identify specific inflammatory conditions through imaging remains limited. There is thus a need for more sensitive and selective cellular and molecular markers, which should facilitate diagnosis and treatment strategies.

6. Influence of genetics: There is a growing recognition of the importance of individual variations and genetic factors in the susceptibility, progression, and response to treatment in cardiomyopathy and cardiotoxicity. Understanding the interplay between genetic variations, inflammation, and disease outcomes could contribute to the development of tailored therapeutic approaches.

7. Influences of sex and gender differences: Sex is known to influence susceptibility to myocarditis and stroke, with men being more susceptible to the former and women more susceptible to the latter. These differences are not fully understood. In addition, the role of biologic sex compared to gender, a social construct, in susceptibility to these conditions is not clear. Understanding the contributions of these factors to myocarditis and stroke should greatly facilitate treatment approaches.

STUDY POPULATION(S)

- For studies involving human subjects, projects must include study participants who are under-represented and/or underserved with regard to healthcare delivery. The proportion of these individuals in proposed studies should be reflective, at a minimum, of their representation in the local/regional population from which subjects will be recruited.

- It will be important for applicants to design studies that incorporate both realistic recruitment goals and sufficient statistical power to ensure valid results.

ADDITIONAL EXPECTATIONS AND OPPORTUNITIES

In keeping with AHA's commitment to supporting diverse researchers and institutions, one of the following conditions must be met. A letter will be required as part of the required pre-proposal confirming that the institution meets these conditions.

- Center applications must originate from investigators at academic institutions that primarily serve individuals from groups who are under-represented in science (e.g., Historically Black Colleges and Universities (HBCUs), Hispanic-Serving Institutions (HSIs) or Tribal Colleges and Universities (TCUs)) or from investigators at a non-research-intensive institution as defined by NIH (an average of less than $7.5M in total NIH funding over the past three fiscal years).

  OR

- For center applications originating from research-intensive institutions, those institutions must partner with an institution from one of the two categories noted in the preceding paragraph. Investigators from these partnering institutions must be included in a substantive manner (see Projects section below).

Application Details

NETWORK CENTER APPLICATION DETAILS

Award Duration: Four (4) years

Number of Awards: The AHA anticipates awarding at least three (3) Network Center grants to establish this SFRN. Awardees will be selected based on scientific merit and how each group aligns with AHA's mission and goals.

Collaborative Project: During Year 1 of the Network, the Centers will be required to develop a Network-wide Collaborative project, with cooperation from the Network Oversight Advisory Committee (OAC). The Collaborative project will start in Year 2. AHA has set aside money for this effort, not to exceed $1,800,000 for the Network. More details on the Collaborative project will be made available after the Centers are named.

Award Amount: The maximum budget amount a Center applicant may request is $4,400,000. The AHA reserves the right to determine the final award amount for competitive projects based on need and potential impact.

Appropriate Budget Items:

- Salary and fringe benefits for the Center Director, Principal Investigators, three named fellows, collaborating investigator(s), and other participating research staff or faculty.
- Project-related expenses, such as salaries of technical personnel essential to the conduct of the project, supplies, equipment, travel, and publication costs in accordance with institutional and AHA policies.
- Centers should use award dollars to pay for travel to two required face-to-face (as feasible), network-wide meetings each year and other meetings where SFRN research is presented. Additional details on bi-annual meetings will be conveyed to awarded centers following award activation. Centers should anticipate hosting at least one of the meetings on a rotating basis. The purpose of both meetings is to share results across the network and identify and act on potential collaborative opportunities. Additionally, there will be virtual meetings if face-to-face travel is not available. More information will be provided upon award and once travel options become clear.

    - Institutional indirect costs for operating expenses may be charged up to ten percent (10%) of the total expenditures each year on awards at the awardee institution. Any subcontract awardee institution (if applicable) is allowed institutional indirect costs up to ten percent (10%) of the total expenditures of the subcontract. The awardee institution may not charge indirect costs on the direct costs of a subcontract.

Sample Center Budget	
Projects: THREE projects over four years. One project must be within a basic science dis and one project must be clinical/translational in scope. *Maximum of $3.29M to be divided among three projects. It is not required to s funds equally across projects or years.*	$ 3.29 M
Fellows Each center must train 3 postdoctoral fellows over the four-year grant period (for example, one fellow in years 1-2; one fellow in years 2-3; one fellow in years 3-4). Fellows must maintain a minimum of 75% effort to research training. See additional requirements for fellow appointment in the Named Fellows section of the RFP. *Up to $65,000 per fellow per year: salary + health insurance/fringe.*	$ 390 K
Center Leadership The ONE Center Director (CD) must commit at least 20% effort. *A maximum of $50,000 salary plus fringe/benefits per year to cover effort associated with directing the Center.*	$ 250 K
Center Travel Costs Covers travel for Center personnel to attend network meetings and other integration activities. *$10,000 per year must be allocated to Center Travel.*	$ 40 K
One-time hosting of face-to-face scientific meeting	$ 30 K
Direct Costs (Total) Research Dollars	$ 4.00 M
Indirect Costs AHA Policy allows for a maximum of 10% for indirect costs	$ 400 K
Total	$ 4.4 M

Note for Center Applicants: There may be only one Center Director at each Center. This person will be responsible for the progress of the projects and overseeing the total budget for their grant. If awarded, the principal investigators and the institution assume an obligation to expend grant funds for the research purposes set forth in the application and in accordance with all regulations and policies governing the grant programs of the AHA.

Center Directors and Project Principal Investigators:

- Must possess an MD, PhD, DO, DVM or equivalent doctoral degree at time of application.
- Must have a faculty or staff appointment.
- May hold another AHA award simultaneously.
- Must demonstrate a 20% minimum effort requirement for the Director and a 10% minimum effort requirement for Principal Investigators (PI) of Center projects. These responsibilities are mutually exclusive, i.e., a Center Director who also serves as a Project PI must contribute a

combined effort of 30%. Each named Director and PI must be able to commit the minimum effort required and may not split these efforts across more than one person.

Directors must have one of the following designations:

- U.S. citizen
- Permanent Resident
- Pending Permanent Resident (must have applied for permanent residency and have filed Form I-485 with the U.S. Citizenship and Immigration Services and have received authorization to legally remain in the U.S., having filed an Application for Employment Form I-765)
- G-4 Visa – family member of employee of international organizations and NATO

Principal Investigators of proposed projects must have one of the following designations:

- U.S. citizen
- Permanent Resident
- Pending Permanent Resident (must have applied for permanent residency and have filed Form I-485 with the U.S. Citizenship and Immigration Services and have received authorization to legally remain in the U.S., having filed an Application for Employment Form I-765)
- E-3 Visa – specialty occupation worker
- H1-B Visa – temporary worker in a specialty occupation
- O-1 Visa – temporary worker with extraordinary abilities in the sciences
- TN Visa – NAFTA professional
- G-4 Visa - family member of employee of international organizations and NATO

Named Fellows
The AHA's aim is to help end historical structures and workplace cultures that advertently or inadvertently treat people inequitably based on race, ethnicity, gender, sexual orientation, age, ability, veteran status or other factors. Therefore, at least 50% of the fellows named must be from a racial or ethnic group that is under-represented in science (Black/African American; Hispanic/Latino; Native American or Alaska Native; and/or Hawaiian or other Pacific Islander); or an LGBTQ+ person, or a woman.

Each fellow must have one of the following designations:

- U.S. citizen
- Permanent Resident
- Pending Permanent Resident (must have applied for permanent residency and have filed Form I-485 with the U.S. Citizenship and Immigration Services and have received authorization to legally remain in the U.S., having filed an Application for Employment Form I-765)
- E-3 Visa – specialty occupation worker
- H1-B Visa – temporary worker in a specialty occupation
- O-1 Visa – temporary worker with extraordinary abilities in the sciences
- TN Visa – NAFTA professional
- J-1 Visa – exchange visitor
- F-1 Visa – student
- G-4 Visa - family member of employee of international organizations and NATO

*All awardees must meet the citizenship criteria throughout the duration of the award.

A named fellow may not hold another comparable fellowship award, although the institution may provide supplemental funding. Fellows may not hold a faculty or staff appointment, except for MD or MD/PhD trainees who also maintain clinical responsibilities. These fellows may hold the title of instructor or similar due to their patient care responsibilities but must devote at least 75% effort to research training.

Required Documents for Invited Proposals

Refer to Format/Type Requirements for All Documents below

Center Director Applicant

- Applicant/PI Biosketch (5 pages) - Upload your NIH biosketch OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026). It is not necessary to reformat to AHA page specifications
- Template for Budget Justification (DOC) (2 pages)
- Template for Department Head Letter (5 pages)
- Research Project Environment (DOC) (2 pages)
- Center Science Vison and Synergy (8 pages)
- Center Collaboration (5 pages)
- Current Postdoctoral Training Program (no limit)
- Proposed Multidisciplinary Training Program (8 pages)
- Center Director Qualifications (2 pages)
- Center Administrative Structure (2 pages)
- Literature Cited in Proposal (5 pages) - See instructions below
- 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. We list it here so the applicant may be aware that this is required.
- Publications (up to 3 separate uploads, no page limits)
- Project PIs Letters of Support (3 PIs, 2 pages each)
- Project PI Biosketches (3 PIs, 5 pages each)
- Partnering Institution Letter (2 pages)
- All project professionals listed in third party personnel (i.e., Co-PIs, Co-Is, Collaborators, Consultants) must submit a biosketch

Project PI Applicant

- Applicant/PI Biosketch (5 pages) - Upload your NIH biosketch OMB No. 0925-0001 and 0925-0002 (Rev. 10/2021 Approved Through 01/31/2026). It is not necessary to reformat to AHA page specifications.
- Template for Budget Justification (DOC) (2 pages)
- Template for Department Head Letter (5 pages)
- Research Project Environment (DOC) (2 pages)
- Research Plan (17 pages) – See instructions below. Refer to Peer Review Phase I section for the criteria against which the proposal will be evaluated
- Literature Cited (5 pages) - See instructions below
- Publications (up to 3 separate uploads, no page limits)

- Letter of Support (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. We list it here so the applicant may be aware that this is required.
- Center Director's Vision and Synergy (8 pages)
- All project professionals listed in third party personnel (i.e., Co-PIs, Co-Is, Collaborators, Consultants) must submit a biosketch

Format/Type Requirements

The Research Plan must be created as a Word-processed document, converted to a Portable Document Format (PDF) file, and uploaded to ProposalCentral. Only PDF files will be accepted. When creating the Research Plan, you must comply exactly with the association's format/type requirements and page limits below. Failure to comply will result in the administrative withdrawal (disqualification) of the application.

- Only Portable Document Format (PDF) files will be accepted.
- File must be single-spaced.
- No more than 15 characters per inch (cpi) or an average of no more than 15 cpi (cpi includes symbols, punctuation and spaces).
- No less than ¾" margins allowed.
- 60 lines per page is the maximum allowed.
- Arial Font style, 12 point font size for Windows users; Helvetica Font style, 12 point font size for Macintosh users

Figures, charts, tables, graphics and legends may be smaller in size but must be clear and legible.

Users of other word processing programs must adjust settings appropriately and should measure text after saving and printing as a PDF. Type requirements should be checked using a standard measuring device (such as a ruler), rather than relying on the font selected for a particular word processing/printer combination. Type size specifications must be observed in the text of your research plan or the application will not be reviewed and will be withdrawn. Adherence to font and margin requirements is necessary. No applicant should have an advantage over other applicants by providing more content in his/her application by using smaller, denser type. The AHA has the responsibility to make the final determination of conformance to format requirements and the authority to withdraw applications. This decision is final and not subject to appeal.

Internet Web site addresses (URLs) may not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Moreover, the reviewers are cautioned not to directly access an Internet site as it could compromise their anonymity.

The only place a URL may be used is in the biographical sketch as described in the instructions for that form. Provide a URL to a full list of your published work as found in a publicly available digital database such as SciENcv or My Bibliography, which are maintained by the US National Library of Medicine.

Proposed Research Plan
Type the research plan specifically following the outline given below, in the same sequence. All items should be addressed. Indicate N/A or None if not applicable to this application. The entire proposed research plan must not exceed the 17-page limit.

Specific Aims
Provide a clear, concise summary of the aims of the work proposed. 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. Literature referenced will be included in the Literature Cited upload (4-page limit).

Identify gaps which this project is intended to fill. If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced?

State concisely the importance on advancing the understanding of approaches and factors underlying the crisis of health inequities in rural America. How will the studies improve this area?

Previous Work of Applicant
Concisely describe 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. If applicable, include pilot studies showing the work is feasible.

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 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 any collaborative arrangements that have been made.

Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims.

Ethical Aspects of the Proposed Research
Describe any special consideration you have given to all ethical issues involved in your proposed investigations (biohazards or human subjects, etc.), identifying risks and management. Be sure to address this topic. Discuss the nature of the informed consent that will be obtained if the research involves human subjects. If the proposed project involves no ethical questions, indicate "none."

Notice: A document that exceeds the page limit or file type will be rejected by ProposalCentral.

Literature Cited (5-page maximum)

List all literature citations for your Project Plan. Citation references should be limited to relevant and

current literature; be concise and select only those references cited in the Project Plan. This section is intended ONLY for your citations, and no other materials.

Literature citations should be marked in the text of the Proposed Project Plan. The mark may be a number or letter. You may use superscript, such as1 or a bracket [1]. When citing specific sections or page numbers, you may indicate these with superscript, such as 1, pp. 345-361 or within the bracket [1, pp. 345-361]. The works cited should not be listed in the Proposed Project Plan. Full and complete citations with marks that correspond to those in the Proposed Project Plan are to be listed in this "Literature Cited" upload of up to five pages.

Standard abbreviations are acceptable with two exceptions: full titles and full paging must be provided.

Each reference must list:

- Corresponding mark in the Proposed Project Plan
- Authors in the same order as they appear on the paper (list all or up to 15)
- Full Title
- Name of the book or journal
- Volume number
- Page numbers
- Year of publication

Upload your completed document within ProposalCentral as a PDF.

Note: In the Personal Statement section of your Biosketch, you may cite up to four publications or research products that highlight your experience and qualifications for this project.

Peer Review

General: Peer Review will be a two-phase process. Projects/Science from the Network Centers will be scored during Phase 1. Network Center applications that advance past Phase 1 will undergo a separate Phase 2 review. This review will focus on the overall vision of the center, synergy and collaborative possibilities within a Center (via the Center application) and across Centers, and the training plan and environment. Phase 2 will occur 2-4 weeks after Phase 1 review. Criteria for both phases of review follow.

Peer Review Criteria for PROJECT Applications

Phase 1 Review

Each PROJECT within a Center application will be scored individually according to the criteria below.

Projects – Potential impact of the project on research in the field of the designated research topic; strengths of applicant investigators (qualifications, expertise and productivity); potential for collaboration or synergy of projects; scientific content; background; preliminary studies; detailed specific aims; approach detail; analytical plan; sample size; data management; significance; innovation; individual project scientific merit; and total project coordination (within and among projects). Projects will be rated on the following areas:

- Approach: Are the conceptual framework, design, methods and analyses adequately developed, well-integrated, well-reasoned and feasible (as determined by preliminary data) and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Does each applicant develop a plan for interoperability of data between Centers and with National or International Standards?

  NOTE: Applicants must explain how relevant biological variables, such as sex, are factored into the research design, analysis and reporting. Furthermore, very strong justification from the scientific literature must be provided for applications proposing to study only one sex.

- Innovation: Is the project original and innovative? For example: Does the project challenge existing paradigms and address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools or technologies for this area?

- Investigator(s): Is the investigator(s) appropriately trained and well-suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)? Project PIs must dedicate at least 10% to the project.

- Significance: Does this study address an important problem related to inflammation and cardiac and/or neurovascular disease? If the aims of the application are achieved, how will mechanistic understanding of mediators related to inflammation be advanced? What will be the effect of these studies on the concepts, methods and technologies that drive this field?

- Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

- Impact: How does the project relate to and support the mission of the AHA – To be a relentless force for a world of longer, healthier lives?

- Synergy: How does this project enhance the Center and the additional science project(s)? i.e., does this project enhance the likelihood that the collective Center outcomes will exceed outcomes of the individual sum of its distinct components? For more information, please see this page. Only projects that demonstrate synergy will move forward to Phase 2.

- Lay Summary/Summary for Non-Scientists: How well written is the lay summary in explaining to a non-scientist audience the research proposed and importance? Does the Lay Summary adequately explain the major health problem being addressed by this study? Does it provide specific questions and how the projects will address them? Does it provide information on the overall impact of this work and the potential advances in the field? Does it relay how the proposal supports the mission of the AHA?

Peer Review Criteria for CENTER Applications

Phase 2 Review

Each NETWORK CENTER moving beyond Phase I Review will be scored on the following:

- Synergy – A clear vision of scientific direction is expected. A Center should be viewed as a group of interrelated research projects, each of which is not only individually scientifically meritorious, but also complements the other projects and contributes to an integrating theme. Describe the rationale for the total program. Explain the strategy of achieving the objectives of the overall program and how each individual project relates to the strategy. Describe the synergies and interactions among projects and their investigators. Is there evidence of synergy among the projects and training component of the Center?

- Collaboration – History of collaboration, as well as the ability and commitment to collaborate with other institutions, investigators and within the applicant institution as well as within the awarded Network. Defined and detailed process for collaboration with other sites in addition to within and among the proposed projects; plans to actively participate in a collaborative network. Evidence of formal training in leadership skills with an emphasis on collaborative leadership will be favorably reviewed. What collaborations do you envision between investigators working on individual projects?

- Interaction Plan within and among this Network and other AHA Networks (if appropriate) – Plan for and commitment to sharing knowledge and methods, providing a stimulating atmosphere for research collaborations, and providing networking opportunities for trainees. Cited strategies for communication and interaction among the Centers. Centers proposing clinical projects must document that they have sufficient volume of patients from all identified study populations to ensure robust results are achievable.

- Training Component – A detailed plan for developing and implementing a postdoctoral training program that includes clinical (M.D., D.O., PharmD) or Ph.D. training in research in the field outlined by the RFA; qualifications and characteristics of current and anticipated trainees; didactic and practicum training opportunities; plan for the selection of prospective fellows and how funded fellows' ongoing progress will be guided via an individual development plan (IDP) and evaluated at least annually. Plan for involving fellows in annual Center meetings and Center-to-Center visits, along with identifying opportunities for fellows to work with established investigators at other network Centers; ability to track trainees; conferences and meeting participation for trainees; documentation of a ready supply of fellows; and history of successful fellowship training for researchers in the appropriate research topic.

- Center Director – Qualifications of the Director to provide scientific and administrative leadership for the Center; demonstrated ability to lead others, along with experience and commitment to the success of the Center, the projects contained within, and the Network. Documented evidence of willingness to collaborate with others outside their institution to share ideas, science, etc., to advance the research in the intended area.

- Investigator Team – Qualifications of each PI to provide scientific and administrative leadership for their respective projects; demonstrated commitment of each PI, and experience in the

area(s) of studies proposed; qualifications of investigators, and co-investigators and the research team; training experience.

- Diversity of the Research Team – In keeping with AHA's core values of diversity and inclusivity, AHA is committed to broadening the diversity of investigators supported by programmatic, multi-investigator initiatives it offers. As such, at least 25% of key personnel of the research team must be from groups who are under-represented in science and medicine. Applicants must be able to document the diverse composition of the proposed research team and should comment on steps their institution(s) has taken/is taking to expand and support diverse investigators.

- Environment – Institutional commitment, resources and facilities to sustain the Center; institutional resources available to complete the project; analytical resources available to the project; letter from Center Director's Department Head assuring the department and institution's support of the Center along with confirmation that the Center Director will devote at least 20% effort towards the Center. Other Center personnel may be appointed to assist the Director in the administration of the Center. However, the Director will be required to devote 20% effort to the Center.

For more information on Peer Review of submitted applications, including information on reverse site visits, see the Peer Review section of the SFRN General Information web page on the AHA SFRN website.

Applicants are prohibited from contacting AHA peer reviewers. This is a form of scientific misconduct and will result in removal of the application from funding consideration and institutional notification of misconduct.

AWARD SELECTION - Final funding decisions are subject to approval by the AHA.

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.

The Centers are not transferable to other institutions. An institution may submit only one Center (and related Projects) application in response to this RFP. Individuals at the applicant institution who are not participating in their institution's center and project(s) application may participate in a separate institution's Center application. Individuals other than the Center Director who are participating in their institution's Center application, may participate in a separate institution's Center application. The application may include individuals and/or projects at more than one institution provided there is evidence supporting the likelihood of a successful interaction among research and training personnel.

It is the responsibility of the submitting institution to ensure that only one proposal is submitted for the institution or to coordinate across several institutions to create a single application. The Center Director's institution will maintain fiscal responsibility for the entire award.

Use of AHA's Precision Medicine Platform
Applicants are encouraged to make use of 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. Each Project will receive Amazon Web Services computational credits to offset the cost of using the platform. Because the credits do not cover all costs associated with use of the PMP, funded centers will incur a monthly usage charge that will need to be factored into the award budget. The approximate monthly charge will be $100 for each month the platform is used.
- 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. 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 PMP is HIPAA and FedRAMP compliant.

Interim Assessment
Awardees must report progress on a minimum annual (once per year) basis. Progress 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 the achievement of stated milestones as indicated in the project timeline. The OAC reserves the right to request additional updates, site visits, or reporting.

Links and References to Relevant AHA Policies

- 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 as soon as possible, and no later than the time of an associated publication or the end of the award period (and any no-cost extension), whichever comes first. For more information on the above policies, see AHA's Open Science Policy webpage.
- Preregistration: AHA requires preregistration for any funded clinical trials and encourages preregistration for any studies that make an inferential claim from a sampled group or population, as well as studies that are reporting and testing hypotheses. After a project is

completed, protocols and preregistration analysis plans can be used in conjunction with the final study and analysis by researchers seeking to replicate, reproduce, and build upon findings. See AHA's preregistration information.

- Other: The projects described can have no scientific or budgetary overlap with other funded work. Any inventions, intellectual property, and patents resulting from this funding are governed by the AHA Intellectual Property Policy for Research Funding EXCEPT to the extent modified by specific Intellectual Property terms for this award mechanism, including financial terms, which will be communicated to awardees following the review process. The applicant/awardee and institution are responsible for compliance with all AHA research award policies and guidelines for the duration of any awards they may receive. Visit the Research Programs Awards Policies page for more information on this topic: AHA Policies Governing All Research Awards

Proposal Submission

Pre-proposals must be submitted via email (instructions above), and invited full proposals must be submitted using ProposalCentral, AHA's online submission portal. For explicit Application Instructions, visit the AHA SFRN General Application Information page.

Other Features of this AHA Research Opportunity

- AHA awards are open to an array of academic and health professionals. This includes but is not limited to all academic disciplines (biology, chemistry, mathematics, technology, physics, etc.) and all health-related professions (physicians, nurses, nurse practitioners, pharmacists, dentists, physical and occupational therapists, statisticians, nutritionists, etc.).

- The AHA believes diversity and inclusion is an essential component to driving its mission and strongly encourages applications by 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.

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