Department of Health and Human Services

Part 1. Overview Information

Participating Organization(s)

National Institutes of Health (NIH (http://www.nih.gov))

Components of Participating Organizations

National Institute of Neurological Disorders and Stroke (NINDS (http://www.ninds.nih.gov))

Funding Opportunity Title

Analytical Validation of a Candidate Biomarker for Neurological Disease (U01) (Clinical Trial Optional)

Activity Code

U01 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=u01&Search.x=0&Search.y=0&Search_Type=Activity) Research Project – Cooperative Agreements

Announcement Type

New

Related Notices

NOT-NS-18-015 (https://grants.nih.gov/grants/guide/notice-files/NOT-NS-18-015.html)

NOT-NS-18-020 (https://grants.nih.gov/grants/guide/notice-files/NOT-NS-18-020.html)

Funding Opportunity Announcement (FOA) Number

PAR-18-550

Companion Funding Opportunity

PAR-18-548 (https://grants.nih.gov/grants/guide/pa-files/PAR-18-548.html) U44 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=u44&Search.x=0&Search.y=0&Search_Type=Activity) Small Business Innovation Research (SBIR) Cooperative Agreement – Fast Track

PAR-18-549 (https://grants.nih.gov/grants/guide/pa-files/PAR-18-549.html) U44 (//grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=u44&Search.x=0&Search.y=0&Search_Type=Activity) Small Business Innovation Research (SBIR) Cooperative Agreement – Fast Track

Number of Applications

See Section III. 3. Additional Information on Eligibility.

Catalog of Federal Domestic Assistance (CFDA) Number(s)

93.853

Funding Opportunity Purpose

The purpose of this Funding Opportunity Announcement (FOA) is to support rigorous analytical validation of candidate biomarker measures or endpoints in a manner that is consistent with FDA guidelines. Analytical validation establishes that the performance characteristics of the biomarker measurement or endpoint are acceptable for its intended use. This FOA assumes that 1) a candidate biomarker has already been identified, 2) assay technology has already been developed, and 3) a working hypothesis regarding context of use is in place. The goal of this FOA is to facilitate the advancement of robust and reliable biomarkers of diseases that fall within the mission of NINDS to application in clinical trials and practice (Phase II clinical trials and beyond).

Key Dates

Posted Date

December 22, 2017

Open Date (Earliest Submission Date)

February 14, 2018

Letter of Intent Due Date(s)

30 days prior to the application due date

Application Due Date(s)

March 14, 2018; July 18, 2018; February, 14, 2019; July 18, 2019; February 14, 2020; and July 20, 2020, by 5:00 PM local time of applicant organization. All types of non-AIDS applications allowed for this funding opportunity announcement 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)

May 7, 2018; September 7, 2018; May 7, 2019; September 7, 2019; May 7, 2019; and September 7, 2020, by 5:00 PM local time of applicant organization. All types of AIDS and AIDS-related applications allowed for this funding opportunity announcement 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.

Scientific Merit Review

June 2018; November 2018; June 2019; November 2019; June 2020; November 2020

Advisory Council Review

October 2018; January 2019; October 2019; January 2020; October 2020; January 2021
(http://grants1.nih.gov/grants/funding/submissionschedule.htm#reviewandaward)

Earliest Start Date

December 2018

Expiration Date

September 8, 2020

Due Dates for E.O. 12372

Not Applicable

Required Application Instructions

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), except where instructed to do otherwise (in this FOA or in a Notice from the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/)). 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 available to submit your application through Grants.gov to NIH and Department of Health and Human Services partners. You **must** use one of these submission options to access the application forms for this opportunity.

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) solution to prepare and submit your application to Grants.gov and eRA Commons (http://public.era.nih.gov/commons/) to track your application. Check with your institutional officials regarding availability.

3. Use Grants.gov (../ApplyButtonSplash.cfm?oppNum=PAR-18-550) Workspace to prepare and submit your application and eRA Commons (http://public.era.nih.gov/commons/) to track your application.

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Part 2. Full Text of Announcement

Section I. Funding Opportunity Description

Purpose

The overarching purpose of this Funding Opportunity Announcement (FOA) is to fill critical scientific gaps needed to advance strong candidate biomarkers of neurological disease from discovery to clinical use. Specifically, the focus of this FOA is on the validation of analytical methods for biomarker measurements, including evaluation of the assay, its performance characteristics, and the optimal conditions that will generate reproducibility and accuracy consistent with FDA guidelines that are fit for the purpose of the assay.

Background

A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions. Biomarker modalities are diverse, and can include genetic, protein, cellular, metabolomic, imaging, behavioral and physiologic endpoints.

Biomarkers have become recognized as critical to the discovery and development of therapeutics. For example, they provide an early indication of therapeutic target engagement, and improve signal to noise by stratifying patients, thereby improving clinical trial design and enabling successful therapeutic development. In addition, biomarkers allow the evaluation of therapeutic intervention on disease progression or recurrence, as well as on the clinical manifestation of disease phenotype or severity. They are also being used to improve early diagnosis and therapeutic outcomes in cases where disease or disease manifestation could be significantly attenuated with treatment. Despite the active pace of discovery of novel biomarker candidates, few biomarkers progress beyond discovery to analytical validation and clinical practice, and robust, well-validated biomarkers for use in Phase II and Phase II clinical trials remain scant. Thus, there is a critical need to advance biomarkers to improve public health, particularly for disorders of the nervous system where failures to advance drugs from discovery to the market are notorious.

This FOA is intended to address the gap in biomarker validation by encouraging rigorous analytical validation of the biomarker measurement. This funding opportunity uses a cooperative agreement mechanism that enables significant input from NIH staff to assist investigators with preparing and evaluating their analytical validation strategy.

Research Objectives

Applications to this FOA must propose to conduct biomarker analytical validation studies in order to be supported.

The definitions of the terms assay, analytical validation, and context of use are provided below for the purposes of this FOA:

- **Assay:** An analytic procedure for detecting or measuring the presence, amount, state or functional activity of a biomarker.
- **Analytical Validation:** Establishing that the performance characteristics of a measurement are acceptable in terms of its sensitivity, specificity, accuracy, precision, and other relevant performance characteristics using a specified technical protocol (which may include sample collection and standardization procedures). Although the goal of analytical validation is to ensure a rigorous clinical conclusion, the level of analytical rigor that is necessary depends upon the characteristics of the biomarker, the detection technology, the type of clinical question (exploratory/informational) or its intended use as a biomarker (diagnostic, predictive, pharmacodynamic, etc). Analytical validation establishes the measurement's technical performance, but does not validate the usefulness of the measurement.
- **Context of Use (COU):** A statement that fully and clearly describes the way the biomarker is to be used and the biomarker-related purpose of the use. Considerations involved in defining the COU can include: biomarker modality and method of detection, clinical population characteristics, unmet need for the new biomarker and type of biomarker (response prediction, stratification, prognostic, diagnostic, target engagement, etc). Context of use statements are discussed extensively in the following link: https://fnih.org/sites/default/files/final/pdf/Evidentiary%20Criteria%20Framework%20Final%20Version%20Oct%2020%202016.pdf (https://fnih.org/sites/default/files/final/pdf/Evidentiary%20Criteria%20Framework%20Final%20Version%20Oct%2020%202016.pdf)

Use of the BEST (Biomarkers, EndpointS, and Other Tools Resource) standardized biomarker definitions (https://www.ncbi.nlm.nih.gov/books/NBK338448/ (https://www.ncbi.nlm.nih.gov/books/NBK338448/)) is required for all studies.

Entry Criteria

- **Applicants should have an identified biomarker with a working hypothesis regarding context of use.**

- **The method of detection for the biomarker should be developed, although it is understood that further optimization may occur during the validation process**. Applications are not limited by biomarker type or modality, and may include validation of prognostic, predictive, monitoring, diagnostic, risk, or response biomarkers using molecular, physiological, behavioral or neuroimaging data.
- **Plans for management of pre-analytic variables, such as standardization of biofluid or tissue sample collection, harmonization of instrumentation and image collection procedures across imaging centers, etc. must be in place.**
- **Biological rationale:** Projects should be supported by a cogent biological rationale supporting the candidate biomarker, as well as a discussion regarding the unmet need for the candidate biomarker. The biological rationale should include rigorously obtained evidence that the candidate biomarker is an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention, including therapeutic interventions.
- **Relevance for therapy development:** Projects should address the relevance of the candidate biomarker for therapy development or clinical practice.

Project Characteristics

- The project must focus on assays where the biomarker is likely to be used as a tool in the diagnosis, treatment, or prevention of diseases that fall within the NINDS mission.
- Strong justification of the use of the proposed assay and its biomarker as well as proven ability of the investigative team to perform analytical validation and optimization of assays in their laboratories is important.
- The status of the existing assay and the plan for its optimization in the clinical laboratory are critically important.
- Applications to this FOA should use technologies already in use or soon to be approved for use in clinical laboratories since this is not a technology development FOA.
- Applications to improve standardization or harmonization of assays among laboratories for use in clinical trials are appropriate for this FOA.
- Analytical validation in multiple testing sites is required, if applicable to the method of detection or its intended application.
- Metrics for analytical validation as milestones will be used to assess success in achieving each of the research plan's objectives.

Analytical Validation can include the following metrics with use of FDA guidance standards appropriate for the context of use:

- Accuracy
- Precision
- Analytical sensitivity
- Analytical specificity including interfering substances
- Reportable range of test results for the test system
- Reference intervals (normal values) with controls and calibrators
- Harmonization of analytical performance if the assay is to be performed in multiple laboratories
- Establishment of appropriate quality control and improvement procedures
- Any other performance characteristic required for test performance with determination of calibration and control procedures.

Applicants with assays that have already met the above criteria for analytical validation may apply directly to the companion FOA, "Clinical Validation of a Candidate Biomarker for Neurological Disease (U01 - Clinical Trial Optional)" which addresses retrospective and/or prospective clinical validation of candidate biomarkers for use in clinical trials and/or clinical practice.

Data obtained after completion of this FOA should be appropriate for use as a component of the package required for FDA qualification of the biomarker:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm)

Examples of biomarker validation studies that would be appropriate under this FOA include:

- Determination of the Context of Use for the biomarker
- Analytical validation of a tissue or biofluid biomarker assay or method of detection
- Analytical validation of an imaging biomarker
- Analytical validation of a physiological or behavioral biomarker
- Analytical validation of biomarkers with clinical intervention such as pharmacodynamic/response biomarkers, predictive biomarkers, safety biomarkers, or monitoring biomarkers
- Analytical validation of biomarkers without clinical intervention such as diagnostic, prognostic, or susceptibility/risk biomarkers
- Studies focused on improving standardization or harmonization of assays among laboratories for use in clinical trials
- The goal for analytical validation should be that the biomarker measurement meet**s** FDA analytical performance criteria https://www.fda.gov/downloads/drugs/guidances/ucm368107.pdf (https://www.fda.gov/downloads/drugs/guidances/ucm368107.pdf) within the scope of the intended Context of Use.

Examples of studies that are not appropriate for this FOA

This FOA is not meant to support the discovery of biomarkers or to support trials that assess the clinical utility of a biomarker/assay. Rather, it is intended to advance candidate biomarkers to the point where their clinical utility could be assessed in retrospective and/or prospective correlational clinical studies because the method of detection has been rigorously validated. Therefore, projects that are not appropriate for this FOA include:

- Natural history studies aimed at understanding disease pathophysiology, genetic, or epigenetic mechanisms
- Biomarker identification
- Initial development of the biomarker detection method (although it is recognized that optimization of that detection method will occur during the validation process)
- Therapeutic target identification
- Preclinical animal studies
- Development of candidate therapeutics

- Studies focused on clinical validation of a candidate biomarker

NINDS supports the analytical validation of biomarkers that indicate pharmacodynamic responses to therapeutics, that predict an efficacy or safety response to a therapeutic or that can be used to monitor a therapeutic response. While the studies outlined in an application may be defined as clinical trials, they should not seek to answer specific questions about safety, tolerability, clinical efficacy, effectiveness, and/or clinical management.

Studies focused on examining biomarker clinical validation and evaluation of utility in clinical practice of biomarkers may be more appropriate for the companion FOA, PAR-18-548. Prospective applicants are encouraged to discuss project suitability for this FOA with the NINDS Scientific/Research Contact listed in the Agency Contacts section below.

Collaborations

Multi-disciplinary collaboration among scientific investigators, assay developers, clinicians, statisticians, consultants, and clinical laboratory staff must be an integral part of the application. Projects proposed for this FOA will utilize multi-site design as applicable, and standardized data stewardship to ensure that data is reusable and accessible.

Investigators are encouraged to form collaborations with individuals knowledgeable in the FDA qualification process as well as those familiar with the process of analytical validation, including statistical design and analysis experts.

Leveraging Existing Research Resources

Applicants should leverage existing research resources for their studies. Such resources may include tissue, cellular, or DNA samples from NINDS BioSEND https://pdbp.ninds.nih.gov/biorepository (https://pdbp.ninds.nih.gov/biorepository) or other existing biospecimen, imaging and data repositories. Leveraging the resources and support from advocacy groups, private research foundations, academic institutions, other government agencies and the NIH Intramural program are also encouraged. Studies are also encouraged that leverage the resources of ongoing clinical trials supported through other Federal or private funds.

Project Milestones

A project timeline including milestones is a required component of the application (see Section IV.2). Milestones are quantitative goals that can be used for go/no-go decision making throughout the funding period, and therefore should have quantitative criteria associated with them. All milestones should be useful as a measure of progress toward the overall goal of the project. A list of activities planned for each year are not considered milestones because they do not provide decision-making goals. Annual milestones will provide clear indicators of a project's continued success or emergent difficulties and will be used to evaluate the application as part of the consideration of the awarded project for further funding of non-competing award years by the Program Director(s)/Principal Investigator(s), and Program Official and Project Scientist.

The NIH Program Official will contact the applicant to discuss the proposed milestones prior to the award. The Program Official and Project Scientist will discuss with the Program Director(s)/Principal Investigator(s) any recommended changes to the research plan or suggestions from peer reviewers, and the plan will be revised as appropriate prior to the award.

Studies should include quantitative milestones consistent with the metrics for analytical validation of the biomarker (e.g., sensitivity, reliability and responsiveness of the biomarker).

Pre-Application Consultation

Under this Cooperative Agreement mechanism, NINDS Project Scientist will have substantial communication and involvement with researchers in decision making prior to award and during the conduct of the study to provide oversight of data and safety monitoring, ensure the timely completion of the proposed studies and to maximize the positive impact of the studies on upcoming clinical trials.

Applicants are strongly encouraged to consult with NINDS Scientific/Research Staff early on during the planning for an application. This early contact will provide an opportunity to discuss and clarify NINDS policies and guidelines, including the scope of project relative to the NINDS mission and intent of this FOA. These discussions also provide important information and guidance on how to develop an appropriate timeline and milestone plan, which are subject to peer review under this program.

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

Section II. Award Information

Funding Instrument

Cooperative Agreement: A support mechanism used when there will be substantial Federal scientific or programmatic involvement. Substantial involvement means that, after award, NIH scientific or program staff will assist, guide, coordinate, or participate in project activities. See Section VI.2 for additional information about the substantial involvement for this FOA.

Application Types Allowed

New
Resubmission

Revision

The OER Glossary (//grants.nih.gov/grants/guide/url_redirect.htm?id=11116) and the SF424 (R&R) Application Guide provide details on these application types.

Clinical Trial?

Optional: Accepting applications that either propose or do not propose clinical trial(s)

Need help determining whether you are doing a clinical trial? (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82370)

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 proposed project period for this grant must not exceed 5 years

NIH grants policies as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120) will apply to the applications submitted and awards made from this FOA.

Section III. Eligibility Information

1. Eligible Applicants

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* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11118), **are** allowed.

Required Registrations

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 Late Submission of Grant Applications (//grants.nih.gov/grants/guide/notice-files/NOT-OD-15-039.html) 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) (http://fedgov.dnb.com/webform) - 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) (https://www.sam.gov/portal/public/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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11176) – Foreign organizations must obtain an NCAGE code (in lieu of a CAGE code) in order to register in SAM.
- eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123) - 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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=82300) – Applicants must have an active DUNS number and SAM registration in order to complete the Grants.gov registration.

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

All PD(s)/PI(s) must have an eRA Commons account. PD(s)/PI(s) should work with their organizational officials to either create a new account or to affiliate their existing account with the applicant organization in eRA Commons. 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.

Eligible Individuals (Program Director/Principal Investigator)

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*. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11126)

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 (//grants.nih.gov/grants/guide/notice-files/NOT-OD-11-101.html)).

Section IV. Application and Submission Information

1. Requesting an Application Package

Buttons to access the online ASSIST system or to download application forms are available in Part 1 of this FOA. See your administrative office for instructions if you plan to use an institutional system-to-system solution.

2. Content and Form of Application Submission

It is critical that applicants follow the Research (R) Instructions in the SF424 (R&R) Application Guide (//grants.nih.gov/grants/guide/url_redirect.htm?id=12000), 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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=41137).

Letter of Intent

Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, it is strongly encouraged. The information that it contains will allow IC staff to estimate the potential review workload and plan the review.

By the date listed in Part 1. Overview Information, prospective applicants are encouraged to submit a letter of intent that includes the following information:

- Descriptive title of proposed activity
- Name(s), address(es), and telephone number(s) of the PD(s)/PI(s)
- Names of other key personnel
- Participating institution(s)
- Number and title of this funding opportunity

The letter of intent should be sent to:

Mary Ann Pelleymounter, PhD

National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-451-4551
Fax: 301-219-9346
Email: mary.pelleymounter@nih.gov (mailto:mary.pelleymounter@nih.gov)

Page Limitations

All page limitations described in the SF424 Application Guide and the Table of Page Limits (//grants.nih.gov/grants/guide/url_redirect.htm?id=11133) must be followed.

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 be followed.

Applications should include an Intellectual property (IP) strategy. Applicants are encouraged to prepare this section of the application in consultation with their institution's technology transfer officials.

- Applicants should describe the IP landscape surrounding their biomarker and its measurement. Applicants should describe any known constraints that could impede biomarker development (e.g., certain restrictions under transfer or sharing agreements, applicants' previous or present IP filings and publications, similar biomarkers that are under patent protection and/or on the market, etc.) and how these issues could be addressed with achieving the goals of this program. If the applicant proposes using an agent(s) whose IP is not owned by the applicant's institution, either an investigational therapeutic, FDA-approved therapeutic, or other licensed product, the applicant should include a letter (see letter of support) from any entities owning the IP indicating there will not be any limitations imposed on the studies or the product which would impede achieving the goals of the funding program.
- If patents pertinent to the biomarker being developed under this application have been filed, the applicant should indicate the details of filing dates, what type of patents are filed, and application status, and associated USPTO links, if applicable.
- Applicants should discuss future IP filing plans. For a multiple-PD/PI, multiple-institution application, applicants should describe the infrastructure of each institution for bringing the technologies to practical application and for coordinating these efforts (e.g., licensing, managing IP) among the institutions. Applicants should clarify how IP will be shared or otherwise managed if multiple PD/PIs and institutions are involved.

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:

This FOA supports the validation of analytical methods for biomarker measurements, including evaluation of the assay, its performance characteristics, and the optimal conditions that will generate reproducibility and accuracy consistent with FDA guidelines that are fit for the

purpose of the assay.

Therefore, the potential of the proposed project to provide robust validation of a biomarker assay or method of detection is essential and will be a main factor in assessing the overall merit of the applications. Priority will be given to technologies that: 1) address an unmet medical need, 2) are supported by a strong biological rationale, 3) include a carefully designed plan for performance evaluation, 4) include a plan for standardization of sample and data collection for use in assay validation and 5) consider feasibility in a clinical setting across multiple sites.

Specific Aims:

Briefly provide the context for the proposed set of studies, with an emphasis on the biological research rationale for the identified biomarker, along with a cogent argument outlining its importance and unmet need. In addition, the major objectives of the proposed study should be stated, including the technical questions to be answered to further develop and validate the assay. A scientific hypothesis is not required for work of this nature.

Research Strategy:

The Research Strategy Section should include the following sections:

1. Rationale and Unmet Need

- Define the disease to be addressed.
- Provide a strong biological rationale for the candidate biomarker and strong justification of the use of the proposed assay.
- Describe the candidate biomarker along with its assay (i.e., method of detection,
- measurement methodology), and its potential for affecting the intended clinical
- context in treatment, prevention, diagnosis or clinical trials.
- Define the intended clinical context of use for the biomarker and its assay. Include
- information on characteristics of the sample (i.e., specimen, image, EEG, behavioral endpoint) to be used for the assay and how the assay result will be used.
- Describe the unmet need for the candidate biomarker and why the biomarker and its
- assay will be feasible to conduct in a clinical setting including multiple sites.
- If applicable, provide a comparison to other biomarker approaches for the disease of interest.
- Describe the potential for the proposed studies to significantly advance translational
- medicine in the disease area described.
- Address the probability for the biomarker and its assay to be broadly adopted by the
- health care community for use in treatment or prevention.

2. Preliminary Data

- Provide a clear outline of the preliminary data supporting an argument that the biomarker has been identified.
- Describe the development status of the assay or method of detection and its potential use in a clinical setting.
- Provide a clear outline of the function of the assay or method of detection, including the current reagents, technologies and types of specimens that the assay will use (e.g., fresh frozen or formalin--fixed tissue, serum or plasma or the same types of detail applicable to neuroimaging, behavioral or physiological measures).
- Discuss whether any of the analytical validation metrics listed in Section I above have been analyzed or completed; if so, provide the metrics.
- Provide the preliminary rationale for Context of Use.

3. Approach - address each of the items below.

- Plans to perform analytical validation of the assay or method of detection and its biomarker within its proposed context of use/Plans for refinement of the context of use for the biomarker, including but not limited to:
- Plan to obtain appropriate samples (i.e., specimens, imaging data, EEG, or behavioral data) for further development and optimization of the assay or method of detection
- Plan to ensure appropriate standardization of samples and data that are used to validate the assay or method of detection
- Plan to initiate and complete validation of the assay or method of detection
- Plan for evaluation of (i) Accuracy, (ii) Precision, (iii) Analytical sensitivity, (iv) Analytical specificity including interfering substances, (v) Reportable range of test results for the test system, (vi) Reference intervals (normal values) with controls and calibrators, (vii) Harmonization of analytical performance if the assay is to be performed in multiple laboratories, (viii)
- Establishment of appropriate quality control and improvement procedures, (ix) Any other
- performance characteristic required for test performance with determination of calibration and control procedures
- Plan for additional optimization of analytical validation including establishing threshold or cut-off for assay

4. Timeline and Proposed Milestones (required)

- Milestones and timelines must be provided *under* a separate, specific heading at the end of the Research Strategy Section.
- Please see "Project Milestones" section above for guidance in writing Go-No Go, quantitative milestones.
- There should be at least one milestone proposed for completion at the end of each year. Annual quantitative milestones are required to provide clear indicators of a project's continued progress or emergent difficulties and will be used to evaluate the application not only in peer review but also in consideration of the awarded project for funding of non-competing award years.
- Provide a detailed timeline for the anticipated attainment of each milestone and the overall goal.

- Identify any impediments that could require an addendum to the research plan, milestones, or timeline with a discussion of alternative approaches.

Team Management Plan:

- Applicants are strongly encouraged to form multidisciplinary teams that consist of clinical scientists, clinicians with drug development experience, regulatory experts, statisticians, and other academic/industry experts relevant to the therapeutic modality. Describe the team's ability to design the details of the plans and experiments, and to execute the research strategy.
- Describe how the team will work together (e.g., data generation, reporting of data and integrated review across teams with various disciplines, decision-making, etc.) over the course of the project (and include letters of support below). This description should include an outline of roles and responsibilities for each team member.

Letters of Support:

- Applicants should include letters of support from consultants, contractors, and collaborators.
- If applying from an academic institution, include a letter of support from the technology transfer official who will be managing intellectual property associated with this project.
- If research will be performed at more than one institution, include a letter of support from each institution clarifying how intellectual property will be shared or otherwise managed across the institutions.
- If collaborating with a private entity, include a letter of support that addresses any agreement to provide agent(s), any limits on the studies that can be performed with said agent(s), any limitations on sharing of data (including negative results), and whether a licensing agreement(s) will be needed and in place once the project is funded. This letter should come from a high official within the private entity who has authority to speak on these issues.
- If an application plans to utilize the infrastructure or resources of existing projects, whether funded by the NINDS, other governmental or non-governmental entities, letters of support detailing the terms of collaboration and data sharing must be included.
- If utilization of extant samples is proposed as a component of the study, letters of support or approval for use of those samples should be included. For example, if samples include those adjudicated by the Parkinson's Disease Biospecimen Review Access Committee (PD-BRAC), a letter indicating BRAC approval should be included (https://pdbp.ninds.nih.gov/pd-brac (https://pdbp.ninds.nih.gov/pd-brac)).

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, with the following addition:

- If patent protection is being sought, investigators should explain how data will be shared after filing for patent protection to allow for both further research and the development of commercial products to advance forward, consistent with achieving the goals of the program.

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 with the following additional instructions:

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* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11137), 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 (https://grants.nih.gov/grants/guide/url_redirect.htm?id=82380), the application deadline is automatically extended to the next business day.

Organizations must submit applications to Grants.gov (//grants.nih.gov/grants/guide/url_redirect.htm?id=11128) (the online portal to find and apply for grants across all Federal agencies). Applicants must then complete the submission process by tracking the status of the application in the eRA Commons (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123), 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. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11142)

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* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

Pre-award costs are allowable only as described in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11143).

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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11144). 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 (//grants.nih.gov/grants/ElectronicReceipt/support.htm#guidelines). 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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11146) for avoiding common errors.

Upon receipt, applications will be evaluated for completeness and compliance with application instructions by the Center for Scientific Review, NIH. Applications that are incomplete or non-compliant 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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=82299).

In addition, the NINDS Scientific Review Officer (SRO) will accept regulatory meeting minutes and transcripts, patents, and late-breaking data not to exceed 2 pages and not later than 30 calendar days prior to the peer review meeting.

Any instructions provided here are in addition to the instructions in the policy.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the NIH mission (//grants.nih.gov/grants/guide/url_redirect.htm?id=11149), 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.

This FOA supports the validation of analytical methods for biomarker measurements, including evaluation of the assay, its performance characteristics, and the optimal conditions that will generate reproducibility and accuracy consistent with FDA guidelines that are fit for the purpose of the assay.

Therefore, the potential of the proposed project to provide robust validation of a biomarker assay or method of detection is essential and will be a main factor in assessing the overall merit of the applications. Priority will be given to technologies that: 1) address an unmet medical need, 2) are supported by a strong biological rationale, 3) include a carefully designed plan for performance evaluation, 4) include a plan for standardization of sample and data collection for use in assay validation and 5) consider feasibility in a clinical setting across multiple sites.

In addition, for applications involving clinical trials

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? Is there a strong scientific premise for the project? 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?

Further criteria specific to this opportunity: 1) What is the potential of the candidate biomarker to address an unmet medical need? 2) What is the strength of the biological rationale for the biomarker? 3) What is the strength of the data supporting the rationale? 4) What is the feasibility of measurement of the biomarker from a clinical perspective? 5) How carefully have the investigators considered the phenotype, physiology, and feasibility of measurement of the targeted clinical population in the design of their biomarker assay? 6) Has the investigator carefully considered plans to obtain and refine context of use? 7) What is the overall potential for the proposed studies to significantly advance translational medicine in the disease area described? 8) How likely are the biomarker and its assay to be broadly adopted by the health care community for use in treatment or prevention?

In addition, for applications involving clinical trials

Are the scientific rationale and need for a clinical trial to test the proposed hypothesis or intervention well supported by preliminary data, clinical and/or preclinical studies, or information in the literature or knowledge of biological mechanisms? For trials focusing on clinical or public health endpoints, is this clinical trial necessary for testing the safety, efficacy or effectiveness of an intervention that could lead to a change in clinical practice, community behaviors or health care policy? For trials focusing on mechanistic, behavioral, physiological, biochemical, or other biomedical endpoints, is this trial needed to advance scientific understanding?

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?

Further criteria specific to this opportunity:

1) Are the investigators knowledgeable and experienced about the biological target and/or disease biology? 2) Do the investigators have sufficient expertise in the areas of development and analytical validation of the assay within the specified clinical context of use, statistical analysis, experimental design as appropriate for the project? 3) Will the team be able to manage the further development of the assay should the assay be successful so that it is distributed and available ultimately to the healthcare community?4) Are the roles of each collaborator carefully defined in the research plan?

In addition, for applications involving clinical trials

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?

Further criteria specific to this opportunity: How is the applicant's proposed use of the assay and its marker within the clinical context innovative?

In addition, for applications involving clinical trials

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?

Further criteria specific to this opportunity: >1) Are the plans to further optimize and validate the biomarker assay appropriate? 2) Does the application include a plan to ensure that samples and data used to validate the assay have been collected in a standardized and representative fashion? 3) Does the application include a carefully detailed plan for assay validation? 4) Does the application address the required assay performance metrics needed within the context of use? 5) Is the proposed statistical analysis appropriate for the experimental design and the quantitative characteristics of the end points? 6) Are the methods for evaluating the analytical method of the assay systematically outlined and scientifically sound? 7) What is the potential of the application to produce a biomarker assay or method of detection that will be feasible to implement and will meaningfully translate to human biology? 8) Havethe investigators included testing in multiple sites as part of the validation plan (if appropriate for the intended use of the assay)?

In addition, for applications involving clinical trials

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?

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?

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?

In addition, for applications involving clinical trials

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

Milestones and Timelines

Are the milestones robust and associated with clear, quantitative criteria for success that allow

go/no-go decisions? If a criterion is not to be used for go/no-go decisions, is it justifiable? Are the

timelines proposed for achieving the milestones realistic and inclusive of necessary steps, but

also efficient without adding unnecessary steps? Does the set of milestones allow the evaluation of progress and

will successful completion of these milestones provide confidence that the investigator will be able

to successfully implement future phases of the study and achieve its end goals within the timeline

of the grant mechanism?

Specific to applications involving clinical trials

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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11175).

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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11174).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following criteria: (1) description of proposed procedures involving animals, including species, strains, ages, sex, and total number to be used; (2) justifications for the use of animals versus alternative models and for the appropriateness of the species proposed; (3) interventions to minimize discomfort, distress, pain and injury; and (4) justification for euthanasia method if NOT consistent with the AVMA Guidelines for the Euthanasia of Animals. Reviewers will assess the use of chimpanzees as they would any other application proposing the use of vertebrate animals. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (//grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

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

Not Applicable.

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.

Intellectual Property

1) Does the application outline any known constraints that could impede biomarker development (e.g., certain restrictions under transfer or sharing agreements, applicants' previous or present IP filings and publications, similar biomarkers that are under patent protection and/or on the market, etc.) and how these issues could be addressed while achieving the goals of this program? 2) Does the applicant outline the IP landscape of their biomarker assay or method of detection? 3) If applicable, how strong is the applicant's IP portfolio/position (pertinent to the proposed project), and to what extent does the applicant have a reasonable strategy to protect its IP going forward? 44) If the applicant has filed patents pertinent to the biomarker assay, do they provide details about those patents? 5) If IP will be shared among co-investigators, does the applicant provide details about the plans for IP sharing?

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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11151); (2) Sharing Model Organisms (//grants.nih.gov/grants/guide/url_redirect.htm?id=11152); and (3) Genomic Data Sharing Plan (GDS) (//grants.nih.gov/grants/guide/url_redirect.htm?id=11153).

Authentication of Key Biological and/or Chemical Resources:

For projects involving key biological and/or chemical resources, reviewers will comment on the brief plans proposed for identifying and ensuring the validity of those resources.

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{NINDS}, in accordance with NIH peer review policy and procedures (//grants.nih.gov/grants/guide/url_redirect.htm?id=11154), 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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11123). Refer to Part 1 for dates for peer review, advisory council review, and earliest start date.

Information regarding the disposition of applications is available in the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11156).

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* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157).

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 terms and conditions found on the Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158) website. This includes any recent legislation and policy applicable to awards that is highlighted on this website.

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* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120) 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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11157) and Part II: Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (//grants.nih.gov/grants/guide/url_redirect.htm?id=11159). More information is provided at Award Conditions and Information for NIH Grants (//grants.nih.gov/grants/guide/url_redirect.htm?id=11158).

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 (http://www.hhs.gov/ocr/civilrights/understanding/section1557/index.html); and http://www.hhs.gov/ocr/civilrights/understanding/index.html (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 (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 (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 (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

The following special terms of award are in addition to, and not in lieu of, otherwise applicable U.S. Office of Management and Budget (OMB) administrative guidelines, U.S. Department of Health and Human Services (HHS) grant administration regulations at 45 CFR Parts 74 and 92 (Part 92 is applicable when State and local Governments are eligible to apply), and other HHS, PHS, and NIH grant administration policies.

The administrative and funding instrument used for this program will be the cooperative agreement, an "assistance" mechanism (rather than an "acquisition" mechanism), in which substantial NIH programmatic involvement with the awardees is anticipated during the performance of the activities

Under the cooperative agreement, the NIH purpose is to support and stimulate the recipients' activities by involvement in and otherwise working jointly with the award recipients in a partnership role; it is not to assume direction, prime responsibility, or a dominant role in the activities. Consistent with this concept, the dominant role and prime responsibility resides with the awardees for the project as a whole, although specific tasks and activities may be shared among the awardees and the NIH as defined below.

The PD(s)/PI(s) will have the primary responsibility (as appropriate) for:

- Defining the overall research objectives and approaches, and for planning, conducting, analyzing, interpreting, drawing conclusions on their studies, publishing and sharing the results.
- Determining experimental approaches, designing protocols, and overseeing the conduct of experiments.
- Developing and proposing rigorous milestones that will be achieved during the project period.
- Overseeing and coordinating the effort of the multi-disciplinary team and participating institutions and ensuring their optimal integration.
- Overseeing the conduct of research projects and ensuring their scientific rigor, including assumptions for the design of the experiments, the results of the investigations, interpretations of the results, and for concluding whether milestones have been met or not. In cases when NINDS Program staff request raw data, awardees agree to provide the data.
- Ensuring compliance with the applicable mandatory regulations (including protection of human subjects).
- Adhering to the NIH policies regarding intellectual property, data release, and other policies that might be established during the course of this activity.
- Submitting updates on progress and problems in a brief format as agreed upon with the NIH.
- Submitting monthly updates on human subject and accrual reports upon initiation of validation studies if applicable.
- Participating in monthly teleconferences with NIH program staff;
- Participating in at least once a year in progress meetings (teleconferences) that are organized by NIH staff.
- Regarding meetings and interactions with regulatory agencies, awardees agree to communicate meeting dates and agenda to the NIH Program staff and invite their participation.
- Awardees agree to communicate study reports from CROs, meeting minutes (and associated data packages if applicable), letters and other forms of communications with FDA, and other authorities, and to provide IND# and registration numbers in clinical trial.gov, if applicable.
- Awardees will retain custody of and have primary rights to the data, technologies, and software developed under these awards, subject to Government rights of access consistent with current HHS, PHS, and NIH policies.

NIH staff will have substantial programmatic involvement that is above and beyond the normal stewardship role in awards, as described below (as appropriate regarding clinical trials):

- Each project will have the support of one or more Project Scientists from NIH Program staff who are assigned an administrative role for the neurological disorder being studied and have expertise in the implementation of the NINDS Biomarker Program in Translational Research.
- The Project Scientists will have substantial scientific/programmatic involvement during the conduct of this activity, through technical assistance, advice, and coordination above and beyond normal program stewardship for grants.
- Providing input on the milestones and makes decisions regarding their finalization.
- Providing input on experimental and clinical approaches, assisting in designing protocols, and consulting on updates to project milestones.
- Assessing the progress of the project towards the specified milestones, and for recommending if further funds should be released to the project.
- In consultation with the PDs/PIs, may make suggestions for critical experiments to be conducted prior to or during the award as an additional milestone(s). In most cases, these studies will be supported by additional funds.
- Participates in meetings together with PDs/PIs with regulatory agencies related to the funded project if applicable.
- Providing advice to the awardees on specific scientific, analytical, and clinical issues if applicable.
- Assisting and advising awardees with regard to various regulatory and compliance issues if applicable.
- Participating in monthly teleconferences with PDs/PIs to monitor progress and facilitate cooperation if applicable.
- Tracking monthly accrual of participants for clinical testing to ensure proper completion of this essential step if applicable.
- Contributing to publications and presentations resulting from the project if appropriate.
- An important part of the NINDS Biomarker program is the coordination of research efforts across different funding mechanisms and research capabilities, and the coordination among efforts aimed at different neurological disorders. NINDS Project Scientists will have the primary responsibility for this overall coordination.
- Additionally, an NINDS Program Official will be responsible for the normal scientific and programmatic stewardship of the award and will be named in the award notice. Some Program Officials may also have substantial programmatic involvement (as Project Scientists/Coordinators). In that case, the individual involved will not attend peer review meetings of renewal (competing continuation) and/or supplemental applications or will seek NINDS waiver as stated above.

- NIH leadership will make decisions on project continuation based on Program staff recommendations, programmatic prioritizations and budget considerations. NINDS Program staff may consult as necessary with independent consultants with relevant expertise. If justified, future year milestones may be revised based on data and information obtained during the previous year. If, based on the progress report, a funded project does not meet the milestones, funding for the project may be discontinued. In addition to milestones, the decision regarding continued funding will also be based on the overall robustness of the entire data package that adequately allows an interpretation of the results (regardless if they have been captured in the milestones), overall progress, NINDS portfolio balance and program priorities, competitive landscape, and availability of funds.

Areas of Joint Responsibility include:

- Clarifying, negotiating and finalizing the milestones and timelines.

Dispute Resolution:

Any disagreements that may arise in scientific and/or programmatic matters (within the scope of the award) between award recipients and the NIH may be brought to Dispute Resolution. A Dispute Resolution Panel composed of three members will be convened. It will have three members: a designee of the Steering Committee chosen without NIH staff voting; one NIH designee; and a third designee with expertise in the relevant area who is chosen by the other two; in the case of individual disagreement, the first member may be chosen by the individual awardee. This special dispute resolution procedure does not alter the awardee's right to appeal an adverse action that is otherwise appealable in accordance with PHS regulation 42 CFR Part 50, Subpart D and HHS regulation 45 CFR Part 16.

3. Reporting

When multiple years are involved, awardees will be required to submit the Research Performance Progress Report (RPPR) (//grants.nih.gov/grants/rppr/index.htm) annually and financial statements as required in the NIH Grants Policy Statement. (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161)

A final RPPR, 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* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11161).

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 (//grants.nih.gov/grants/guide/url_redirect.htm?id=11170) on all subawards over $25,000. See the *NIH Grants Policy Statement* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11171) for additional information on this reporting requirement.

In accordance with the regulatory requirements provided at 45 CFR 75.113 and Appendix XII to 45 CFR Part 75, recipients that have currently active Federal grants, cooperative agreements, and procurement contracts from all Federal awarding agencies with a cumulative total value greater than $10,000,000 for any period of time during the period of performance of a Federal award, must report and maintain the currency of information reported in the System for Award Management (SAM) about civil, criminal, and administrative proceedings in connection with the award or performance of a Federal award that reached final disposition within the most recent five-year period. The recipient must also make semiannual disclosures regarding such proceedings. Proceedings information will be made publicly available in the designated integrity and performance system (currently FAPIIS). This is a statutory requirement under section 872 of Public Law 110-417, as amended (41 U.S.C. 2313). As required by section 3010 of Public Law 111-212, all information posted in the designated integrity and performance system on or after April 15, 2011, except past performance reviews required for Federal procurement contracts, will be publicly available. Full reporting requirements and procedures are found in Appendix XII to 45 CFR Part 75 – Award Term and Conditions for Recipient Integrity and Performance Matters.

Section VII. Agency Contacts

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

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: http://grants.nih.gov/support/ (//grants.nih.gov/support/) (preferred method of contact)
Telephone: 301-402-7469 or 866-504-9552 (Toll Free)

Grants.gov Customer Support (//grants.nih.gov/grants/guide/url_redirect.htm?id=82301) (Questions regarding Grants.gov registration and submission, downloading forms and application packages)
Contact Center Telephone: 800-518-4726
Email: support@grants.gov (mailto:support@grants.gov)

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

Scientific/Research Contact(s)

Mary Ann Pelleymounter, PhD
National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-496-1779
Email: mary.pelleymounter@nih.gov (mailto:mary.pelleymounter@nih.gov)

Victoria Smith, PhD
National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-496-1779
Email: victoria.smith@ninds.nih.gov (mailto:victoria.smith@ninds.nih.gov)

Peer Review Contact(s)

Chief, Scientific Review Branch
National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-496-9223
Email: nindsreview@mail.nih.gov (mailto:nindsreview@mail.nih.gov)

Financial/Grants Management Contact(s)

Tijuanna DeCoster, PhD
National Institute of Neurological Disorders and Stroke (NINDS)
Telephone: 301-496-9231
Email: decostert@mail.nih.gov (mailto:decostert@mail.nih.gov)

Section VIII. Other Information

Recently issued trans-NIH policy notices (//grants.nih.gov/grants/guide/url_redirect.htm?id=11163) may affect your application submission. A full list of policy notices published by NIH is provided in the *NIH Guide for Grants and Contracts* (//grants.nih.gov/grants/guide/url_redirect.htm?id=11164). All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement (//grants.nih.gov/grants/guide/url_redirect.htm?id=11120).

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 Part 75.

Weekly TOC for this Announcement (/grants/guide/WeeklyIndex.cfm?12-22-17)
NIH Funding Opportunities and Notices (/grants/guide/index.html)

Note: For help accessing PDF, RTF, MS Word, Excel, PowerPoint, Audio or Video files, see Help Downloading Files (/grants/edocs.htm).