Follow the tips in the blue boxes below to help you understand the importance of key pieces of information in funding opportunity announcements (FOA).

Department of Health and Human Services
Part 1. Overview Information

Participating Organization(s)	National Institutes of Health (NIH)
Components of Participating Organizations	National Heart, Lung, and Blood National Institute on Aging (NIA) National Institute on Alcohol Abuse and Alcoholism (NIAAA) National Institute of Allergy and Infectious Diseases (NIAID) National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) National Institute on Drug Abuse (NIDA) National Institute of Environmental Health Sciences (NIEHS) National Institute of General Medical Sciences (NIGMS) National Human Genome Research Institute (NHGRI) National Institute of Mental Health (NIMH) National Institute on Minority Health and Health Disparities (NIMHD) National Institute of Neurological Disorders and Stroke (NINDS) National Institute of Nursing Research (NINR) National Center for Complementary and Integrative Health (NCCIH) Note: Not all NIH Institutes and Centers (ICs) participate in Parent Announcements. Applicants should carefully note which ICs participate in this announcement and view their respective areas of research interest at the R01 Clinical Trial Required IC-Specific Scientific Interests and Contact website. Applicants should also carefully note which ICs accept only mechanistic wing the Related Notices. ICs that do not participate uncement will not consider applications for funding.
Funding Opportunity Title	**NIH Research Project Grant (Parent RO1 Clinical Trial Required)**
Activity Code	R01 Research Project Grant

Your research has to fit within the mission of one of these participating organizations for your application to be assigned for funding consideration.

Most Titles include activity code and clinical trial information.

The activity code tells you the type of grant program that is being advertised. Talk to a scientific/program contact listed in section VII of the FOA to ensure that you apply to the right grant program for you and your science.

Announcement Type	New
Related Notices A must-read. The related notices provide updates to instructions after the FOA was issued. Revisit the FOA before submitting your application to check for any new related notices. Information in the notice augments/supersedes the information in the FOA.	December 18, 2017 - Notice of NINDS Policy for Submission of Applications and Participation in PA-18-345.See Notice NOT-NS-18-011. NOT-AR-18-008 NIAMS Only Accepts Clinical Trial Applications Proposing Mechanistic Studies for Clinical Trial Parent R01 and R21 Announcements NOT-HL-17-546 NHLBI Only Accepts Clinical Trial Applications Proposing Mechanistic Studies for the NIH Parent R01 Clinical Trial Required Announcement NOT-AT-18-001 NCCIH Policy for Submission of Parent R01 Applications Proposing Clinical Trials NOT-MH-18-004 NIMH Only Accepts Clinical Trial Applications Proposing Mechanistic Studies for Clinical Trial Parent R01 and R21 Announcements NOT-MH-18-006 Notice of NIMH Participation in (PA-18-345) NIH Research Project Grant (Parent R01 Clinical Trial Required)

Funding Opportunity Announcement (FOA) Number	**PA-18-345**
Companion Funding Opportunity	PA-18-484 - Parent R01 Clinical Trial Not Allowed Check Componer Notices for restric Companion FOAs focus on similar areas of science but use different activity codes
Number of Applications	See Section III. 3. Additional Information on Eligibility.
Catalog of Federal Domestic Assistance (CFDA) Number(s)	93.307; 93.213; 93.113; 93.846; 93.233; 93.840; 93.839; 93.838; 93.837; 93.172; 93.859; 93.279; 93.855; 93.866; 93.361; 93.273, 93.853
Funding Opportunity Purpose	The NIH Research Project Grant supports a discrete, specified, circumscribed project in areas representing the specific interests and competencies of the investigator(s). This Parent Funding Opportunity Announcement requires that at least 1 clinical trial be proposed. The proposed project must be related to the programmatic interests of one or more of the participating NIH Institutes and Centers (ICs) based on their scientific missions. Applicants should note that some ICs (see Related Notices) only

	accept applications proposing mechanistic studies that meet NIH's definition of a clinical trial through this funding opportunity announcement.

Key Dates

Posted Date	November 3, 2017
Open Date (Earliest Submission Date)	Jan 5, 2018
Letter of Intent Due Date(s)	Not Applicable Letters of Intent are requested for planning purposes. They are not required.
Application Due Date(s)	Standard dates apply, by 5:00 PM local time of applicant organization. All types of non-AIDS applications allowed for this funding opportunity are due on these dates. Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.
AIDS Application Due Date(s)	Standard AIDS dates apply, by 5:00 PM local time of applicant organization. If your application has a strong focus on AIDS research, special due dates apply. first AIDS application due date for this FOA is May 7, 2018. licants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.
Scientific Merit Review	Standard dates apply
Advisory Council Review	Standard dates apply
Earliest Start Date	Standard dates apply
Expiration Date	January 8, 2021 You cannot apply to an expired FOA.
Due Dates for E.O. 12372	Not Applicable

Required Application Instructions

Your application may not be accepted for review unless you closely follow the instructions in the FOA and the SF424 (R&R) Application Guide.

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide, except where instructed to do otherwise (in this FOA or in a Notice from the *NIH Guide for Grants and Contracts*). Conformance to all requirements (both in the Application Guide and the FOA) is

required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions. **Applications that do not comply with these instructions may be delayed or not accepted for review.**

There are several options to submit your application to the agency through Grants.gov. to NIH and Department of Health and Human Services partners.

1. Use the NIH ASSIST system to prepare, submit and track your application online.

   Apply Online Using ASSIST

2. Use an institutional system-to-system (S2S) solu
   application to Grants.gov and eRA Commons to
   institutional officials regarding availability.
3. Use Grants.gov Workspace to prepare and submit your application and eRA Commons to track your application.

Application forms are specific to each FOA. Access the forms using these buttons in the FOA, then select the submission method that works best for you (ASSIST or downloadable forms). If your institution has its own system-to-system submission method, the system should pull the correct forms for you.

Table of Contents

Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

The NIH Research Project Grant supports a discrete, specified, circumscribed project in scientific areas that represent the investigators' specific interests and competencies and that fall within the mission of the participating NIH Institutes and Centers (ICs). The R01 is the original, and historically the oldest, grant mechanism used by the NIH to support health-related research and development.

All applications submitted to this Parent Funding Opportunity Announcement must propose clinical trial(s).

Research grant applications are assigned to participating ICs based on receipt and referral guidelines and many applications are assigned to multiple participating ICs with related research interests. Applicants are encouraged to identify a participating IC that supports their area of research via the R01 Clinical Trial Required IC-Specific Scientific Interests and Contact website and contact Scientific/Research staff from relevant ICs to inquire about their interest in supporting the proposed research project.

For specific information about the mission of each NIH IC, visit the List of NIH Institutes, Centers, and Offices website.

NIH defines a clinical trial as "A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes." (NOT-OD-15-015)

NIH not only supports trials of safety and efficacy, it also supports mechanistic exploratory studies that meet the definition of a clinical trial and are designed to explore or understand a biological or behavioral process, the pathophysiology of a disease, or the mechanism of action of an intervention. These studies may focus on basic and/or translational discovery research in healthy human subjects and in human subjects who are affected by the pathophysiology of

diseases and disorders. By addressing basic questions and concepts in biology, behavior, and pathophysiology, these studies may provide insight into understanding human diseases and disorders along with potential treatments or preventive strategies. NIH also supports biomarker studies that meet the definition of a clinical trial and that may provide information about physiological function, target engagement of novel therapeutics, and/or the impact of therapeutics on treatment response. NIH thus supports studies that meet the definition of clinical trials (as noted above) but do not seek to establish safety, clinical efficacy, effectiveness, clinical management, and/or implementation of preventive, therapeutic, and services interventions.

Applicants should note that some ICs (see the Related Notices section above) only accept applications proposing mechanistic studies that meet NIH's definition of a clinical trial through this funding opportunity announcement. A mechanistic study is designed to understand a biological or behavioral process, the pathophysiology of a disease, or the mechanism of action of an intervention. If the proposed research project includes clinical trial other than a mechanistic study that would be assigned to one of these ICs, applicants are advised to contact relevant Scientific/Research staff to discuss alternative mechanisms of support of these studies.

See Section VIII. Other Information for award authorities and regulations.

Section II. Award Information

Funding Instrument	Grant: A support mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity.
Application Types Allowed	New Renewal Resubmission Revision The OER Glossary and the SF424 (R&R) Application Guide provide details on these
Clinical Trial?	Required: Only accepti trial(s) Need help determining whether you are doing a clinical trial?
Funds Available and Anticipated Number of Awards	The number of awards is contingent upon NIH appropriations and the submission of a sufficient number of meritorious applications.
Award Budget	Application budgets are not limited but need to reflect the actual needs of the proposed project.
Award Project Period	The scope of the proposed project should determine the project period. The maximum project period is 5 years.

Check to see if the FOA will accept clinical trial applications (clinical trial required, not allowed, or optional.) The hyperlinked question provides more details on the NIH definition of a clinical trial.

NIH grants policies as described in the *NIH Grants Policy Statement* will apply to the applications submitted and awards made in response to this FOA.

Section III. Eligibility Information

1. Eligible Applicants

Be sure both you and your organization are eligible before applying.

Eligible Organizations

Higher Education Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

The following types of Higher Education Institutions are always encouraged to apply for NIH support as Public or Private Institutions of Higher Education:

- Hispanic-serving Institutions
- Historically Black Colleges and Universities (HBCUs)
- Tribally Controlled Colleges and Universities (TCCUs)
- Alaska Native and Native Hawaiian Serving Institutions
- Asian American Native American Pacific Islander Serving Institutions (AANAPISIs)

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)

Governments

- State Governments
- County Governments
- City or Township Governments
- Special District Governments
- Indian/Native American Tribal Governments (Federally Recognized)
- Indian/Native American Tribal Governments (Other than Federally Recognized)
- Eligible Agencies of the Federal Government

- U.S. Territory or Possession

Other

- Independent School Districts
- Public Housing Authorities/Indian Housing Authorities
- Native American Tribal Organizations (other than Federally recognized tribal governments)
- Faith-based or Community-based Organizations
- Regional Organizations
- Non-domestic (non-U.S.) Entities (Foreign Institutions)

Foreign Institutions

Non-domestic (non-U.S.) Entities (Foreign Institutions) **are** eligible to apply.
Non-domestic (non-U.S.) components of U.S. Organizations **are** eligible to apply.

Foreign components, as defined in the *NIH Grants Policy Statement*, **are** allowed.

Required Registrations

All registrations must be complete in order to submit you application. Details on required institutional and investigator registrations may be found on our Prepare to Apply & Register website.

Applicant Organizations

Applicant organizations must complete and maintain the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. All registrations must be completed prior to the application being submitted. Registration can take 6 weeks or more, so applicants should begin the registration process as soon as possible. The NIH Policy on Simplifying the NIH Policy for Late Application Submission states that failure to complete registrations in advance of a due date is not a valid reason for a late submission.

- Dun and Bradstreet Universal Numbering System (DUNS) - All registrations require that applicants be issued a DUNS number. After obtaining a DUNS number, applicants can begin both SAM and eRA Commons registrations. The same DUNS number must be used for all registrations, as well as on the grant application.
- System for Award Management (SAM) (formerly CCR) – Applicants must complete and maintain an active registration, **which requires renewal at least annually**. The renewal process may require as much time as the initial registration. SAM registration includes the assignment of a Commercial and Government Entity (CAGE) Code for domestic organizations which have not already been assigned a CAGE Code.
- NATO Commercial and Government Entity (NCAGE) Code – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons - Applicants must have an active DUNS number and SAM registration in order to complete the eRA Commons registration. Organizations can register with the eRA Commons as they are working through their SAM or Grants.gov registration. eRA Commons requires organizations to identify at least one Signing Official (SO) and at least one Program Director/Principal Investigator (PD/PI) account in order to submit an application.

- Grants.gov – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

Some of the relevant roles at your organization are described in our Understanding Your Role website.

Program Directors/Principal Investigators (PD(s)/PI(s))

All PD(s)/PI(s) must have an eRA Commons account and should work with their organizational officials to either create a new account or to affiliate an existing account with the applicant organization's eRA Commons account. If the PD/PI is also the organizational Signing Official, they must have two distinct eRA Commons accounts, one for each role. Obtaining an eRA Commons account can take up to 2 weeks.

Individual eligibility requirements only apply to the program director/principal investigator, not to collaborators or consultants

Eligible Individuals (Program Director/Principal Investiga

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Program Director(s)/Principal Investigator(s) (PD(s)/PI(s)) is invited to work with his/her organization to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH support.

For institutions/organizations proposing multiple PDs/PIs, visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF424 (R&R) Application Guide.

2. Cost Sharing

This FOA does not require cost sharing as defined in the *NIH Grants Policy Statement*.

3. Additional Information on Eligibility

Number of Applications

Applicant organizations may submit more than one application, provided that each application is scientifically distinct.

The NIH will not accept duplicate or highly overlapping applications under review at the same time. This means that the NIH will not accept:

- A new (A0) application that is submitted before issuance of the summary statement from the review of an overlapping new (A0) or resubmission (A1) application.
- A resubmission (A1) application that is submitted before issuance of the summary statement from the review of the previous new (A0) application.
- An application that has substantial overlap with another application pending appeal of initial peer review (see NOT-OD-11-101).

Section IV. Application and Submission Information

Section IV provides details of where to put information in your application. Follow these instructions closely to help ensure a successful submission.

1. Requesting an Application Package

Applicants must download the SF424 (R&R) application package associated with this funding opportunity using the "Apply for Grant Electronically" button in this FOA or following the directions provided at Grants.gov.

2. Content and Form of Application Submission

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide, i except where instructed in this funding opportunity announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

For information on Application Submission and Receipt, visit Frequently Asked Questions – Application Guide, Electronic Submission of Grant Applications.

Page Limitations

All page limitations described in the SF42 Limits must be followed.

Remember to follow the instructions in the application guide in addition to the instructions listed in this section of the FOA.

Instructions for Application Submission

The following section supplements the instructions found in the SF424 (R&R) Application Guide and should be used for preparing an application to this FOA.

SF424(R&R) Cover

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Project/Performance Site Locations

All instructions in the SF424 (R&R) Application Guide must be followed.

SF424(R&R) Other Project Information

All instructions in the SF424 (R&R) Application Guide must b

The forms for the funding opportunity are available within the application.

SF424(R&R) Senior/Key Person Profile

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R or Modular Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

R&R Subaward Budget

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Cover Page Supplement

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS 398 Research Plan

All instructions in the SF424 (R&R) Application Guide must be followed, with the following additional instructions:

Resource Sharing Plan: Individuals are required to comply with the instructions for the Resource Sharing Plans as provided in the SF424 (R&R) Application Guide.

Appendix: Only limited Appendix materials are allowed. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

PHS Human Subjects and Clinical Trials Information

When involving NIH-defined human subjects research, clinical research, and/or clinical trials (and when applicable, clinical trials research experience) follow all instructions for the PHS Human Subjects and Clinical Trials Information form in the SF424 (R&R) Application Guide, with the following additional instructions:

If you answered "Yes" to the question "Are Human Subjects Involved?" on the R&R Other Project Information form, you must include at least one human subjects study record using the **Study Record: PHS Human Subjects and Clinical Trials Information** form or **Delayed Onset Study** record.

Study Record: PHS Human Subjects and Clinical Trials Information

All instructions in the SF424 (R&R) Application Guide must be followed.

Delayed Onset Study

All instructions in the SF424 (R&R) Application Guide must be followed.

PHS Assignment Request Form

All instructions in the SF424 (R&R) Application Guide must be followed.

Foreign Institutions

Foreign (non-U.S.) institutions must follow policies described in the *NIH Grants Policy Statement*, and procedures for foreign institutions.

3. Unique Entity Identifier and System for Award Management (SAM)

See Part 1. Section III.1 for information regarding the requirement for obtaining a unique entity identifier and for completing and maintaining active registrations in System for Award Management (SAM), NATO Commercial and Government Entity (NCAGE) Code (if applicable), eRA Commons, and Grants.gov

4. Submission Dates and Times

Part I. Overview Information contains information about Key Dates and times. Applicants are encouraged to submit applications before the due date to ensure they have time to make any application corrections that might be necessary for successful submission. When a submission date falls on a weekend or Federal holiday, the application deadline is automatically extended to the next business day.

Organizations must submit applications to Grants.gov (the online po
grants across all Federal agencies). Applicants must then complete

All system-detected errors in your application must be addressed by the application deadline to be considered an on-time application.

[Understanding Funding Opportunity Announcements: PA-18-345.]

tracking the status of the application in the eRA Commons, NIH's electronic system for grants administration. NIH and Grants.gov systems check the application against many of the application instructions upon submission. Errors must be corrected and a changed/corrected application must be submitted to Grants.gov on or before the application due date and time. If a Changed/Corrected application is submitted after the deadline, the application will be considered late. Applications that miss the due date and time are subjected to the NIH Policy on Late Application Submission.

Applicants are responsible for viewing their application before the due date in the eRA Commons to ensure accurate and successful submission.

Information on the submission process and a definition of on-time submission are provided in the SF424 (R&R) Application Guide.

5. Intergovernmental Review (E.O. 12372)

This initiative is not subject to intergovernmental review.

6. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement*.

Pre-award costs are allowable only as described in the *NIH Grants Policy Statement*.

7. Other Submission Requirements and Information

Applications must be submitted electronically following the instructions described in the SF424 (R&R) Application Guide. Paper applications will not be accepted.

Applicants must complete all required registrations before the application due date. Section III. Eligibility Information contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically. If you encounter a system issue beyond your control that threatens your ability to complete the submission process on-time, you must follow the Guidelines for Applicants Experiencing System Issues. For assistance with application submission, contact the Application Submission Contacts in Section VII.

Important reminders:
All PD(s)/PI(s) must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF424(R&R) Application Package**.** Failure to register in the Commons and to include a valid PD/PI Commons ID in the credential field will prevent the successful submission of an electronic application to NIH. See Section III of this FOA for information on registration requirements.

The applicant organization must ensure that the DUNS number it provides on the application is the same number used in the organization's profile in the eRA Commons and for the System for Award Management. Additional information may be found in the SF424 (R&R) Application Guide.

See more tips for avoiding common errors.

Upon receipt, applications will be evaluated for completeness by the Center for Scientific Review, NIH. Applications that are incomplete will not be reviewed.

Requests of $500,000 or more for direct costs in any year

Applicants requesting $500,000 or more in direct costs in any year (excluding consortium F&A) must contact a Scientific/ Research Contact at least 6 weeks before submitting the application and follow the Policy on the Acceptance for Review of Unsolicited Applications that Request $500,000 or More in Direct Costs as described in the SF424 (R&R) Application Guide.

Post Submission Materials

Applicants are required to follow the instructions for post-submission materials, as described in the policy. Any instructions provided here are in addition to the instructions in the policy.

Section V. Application Review Information

Write your research strategy to respond to the review criteria to ensure reviewers have what they need to properly evaluate the scientific merit of your application. Be sure to note any special criteria involving Clinical Trials.

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the NIH mission, all applications submitted to the NIH in support of biomedical and behavioral research are evaluated for scientific and technical merit through the NIH peer review system.

A proposed Clinical Trial application may include study design, methods, and intervention that are not by themselves innovative but address important questions or unmet needs. Additionally, the results of the clinical trial may indicate that further clinical development of the intervention is unwarranted or lead to new avenues of scientific investigation.

Overall Impact

Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following review criteria and additional review criteria (as applicable for the project proposed).

Scored Review Criteria

Reviewers will consider each of the review criteria below in the determination of scientific merit, and give a separate score for each. An application does not need to be strong in all categories to be judged likely to have major scientific impact. For example, a project that by its nature is not innovative may be essential to advance a field.

Significance

Does the project address an important problem or a critical barrier to progress in the field? If the aims of the project are achieved, how will scientific knowledge, technical capability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

Investigator(s)

Are the PD(s)/PI(s), collaborators, and other researchers well suited to the project? If Early Stage Investigators or those in the early stages of independent careers, do they have appropriate experience and training? If established, have they demonstrated an ongoing record of accomplishments that have advanced their field(s)? If the project is collaborative or multi-PD/PI, do the investigators have complementary and integrated expertise; are their leadership approach, governance and organizational structure appropriate for the project?

With regard to the proposed leadership for the project, do the PD/PI(s) and key personnel have the expertise, experience, and ability to organize, manage and implement the proposed clinical trial and meet milestones and timelines? Do they have appropriate expertise in study coordination, data management and statistics? For a multicenter trial, is the organizational structure appropriate and does the application identify a core of potential center investigators and staffing for a coordinating center?

Innovation

Does the application challenge and seek to shift current research or clinical practice paradigms by utilizing novel theoretical concepts, approaches or methodologies, instrumentation, or interventions? Are the concepts, approaches or methodologies, instrumentation, or interventions novel to one field of research or novel in a broad sense? Is a refinement, improvement, or new application of theoretical concepts, approaches or methodologies, instrumentation, or interventions proposed?

Does the design/research plan include innovative elements, as appropriate, that enhance its sensitivity, potential for information or potential to advance scientific knowledge or clinical practice?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed? Are potential problems, alternative strategies, and benchmarks for success presented? If the project is in the early stages of development, will the strategy establish feasibility and will particularly risky aspects be managed? Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?

If the project involves human subjects and/or NIH-defined clinical research, are the plans to address 1) the protection of human subjects from research risks, and 2) inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion or exclusion of children, justified in terms of the scientific goals and research strategy proposed?

Does the application adequately address the following, if applicable

Study Design

Is the study design justified and appropriate to address primary and secondary outcome variable(s)/endpoints that will be clear, informative and relevant to the hypothesis being tested? Is the scientific rationale/premise of the study based on previously well-designed preclinical and/or clinical research? Given the methods used to assign participants and deliver interventions, is the study design adequately powered to answer the research question(s), test the proposed hypothesis/hypotheses, and provide interpretable results? Is the trial appropriately designed to conduct the research efficiently? Are the study populations (size, gender, age, demographic group), proposed intervention arms/dose, and duration of the trial, appropriate and well justified?

Are potential ethical issues adequately addressed? Is the process for obtaining informed consent or assent appropriate? Is the eligible population available? Are the plans for recruitment outreach, enrollment, retention, handling dropouts, missed visits, and losses to follow-up appropriate to ensure robust data collection? Are the planned recruitment timelines feasible and is the plan to monitor accrual adequate? Has the need for randomization (or not), masking (if appropriate), controls, and inclusion/exclusion criteria

been addressed? Are differences addressed, if applicable, in the intervention effect due to sex/gender and race/ethnicity?

Are the plans to standardize, assure quality of, and monitor adherence to, the trial protocol and data collection or distribution guidelines appropriate? Is there a plan to obtain required study agent(s)? Does the application propose to use existing available resources, as applicable?

Data Management and Statistical Analysis

Are planned analyses and statistical approach appropriate for the proposed study design and methods used to assign participants and deliver interventions? Are the procedures for data management and quality control of data adequate at clinical site(s) or at center laboratories, as applicable? Have the methods for standardization of procedures for data management to assess the effect of the intervention and quality control been addressed? Is there a plan to complete data analysis within the proposed period of the award?

Environment

Will the scientific environment in which the work will be done contribute to the probability of success? Are the institutional support, equipment and other physical resources available to the investigators adequate for the project proposed? Will the project benefit from unique features of the scientific environment, subject populations, or collaborative arrangements?

If proposed, are the administrative, data coordinating, enrollment and laboratory/testing centers, appropriate for the trial proposed?

Does the application adequately address the capability and ability to conduct the trial at the proposed site(s) or centers? Are the plans to add or drop enrollment centers, as needed, appropriate?

If international site(s) is/are proposed, does the application adequately address the complexity of executing the clinical trial?

If multi-sites/centers, is there evidence of the ability of the individual site or center to: (1) enroll the proposed numbers; (2) adhere to the protocol; (3) collect and transmit data in an accurate and timely fashion; and, (4) operate within the proposed organizational structure?

Additional Review Criteria

As applicable for the project proposed, reviewers will evaluate the following additional items while determining scientific and technical merit, and in providing an overall impact score, but will not give separate scores for these items.

Study Timeline

Is the study timeline described in detail, taking into account start-up activities, the anticipated rate of enrollment, and planned follow-up assessment? Is the projected timeline feasible and well justified? Does the project incorporate efficiencies and utilize existing resources (e.g., CTSAs, practice-based research networks, electronic medical

records, administrative database, or patient registries) to increase the efficiency of participant enrollment and data collection, as appropriate?

Are potential challenges and corresponding solutions discussed (e.g., strategies that can be implemented in the event of enrollment shortfalls)?

Protections for Human Subjects

For research that involves human subjects but does not involve one of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate the justification for involvement of human subjects and the proposed protections from research risk relating to their participation according to the following five review criteria: 1) risk to subjects, 2) adequacy of protection against risks, 3) potential benefits to the subjects and others, 4) importance of the knowledge to be gained, and 5) data and safety monitoring for clinical trials.

For research that involves human subjects and meets the criteria for one or more of the six categories of research that are exempt under 45 CFR Part 46, the committee will evaluate: 1) the justification for the exemption, 2) human subjects involvement and characteristics, and 3) sources of materials. For additional information on review of the Human Subjects section, please refer to the Guidelines for the Review of Human Subjects.

Inclusion of Women, Minorities, and Children

When the proposed project involves human subjects and/or NIH-defined clinical research, the committee will evaluate the proposed plans for the inclusion (or exclusion) of individuals on the basis of sex/gender, race, and ethnicity, as well as the inclusion (or exclusion) of children to determine if it is justified in terms of the scientific goals and research strategy proposed. For additional information on review of the Inclusion section, please refer to the Guidelines for the Review of Inclusion in Clinical Research.

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section.

Biohazards

Reviewers will assess whether materials or procedures proposed are potentially hazardous to research personnel and/or the environment, and if needed, determine whether adequate protection is proposed.

Resubmissions

For Resubmissions, the committee will evaluate the application as now presented, taking into consideration the responses to comments from the previous scientific review group and changes made to the project.

Renewals

For Renewals, the committee will consider the progress made in the last funding period.

Revisions

For Revisions, the committee will consider the appropriateness of the proposed expansion of the scope of the project. If the Revision application relates to a specific line of investigation presented in the original application that was not recommended for approval by the committee, then the committee will consider whether the responses to comments from the previous scientific review group are adequate and whether substantial changes are clearly evident.

Additional Review Considerations

As applicable for the project proposed, reviewers will consider each of the following items, but will not give scores for these items, and should not consider them in providing an overall impact score.

Applications from Foreign Organizations

Reviewers will assess whether the project presents special opportunities for furthering research programs through the use of unusual talent, resources, populations, or environmental conditions that exist in other countries and either are not readily available in the United States or augment existing U.S. resources.

Select Agent Research

Reviewers will assess the information provided in this section of the application, including 1) the Select Agent(s) to be used in the proposed research, 2) the registration status of all entities where Select Agent(s) will be used, 3) the procedures that will be used to monitor possession use and transfer of Select Agent(s), and 4) plans for appropriate biosafety, biocontainment, and security of the Select Agent(s).

Resource Sharing Plans

Reviewers will comment on whether the following Resource Sharing Plans, or the rationale for not sharing the following types of resources, are reasonable: 1) Data Sharing Plan; 2) Sharing Model Organisms; and 3) Genome Wide Association Studies (GWAS).

Budget and Period of Support

Reviewers will consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

2. Review and Selection Process

Applications will be evaluated for scientific and technical merit by (an) appropriate Scientific Review Group(s) convened by the Center for Scientific Review, in accordance with NIH peer review policy and procedures, using the stated review criteria. Assignment to a Scientific Review Group will be shown in the eRA Commons.

As part of the scientific peer review, all applications:

- May undergo a selection process in which only those applications deemed to have the highest scientific and technical merit (generally the top half of applications under review) will be discussed and assigned an overall impact score.
- Will receive a written critique.

Applications will be assigned on the basis of established PHS referral guidelines to the appropriate NIH Institute or Center. Applications will compete for available funds with all other recommended applications. Following initial peer review, recommended applications will receive a second level of review by the appropriate national Advisory Council or Board. The following will be considered in making funding decisions:

- Scientific and technical merit of the proposed project as determined by scientific peer review.
- Availability of funds.
- Relevance of the proposed project to program priorities.

3. Anticipated Announcement and Award Dates

After the peer review of the application is completed, the PD/PI will be able to access his or her Summary Statement (written critique) via the eRA Commons.

Information regarding the disposition of applications is available in the *NIH Grants Policy Statement*.

Section VI. Award Administration Information

1. Award Notices

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant as described in the *NIH Grants Policy Statement*.

A formal notification in the form of a Notice of Award (NoA) will be provided to the applicant organization for successful applications. The NoA signed by the grants management officer is the authorizing document and will be sent via email to the grantee's business official.

Awardees must comply with any funding restrictions described in Section IV.5. Funding

Restrictions. Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NoA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Any application awarded in response to this FOA will be subject to the DUNS, SAM Registration, and Transparency Act requirements as noted on the Award Conditions and Information for NIH Grants website.

Additionally, ICs may specify any special reporting requirements for the proposed clinical trial to be included under IC-specific terms and conditions in the NoA. For example: If the proposed clinical trial has elevated risks, ICs may require closer programmatic monitoring and it may be necessary to require the awardee to provide more frequent information and data as a term of the award (e.g., to clarify issues, address and evaluate concerns, provide documentation). All additional communications and information related to programmatic monitoring must be documented and incorporated into the official project file. Individual awards are based on the application submitted to, and as approved by, the NIH and are subject to the IC-specific terms and conditions identified in the NoA. ClinicalTrials.gov: If an award provides for one or more clinical trials. By law (Title VIII, Section 801 of Public Law 110-85), the "responsible party" must register and submit results information for certain "applicable clinical trials" on the ClinicalTrials.gov Protocol Registration and Results System Information Website (https://register.clinicaltrials.gov). NIH expects registration of all trials whether required under the law or not. For more information, see http://grants.nih.gov/ClinicalTrials_fdaaa/

Institutional Review Board or Independent Ethics Committee Approval: Grantee institutions must ensure that the application as well as all protocols are reviewed by their IRB or IEC. To help ensure the safety of participants enrolled in NIH-funded studies, the awardee must provide NIH copies of documents related to all major changes in the status of ongoing protocols. Data and Safety Monitoring Requirements: The NIH policy for data and safety monitoring requires oversight and monitoring of all NIH-conducted or -supported human biomedical and behavioral intervention studies (clinical trials) to ensure the safety of participants and the validity and integrity of the data. Further information concerning these requirements is found at http://grants.nih.gov/grants/policy/hs/data_safety.htm and in the application instructions (SF424 (R&R) and PHS 398).

Investigational New Drug or Investigational Device Exemption Requirements: Consistent with federal regulations, clinical research projects involving the use of investigational therapeutics, vaccines, or other medical interventions (including licensed products and devices for a purpose other than that for which they were licensed) in humans under a research protocol must be performed under a Food and Drug Administration (FDA) investigational new drug (IND) or investigational device exemption (IDE).

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the *NIH Grants Policy Statement* as part of the NoA. For these terms of award, see the *NIH Grants Policy Statement* Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees,

and Activities. More information is provided a tAward Conditions and Information for NIH Grants.

Recipients of federal financial assistance (FFA) from HHS must administer their programs in compliance with federal civil rights law. This means that recipients of HHS funds must ensure equal access to their programs without regard to a person's race, color, national origin, disability, age and, in some circumstances, sex and religion. This includes ensuring your programs are accessible to persons with limited English proficiency. HHS recognizes that research projects are often limited in scope for many reasons that are nondiscriminatory, such as the principal investigator's scientific interest, funding limitations, recruitment requirements, and other considerations. Thus, criteria in research protocols that target or exclude certain populations are warranted where nondiscriminatory justifications establish that such criteria are appropriate with respect to the health or safety of the subjects, the scientific study design, or the purpose of the research.

For additional guidance regarding how the provisions apply to NIH grant programs, please contact the Scientific/Research Contact that is identified in Section VII under Agency Contacts of this FOA. HHS provides general guidance to recipients of FFA on meeting their legal obligation to take reasonable steps to provide meaningful access to their programs by persons with limited English proficiency. Please see http://www.hhs.gov/ocr/civilrights/resources/laws/revisedlep.html. The HHS Office for Civil Rights also provides guidance on complying with civil rights laws enforced by HHS. Please see http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html; and http://www.hhs.gov/ocr/civilrights/understanding/index.html. Recipients of FFA also have specific legal obligations for serving qualified individuals with disabilities. Please see http://www.hhs.gov/ocr/civilrights/understanding/disability/index.html. Please contact the HHS Office for Civil Rights for more information about obligations and prohibitions under federal civil rights laws at http://www.hhs.gov/ocr/office/about/rgn-hqaddresses.html or call 1-800-368-1019 or TDD 1-800-537-7697. Also note it is an HHS Departmental goal to ensure access to quality, culturally competent care, including long-term services and supports, for vulnerable populations. For further guidance on providing culturally and linguistically appropriate services, recipients should review the National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care at http://minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=53.

In accordance with the statutory provisions contained in Section 872 of the Duncan Hunter National Defense Authorization Act of Fiscal Year 2009 (Public Law 110-417), NIH awards will be subject to the Federal Awardee Performance and Integrity Information System (FAPIIS) requirements. FAPIIS requires Federal award making officials to review and consider information about an applicant in the designated integrity and performance system (currently FAPIIS) prior to making an award. An applicant, at its option, may review information in the designated integrity and performance systems accessible through FAPIIS and comment on any information about itself that a Federal agency previously entered and is currently in FAPIIS. The Federal awarding agency will consider any comments by the applicant, in addition to other information in FAPIIS, in making a judgement about the applicant's integrity, business ethics, and record of performance under Federal awards when completing the review of risk posed by applicants as described in 45 CFR Part 75.205 "Federal awarding agency

review of risk posed by applicants." This provision will apply to all NIH grants and cooperative agreements except fellowships.

Cooperative Agreement Terms and Conditions of Award

Not Applicable

3. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) annually and financial statements as required in the NIH Grants Policy Statement.

A final progress report, invention statement, and the expenditure data portion of the Federal Financial Report are required for closeout of an award, as described in the *NIH Grants Policy Statement*.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable NIH grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over $25,000. See the *NIH Grants Policy Statement* for additional information on this reporting requirement.

Section VII. Agency Contacts

We encourage inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants.

Use the information in this section to save time by contacting the appropriate help desk to answer your question.

Application Submission Contacts

eRA Service Desk (Questions regarding ASSIST, eRA Commons registration, submitting and tracking an application, documenting system problems that threaten submission by the due date, post submission issues)
Finding Help Online: https://grants.nih.gov/support/ (preferred method of contact)
Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

Grants.gov Customer Support (Questions regarding Grants.gov registration and submission, downloading forms and application packages)
Contact Center Telephone: 800-518-4726
Email: support@grants.gov

GrantsInfo (Questions regarding application instructions and process, finding NIH grant resources)
Email: GrantsInfo@nih.gov (preferred method of contact)
Telephone: 301-945-7573

Contact the scientific research (program staff) contact to find out if the FOA is right for you and your project, to obtain approval to submit an application for >$500k/yr, or before submitting a conference grant application.

Scientific/Research Contact(s)

Participating NIH Institutes and Centers are listed in "
Organizations" in Part 1. Overview. Scientific/Researc
Clinical Trial Required IC-Specific Scientific Interests and Contact website.

Peer Review Contact(s)

Examine your eRA Commons account for review assignment and contact information (information appears two weeks after the submission due date).

Contact the peer review contact (Scientific Review Officer) for questions about your review assignment (after the information appears in the eRA Commons), or see the Notice of NIH Policy Changes.

Financial/Grants Management Contact(s)

Contact grants management contacts for non-scientific questions on grants policy and budgets.

Participating NIH Institutes and Centers are listed in "Components of Participating Organizations" in Part 1. Overview. Financial/Grants Management Contact information is listed on the R01 Clinical Trial Required IC-Specific Scientific Interests and Contact website.

Section VIII. Other Information

Recently issued trans-NIH policy notices may affect your application submission. A full list of policy notices published by NIH is provided in the NIH Guide for Grants and Contracts. All awards are subject to the terms and conditions, cost principles, and other considerations described in the *NIH Grants Policy Statement*.

Authority and Regulations

Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR Part 52 and 45 CFR Parts 75.
