Centers for Disease Control and Prevention

Agency for Toxic Substances and Disease Registry Extramural Research Program Office

Identify and Evaluate Potential Risk Factors for Amyotrophic Lateral Sclerosis (ALS)

RFA-TS-20-001

Application Due Date: 03/04/2020

Identify and Evaluate Potential Risk Factors for Amyotrophic Lateral Sclerosis (ALS)
RFA-TS-20-001
TABLE OF CONTENTS

Part 1. Overview Information
- Key Dates
- Required Application Instructions
- Executive Summary

Part 2. Full Text
- Section I. Funding Opportunity Description
- Section II. Award Information
- Section III. Eligibility Information
- Section IV. Application and Submission Information
- Section V. Application Review Information
- Section VI. Award Administration Information
- Section VII. Agency Contacts
- Section VIII. Other Information

Part 1. Overview Information

Participating Organization(s)

Centers for Disease Control and Prevention

Components of Participating Organizations

Agency for Toxic Substances and Disease Registry

Notice of Funding Opportunity (NOFO) Title

Identify and Evaluate Potential Risk Factors for Amyotrophic Lateral Sclerosis (ALS)

Activity Code

Applications in response to this NOFO will be funded using the R-01 activity code.

Notice of Funding Opportunity Type

New

Agency Notice of Funding Opportunity Number

RFA-TS-20-001

Assistance Listings (CFDA) Number(s)

93.061

Category of Funding Activity:

Health

NOFO Purpose

The Agency for Toxic Substances and Disease Registry (ATSDR) is soliciting investigator initiated research that will further the understanding of potential risk factors for ALS, while supporting the ATSDR National ALS Registry's mission. The National ALS Registry's goals are to estimate the number of new ALS cases each year, estimate the number of people who have ALS at a specific point in time, better understand who gets ALS, and identify what contributing factors, including environmental, may affect ALS. ATSDR is seeking investigator-initiated research that will identify and evaluate risk factors contributing to ALS, with preferred focus in this Notice of Funding Opportunity on factors related to military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents.

The purpose of Amendment 1 to NOFO RFA-TS-20-001 is to provide additional clarifying information based on questions received from potential applicants prior to and during the Pre-Application Conference Call held on January 8, 2020. A summary of the questions and answers can be found in *Section VIII. Other Information* of the amended NOFO.

Key Dates

Publication Date:	**To receive notification of any changes to RFA-TS-20-001, return to the synopsis page of this announcement at www.grants.gov and click on the**

	"Send Me Change Notification Emails" link. An email address is needed for this service.
Letter of Intent Due Date:	**01/13/2020**

Letters of Intent are requested by January 13, 2020. Although a letter of intent is not required to apply to this NOFO, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows ATSDR staff to estimate the potential review workload and plan the review.

Application Due Date:	**03/04/2020**

Applications are due March 4, 2020 at 5:00PM EST.

On-time submission requires that electronic applications be error-free and made available to CDC for processing from the NIH eRA system on or before the deadline date. Applications must be submitted to and validated successfully by Grants.gov no later than 5:00 PM U.S. Eastern Time. Applications must be submitted using the Application Submission System & Interface for Submission Tracking (ASSIST) module which is a web-based service used for the preparation and submission of grant applications to CDC through Grants.gov. ASSIST provides the ability for applicants to prepare their applications online, and offers the applicant additional capabilities including the ability to preview the application image, validate the application against required business rules, and prepopulate data from an applicant organization's records, therefore identifying issues earlier in the application submission process.

Note: HHS/CDC grant submission procedures do not provide a grace period beyond the application due date time to correct any error or warning notices of noncompliance with application instructions that are identified by Grants.gov or eRA systems (i.e., error correction window).

Scientific Merit Review:	**05/13/2020**

Estimated date is May 13, 2020. The actual review may occur in May or June 2020.

Secondary Review:	**06/17/2020**

Estimated date is June 17, 2020. The actual review may occur in June or July 2020.

Estimated Start Date:	**09/30/2020**

Estimated start date is September 30, 2020.

Expiration Date:	**05/01/2020**
Due Dates for E.O. 12372:	**Due no later than 60 days after the application receipt date.**

Required Application Instructions

ELECTRONIC APPLICATION SUBMISSION VIA ASSIST IS PREFERRED

It is recommended that applicants use ASSIST for the electronic preparation and submission of applications through Grants.gov to CDC. ASSIST is an alternative method to prepare and submit applications, and provides many features to facilitate the application submission process which improves data quality (e.g., pre-population of organization data, pre-submission validation of business rules, and preview of the application image used for review). Use of the

Grants.gov downloadable Adobe application packages and submission process will still be supported.

It is critical that applicants follow the instructions in the SF 424 (R&R) Application Guide except where instructed to do otherwise in this NOFO. Conformance to all requirements (both in the Application Guide and the NOFO) 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.

Note: The Research Strategy component of the Research Plan is limited to 25 pages.

Applications that do not comply with these instructions may be delayed or not accepted for review.

Pages that exceed page limits described in this NOFO will be removed and not forwarded for peer review, potentially affecting an application's score.

Telecommunications for the Hearing Impaired: TTY 1-888-232-6348

Executive Summary

The Agency for Toxic Substances and Disease Registry (ATSDR) is committed to protecting people's health from environmental hazards by investigating the relationship between environmental factors and health, developing guidance, and building partnerships to support healthy decision making. The intent of the ATSDR extramural research program is to fund research that promotes healthy community environments by assessing the available scientific data to determine whether or not people are at risk because of their exposures to harmful chemicals in the environment.

Approximately 5-10% of ALS cases can be attributed to familial, or heritable, genetic mutations. However, the majority of ALS cases are sporadic, for which the underlying cause(s) are largely unknown, and for which a complex set of risk factors including genetic susceptibility, environment, time, and occupation may interact to produce clinical disease. Many epidemiological investigations have shown a role for specific genetic mutations in multiple genes and exposures to persistent organic pollutants (POPs), organophosphate pesticides, and cyanobacteria.

Purpose: In this Notice of Funding Opportunity, ATSDR is seeking investigator-initiated research that will identify and evaluate risk factors contributing to ALS, **with preferred focus on research proposals that will examine factors related to military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents.**

Past studies suggest that prior military service increases risk for ALS due to potential exposures to pollutants, radiation or explosion blast overpressure mediated traumatic brain injury (TBI). Other studies have suggested a role for impact mediated TBI in the development of ALS, in the context of intense contact sports, possibly from the initiation of ALS related proteinopathies

and/or dysregulated neuroinflammation leading to neuronal toxicity. Finally, studies have evaluated the role of infectious agents, include mycoplasma, neurotoxin producing cyanobacteria and fungi, and viruses in increased ALS risk. ATSDR seeks additional research to identify and determine how environmental and other factors may contribute to increased risk of ALS, with an emphasis on statistically well powered study approaches adequately controlling for potential biases and confounding factors.

This Notice of Funding Opportunity aligns with the National Center for Environmental Health (NCEH)/ATSDR 2014-2016 strategic plan, available at https://www.atsdr.cdc.gov/about/mission_vision_goals.html, and supports the specific ATSDR goal to identify, characterize, and monitor health outcomes and environmental exposures to guide actions that protect and promote health. Additional information about ATSDR priorities is available at https://www.atsdr.cdc.gov/about/docs/NCEHATSDR_priorities_2014_final.pdf.

Mechanism of Support: The funding mechanism for this Notice of Funding Opportunity (NOFO) will be a research grant.

Funds Available and Anticipated Number of Awards: ATSDR intends to commit approximately up to $2,500,000 in FY 2020 to fund up to five (5) applications. Awards issued under this NOFO are contingent upon availability of funds and a sufficient number of meritorious applications. Because the nature and scope of the proposed research will vary from application to application, it is also anticipated that the size and duration of each award may also vary. The total amount awarded and the number of awards will depend upon the number, quality, duration and cost of the applications received and approved.

Budget and Project Period: The maximum award amount will be $500,000 per award for the first 12 month budget period. This includes both direct and indirect costs. An applicant may request a project period of up to three (3) years. The maximum total project funding amount is $1,500,000 (including both direct and indirect costs) over the expected three year project period length, with a maximum of $500,000 per award per year. The project period for this award is expected to run from 9/30/2020 to 9/29/2023. Throughout the project period, ATSDR's commitment to continuation of awards will be conditional on the availability of funds, evidence of satisfactory progress by the recipient (as documented in required reports), and the determination that continued funding is in the best interest of the Federal government.

Application Research Strategy Length: Page limits for the Research Strategy are clearly specified in *Section IV. Application and Submission Information* of this announcement.

Eligible Institutions/Organizations: Institutions/organizations listed in *Section III. Eligibility Information 1. Eligible Applicants* are eligible to apply.

Eligible Project Directors/Principal Investigators (PDs/PIs): Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institution/organization to develop an application for support. NOTE: CDC/ATSDR does not make awards to individuals directly. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply.

Number of PDs/PIs: An application may name more than one PD/PI; their names must appear on the face page of the application. However:

- One (1) principal investigator must be designated as the contact PI for all correspondence related to the application.
- All PD/PIs must include their eRA Commons Identification in the Credential Field of the Senior/Key Person Profile Component of the SF424 (R&R) Application Package.
- Institutions/organizations proposing multiple PDs/PIs must visit the Multiple Program Director/Principal Investigator Policy and submission details in the Senior/Key Person Profile (Expanded) Component of the SF 424 (R&R) Application Guide.

Number of Applications: Applicant organizations may submit more than one application, provided that each application is scientifically distinct. However, applicant institutions can submit only one grant application with the same principal investigator in response to this NOFO. Only one application per principal investigator will be funded under this NOFO. Additionally, applicant institutions submitting applications with essentially the same proposed research to two or more CDC/ATSDR NOFOs will not be funded under more than one NOFO.

Application Type: NEW

Special Date(s): A pre-application teleconference call will be conducted on **January 8, 2020** to address questions from prospective applicants regarding NOFO RFA-TS-20-001, *Identify and Evaluate Potential Risk Factors for Amyotrophic Lateral Sclerosis (ALS)*. The call will begin at 3:00PM Eastern Standard Time (EST) and end at 4:00PM Eastern Standard Time (EST), or sooner if all questions are addressed. Questions and answers from the discussion will be included in an amended NOFO approximately 3 weeks after the call.

Participant Access Information

- Call Date: January 8, 2020
- Call Start Time: 3:00 PM Eastern Standard Time (EST)
- Call End Time: 4:00 PM Eastern Standard Time (EST)
- Call Leader: Marcienne Wright, PhD, Scientific Program Official
- Toll-Free Number: 1-866-600-6035

- Use Passcode 23198543 when prompted.

Application Materials. See Section IV.1 for application materials.

Part 2. Full Text

Section I. Funding Opportunity Description

Statutory Authority

This program is authorized under the Public Health Service Act, Title 42, Part 247b, Section 317(k)(2) and Section 399S of the Public Health Service Act [42 U.S.C. Section 280g-7], as amended.

1. Background and Purpose

Amyotropic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive and often fatal neuromuscular disease that presents in familial (fALS) or sporadic (sALS) forms. Almost 16,000 people in the U.S. lived with ALS in 2013 and most people die within two to five years of being diagnosed with the disease (Mehta et al., 2018). Approximately 5-10% of all ALS cases can be attributed to familial, or heritable, genetic mutations. However, the majority of ALS cases are sporadic, for which the underlying cause(s) are largely unknown, and for which a complex set of risk factors including genetic susceptibility, environment, time, and occupation may interact to produce clinical disease (Bradley, 2018; Oskarsson, 2018; Wang, 2016; Al-Chalabi, 2013). Studies have evaluated possible ALS risk factors including familial and sporadic genetic susceptibility, employment in certain occupations, exposure to heavy metals, cyanotoxins and infectious agents, physical activity, and trauma (Andrew, 2017; Sutedja, 2009; Factor-Litvak, 2013; Bettencourt, 2015; Bradley, 2013; Watanabe, 2017; Pupillo, 2017; Fang, 2011). ATSDR is seeking investigator-initiated research that will identify and evaluate risk factors contributing to ALS, **with preferred focus in this Notice of Funding Opportunity on factors related to military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents**.

Military Service

Past population-based cohort studies provide limited and suggestive evidence of associations between military service in World War II and the Korean, Vietnam, and Gulf Wars and the development of ALS (Cragg, 2017; Beard, 2016; Weisskopf, 2015; Weisskopf, 2005; Horner, 2005; Haley, 2003). While the reasons for increased ALS risk among military veterans are unknown, selective environmental exposures to persistent organic pollutants, herbicides (including Agent Orange), ionizing radiation, burn agents, cyanotoxins etc. may play a part in increased risk during military service (Beard, 2016; Oskarsson, 2015; Cox, 2009; Weisskopf, 2005). Additionally, duration of time served and exposure to repetitive explosion-mediated blast overpressure leading to traumatic brain injury (TBI) in combat settings may also contribute to ALS susceptibility and severity of disease (Beard, 2016; Heyburn, 2019). ATSDR seeks additional research to determine if and how these or other military service-related factors contribute to increased risk of ALS, with an emphasis on statistically well powered study approaches adequately controlling for potential biases and confounding factors (Academies

IoMotN, 2006).

Sports and Traumatic Brain Injury

Participation by athletes in certain contact sports is associated with an increased risk of developing ALS. Past studies cite intense physical activity, head and neck musculoskeletal trauma, and repeated concussions leading to mild, moderate, or severe TBI as potential contributing factors (Blecher, 2019; Gotkine M, 2014; Lehman EJ, 2012; Chio A, 2009; Chio A, 2005). However, it is unclear to what degree contact sports related trauma, and the severity and repetition of TBI, influence ALS development. Additional research is needed that examines the role of impact mediated TBI from participation in contact sports in the development of ALS, including consideration of differential diagnosis of and co-morbidity with ALS and chronic traumatic encephalopathy post-TBI (Walt, 2018; Lehman EJ, 2012). Research on TBI that investigates whether and how additional risk factors can work in concert with TBI to increase ALS risk is also sought. Such risk factors may include, but are not limited to, athletic exposure to playing field pesticides or grass or soil-associated infectious agents, the intensity of physical activity, and athlete participant demographics including pre-existing genetic susceptibility, gender, and age at the time of exposure (Franz, 2019).

Neuroinflammation and Infectious Agents

Neuroinflammation is a primary cause of secondary brain injury following TBI (Kumar, 2012). Emerging research suggests that neuroinflammation, including dysregulated innate immune system activation, may contribute to the development of ALS through neuronal toxicity (McCauley, 2018; Kjaeldgaard, 2018). Research evaluating the role of TBI in neuroinflammatory and innate immune response pathways in the development of ALS, including identification of relevant inflammatory and immune biomarkers in persons with ALS, is sought. Past studies have suggested that exposure to microbial infectious agents, including mycoplasma, cyanobacterial neurotoxins, fungal neurotoxins, and viruses, may be a risk factor for ALS (French, 2019; Douville, 2011; Caller, 2009; Cox, 2009; Nicolson, 2002). ATSDR solicits further research on the etiologic role that infectious agents may have in contributing to ALS, including their impact on neuroinflammation and innate immune response activation.

ATSDR National ALS Registry

Uncertainty about the incidence and prevalence of ALS, the etiology of the disease, and risk factors associated with disease development and progression created a need for structured data collection. The ALS Registry Act (H.R. 2295), passed in October 2008, amends the Public Health Service Act to require the Secretary of DHHS, acting through the Director of CDC, to (1) develop a system to collect data on ALS; and (2) establish a national registry for the collection and storage of ALS data. In October 2010, the federal Agency for Toxic Substances and Disease Registry (ATSDR) launched the National ALS Registry to collect data that would:

- describe the incidence and prevalence of ALS in the US;
- examine factors such as environmental, occupational, genetics, that might be associated

with the disease;
- better outline key demographic factors (such as age, race or ethnicity, gender, and family history of individuals who are diagnosed with the disease) associated with the disease; and
- facilitate examination of the connection between ALS and other motor neuron disorders that can be confused with ALS, misdiagnosed as ALS, and in some cases progress to ALS.

ATSDR National ALS Registry data are available for researchers to identify potential risk factors for ALS. **Applicants are encouraged to consider submitting proposals on research topic areas not currently funded by the ATSDR National ALS Registry.** ATSDR is especially interested in innovative research applications that propose to conduct an epidemiological investigation using the ATSDR National ALS Registry and/or using a third party ALS registry on risk factors related to military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents. Examples of ALS registry research previously funded by ATSDR can be found at https://www.cdc.gov/als/ALSExternalResearchfundedbyRegistry.html.

For NOFO RFA-TS-20-001, through the use of human ALS epidemiological data sources, including those that contain information on potential environmental, demographic, occupational, behavioral and familial associations, and through the use of epidemiological, environmental health, and laboratory research approaches, applications funded under this NOFO must address both of the following objectives:

Objective One: Identify potential risk factors for ALS in humans including, but not limited to, risk factors listed below:

- environmental and occupational risks, including from **past military service**
- **traumatic brain injuries**, including blast or impact TBI associated with military service or contact sports
- injury or microbial infection (e.g., bacterial, fungal, viral) resulting in **neuroinflammation or innate immune system activation**
- nutritional intake, and
- pharmaceutical use (e.g., statins)

Objective Two: Characterize how or why the(se) risk factor(s) are potentially associated with or contribute to the etiology, progression, and pathophysiology of ALS in humans.

Research funded under this NOFO is expected to be innovative and produce outcomes that will help ATSDR better understand the etiology and epidemiology of ALS, prioritize topics for future research initiatives, and inform the development of new ATSDR ALS Registry risk factor

surveys for persons with ALS.

Healthy People 2020 and other National Strategic Priorities

ATSDR is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2020" and to measuring program performance as stipulated by the Government Performance and Review Act (GPRA). This research NOFO directly supports the DHHS Healthy People 2020 goals and objectives as described in: http://www.healthypeople.gov/.

The proposed program of research addresses the Healthy People 2020 priority area of environmental health infrastructure and surveillance and is in alignment with ATSDR's performance goal to conduct a targeted program of research to identify, characterize, and monitor health outcomes and environmental exposures to guide actions that protect and promote health. Specifically this research NOFO supports the Healthy People 2020 goal for promoting high-quality, longer lives free of preventable disease and Healthy People Objective EH-21 to improve the quality, utility, awareness, and use of existing information systems for environmental health.

Public Health Impact

The public health impact of applications funded under RFA-TS-20-001 will result in the addition of new information to existing literature on epidemiological associations between environmental and other risk factors and ALS and a stronger understanding of the etiology of ALS pathogenesis. Research outcomes will help ATSDR prioritize topics for future National ALS Registry research initiatives and the ALS Registry risk factor surveys.

Relevant Work

The ALS Registry Act (P.L. 110-373), passed in October 2008, amends the Public Health Service Act to require the Secretary of DHHS, acting through the Director of CDC, to (1) develop a system to collect data on ALS; and (2) establish a national registry for the collection and storage of ALS data. ATSDR, in coordination with CDC, launched the National ALS Registry in October 2010. The Registry tracks ALS cases in the United States by using existing national administrative databases and a secure web portal that allows patients to self-enroll and take brief risk factor surveys. ATSDR released the first National ALS Registry Report in July 2014 (covering 2010-2011), the second National ALS registry Report in August 2016 (covering 2012-2013), and the third National ALS registry Report in February 2018 (covering 2014).

References:

1. US Public Health Service. ALS Registry Act. Washington, DC: 110th Congress. Public Law 2008;122 Stat 4047:110-373.

2. Mehta, P; Kaye, W; Raymond, J; et. al.; Prevalence of Amyotrophic Lateral Sclerosis - United States, 2014. MMWR February 23, 2018; 67(7):216?218

3. Mehta, P; Kaye, W; Bryan, L; et. al.; Prevalence of Amyotrophic Lateral Sclerosis: United States, 2012-2013. MMWR August 5, 2016; 65 (8); 1-12

4. Mehta, P; Antao, A; Kaye, W; et. al.; Prevalence of Amyotrophic Lateral Sclerosis: United States, 2010-2011; MMWR July 25, 2014; 63 (SS07); 1-14

5. Horton DK, Mehta P, Antao VC. Quantifying a nonnotifiable disease in the United States: the

National Amyotrophic Lateral Sclerosis Registry model. JAMA 2014;312:1097-8.

6. Bryan L, Kaye W, Antao V, Mehta P, Muravov O, Horton DK. Preliminary results of National Amyotrophic Lateral Sclerosis (ALS) Registry risk factor survey data. PLoS One 2016;11:e0153683.

2. Approach

ATSDR is soliciting innovative investigator-initiated research that will help expand and advance our current knowledge of the role that potential risk factors, including environmental risk factors, may have on ALS etiology, with special emphasis on identification and evaluation of ALS risk factors related to military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents.

It is expected that the application's research plan will reflect rigorous quantitative and qualitative experimental designs and include data analytic plans that are appropriate to the research design and hypotheses, data collection measures, and project period. The experimental approach should anticipate and evaluate the effects of methodological challenges to the internal and external validity of the specified research design. The statistical power for investigations must be sufficiently high to provide meaningful toxicological and epidemiological analyses.

Research approaches may include, but are not limited to: population-based case-controlled epidemiological studies, including direct and indirect exposure assessments and dataset analyses, environmental toxicant composition and concentration analyses in human biospecimens; genome wide association and next generation sequencing studies; and molecular, histological and computational analyses of phenotypic biological effects (including biochemical, genetic, epigenetic, and physiological) that can help identify potential risk factors for ALS in humans and evaluate how or why the(se) risk factor(s) are potentially associated with or contribute to the etiology, progression, and pathophysiology of ALS in humans.

ALS case control studies and epidemiological datasets: Prospective cohort studies are preferred. Retrospective case-control studies and ecological studies may also be considered. Analyses of existing ALS epidemiological datasets, such as from large observational studies, are acceptable. Datasets should be of sufficient size to support robust analyses. ALS epidemiological data may include environmental, demographic, occupational, behavioral and familial risk factors, etc. as appropriate for the research plan. ALS epidemiological data may be provided by the applicant and/or may be requested from the ATSDR National ALS Registry.

Use of the ATSDR National ALS Registry: ATSDR National ALS Registry data are available for researchers to identify potential risk factors for ALS. Use of the ATSDR National ALS Registry is not required for consideration of funding under this announcement. However, applicants are encouraged to include ATSDR National ALS Registry enrollees, as appropriate, in their research plans. Applicants are encouraged to consider submitting an application to use ATSDR's ALS Research Notification tool to recruit ALS patients from the National ALS

Registry, when applicable to the research plan, available at https://www.cdc.gov/als/ALSRegistryResearchApplicationInfo.html (pending OMB re-authorization). The ATSDR ALS Research Notification tool will enable Registry grantees to receive email notifications about their approved studies sent to persons with ALS enrolled in the Registry. Applicants awarded a grant under NOFO RFA-TS-20-001 and who wish to use the ATSDR National ALS Registry will be required to enter into a Data Use Agreement (DUA) with ATSDR to protect the confidentiality of data in accordance with the terms of the DUA and applicable laws. Applicants may use, alone or in conjunction with the ATSDR National ALS Registry, applicant-provided or third-party sourced ALS and case-control registries in their research plans, as appropriate for their research proposals.

Use of the ATSDR National ALS Biorepository: Applicants should **not** submit proposals that intend to use biospecimens from the ATSDR National ALS Biorepository for the RFA-TS-20-001 funding cycle. However, applicants may use applicant-provided or third-party sourced ALS biospecimens in their research plans, as appropriate for the research design. Applicants using applicant-provided or third-party sourced ALS biospecimens must include, as part of their research plan, use of a matched ALS epidemiological registry for identification and evaluation of ALS risk factors. The statistical power for the applicant-provided or third-party sourced ALS biospecimen repository must be sufficiently high to provide meaningful epidemiological analyses.

Applications must be scientifically responsive to NOFO RFA-TS-20-001 in order to be forwarded for peer review. Responsiveness criteria are listed in ***Section III. Eligibility Information 5. Responsiveness*** of this NOFO. It is the applicant's responsibility to ensure that the submitted research proposal meets all responsiveness criteria listed in ***Section III. Eligibility Information 5. Responsiveness***.

Objectives/Outcomes

For NOFO RFA-TS-20-001, through the use of human ALS epidemiological data sources, including those that contain information on potential environmental, demographic, occupational, behavioral and familial associations, and through the use of epidemiological, environmental health, and laboratory research approaches, applications funded under this NOFO must address both of the following objectives:

Objective One: Identify potential risk factors for ALS in humans including, but not limited to, risk factors listed below:

- environmental and occupational risks, including from **past military service**
- **traumatic brain injuries**, including blast or impact TBI associated with military service or contact sports
- injury or microbial infection (e.g., bacterial, fungal, viral) resulting in **neuroinflammation or innate immune system activation**
- nutritional intake, and

- pharmaceutical use (e.g., statins)

Objective Two: Characterize how or why the(se) risk factor(s) are potentially associated with or contribute to the etiology, progression, and pathophysiology of ALS in humans.

Research funded under this NOFO is expected to be innovative and produce outcomes that will help ATSDR better understand the etiology and epidemiology of ALS, prioritize topics for future research initiatives, and inform the development of new ATSDR ALS Registry risk factor surveys for persons with ALS.

Target Population

NOFO RFA-TS-20-001 supports the conduct of research that will benefit all persons with ALS and those at risk for developing ALS such as males, non-Hispanics, persons with a history of military service, and persons with a history of participation in contact sports. Although it is not required for consideration of funding under this announcement, applicants are encouraged to include the ATSDR National ALS Registry enrollees, as appropriate, in their research plans. The ATSDR National ALS Registry tool for researcher access can be found at https://www.cdc.gov/als/ALSRegistryResearchApplicationInfo.html (pending OMB re-authorization).

Collaboration/Partnerships

The application must include letters of support, or memoranda of understanding, documenting the proposed partnership(s). Specifically, for all collaborations, documentation must clearly describe the nature of the proposed partnership, including the roles and responsibilities of the Principal Investigator(s) and of the outside entities or partner agencies, the existing working relationship, plans for the proposed research, the nature and extent of the involvement to be provided by the applicant institution and outside entity, the outside entity's scope of work, and how the partnership will ensure implementation and sustainability of the proposed research plan. Applicants must describe all data sources and processes used to ensure data access. Evidence of access to the data from outside entities may be demonstrated by data sharing agreements, memoranda of understanding, or Letters of Support detailing the data availability. The proposed budget should include travel funding for research staff to directly meet with and monitor study implementation within both the program and partner sites if the sites are not local to the research investigators.

For all applications the majority (**60% or greater**) of the proposed research work plan, as evidenced by the proposed budget, must be directly carried out by the applicant organization throughout the project period. The applicant organization cannot serve as a "pass through" to fund another entity to conduct the majority of the research. **Applications that submit a research plan budget in SF-424 Research and Related Budget, and in the detailed budget narrative, reflecting less than 60% of direct effort from the applicant organization will be considered nonresponsive and will not be forwarded for peer review**.

Documentation of collaboration/partnerships and data access must be included in the Letters of Support section of the application. **Applications that do not include appropriate Letters of Support or memoranda of understanding between the applicant organization and every outside entity that will participate in the research or provide data access will be considered nonresponsive and will not be forwarded for peer review**.

Evaluation/Performance Measurement

Applicants are expected to provide an evaluation and performance measurement plan with measures of effectiveness. The plan must be able to demonstrate the feasibility of accomplishing the proposed project objectives. Measures of effectiveness must relate to the goals stated in the "Purpose" section of this announcement and be able to measure the intended outputs and outcomes described. Outcomes to be evaluated should be clearly specified. Performance measures should include the number of participants recruited into the study, the participation rate, and types of samples collected.

Translation Plan

Applicants should provide evidence of the potential for widespread dissemination, implementation, and sustainability of the proposed strategy to ensure that the approach, if effective, is scalable without prohibitive costs or resources. Research findings should be disseminated through publications, including articles in peer reviewed journals and research briefs for diverse audiences, as well as presentations at professional conferences and other venues. An explanation for how the scientific findings could be translated into public health programs, policies or practice should be included in the application.

Grant awardees will be required to attend at least one reverse site visit in Atlanta with ATSDR program staff during the period of performance to review their progress and findings and to discuss opportunities for widespread dissemination of their research achievements and lessons learned. **Travel costs for attending this meeting must be included the application's travel budget submitted in response to this NOFO.**

Section II. Award Information

Funding Instrument Type:	Grant A support mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity.

Application Types Allowed:

New - An application that is submitted for funding for the first time. Includes multiple submission attempts within the same round.

Estimated Total Funding:	$7,500,000
Anticipated Number of Awards:	5

Awards issued under this NOFO are contingent on the availability of funds and submission of a sufficient number of meritorious applications.

Award ceiling and floor are for the first 12-month budget period only.

Award Ceiling:	$500,000 Per Budget Period
Award Floor:	$0 Per Budget Period
Total Period of Performance Length:	3 year(s)

Throughout the Period of Performance, CDC's commitment to continuation of awards will depend on the availability of funds, evidence of satisfactory progress by the recipient (as documented in required reports), and CDC's determination that continued funding is in the best interest of the Federal government.

HHS/CDC grants policies as described in the HHS Grants Policy Statement (http://www.hhs.gov/ sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf) will apply to the applications submitted and awards made in response to this NOFO.

Section III. Eligibility Information

1. Eligible Applicants

Eligibility Category:	State governments County governments City or township governments Special district governments Independent school districts Public and State controlled institutions of higher education Native American tribal governments (Federally recognized) Public housing authorities/Indian housing authorities Native American tribal organizations (other than Federally recognized tribal governments) Nonprofits having a 501(c)(3) status with the IRS, other than institutions of higher education Nonprofits without 501(c)(3) status with the IRS, other than institutions of higher education Private institutions of higher education Others (see text field entitled "Additional Information on Eligibility" for clarification)

Additional Eligibility Category:

The following types of Higher Education Institutions are always encouraged to apply for CDC 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

Nonprofits (Other than Institutions of Higher Education):

Nonprofits (Other than Institutions of Higher Education)

Other:

Faith-based or Community-based Organizations
Regional Organizations
Foreign Organizations: a Foreign Organization is a public or private organization, whether non-profit or for-profit, located in a country other than the United States (U.S.) and its territories that is subject to the laws of the country in which it is located, irrespective of the citizenship of project staff or place of performance.
Bona Fide Agents: A Bona Fide Agent is an agency/organization identified by the state as eligible to submit an application under the state eligibility in lieu of a state application. If applying as a bona fide agent of a state or local government, a legal, binding agreement from the state or local government as documentation of the status is required. Attach with "Other Attachment Forms."
Federally Funded Research and Development Centers (FFRDCs): FFRDCs are operated, managed, and/or administered by a university or consortium of universities, other not-for-profit or nonprofit organization, or an industrial firm, as an autonomous

organization or as an identifiable separate operating unit of a parent organization. A FFRDC meets some special long-term research or development need which cannot be met as effectively by an agency's existing in-house or contractor resources. FFRDC's enable agencies to use private sector resources to accomplish tasks that are integral to the mission and operation of the sponsoring agency. For more information on FFRDCs, go to https://gov.ecfr.io/cgi-bin/searchECFR

2. Foreign Organizations

Foreign Organizations are eligible to apply.

Foreign (non-US) organizations must follow policies described in the HHS Grants Policy Statement (http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf), and procedures for foreign organizations described throughout the SF424 (R&R) Application Guide. International registrants can confirm DUNS by sending an e-mail to ccrhelp@dnb.com, including Company Name, D-U-N-S Number, and Physical Address, and Country. Special Instructions for acquiring a Commercial and Governmental Entity (NCAGE) Code: https://eportal.nspa.nato.int/AC135 Public/Docs/US%20Instructions%20for%20NSPA%20NCAGE.pdf.

Foreign components of U.S. Organizations are eligible to apply.

For this announcement, applicants may include collaborators or consultants from foreign institutions. All applicable federal laws and policies apply.

3. Additional Information on Eligibility

Additional Eligibility Category:
The following types of Higher Education Institutions are always encouraged to apply for CDC 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, Native American tribal organizations (other than Federally recognized tribal governments), Faith-based or Community-based Organizations, Regional Organizations

Bona Fide Agents: A Bona Fide Agent is an agency/organization identified by the state as eligible to submit an application under the state eligibility in lieu of a state application. If applying as a bona fide agent of a state or local government, a legal, binding agreement from the state or local government as documentation of the status is required. Attach with "Other Attachment Forms."

Federally Funded Research and Development Centers (FFRDCs): FFRDCs are operated, managed, and/or administered by a university or consortium of universities, other not-for-profit

or nonprofit organization, or an industrial firm, as an autonomous organization or as an identifiable separate operating unit of a parent organization. A FFRDC meets some special long-term research or development need which cannot be met as effectively by an agency's existing in-house or contractor resources. FFRDC's enable agencies to use private sector resources to accomplish tasks that are integral to the mission and operation of the sponsoring agency. For more information on FFRDCs, go to https://dap.dau.mil/acquipedia/Pages/ArticleDetails.aspx?aid=5e3079b8-44f2-43df-a0e7-9f379e8c48ed

Foreign Organizations are eligible to apply.

4. Justification for Less than Maximum Competition

5. Responsiveness

There must be an overall match between the proposed research objectives as described in the applicant's abstract and the research objectives of this announcement as described in Section I under the heading *Objectives/Outcomes*. **Applications that do not provide an overall match between the proposed research objectives (as described in the applicant's abstract) and the research objectives of this announcement (as described in Section I under the heading *Objectives/Outcomes*) will be considered non-responsive and will not be forwarded for peer review**.

- Funds are available for the identification of potential risk factors, including environmental, for ALS development and progression that uses data from a human ALS registry. Applications proposing **research outside of the stated focus area of this NOFO (e.g., research on non-ALS diseases, etc.) will be considered non-responsive and will not be forwarded for peer review**.

- While applicants may include specific aims comparing environmental toxicant-mediated etiology of ALS to the etiology of other non-ALS neuromuscular diseases (e.g. chronic traumatic encephalopathy, CTE), applications proposing **research which focuses <u>primarily</u> on non-ALS neuromuscular diseases will be considered non-responsive and will not be forwarded for peer review**.

- ATSDR National ALS Biorepository biospecimens will not be provided to applicants for the RFA-TS-20-001 funding cycle. However, applicants may use applicant-provided or third-party sourced ALS biospecimens in their research plans, as appropriate for the research design. Applicants must include, as part of the research plan, use of a matched applicant-provided or third-party sourced ALS epidemiological registry alongside the use of their selected biospecimen repository for identification and evaluation of ALS risk

factors. Applications proposing **research using applicant-provided or third-party sourced ALS biospecimens in the research plan without also using a matched ALS epidemiological registry as the primary aim for identification and evaluation of ALS risk factors will be considered non-responsive and will not be forwarded for peer review.**

- Applicants may use human ALS or ALS-like animal models (e.g. SOD1 or TDP-43 mouse models or other mammalian) in their research plans as appropriate for their research proposals. However, applicants must include in the research plan, as the primary research aim, a human health epidemiological investigation to identify and evaluate ALS risk factors from **human ALS epidemiological data sources** as described in Section I under the heading Objectives/Outcomes. Applications using animal models must clearly describe and justify in their research plan how the animal model will be used to support the primary human epidemiological investigation to identify and evaluate potential risk factors for human ALS through the use of a human ALS epidemiological registry. Applications **proposing research on ALS risk factors in non-human species, including mammalian animal models, as the primary aim of the proposal will be considered non-responsive and will not be forwarded for peer review**.

The biosketch for the PI, Co-PI, or Co-Investigator must include documentation of prior expertise, experience, and knowledge directing human epidemiological, environmental health and ecological empirical research on ALS risk factors, including the use of prospective and retrospective case-controls, large epidemiological datasets, and toxicological/molecular laboratory approaches, as appropriate to the research plan. Expertise must be documented with at least one first-authored, peer-reviewed publication directly relevant to the research plan proposed or by serving as a principal investigator on a grant, cooperative agreement, or contract in these subject matter areas (include description and references in the biographical sketch). Experience requirements may be demonstrated through the combined experiences of a Principal and Co-Investigator (if applicable). The citation of the relevant publication(s) or research experience must be clearly identified (by bold text or highlight) in the appropriate SF 424 Biographical Sketch. **Applications that do not meet this requirement will be considered non-responsive and will not be forwarded for peer review.**

Partnerships between the applicant institution and outside entities may be necessary to complete the proposed work. However, the majority (**60% or greater**) of the proposed research work plan, as evidenced by the proposed budget, must be directly carried out by the applicant organization throughout the project period. The applicant organization cannot serve as a "pass through" to fund another entity to conduct the majority of the research. **Applications that submit a research plan budget in SF-424 Research and Related Budget, and in the detailed budget narrative, reflecting less than 60% of direct effort from the applicant organization will be considered non-responsive and will not be forwarded for peer review**.

If partnerships are necessary, the application must include letters of support, or memoranda of understanding, documenting the proposed partnership(s). Specifically, for each proposed collaboration, documentation must clearly describe the nature of the proposed partnership, including the roles and responsibilities of the Principal Investigator(s) and of the outside entities or partner agencies, the existing working relationship, plans for the proposed research, the nature and extent of the involvement to be provided by the applicant institution and outside entity, the outside entity's scope of work, and how the partnership will ensure implementation and sustainability of the proposed research plan. Applicants must describe all data sources and processes used to ensure data access. Evidence of access to the data from outside entities may be demonstrated by data sharing agreements, memoranda of understanding, or Letters of Support detailing the data availability. The proposed budget should include travel funding for research staff to directly meet with and monitor study implementation within both the program and partner sites if the sites are not local to the research investigators. Documentation of collaboration/partnerships and data access must be included in the Letters of Support section of the application. **Applications that do not include appropriate Letters of Support or memoranda of understanding between the applicant organization and every outside entity that will participate in the research or provide data access will be considered non-responsive and will not be forwarded for peer review**.

6. Required Registrations

Applicant organizations must complete the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award. Applicants must have a valid Dun and Bradstreet Universal Numbering System (DUNS) number in order to begin each of the following registrations.

- (Foreign entities only): Special Instructions for acquiring a Commercial and Governmental Entity (NCAGE) Code: https:// eportal.nspa.nato. int/ AC135Public/ Docs/ US%20Instructions%2 0for%20NSPA%20NCAGE.pdf
- System for Award Management (SAM) – must maintain current registration in SAM (the replacement system for the Central Contractor Registration) to be renewed annually, https://www.sam.gov/portal/SAM/.
- Grants.gov
- eRA Commons

All applicant organizations must register with Grants.gov. Please visit www.Grants.gov at least 30 days prior to submitting your application to familiarize yourself with the registration and submission processes. The “one-time” registration process will take three to five days to complete. However, it is best to start the registration process at least two weeks prior to application submission.

All Program Directors/Principal Investigators (PD/PIs) must also work with their institutional officials to register with the eRA Commons or ensure their existing Principle Investigator (PD/PI) eRA Commons account is affiliated with the eRA commons account of the applicant organization. All registrations must be successfully completed and active before the application due date. Applicant organizations are strongly encouraged to start the eRA Commons registration process at least four (4) weeks prior to the application due date. ASSIST requires that applicant

users have active eRA Commons account in order to prepare an application. It also requires that the applicant organization's Signing Official have an active eRA Commons Signing Official account in order to initiate the submission process. During the submission process, ASSIST will prompt the Signing Official to enter their Grants.gov Authorized Organizational Representative (AOR) credentials in order to complete the submission, therefore the applicant organization must ensure that their Grants.gov AOR credentials are active.

7. Universal Identifier Requirements and System for Award Management (SAM)

All applicant organizations **must obtain** a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number is a nine-digit number assigned by Dun and Bradstreet Information Services. An AOR should be consulted to determine the appropriate number. If the organization does not have a DUNS number, an AOR should complete the US D&B D-U-N-S Number Request Web Form or contact Dun and Bradstreet by telephone directly at 1-866-705-5711 (toll-free) to obtain one. A DUNS number will be provided immediately by telephone at no charge. Note this is an organizational number. Individual Program Directors/Principal Investigators do not need to register for a DUNS number.
Additionally, all applicant organizations must register in the **System for Award Management (SAM)**. Organizations must maintain the registration with current information at all times during which it has an application under consideration for funding by CDC and, if an award is made, until a final financial report is submitted or the final payment is received, whichever is later. SAM is the primary registrant database for the Federal government and is the repository into which an entity must provide information required for the conduct of business as a recipient. Additional information about registration procedures may be found at the SAM internet site at https://www.sam.gov/index.html.
If an award is granted, the recipient organization **must** notify potential sub-recipients that no organization may receive a subaward under the grant unless the organization has provided its DUNS number to the recipient organization.

8. Eligible Individuals (Project Director/Principal Investigator) in Organizations/Institutions

Any individual(s) with the skills, knowledge, and resources necessary to carry out the proposed research as the Project Director/Principal Investigator (PD/PI) 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 HHS/CDC support.

9. Cost Sharing

This FOA does not require cost sharing as defined in the HHS Grants Policy Statement (http://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf).

10. Number of Applications

As defined in the HHS Grants Policy Statement, (https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf), applications received in response to the same Notice of Funding Opportunity generally are scored

individually and then ranked with other applications under peer review in their order of relative programmatic, technical, or scientific merit. HHS/CDC will not accept any application in response to this NOFO that is essentially the same as one currently pending initial peer review unless the applicant withdraws the pending application.

Applicant institutions may not submit applications with the same, or similar, proposed research to two or more funding opportunities from CDC/ATSDR. Eligible applicant organizations may submit more than one application to this NOFO, provided that each application is scientifically distinct. However, applicant institutions can submit only one application with the same principal investigator. Only one application per principal investigator will be funded under this announcement. If two or more applications from the same PI are received, the only application that will be submitted for review will be the first application received based on the time and date stamp for submission in Grants.gov (http://www.grants.gov).

Section IV. Application and Submission Information

1. Address to Request Application Package

In order to use ASSIST, applicants must visit https://public.era.nih.gov/assist where you can login using your eRA Commons credentials, and enter the Notice of Funding Opportunity Number to initiate the application, and begin the application preparation process.
If you experience problems accessing or using ASSIST, you can refer to the ASSIST Online Help Site at: https://era.nih.gov/erahelp/assist. Additional support is available from the NIH eRA Service desk via:

- E-mail: http://grants.nih.gov/support/index.html
- Phone: 301-402-7469 or (toll-free) 1-866-504-9552. The NIH eRA Service desk is available Monday - Friday, 7 a.m. to 8 p.m. Eastern Time, excluding federal holidays.

2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the SF-424 (R&R) Application Guide http://grants.nih.gov/grants/how-to-apply-application-guide.htm and here: https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general-forms-e.pdf, except where instructed in this Notice of Funding Opportunity 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. The package associated with this NOFO includes all applicable mandatory and optional forms. Please note that some forms marked optional in the application package are required for submission of applications for this NOFO. Follow the instructions in the SF-424 (R&R) Application Guide to ensure you complete all appropriate “optional” components.
When using ASSIST, all mandatory forms will appear as separate tabs at the top of the Application Information screen; applicants may add optional forms available for the NOFO by selecting the Add Optional Form button in the left navigation panel.

3. Letter of Intent

Due Date for Letter of Intent: **01/13/2020**

Letters of Intent are optional but requested. Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information it contains allows CDC/ATSDR staff to plan the review. **The request submission date of the Letter of Intent is January 13, 2020**.

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

Name of the applicant:

Description of the research topic (not to exceed one page):

Descriptive title of the proposed research:

Name, address, and telephone number of the PD(s)/PI(s):

Name of other key personnel: Participating institutions:

Number and title of this Notice of Funding Opportunity (NOFO):

The letter of intent should be sent to:

Kimberly Leeks, PhD, MPH
Scientific Review Officer

Agency for Toxic Substances and Disease Registry (ATSDR)

and

Centers for Disease Control and Prevention (CDC)

4770 Buford Hwy, NE, Mailstop S106-9

Atlanta, GA 30341

Telephone: 770.488.6562

Email: kleeks@cdc.gov

4. Required and Optional Components

A complete application has many components, both required and optional. The forms package associated with this NOFO in Grants.gov includes all applicable components for this NOFO, required and optional. In ASSIST, all required and optional forms will appear as separate tabs at the top of the Application Information screen.

5. PHS 398 Research Plan Component

The SF424 (R&R) Application Guide includes instructions for applicants to complete a PHS 398 Research Plan that consists of components. Not all components of the Research Plan apply to all Notices of Funding Opportunities (NOFOs). Specifically, some of the following components are for Resubmissions or Revisions only. See the SF 424 (R&R) Application Guide https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/generalforms-e.pdf and http://grants.nih.gov/grants/how-to-apply-application-guide.htm for additional information. Please attach applicable sections of the following Research Plan components as

directed in Part 2, Section 1 (Notice of Funding Opportunity Description).
Follow the page limits stated in the SF 424 unless otherwise specified in the NOFO. As applicable to and specified in the NOFO, the application should include the bolded headers in this section and should address activities to be conducted over the course of the entire project, including but not limited to:

1. **Introduction to Application** (for Resubmission and Revision ONLY) - provide a clear description about the purpose of the proposed research and how it addresses the specific requirements of the NOFO.
2. **Specific Aims** – state the problem the proposed research addresses and how it will result in public health impact and improvements in population health.
3. **Research Strategy** – the research strategy should be organized under 3 headings: Significance, Innovation and Approach. Describe the proposed research plan, including staffing and time line.
4. **Progress Report Publication List** (for Continuation ONLY)

Other Research Plan Sections

5. **Vertebrate Animals**
6. **Select Agent Research**
7. **Multiple PD/PI Leadership Plan.**
8. **Consortium/Contractual Arrangements**
9. **Letters of Support**
10. **Resource Sharing Plan(s)**
11. **Authentication of Key Biological and/or Chemical Resources**
12. **Appendix**

All instructions in the SF424 (R&R) Application Guide https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general-forms-e.pdf and here: http://grants.nih.gov/grants/how-to-apply-application-guide.htm must be followed along with any additional instructions provided in the NOFO.
Applicants that plan to collect public health data must submit a Data Management Plan (DMP) in the Resource Sharing Plan section of the PHS 398 Research Plan Component of the application. A DMP is required for each collection of public health data proposed. Applicants who contend that the public health data they collect or create are not appropriate for release must justify that contention in the DMP submitted with their application for CDC funds.
The DMP may be outlined in a narrative format or as a checklist but, at a minimum, should include:
• A description of the data to be collected or generated in the proposed project;
• Standards to be used for the collected or generated data;
• Mechanisms for, or limitations to, providing access to and sharing of the data (include a description of
provisions for the protection of privacy, confidentiality, security, intellectual property, or other rights -

this section should address access to identifiable and de-identified data);
• Statement of the use of data standards that ensure all released data have appropriate documentation that
describes the method of collection, what the data represent, and potential limitations for use; and
• Plans for archiving and long-term preservation of the data, or explaining why long-term preservation
and access are not justified (this section should address archiving and preservation of identifiable and deidentified
data).
Examples of DMPs may be found here: USGS, http://www.usgs.gov/products/data-and-tools/data-management/data-management-plans

6. Appendix

Do not use the appendix to circumvent page limits. A maximum of 10 PDF documents are allowed in the appendix. Additionally, up to 3 publications may be included that are not publically available. Follow all instructions for the Appendix as described in the SF424 (R&R) Application Guide.

7. Page Limitations

All page limitations described in this individual NOFO must be followed. For this specific NOFO, the Research Strategy component of the Research Plan narrative is limited to 25 pages. Supporting materials for the Research Plan narrative included as appendices may not exceed 5 PDF files with a maximum of 25 pages for all appendices. Pages that exceed page limits described in this NOFO will be removed and not forwarded for peer review, potentially affecting an application's score.

8. Format for Attachments

Designed to maximize system-conducted validations, multiple separate attachments are required for a complete application. When the application is received by the agency, all submitted forms and all separate attachments are combined into a single document that is used by peer reviewers and agency staff. Applicants should ensure that all attachments are uploaded to the system.
CDC requires all text attachments to the Adobe application forms be submitted as PDFs and that all text attachments conform to the agency-specific formatting requirements noted in the SF424 (R&R) Application Guide https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general-forms-e.pdf.

9. Submission Dates & Times

Part I. Overview Information contains information about Key Dates. Applicants are strongly encouraged to allocate additional time and submit in advance of the deadline to ensure they have time to make any corrections that might be necessary for successful submission. This

includes the time necessary to complete the application resubmission process that may be necessary, if errors are identified during validation by Grants.gov and the NIH eRA systems. The application package is not complete until it has passed the Grants.gov and NIH eRA Commons submission and validation processes.
Organizations must submit applications using the ASSIST web-based application preparation and submission process.
ASSIST will validate applications before submission. If the system detects errors, then the applicant must correct errors before their application can be submitted.
Applicants are responsible for viewing their application in ASSIST after submission to ensure accurate and successful submission through Grants.gov. If the submission is not successful and post-submission errors are found, then those errors must be corrected and the application resubmitted in ASSIST.
Applicants are able to access, view, and track the status of their applications in the eRA Commons.
Information on the submission process is provided in the SF-424 (R&R) Application Guidance and ASSIST User Guide at https://era.nih.gov/files/ASSIST_user_guide.pdf.
Note: HHS/CDC grant submission procedures do not provide a grace period beyond the grant application due date time to correct any error or warning notices of noncompliance with application instructions that are identified by Grants.gov or eRA systems (i.e. error correction window).
Applicants who encounter problems when submitting their applications must attempt to resolve them by contacting the NIH eRA Service desk at:
Toll-free: 1-866-504-9552; Phone: 301-402-7469
http://grants.nih.gov/support/index.html
Hours: Mon-Fri, 7 a.m. to 8 p.m. Eastern Time (closed on federal holidays)

Problems with Grants.gov can be resolved by contacting the Grants.gov Contact Center at:
Toll-free: 1-800-518-4726
https://www.grants.gov/web/grants/support.html
support@grants.gov
Hours: 24 hours a day, 7 days a week; closed on Federal holidays

It is important that applicants complete the application submission process well in advance of the due date time.
After submission of your application package, applicants will receive a "submission receipt" email generated by Grants.gov. Grants.gov will then generate a second e-mail message to applicants which will either validate or reject their submitted application package. A third and final e-mail message is generated once the applicant's application package has passed validation and the grantor agency has confirmed receipt of the application.

Unsuccessful Submissions: If an application submission was unsuccessful, the **applicant** must:

1. Track submission and verify the submission status (tracking should be done initially regardless of rejection or success).

    a. If the status states "rejected," be sure to save time stamped, documented rejection

notices, and do #2a or #2b

2. Check emails from both Grants.gov and NIH eRA Commons for rejection notices.

a. If the deadline has passed, he/she should email the Grants Management contact listed in the Agency Contacts section of this announcement explaining why the submission failed.
b. If there is time before the deadline, correct the problem(s) and resubmit as soon as possible.

Due Date for Applications: **03/04/2020**

Electronically submitted applications must be submitted no later than 5:00 p.m., ET, on the listed application due date.

10. Intergovernmental Review (E.O. 12372)

Your application is subject to Intergovernmental Review of Federal Programs, as governed by Executive Order 12372 (http://www.archives.gov/federal-register/codification/executive-order/12372.html). This order sets up a system for state and local review of proposed federal assistance applications. You should contact your state single point of contact (SPOC) as early as possible to alert the SPOC to prospective applications, and to receive instructions on your state's process. Click on the following link to get the current SPOC list: https://www.whitehouse.gov/wp-content/uploads/2017/11/Intergovernmental_-Review-_SPOC_01_2018_OFFM.pdf.

11. Funding Restrictions

All HHS/CDC awards are subject to the federal regulations, 45 CFR 75, terms and conditions, and other requirements described in the HHS Grants Policy Statement. Pre-award costs may be allowable as an expanded authority, but only if authorized by CDC.
In accordance with the United States Protecting Life in Global Health Assistance policy, all non-governmental organization (NGO) applicants acknowledge that foreign NGOs that receive funds provided through this award, either as a prime recipient or subrecipient, are strictly prohibited, regardless of the source of funds, from performing abortions as a method of family planning or engaging in any activity that promotes abortion as a method of family planning, or to provide financial support to any other foreign non-governmental organization that conducts such activities. See Additional Requirement (AR) 35 for applicability (https://www.cdc.gov/grants/additionalrequirements/ar-35.html).
For more information on expanded authority and pre-award costs, go to: https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf.
CDC requires that mechanisms for, and cost of, public health data sharing be included in grants, cooperative agreements, and contracts. The cost of sharing or archiving public health data may also be included as part of the total budget requested for first-time or continuation awards. Fulfilling the data-sharing requirement must be documented in a Data Management Plan (DMP) that is developed during the project planning phase prior to the initiation of generating or collecting public health data and must be included in the Resource Sharing Plan(s) section of the PHS398 Research Plan Component of the application.
Applicants who contend that the public health data they collect or create are not appropriate for

release must justify that contention in the DMP submitted with their application for CDC funds (for example, privacy and confidentiality considerations, embargo issues).
Recipients who fail to release public health data in a timely fashion will be subject to procedures normally used to address lack of compliance (for example, reduction in funding, restriction of funds, or award termination) consistent with 45 CFR 74.62 or other authorities as appropriate. For further information, please
see: https://www.cdc.gov/grants/additionalrequirements/ar-25.html for revised AR-25.

12. Other Submission Requirements and Information

Risk Assessment Questionnaire Requirement

CDC is required to conduct pre-award risk assessments to determine the risk an applicant poses to meeting federal programmatic and administrative requirements by taking into account issues such as financial instability, insufficient management systems, non-compliance with award conditions, the charging of unallowable costs, and inexperience. The risk assessment will include an evaluation of the applicant's CDC Risk Questionnaire, located at https://www.cdc.gov/grants/documents/PPMR-G-CDC-Risk-Questionnaire.pdf, as well as a review of the applicant's history in all available systems; including OMB-designated repositories of government-wide eligibility and financial integrity systems (see 45 CFR 75.205(a)), and other sources of historical information. These systems include, but are not limited to: FAPIIS (https://www.fapiis.gov/), including past performance on federal contracts as per Duncan Hunter National Defense Authorization Act of 2009; Do Not Pay list; and System for Award Management (SAM) exclusions.
CDC requires all applicants to complete the Risk Questionnaire, OMB Control Number 0920-1132 annually. This questionnaire, which is located at https://www.cdc.gov/grants/documents/PPMR-G-CDC-Risk-Questionnaire.pdf, along with supporting documentation must be submitted with your application by the closing date of the Notice of Funding Opportunity Announcement. Upload the questionnaire and supporting documents as an attachment in the "12. Other Attachments" section of the "RESEARCH & RELATED Other Project Information" section of the application. If your organization has completed CDC's Risk Questionnaire within the past 12 months of the closing date of this NOFO, then you must submit a copy of that questionnaire, or submit a letter signed by the authorized organization representative to include the original submission date, organization's EIN and DUNS.

When uploading supporting documentation for the Risk Questionnaire into this application package, clearly label the documents for easy identification of the type of documentation. For example, a copy of Procurement policy submitted in response to the questionnaire may be labeled using the following format: Risk Questionnaire Supporting Documents _ Procurement Policy.

Duplication of Efforts

Applicants are responsible for reporting if this application will result in programmatic,

budgetary, or commitment overlap with another application or award (i.e. grant, cooperative agreement, or contract) submitted to another funding source in the same fiscal year. Programmatic overlap occurs when (1) substantially the same project is proposed in more than one application or is submitted to two or more funding sources for review and funding consideration or (2) a specific objective and the project design for accomplishing the objective are the same or closely related in two or more applications or awards, regardless of the funding source. Budgetary overlap occurs when duplicate or equivalent budgetary items (e.g., equipment, salaries) are requested in an application but already are provided by another source. Commitment overlap occurs when an individual's time commitment exceeds 100 percent, whether or not salary support is requested in the application. Overlap, whether programmatic, budgetary, or commitment of an individual's effort greater than 100 percent, is not permitted. Any overlap will be resolved by the CDC with the applicant and the PD/PI prior to award. Report Submission: The applicant must upload the report under "Other Attachment Forms." The document should be labeled: "Report on Programmatic, Budgetary, and Commitment Overlap."

Application Submission
Applications must be submitted electronically following the instructions described in the SF 424 (R&R) Application Guide. **PAPER APPLICATIONS WILL NOT BE ACCEPTED.**

Applicants must complete all required registrations before the application due date. Section III.6 "Required Registrations" contains information about registration.

For assistance with your electronic application or for more information on the electronic submission process, visit Applying Electronically (http://grants.nih.gov/grants/guide /url_ redirect.htm? id=11144).

Important reminders:
All PD/PIs must include their eRA Commons ID in the Credential field of the Senior/Key Person Profile Component of the SF 424(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 CDC.
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 (SAM). Additional information may be found in the SF424 (R&R) Application Guide.
If the applicant has an FWA number, enter the 8-digit number. Do not enter the letters "FWA" before the number. If a Project/Performance Site is engaged in research involving human subjects, the applicant organization is responsible for ensuring that the Project/Performance Site operates under and appropriate Federal Wide Assurance for the protection of human subjects and complies with 45 CFR Part 46 and other CDC human subject related policies described in Part II of the SF 424 (R&R) Application Guide and in the HHS Grants Policy Statement.

See more resources to avoid common errors and submitting, tracking, and viewing

applications:

- http://grants.nih.gov/grants/ElectronicReceipt/avoiding_errors.htm
- http://grants.nih.gov/grants/ElectronicReceipt/submit_app.htm
- https://era.nih.gov/files/ASSIST_user_guide.pdf
- http://era.nih.gov/erahelp/ASSIST/

Upon receipt, applications will be evaluated for completeness by the CDC Office of Grants Services (OGS) and responsiveness by OGS and the Center, Institute or Office of the CDC. Applications that are incomplete and/or nonresponsive will not be reviewed.

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process. As part of the CDC mission (http:// www.cdc.gov/ about/ organization/ mission.htm), all applications submitted to the CDC in support of public health research are evaluated for scientific and technical merit through the CDC peer review system.

Overall Impact

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

Scored Review Criteria

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

Significance

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

If successfully completed, to what extent will the proposed activities significantly advance the current knowledge of risk factors for ALS?

Does the applicant provide a rationale or justification for the proposed research plan with respect to its significance in identifying and evaluating the specific ALS risk factor(s) to be

investigated?

Investigator(s)

Are the PD/PIs, collaborators, and other researchers well suited to the project? 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?

Does the application include adequate information on the project team's experience in conducting research consistent with that proposed in the application's research plan?

Does the PI/Co-PI, collaborator, or key research team have sufficient prior expertise, experience, and knowledge directing human epidemiological, environmental health and ecological empirical research on ALS risk factors, including the use of prospective and retrospective case-controls, large epidemiological datasets, and toxicological/molecular laboratory approaches, as appropriate to the research plan?

For proposals that are collaborative or multi-PD/PI, do the investigators have the experience to conduct the proposed research? Is there evidence of past collaboration with the proposed research team to support the success of the proposed research?

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?

Is the proposed research innovative and yet offer a reasonable potential of meeting the Purpose and Research Objectives of this NOFO?

To what extent is innovation balanced with a well described research strategy?

To what extent does the proposed research include innovative methods to identify potential risk factors for ALS in humans?

Approach

Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the specific aims of the project? 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?
If the project involves clinical research, are there plans for 1) protection of human subjects from research risks, and 2) inclusion of minorities and members of both sexes/genders, as well

as the inclusion of children, justified in terms of the scientific goals and research strategy proposed?

Does the applicant address the research objectives as stated in Section I of the NOFO?

Does the applicant propose using a rigorous experimental design, that includes data analytic plans appropriate to the research design, and hypotheses, data collection measures, and project period?

To what extent does the proposal describe how the potential risk factors for ALS in humans be identified? To what extent has the applicant identified and described the target population for the proposed research? Is the sample size for the proposed research adequate to test the proposed hypotheses?

To what extent does the applicant describe methods to translate the proposed research?

Does the applicant demonstrate the ability to access the necessary data to execute the research plan? Are these data appropriate for the research? Does the research plan address the following:

- the availability and quality of ALS epidemiological data research resources proposed for evaluation, and
- limitations in the analysis of the ALS epidemiological data proposed for evaluation?

Does the applicant propose a sufficient plan for addressing data management, access, and security?

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?

Does the proposed research benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements?

Are the partnerships necessary and critical for the successful completion of the proposed research documented in the application by letters of support or memoranda of understanding that include detailed information about the nature of existing relationships?

Does the applicant organization clearly demonstrate that it will conduct a substantial portion of the research plan, including a proposed budget that does not reflect an intent to act as a "pass through" organization for partner entities?

Do the letters of support or memoranda of understanding clearly describe the working relationships between the research institution and all partner organizations?

Is the nature of and extent of each entity's involvement sufficient for the successful completion of the proposed research project as a whole?

2. 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/priority score, but *will not give separate scores* for these items.

Protections for Human Subjects

If the research 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 HHS/CDC Requirements under AR-1 Human Subjects Requirements (https://www.cdc.gov/grants/additionalrequirements/ar-1.html).

If your proposed research involves the use of human data and/or biological specimens, you must provide a justification for your claim that no human subjects are involved in the Protection of Human Subjects section of the Research Plan.

Inclusion of Women, Minorities, and Children

When the proposed project involves clinical research, the committee will evaluate the proposed plans for inclusion of minorities and members of both genders, as well as the inclusion of children. For additional information on review of the Inclusion section, please refer to the policy on the Inclusion of Women and Racial and Ethnic Minorities in Research (https://www.cdc.gov/maso/Policy/Policy_women.pdf and the policy on the Inclusion of Persons Under 21 in Research (https://www.cdc.gov/maso/Policy/policy496.pdf).

Vertebrate Animals

The committee will evaluate the involvement of live vertebrate animals as part of the scientific assessment according to the following four points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable

restraining devices; and 4) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (https://grants.nih.gov/grants/olaw/VAChecklist.pdf).

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.

Dual Use Research of Concern
Reviewers will identify whether the project involves one of the agents or toxins described in the US Government Policy for the Institutional Oversight of Life Sciences Dual Use Research of Concern, and, if so, whether the applicant has identified an IRE to assess the project for DURC potential and develop mitigation strategies if needed.

For more information about this Policy and other policies regarding dual use research of concern, visit the U.S. Government Science, Safety, Security (S3) website at: http://www.phe.gov/s3/dualuse. Tools and guidance for assessing DURC potential may be found at: http://www.phe.gov/s3/dualuse/Pages/companion-guide.aspx.

3. 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/priority score.

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

Resource Sharing Plan(s)
HHS/CDC policy requires that recipients of grant awards make research resources and data readily available for research purposes to qualified individuals within the scientific community after publication. Please see: https://www.cdc.gov/grants/additionalrequirements/ar-25.html

New additional requirement: CDC requires recipients for projects and programs that involve data collection or generation of data with federal funds to develop and submit a Data Management Plan (DMP) for each collection of public health data.

Investigators responding to this Notice of Funding Opportunity should include a detailed DMP in the Resource Sharing Plan(s) section of the PHS 398 Research Plan Component of the application. The AR-25 outlines the components of a DMP and provides

additional information for investigators regarding the requirements for data accessibility, storage, and preservation.

The DMP should be developed during the project planning phase prior to the initiation of collecting or generating public health data and will be submitted with the application. The submitted DMP will be evaluated for completeness and quality at the time of submission.

The DMP should include, at a minimum, a description of the following:

- A description of the data to be collected or generated in the proposed project;
- Standards to be used for the collected or generated data;
- Mechanisms for, or limitations to, providing access to and sharing of the data (include a description of provisions for the protection of privacy, confidentiality, security, intellectual property, or other rights - this section should address access to identifiable and de-identified data);
- Statement of the use of data standards that ensure all released data have appropriate documentation that describes the method of collection, what the data represent, and potential limitations for use; and
- Plans for archiving and long-term preservation of the data, or explaining why long-term preservation and access are not justified (this section should address archiving and preservation of identifiable and de-identified data).

Applications submitted without the required DMP may be deemed ineligible for award unless submission of DMP is deferred to a later period depending on the type of award, in which case, funding restrictions may be imposed pending submission and evaluation.

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. The applicant can obtain guidance for completing a detailed justified budget on the CDC website, at the following Internet address: http://www.cdc.gov/grants/interestedinapplying/applicationresources.html

The budget can include both direct costs and indirect costs as allowed.

Indirect costs could include the cost of collecting, managing, sharing and preserving data.

Indirect costs on grants awarded to foreign organizations and foreign public entities and performed fully outside of the territorial limits of the U.S. may be paid to support the costs of compliance with federal requirements at a fixed rate of eight percent of modified total direct costs exclusive of tuition and related fees, direct expenditures for equipment, and subawards in excess of $25,000. Negotiated indirect costs may be paid to the American University, Beirut, and the World Health Organization.

Indirect costs on training grants are limited to a fixed rate of eight percent of MTDC exclusive of tuition and related fees, direct expenditures for equipment, and sub-awards in excess of $25,000.

If requesting indirect costs in the budget based on a federally negotiated rate, a copy of the indirect cost rate agreement is required. Include a copy of the current negotiated federal indirect cost rate agreement or cost allocation plan approval letter.

4. Review and Selection Process

Applications will be evaluated for scientific and technical merit by an appropriate peer review group, in accordance with CDC peer review policy and procedures, using the stated review criteria.
As part of the scientific peer review, all applications:

- Will 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/priority score.

- Will receive a written critique.

Applications will be assigned to the appropriate HHS/CDC Center, Institute, or Office. Applications will compete for available funds with all other recommended applications submitted in response to this NOFO. Following initial peer review, recommended applications will receive a second level of review. The following will be considered in making funding recommendations:

- 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.

ATSDR program may prioritize funding meritorous applications proposing to identify and evaluate risk factors for ALS in the context of past military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents.

Review of risk posed by applicants.
Prior to making a Federal award, CDC is required by 31 U.S.C. 3321 and 41 U.S.C. 2313 to review information available through any OMB-designated repositories of government-wide eligibility qualification or financial integrity information as appropriate. See also suspension and debarment requirements at 2 CFR parts 180 and 376.

In accordance 41 U.S.C. 2313, CDC is required to review the non-public segment of the OMB-designated integrity and performance system accessible through SAM (currently the Federal Recipient Performance and Integrity Information System (FAPIIS)) prior to making a Federal award where the Federal share is expected to exceed the simplified acquisition threshold, defined in 41 U.S.C. 134, over the period of performance. At a minimum, the information in the system for a prior Federal award recipient must demonstrate a satisfactory record of executing programs or activities under Federal grants, cooperative agreements, or procurement awards; and integrity and business ethics. CDC may make a Federal award to a recipient who does not fully meet these standards, if it is determined that the information is not relevant to the current Federal award under consideration or there are specific conditions that

can appropriately mitigate the effects of the non-Federal entity's risk in accordance with 45 CFR §75.207.

CDC's framework for evaluating the risks posed by an applicant may incorporate results of the evaluation of the applicant's eligibility or the quality of its application. If it is determined that a Federal award will be made, special conditions that correspond to the degree of risk assessed may be applied to the Federal award. The evaluation criteria is described in this Notice of Funding Opportunity.

In evaluating risks posed by applicants, CDC will use a risk-based approach and may consider any items such as the following:

(1) Financial stability;
(2) Quality of management systems and ability to meet the management standards prescribed in this part;
(3) History of performance. The applicant's record in managing Federal awards, if it is a prior recipient of Federal awards, including timeliness of compliance with applicable reporting requirements, conformance to the terms and conditions of previous Federal awards, and if applicable, the extent to which any previously awarded amounts will be expended prior to future awards;
(4) Reports and findings from audits performed under subpart F 45 CFR 75 or the reports and findings of any other available audits; and
(5) The applicant's ability to effectively implement statutory, regulatory, or other requirements imposed on non-Federal entities.

CDC must comply with the guidelines on government-wide suspension and debarment in 2 CFR part 180, and require non-Federal entities to comply with these provisions. These provisions restrict Federal awards, subawards and contracts with certain parties that are debarred, suspended or otherwise excluded from or ineligible for participation in Federal programs or activities.

5. 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) and other pertinent information via the eRA Commons.

Section VI. Award Administration Information

1. Award Notices

Any applications awarded in response to this NOFO will be subject to the DUNS, SAM Registration, and Transparency Act requirements. If the application is under consideration for funding, HHS/CDC will request "just-in-time" information from the applicant as described in the HHS Grants Policy Statement (https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf).

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.

Recipient must comply with any funding restrictions as described in Section IV.11. 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 allowable as an expanded authority, but only if authorized by CDC.

2. CDC Administrative Requirements

Overview of Terms and Conditions of Award and Requirements for Specific Types of Grants

Administrative and National Policy Requirements, Additional Requirements (ARs) outline the administrative requirements found in 45 CFR Part 75 and the HHS Grants Policy Statement and other requirements as mandated by statute or CDC policy. Recipients must comply with administrative and national policy requirements as appropriate. For more information on the Code of Federal Regulations, visit the National Archives and Records Administration: http://www.access.gpo.gov/nara/cfr/cfr-table- search.html.

Specific requirements that apply to this NOFO are the following:

Generally applicable ARs:

AR-1: Human Subjects Requirements

AR-2: Requirements for Inclusion of Women and Racial and Ethnic Minorities in Research

AR-3: Animal Subjects Requirements

AR-7: Executive Order 12372 Review

AR-9: Paperwork Reduction Act Requirements

AR-10: Smoke-Free Workplace Requirements

AR-11: Healthy People 2020

AR-12: Lobbying Restrictions

AR-13: Prohibition on Use of CDC Funds for Certain Gun Control Activities

AR-14: Accounting System Requirements

AR-16: Security Clearance Requirement

AR-17: Peer and Technical Reviews of Final Reports of Health Studies – ATSDR

AR-21: Small, Minority, And Women-owned Business

AR-22: Research Integrity

AR-24: Health Insurance Portability and Accountability Act Requirements

AR-25: Data Management and Access

AR-26: National Historic Preservation Act of 1966

AR-28: Inclusion of Persons Under the Age of 21 in Research

AR-29: Compliance with EO13513, “Federal Leadership on Reducing Text Messaging while Driving”, October 1, 2009

AR-30: Information Letter 10-006, - Compliance with Section 508 of the Rehabilitation Act of 1973

AR-31: Research Definition

AR-32: Appropriations Act, General Provisions

AR-33: United States Government Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern

AR-34: Language Access for Persons with Limited English Proficiency

AR-36: ; Certificates of Confidentiality

ARs applicable to HIV/AIDS Awards:

AR-4: HIV/AIDS Confidentiality Provisions

AR-5: HIV Program Review Panel Requirements

AR-6: Patient Care

ARs applicable to Conference Awards:

AR-20: Conference Support

AR-27: Conference Disclaimer and Use of Logos

Organization Specific ARs:

AR-8: Public Health System Reporting Requirements

AR-15: Proof of Non-profit Status

AR 23: Compliance with 45 C.F.R. Part 87

ARs applicable to Global Health Assistance Awards:

AR-35: Protecting Life in Global Health Assistance

The full text of the Uniform Administrative Requirements, Cost Principles, and Audit Requirements for HHS Awards, 45 CFR 75, can be found at: https://www.ecfr.gov/cgi-bin/text-idx?node=pt45.1.75

To view brief descriptions of relevant CDC requirements visit: https://www.cdc.gov/grants/additionalrequirements/index.html

Paperwork Reduction Act / Information Collection:

Applicants are advised that any activities involving information collection (i.e., posting similar questions or requirements via surveys, questionnaires, telephonic requests, focus groups, etc.) from 10 or more non-Federal entities/persons, including states, are subject to Paperwork Reduction Act (PRA) requirements and may or may not be subject to approval by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA) prior to the start of information collection activities. PRA applicability will depend on the level of CDC involvement with the development, collection, and management of information/data.

CDC Assurances and Certifications:

All applicants are required to sign and submit "Assurances and Certifications" documents indicated at http://www.cdc.gov/od/pgo/funding/grants/foamain.shtm.

Applicants may follow either of the following processes:

- Complete the applicable assurances and certifications on an annual basis, name the file "Assurances and Certifications" and upload it as a PDF file at www.grants.gov ;or
- Complete the applicable assurances and certifications and submit them directly to CDC on an annual basis at: http://wwwn.cdc.gov/grantassurances/(S(mj444mxct51lnrv1hljjjmaa))/Homep ;age.aspx

Assurances and certifications submitted directly to CDC will be kept on file for one year and will apply to all applications submitted to CDC by the applicant within one year of the submission date.

3. Additional Policy Requirements

The following are additional policy requirements relevant to this NOFO:
HHS Policy on Promoting Efficient Spending: Use of Appropriated Funds for Conferences and Meetings, Food, Promotional Items and Printing Publications This policy supports the Executive Order on Promoting Efficient Spending (EO 13589), the Executive Order on Delivering and Efficient, Effective, and Accountable Government (EO 13576) and the Office of Management and Budget Memorandum on Eliminating Excess Conference Spending and Promoting Efficiency in Government (M-35-11). This policy apply to all new obligations and all funds appropriated by Congress. For more information, visit the HHS website at: https://www.hhs.gov/grants/contracts/contract-policies-regulations/efficient-spending/index.html.

Federal Funding Accountability and Transparency Act of 2006 Federal Funding Accountability and Transparency Act of 2006 (FFATA), P.L. 109–282, as amended by section 6202 of P.L. 110–252, requires full disclosure of all entities and organizations receiving Federal funds including grants, contracts, loans and other assistance and payments through a single,

publicly accessible website, www.usaspending.gov. For the full text of the requirements, please review the following website: https://www.fsrs.gov/.

Plain Writing Act The Plain Writing Act of 2010, Public Law 111-274 was signed into law on October 13, 2010. The law requires that federal agencies use "clear Government communication that the public can understand and use" and requires the federal government to write all new publications, forms, and publicly distributed documents in a "clear, concise, well-organized" manner. For more information on this law, go to: http://www.plainlanguage.gov/plLaw/index.cfm.

Pilot Program for Enhancement of Employee Whistleblower Protections All applicants will be subject to a term and condition that applies the terms of 48 CFR section 3.908 to the award and requires that grantees inform their employees in writing (in the predominant native language of the workforce) of employee whistleblower rights and protections under 41 U.S.C. 4712.

Copyright Interests Provision This provision is intended to ensure that the public has access to the results and accomplishments of public health activities funded by CDC. Pursuant to applicable grant regulations and CDC's Public Access Policy, Recipient agrees to submit into the National Institutes of Health (NIH) Manuscript Submission (NIHMS) system an electronic version of the final, peer-reviewed manuscript of any such work developed under this award upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. Also at the time of submission, Recipient and/or the Recipient's submitting author must specify the date the final manuscript will be publicly accessible through PubMed Central (PMC). Recipient and/or Recipient's submitting author must also post the manuscript through PMC within twelve (12) months of the publisher's official date of final publication; however the author is strongly encouraged to make the subject manuscript available as soon as possible. The recipient must obtain prior approval from the CDC for any exception to this provision.
The author's final, peer-reviewed manuscript is defined as the final version accepted for journal publication, and includes all modifications from the publishing peer review process, and all graphics and supplemental material associated with the article. Recipient and its submitting authors working under this award are responsible for ensuring that any publishing or copyright agreements concerning submitted articles reserve adequate right to fully comply with this provision and the license reserved by CDC. The manuscript will be hosted in both PMC and the CDC Stacks institutional repository system. In progress reports for this award, recipient must identify publications subject to the CDC Public Access Policy by using the applicable NIHMS identification number for up to three (3) months after the publication date and the PubMed Central identification number (PMCID) thereafter.

Language Access for Persons with Limited English Proficiency Recipients of federal financial assistance 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. Recipients of federal financial assistance must take the

reasonable steps to provide meaningful access to their programs by persons with limited English proficiency.

Dual Use Research of Concern On September 24, 2014, the US Government Policy for the Institutional Oversight of Life Sciences Dual Use Research of Concern was released. Grantees (foreign and domestic) receiving CDC funding on or after September 24, 2015 are subject to this policy. Research funded by CDC involving the agents or toxins named in the policy, must be reviewed to determine if it involves one or more of the listed experimental effects and if so, whether it meets the definition of DURC. This review must be completed by an Institutional Review Entity (IRE) identified by the funded institution.

Recipients also must establish an Institutional Contact for Dual Use Research (ICDUR). The award recipient must maintain records of institutional DURC reviews and completed risk mitigation plans for the term of the research grant, cooperative agreement or contract plus three years after its completion, but no less than eight years, unless a shorter period is required by law or regulation.

If a project is determined to be DURC, a risk/benefit analysis must be completed. CDC will work collaboratively with the award recipient to develop a risk mitigation plan that the CDC must approve. The USG policy can be found at http://www.phe.gov/s3/dualuse.

Non-compliance with this Policy may result in suspension, limitation, restriction or termination of USG funding, or loss of future USG funding opportunities for the non-compliant USG-funded research project and of USG funds for other life sciences research at the institution, consistent with existing regulations and policies governing USG funded research, and may subject the institution to other potential penalties under applicable laws and regulations.

Data Management Plan(s)
CDC requires that all new collections of public health data include a Data Management Plan (DMP). For purposes of this announcement, "public health data" means digitally recorded factual material commonly accepted in the scientific community as a basis for public health findings, conclusions, and implementation.

This new requirement ensures that CDC is in compliance with the following; Office of Management and Budget (OMB) memorandum titled "Open Data Policy–
Managing Information as an Asset" (OMB M-13-13); Executive Order 13642 titled "Making Open and Machine Readable the New Default for Government Information"; and the Office of Science and Technology Policy (OSTP) memorandum titled "Increasing Access to the Results of Federally Funded Scientific Research" (OSTP Memo).

The AR-25 https://www.cdc.gov/grants/additionalrequirements/ar-25.html outlines the components of a DMP and provides additional information for investigators regarding the requirements for data accessibility, storage, and preservation.
Certificates of Confidentiality: Institutions and investigators are responsible for determining whether research they conduct is subject to Section 301(d) of the Public Health Service (PHS) Act. Section 301(d), as amended by Section 2012 of the 21st Century Cures Act, P.L. 114-255

(42 U.S.C. 241(d)), states that the Secretary shall issue Certificates of Confidentiality (Certificates) to persons engaged in biomedical, behavioral, clinical, or other research activities in which identifiable, sensitive information is collected. In furtherance of this provision, CDC supported research commenced or ongoing after December 13, 2016 in which identifiable, sensitive information is collected, as defined by Section 301(d), is deemed issued a Certificate and therefore required to protect the privacy of individuals who are subjects of such research. Certificates issued in this manner will not be issued as a separate document, but are issued by application of this term and condition to this award. See Additional Requirement 36 to ensure compliance with this term and condition. The link to the full text is at: https://www.cdc.gov/grants/additionalrequirements/ar-36.html.

4. Cooperative Agreement Terms and Conditions

N/A

5. Reporting

Recipients will be required to complete Research Performance Progress Report (RPPR) in eRA Commons at least annually (see https://grants.nih.gov/grants/rppr/index.htm; https://grants.nih.gov/grants/forms/report_on_grant.htm) and financial statements as required in the HHS Grants Policy Statement.

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

Although the financial plans of the HHS/CDC CIO(s) provide support for this program, awards pursuant to this funding opportunity depend upon the availability of funds, evidence of satisfactory progress by the recipient (as documented in required reports) and the determination that continued funding is in the best interest of the Federal government.

The Federal Funding Accountability and Transparency Act of 2006 (Transparency Act), includes a requirement for recipients of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later.
Compliance with this law is primarily the responsibility of the Federal agency. However, two elements of the law require information to be collected and reported by recipients:
1) Information on executive compensation when not already reported through the SAM Registration; and
2) Similar information on all sub-awards/ subcontracts/ consortiums over $25,000. It is a requirement for recipients of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later.
All recipients of applicable CDC grants and cooperative agreements are required to report to the Federal Subaward Reporting System (FSRS) available at www.fsrs.gov on all subawards over $25,000. See the HHS Grants Policy Statement (https://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf).

Technical Review Statement Response Requirements

Recipients will be required to electronically submit a response to the peer reviewers' comments and/or concerns, as appropriate, within 30 days of the notification of their initial award. Recipients will also be required to electronically submit a response to any progress concerns or areas for improvement noted on their annual Technical Review, within the time period specified in the annual award continuation notice.

A. Submission of Reports

The Recipient Organization must provide HHS/CDC with an original, plus one hard copy of the following reports:

1. **Yearly Non-Competing Grant Progress Report**, is due 90 to 120 days before the end of the current budget period. The RPPR form (https://grants.nih.gov/grants/rppr/index.htm; https://grants.nih.gov/grants/rppr/rppr_instruction_guide.pdf) is to be completed on the eRA Commons website. The progress report will serve as the non-competing continuation application. Although the financial plans of the HHS/CDC CIO(s) provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds, evidence of satisfactory progress by the recipient (as documented in required reports) and the determination that continued funding is in the best interest of the Federal government.

2. **Annual Federal Financial Report (FFR) SF 425** (https://grants.nih.gov/grants/forms/report_on_grant/federal_financial_report_ffr.htm) is required and must be submitted through eRA Commons **within 90 days after the end of the calendar quarter in which the budget period ends**.

3. **A final progress report**, invention statement, equipment/inventory report, and the final FFR are required **90 days after the end of the period of performance**.

B. Content of Reports

1. Yearly Non-Competing Grant Progress Report: The grantee's continuation application/progress should include:

- Description of Progress during Annual Budget Period: Current Budget Period Progress reported on the RPPR form in eRA Commons (https://grants.nih.gov/grants/rppr/index.htm). Detailed narrative report for the current budget period that directly addresses progress towards the Measures of Effectiveness included in the current budget period proposal.
- Research Aims: list each research aim/project

a) Research Aim/Project: purpose, status (met, ongoing, and unmet), challenges, successes, and lessons learned

b) Leadership/Partnership: list project collaborations and describe the role of external partners.

- Translation of Research (1 page maximum). When relevant to the goals of the research project, the PI should describe how the significant findings may be used to promote, enhance, or advance translation of the research into practice or may be used to inform public health policy. This section should be understandable to a variety of audiences, including policy makers, practitioners, public health programs, healthcare institutions, professional organizations, community groups, researchers, and other potential users. The PI should identify the research findings that were translated into public health policy or practice and how the findings have been or may be adopted in public health settings. Or, if they cannot be applied yet, this section should address which research findings may be translated, how these findings can guide future research or related activities, and recommendations for translation. If relevant, describe how the results of this project could be generalized to populations and communities outside of the study. Questions to consider in preparing this section include:

- How will the scientific findings be translated into public health practice or inform public health policy?
- How will the project improve or effect the translation of research findings into public health practice or inform policy?
- How will the research findings help promote or accelerate the dissemination, implementation, or diffusion of improvements in public health programs or practices?
- How will the findings advance or guide future research efforts or related activities?

- Public Health Relevance and Impact (1 page maximum). This section should address improvements in public health as measured by documented or anticipated outcomes from the project. The PI should consider how the findings of the project relate beyond the immediate study to improved practices, prevention or intervention techniques, inform policy, or use of technology in public health. Questions to consider in preparing this section include:
- How will this project lead to improvements in public health?
- How will the findings, results, or recommendations been used to influence practices, procedures, methodologies, etc.?
- How will the findings, results, or recommendations contributed to documented or projected reductions in morbidity, mortality, injury, disability, or disease?

- Current Budget Period Financial Progress: Status of obligation of current budget period funds and an estimate of unobligated funds projected provided on an estimated FFR.

- New Budget Period Proposal:
- Detailed operational plan for continuing activities in the upcoming budget period, including updated Measures of Effectiveness for evaluating progress during the upcoming budget period. Report listed by Research Aim/Project.
- Project Timeline: Include planned milestones for the upcoming year (be specific and provide deadlines).

- New Budget Period Budget: Detailed line-item budget and budget justification for the new budget period. Use the CDC budget guideline format.

- Publications/Presentations: Include publications/presentations resulting from this CDC grant only during this budget period. If no publication or presentations have been made at this stage in the project, simply indicate “Not applicable: No publications or presentations have been made."

- IRB Approval Certification: Include all current IRB approvals to avoid a funding restriction on your award. If the research does not involve human subjects, then please state so. Please provide a copy of the most recent local IRB and CDC IRB, if applicable. If any approval is still pending at time of APR due date, indicate the status in your narrative.

- Update of Data Management Plan: The DMP is considered a living document that will require updates throughout the lifecycle of the project. Investigators should include any updates to the project’s data collection such as changes to initial data collection plan, challenges with data collection, and recent data collected. Applicants should update their DMP to reflect progress or issues with planned data collection and submit as required for each reporting period.

- Additional Reporting Requirements:

2. Annual Federal Financial Reporting The Annual Federal Financial Report (FFR) SF 425 is required and must be submitted through eRA Commons within 90 days after the end of the calendar quarter in which the budget period ends. The FFR should only include those funds authorized and disbursed during the timeframe covered by the report. The final FFR must indicate the exact balance of unobligated funds and may not reflect
any unliquidated obligations. There must be no discrepancies between the
final FFR expenditure data and the Payment Management System's (PMS) cash transaction data.
Failure to submit the required information in a timely manner may adversely affect the future funding of this project. If the information cannot be provided by the due date, you are required to submit a letter explaining the reason and date by which the Grants Officer will receive the information.
The due date for final FFRs will continue to be 90 days after the Period of Performance end date.
Recipients must submit closeout reports in a timely manner. Unless the Grants Management Officer (GMO) of the awarding Institute or Center approves an extension, recipients must submit a final FFR, final progress report, and Final Invention Statement and Certification within 90 days of the end of grant period. Failure to submit timely and accurate final reports may affect future funding to the organization or awards under the direction of the same Project Director/Principal Investigator (PD/PI).

FFR (SF 425) instructions for CDC recipients are now available at https://grants.nih.gov/grants/forms/report_on_grant/federal_financial_report_ffr.htm. For further information, contact GrantsInfo@nih.gov. Additional resources concerning the eFSR/FFR system, including a User Guide and an on-line demonstration, can be found on the eRA Commons Support Page: https://grants.nih.gov/support/index.html

FFR Submission: The submission of FFRs to CDC will require organizations to register with eRA Commons (Commons) (https:// commons. era.nih.gov/ commons/). CDC recommends that this one time registration process be completed at least 2 weeks prior to the submittal date of a FFR submission.

Organizations may verify their current registration status by running the "List of Commons Registered Organizations" query found at: https://era.nih.gov/registration_accounts.cfm. Organizations not yet registered can go to https://commons.era.nih.gov/commons for instructions. It generally takes several days to complete this registration process. This registration is independent of Grants.gov and may be done at any time.

The individual designated as the PI on the application must also be registered in the Commons. The PI must hold a PI account and be affiliated with the applicant organization. This registration must be done by an organizational official or their delegate who is already registered in the Commons. To register PIs in the Commons, refer to the eRA Commons User Guide found at: https://era.nih.gov/docs/Commons_UserGuide.pdf.

3. Final Reports: Final reports should provide sufficient detail for CDC to determine if the stated outcomes for the funded research have been achieved and if the research findings resulted in public health impact based on the investment. The grantee's final report should include:

- Research Aim/Project Overview: The PI should describe the purpose and approach to the project, including the outcomes, methodology and related analyses. Include a discussion of the challenges, successes and lessons learned. Describe the collaborations/partnerships and the role of each external partner.

- Translation of Research Findings: The PI should describe how the findings will be translated and how they will be used to inform policy or promote, enhance or advance the impact on public health practice. This section should be understandable to a variety of audiences, including policy makers, practitioners, public health programs, healthcare institutions, professional organizations, community groups, researchers and other potential end users. The PI should also provide a discussion of any research findings that informed policy or practice during the course of the period of performance. If applicable, describe how the findings could be generalized and scaled to populations and communities outside of the funded project.

- Public Health Relevance and Impact: This section should address improvements in public health as measured by documented or anticipated outcomes from the project. The

PI should consider how the findings of the project related beyond the immediate study to improved practices, prevention or intervention techniques, or informed policy, technology or systems improvements in public health.

- Publications; Presentations; Media Coverage: Include information regarding all publications, presentations or media coverage resulting from this CDC funded activity. Please include any additional dissemination efforts that did or will result from the project.

- Final Data Management Plan: Applicants must include an updated final Data Management Plan that describes the data collected, the location of where the data is stored (example: a repository), accessibility restrictions (if applicable), and the plans for long term preservation of the data.

Section VII. Agency Contacts

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

Application Submission Contacts
Grants.gov Customer Support (Questions regarding Grants.gov registration and submission, downloading or navigating forms)
Contact Center Phone: 800-518-4726
Email: support@grants.gov
Hours: 24 hours a day, 7 days a week; closed on Federal holidays

eRA Commons Help Desk (Questions regarding eRA Commons registration, tracking application status, post submission issues, FFR submission)
Phone: 301-402-7469 or 866-504-9552 (Toll Free)
TTY: 301-451-5939
Email: commons@od.nih.gov
Hours: Monday - Friday, 7am - 8pm U.S. Eastern Time

Scientific/Research Contact:

Marcienne Wright, PhD

Scientific Program Official

Agency for Toxic Substances and Disease Registry

and

Centers for Disease Control and Prevention (CDC)

Telephone: 770-488-4850

Email: lxv8@cdc.gov

Peer Review Contact:

Kimberly Leeks, PhD, MPH

Scientific Review Officer

Agency for Toxic Substances and Disease Registry

and

Centers for Disease Control and Prevention (CDC)

Telephone: 770.488.6562

Email: kleeks@cdc.gov

Financial/Grants Management Contact:

Mary Pat Shanahan

Grants Management Specialist

CDC/ATSDR Office of Grants Services

Centers for Disease Control and Prevention (CDC)

Telephone: 412.386.4453

Email: mpu0@cdc.gov

Section VIII. Other Information

Other CDC Notices of Funding Opportunities can be found at www.grants.gov.
All awards are subject to the terms and conditions, cost principles, and other considerations described in the HHS Grants Policy Statement.

Authority and Regulations
Awards are made under the authorization of Sections of the Public Health Service Act as amended and under the Code Federal Regulations.

All applications submitted for this NOFO must be responsive to the specific requirements and objectives of this NOFO and must be submitted as a new application through www.grants.gov.

Application documents included in an application to a previous NOFO may be submitted as part of this application process. Please read the current NOFO carefully to make sure that what is submitted is consistent with the intent of this NOFO, and that there is an overall match between the proposed research objectives as described in the applicant's abstract and the research objectives of this NOFO.

All applicants are advised to carefully review the responsiveness requirements and instructions on how applicants must document responsiveness in *Section III. Eligibility Information Part 5. Responsiveness* of this NOFO.

Successful Recipients will be permitted expanded authorities in the administration of this award as provided for in the Code of Federal Regulations, 45 CRF 75. Specific authorities granted will be detailed in the official Notice of Award document.

References - Background and Purpose

References:

1. Mehta P, Kaye W, Raymond J, et al. Prevalence of Amyotrophic Lateral Sclerosis - United States, 2014. MMWR Morb Mortal Wkly Rep. 2018 Feb 23;67(7):216-218
2. Bradley WG, Andrew AS, Traynor BJ, et al. Gene-Environment-Time Interactions in Neurodegenerative Diseases: Hypotheses and Research Approaches. Ann Neurosci. 2018 Dec;25(4):261-267
3. Oskarsson B, Gendron TF, and Staff NP. Amyotrophic Lateral Sclerosis: An Update for 2018. Mayo Clin Proc. 2018 Nov;93(11):1617-1628
4. Wang MD, Little J, Gomes J, et al. Identification of risk factors associated with the onset and progression of amyotropic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology. 2017 Jul;61:101-130
5. Al-Chalabi A and Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment, and time. Nat Rev Neurol. 2013 Nov;9(11):617-28
6. Andrew AS, Caller TA, Tandan R, et al. Environmental and Occupational Exposures and Amyotrophic Lateral Sclerosis in New England. Neurodegener Dis. 2017;17(2-3):110-116
7. Sutedja N, Veldink JH, Fischer K et al. Exposure to chemicals and metals and risk of amyotrophic lateral sclerosis: A systematic review. Amyotroph Lateral Scler. 2009 Oct-Dec;10(5-6):302-9
8. Factor-Litvak P, Al-Chalabi A, Ascherio A, et al. Current pathways for epidemiological research in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2013.14 (Suppl 1):33-43.
9. Bettencourt C, Houlden H. Exome sequencing uncovers hidden pathways in familial and sporadic ALS. Nat Neurosci 2015;18:611-13.
10. Bradley WG, Borenstein AR, Nelson LM, et al. Is exposure to cyanobacteria an environmental risk factor for amyotrophic lateral sclerosis and other neurodegenerative diseases: Amyotroph Lateral Scler Frontotemporal Degener 2013.14:325-33.
11. Watanabe Y, Watanabe T. Eur J Epidemiol. 2017 Oct;32(10):867-879.
12. Pupillo E, Poloni M, Bianchi E, Giussani G, Logroscino G, Zoccolella S, Chiò A, Calvo A, Corbo M, Lunetta C, Marin B, Mitchell D, Hardiman O, Rooney J, Stevic Z, Bandettini di Poggio M, Filosto M, Cotelli MS, Perini M, Riva N, Tremolizzo L, Vitelli E, Damiani D, Beghi E; EURALS Consortium?. Amyotroph Lateral Scler Frontotemporal Degener. 2017 Oct 24:1-8
13. Fang F, Chen H, Wirdefeldt K, et al. Infection of the central nervous system, sepsis and amyotrophic lateral sclerosis. PLoS ONE 2011;6:e29749

14. Cragg JJ, Johnson NJ, Weisskopf MG. Military Service and Amyotrophic Lateral Sclerosis in a Population-based Cohort: Extended Follow-up 1979-2011. Epidemiology. 2017 Mar;28(2):e15-e16
15. Beard JD, Engel LS, Richardson DB, et al. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology. Environ Int. 2016 May;91:104-15
16. Weisskopf MG, Cudkowicz ME, and Johnson N. Military Service and Amyotrophic Lateral Sclerosis in a Population-based Cohort. Epidemiology. 2015 Nov;26(6):831-8
17. Weisskopf MG, OReilly EJ, McCullough ML, et al. Prospective study of military service and mortality from ALS. Neurology 2005;64:32-7.
18. Horner RD, Feussner JR, Kasarskis EJ. Prospective study of military service and mortality from ALS. Neurology. 2005 Jul 12;65(1):180-1
19. Haley RW. Excess incidence of ALS in young Gulf War veterans. Neurology. 2003 Sep 23;61(6):750-6
20. Oskarsson B, Horton DK, Mitsumoto H. Potential Environmental Factors in Amyotrophic Lateral Sclerosis. Neurol Clin. 2015 Nov;33(4):877-88
21. Cox PA, Richer R, Metcalf JS, Banack SA, Codd GA, Bradley WG. Cyanobacteria and BMAA exposure from desert dust: a possible link to sporadic ALS among Gulf War veterans. Amyotroph Lateral Scler. 2009;10 Suppl 2:109-17
22. Heyburn L, Sajja VSSS and Long JB. The Role of TDP-43 in Military-Relevant TBI and Chronic Neurodegeneration. Front Neurol. 2019 Jun 27;10:680.
23. Institute of Medicine. 2006. Amyotrophic Lateral Sclerosis in Veterans: Review of the Scientific Literature. Washington, DC: The National Academies Press. https://doi.org/10.17226/11757.
24. Blecher R, Elliott MA, Yilmaz E. Contact Sports as a Risk Factor for Amyotrophic Lateral Sclerosis: A Systematic Review. Global Spine J. 2019 Feb;9(1):104-118.
25. Gotkine M, Friedlander Y, Hochner H. Triathletes are over-represented in a population of patients with ALS. Amyotroph Lateral Scler Frontotemporal Degener. 2014 Dec;15(7-8):534-6
26. Lehman EJ, Hein MJ, Baron SL, Gersic CM. Neurodegenerative causes of death among retired National Football League players. Neurology. 2012 Nov 6;79(19):1970-4.
27. Chio A, Calvo A, Dossena M, Ghiglione P, Mutani R, Mora G. ALS in Italian professional soccer players: the risk is still present and could be soccer-specific. Amyotroph Lateral Scler. 2009 Aug;10(4):205-9
28. Chio A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. Brain. 2005 Mar;128(Pt 3):472-6
29. Walt GS, Burris HM, and Brady CB. Chronic Traumatic Encephalopathy Within an Amyotrophic Lateral Sclerosis Brain Bank Cohort. J Neuropathol Exp Neurol. 2018 Dec 1;77(12):1091-1100
30. Franz CK, Joshi D, Daley EL, Grant RA, Dalamagkas K, Leung A, Finan JD, Kiskinis E. Impact of traumatic brain injury on amyotrophic lateral sclerosis: from bedside to bench. J Neurophysiol. 2019 Sep 1;122(3):1174-1185
31. Kumar A, Loane DJ. Neuroinflammation after traumatic brain injury: opportunities for therapeutic intervention. Brain Behav Immun. 2012 Nov;26(8):1191-201
32. McCauley ME, Baloh RH. Inflammation in ALS/FTD pathogenesis. Acta Neuropathol. 2019 May;137(5):715-730

33. French PW, Ludowyke RI, Guillemin GJ. Fungal-contaminated grass and well water and sporadic amyotrophic lateral sclerosis. Neural Regen Res. 2019 Sep;14(9):1490-1493
34. Douville R, Liu J, Rothstein J, Nath A. Identification of active loci of a human endogenous retrovirus in neurons of patients with amyotrophic lateral sclerosis. Ann Neurol. 2011 Jan;69(1):141-51
35. Caller TA, Doolin JW, Haney JF, Murby AJ, West KG, Farrar HE, Ball A, Harris BT, Stommel EW. A cluster of amyotrophic lateral sclerosis in New Hampshire: a possible role for toxic cyanobacteria blooms. Amyotroph Lateral Scler. 2009;10 Suppl 2:101-8
36. Nicolson GL1, Nasralla MY, Haier J, etal. High frequency of systemic mycoplasmal infections in Gulf War veterans and civilians with Amyotrophic Lateral Sclerosis (ALS). J Clin Neurosci. 2002 Sep;9(5):525-9.

Amendment 1 to RFA-TS20-001

Q & A received before and during the RFA-TS20-001 Pre-Application Conference Call held on 1/08/2020 at 3:00 PM Eastern Time

Q1. Is a foreign, not-for-profit institution eligible to apply as an "applicant organization" to RFA-TS-20-001?

A1. Yes. Per *Section III. Eligibility Information 1. Eligible Applicants* and *Section III. Eligibility Information 2. Foreign Organizations*:

- Nonprofits (Other than Institutions of Higher Education) are eligible applicants.
- Foreign Organizations are eligible to apply.

Q2. Can a foreign applicant organization include Co-Investigators, key personnel, and collaborators from multiple countries?

A2. Yes. Any applicant organization, domestic or foreign, may include Co-Investigators, key personnel, and collaborators from multiple countries.

Q3. If a foreign applicant organization intends to submit an application to RFA-TS-20-001, are all foreign institutions collaborating with the foreign applicant institution also required to complete registrations?

A3. No. Applicable registrations are required from only the single applicant organization applying for an award. All applicant organizations, domestic and foreign, are encouraged to take great care to ensure that all required registrations are completed well before the application due date. Please carefully review ***Section III. Eligibility Information 6. Required Registrations*** and ***7. Universal Identifier Requirements and System for Award Management (SAM)*** (pages 21-22 of RFA-TS-20-001) for required registrations and the projected timeline for completing required registrations.

Per *Section III. Eligibility Information 2. Foreign Organizations*: Foreign Organizations are eligible to apply. Foreign (non-US) organizations must follow policies described in the HHS Grants Policy Statement (http://www.hhs.gov/asfr/ogapa/aboutog/hhsgps107.pdf), and procedures for foreign organizations described throughout the SF424 (R&R) Application Guide. International registrants can confirm DUNS by sending an e-mail to ccrhelp@dnb.com, including Company Name, D-U-N-S Number, and Physical Address, and Country. Special Instructions for acquiring a Commercial and Governmental Entity (NCAGE) Code: https://eportal.nspa.nato.int/AC135Public/Docs/US%20Instructions%20for%20NSPA%20NCAGE.pdf.

Per *Section III. Eligibility Information 6. Required Registrations* and *7. Universal Identifier Requirements and System for Award Management (SAM)*: Applicant organizations must complete the following registrations as described in the SF 424 (R&R) Application Guide to be eligible to apply for or receive an award.

- Applicants must have a valid **Dun and Bradstreet Universal Numbering System (DUNS) number** in order to begin each of the following registrations. All applicant organizations must obtain a DUN and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements.
- (Foreign entities only): Special Instructions for acquiring a **Commercial and Governmental Entity (NCAGE) Code**: https:// eportal.nspa.nato. int/ AC135Public/ Docs/US%20Instructions%2 0for%20NSPA%20NCAGE.pdf
- **System for Award Management (SAM)** – must maintain current registration in SAM to be renewed annually, https://www.sam.gov/portal/SAM/. All applicant organizations must register in the System for Award Management (SAM). Additional information about registration procedures may be found at the SAM internet site at https://www.sam.gov/index.html.
- **Grants.gov** (www.grants.gov). All applicant organizations must register with Grants.gov.
- **eRA Commons** (https://era.nih.gov/reg-accounts/register-commons.htm). All Program Directors/Principal Investigators (PD/PIs) must also work with their institutional officials to register with the eRA Commons or ensure their existing Principal Investigator (PD/PI) eRA Commons account is affiliated with the eRA commons account of the applicant organization. All registrations must be successfully completed and active before the application due date.

Q4. Is there a limit to the number of collaborating institutions that an applicant organization can partner with to complete the research project?

A4. There is no maximum number of U.S. or foreign institutions that can serve as collaborating institutions or study sites. However, there can be only one applicant organization to whom the grant award can be made. Additionally, per *Section III. Eligibility Information 5. Responsiveness*: the applicant organization must meet responsiveness review requirements that:

1. the majority (60% or greater) of the proposed research work plan, as evidenced by the proposed budget, must be directly carried out by the applicant organization throughout the project period in order to be considered responsive to the RFA and forwarded for peer review.
2. the application must include appropriate Letters of Support or memoranda of understanding between the applicant organization and every outside entity that will participate in the research or provide data access in order to be considered responsive to the RFA and forwarded for peer review.

Please review *Section III. Eligibility Information 5. Responsiveness* (pages 19 -21 of the RFA) carefully to ensure that all responsiveness review requirements regarding collaborations and partnerships are met.

Q5. Is a principal investigator or project director required to have a specific academic degree or qualification in order to meet eligibility requirements as PI/PD (ie: age, H-index, specific terminal degree like MD, PhD, etc...)? Is there a special provision in RFA-TS-20-001 for Principal Investigators with early investigator status?

A5. Specific age, H-index, or academic degree criteria are not required for PI/PD eligibility for RFA-TS-20-001, though it is expected that the PI/PD and, if applicable, Co-I have an academic degree suitable for the work proposed. There is no specific, called out, provision for early investigator targeted awards in the RFA. Any principal investigator of any career stage who meets the eligibility requirements in *Part I. Overview Information – Executive Summary* and *Section III. Eligibility Information 5. Responsiveness* is encouraged to work with his or her applicant organization to develop and submit an application:

Part I. Overview Information – Executive Summary: Eligible Project Directors/Principal Investigators (PDs/PIs): Individuals with the skills, knowledge, and resources necessary to carry out the proposed research are invited to work with their institution/organization to develop an application for support.

Section III. Eligibility Information 5. Responsiveness: The biosketch for the PI, Co-PI, or Co-Investigator must include documentation of prior expertise, experience, and knowledge directing human epidemiological, environmental health and ecological empirical research on ALS risk factors, including the use of prospective and retrospective case-controls, large epidemiological datasets, and toxicological/molecular laboratory approaches, as appropriate to the research plan. Expertise must be documented with at least one first-authored, peer-reviewed publication directly relevant to the research plan proposed or by serving as a principal investigator on a grant, cooperative agreement, or contract in these subject matter areas (include description and references in the biographical sketch). Experience requirements may be demonstrated through the combined experiences of a Principal and Co-Investigator (if applicable). The citation of the relevant publication(s) or research experience must be clearly identified (by bold text or highlight) in the appropriate SF 424 Biographical Sketch. **Applications that do not meet this requirement will be considered non-responsive and will not be forwarded for peer review.**

Q6. What is the grant mechanism for RFA-TS-20-001?

A6. RFA-TS-20-001 is an R-01 grant mechanism.

Q7. ATSDR indicates that RFA-TS-20-001 is seeking investigator-initiated research that will identify and evaluate risk factors contributing to ALS, with preferred focus on factors related to military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents. If my research proposal does not address an investigation in one of these preferred focus areas, will my research proposal still be considered for funding?

A7. All administratively eligible applications that have an overall match between the proposed research objectives as described in the applicant's abstract and the research objectives of RFA-TS-20-001 as described in Section I under the heading Objectives/Outcomes, and that meet all other responsiveness criteria (see *Section III. Eligibility Information 5. Responsiveness*) will be found responsive and will be forwarded for peer review. Meritorious applications proposing to identify and evaluate risk factors for ALS in the context of past military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents may be prioritized for funding by ATSDR during the second level review.

Per *Section I. Funding Opportunity Description. 1. Background and Purpose* the objectives and outcomes that are required to be addressed in responsive applications to this NOFO are:

Objectives/Outcomes

For NOFO RFA-TS-20-001, through the use of human ALS epidemiological data sources, including those that contain information on potential environmental, demographic, occupational, behavioral and familial associations, and through the use of epidemiological, environmental health, and laboratory research approaches, applications funded under this NOFO must address both of the following objectives:

- Objective One: Identify potential risk factors for ALS in humans including, but not limited to, risk factors listed below:
    - environmental and occupational risks, including from past military service
    - traumatic brain injuries, including blast or impact TBI associated with military service or contact sports
    - injury or microbial infection (e.g., bacterial, fungal, viral) resulting in neuroinflammation or innate immune system activation
    - nutritional intake, and
    - pharmaceutical use (e.g., statins)

Per *Section V. Application Review Information. 4. Review and Selection Process*: Following initial peer review, recommended applications will receive a second level of review. The following will be considered in making funding recommendations:

- 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.

ATSDR program may prioritize funding meritorious applications proposing to identify and

evaluate risk factors for ALS in the context of past military service, contact sports, traumatic brain injury, neuroinflammation and infectious agents.

Q8. Will a research proposal that intends to evaluate neuroinflammation in the context of neurotoxin producing cyanobacteria and/or fungi meet the scientific requirements of RFA-TS-20-001?

A8. Yes. Neurotoxin producing cyanobacteria and fungi qualify as infectious agents. A proposal evaluating neurotoxin producing cyanobacteria and/or fungi as ALS risk factors will meet a preferred focus area of the RFA.

Q9. Can ATSDR define what is meant by a "matched ALS epidemiological registry" in *Section III. Eligibility Information 5. Responsiveness*? Can an investigator evaluate ALS biospecimens from a large general health surveillance epidemiological database that is not specifically an "ALS Registry", but contains information on selected ALS risk factors? Will that research approach be responsive to the RFA?

A9. An investigator may use a larger general health surveillance epidemiological dataset to evaluate biospecimens for ALS risk factors in provided that 1. It includes epidemiological data from persons with ALS **and** 2. provided that the data for persons with ALS in this general health surveillance epidemiological dataset can be matched to the biospecimens the investigator wishes to evaluate.

Q10. For RFA-TS-20-001, are applicants invited to use the ATSDR National ALS Registry and/or the ATSDR National ALS Biorepository?

A10. Per *Section I. Funding Opportunity Description 2. Approach:* **ATSDR National ALS Registry**: ATSDR National ALS Registry data are available for researchers to identify potential risk factors for ALS. Use of the ATSDR National ALS Registry is not required for consideration of funding under this announcement. However, applicants are encouraged to include ATSDR National ALS Registry enrollees, as appropriate, in their research plans. Applicants are encouraged to consider submitting an application to use ATSDR's ALS Research Notification tool to recruit ALS patients from the National ALS Registry, when applicable to the research plan, available at https://www.cdc.gov/als/ALSRegistryResearchApplicationInfo.html (pending OMB re-authorization). The ATSDR ALS Research Notification tool will enable Registry grantees to receive email notifications about their approved studies sent to persons with ALS enrolled in the Registry. Applicants awarded a grant under NOFO RFA-TS-20-001 and who wish to use the ATSDR National ALS Registry will be required to enter into a Data Use Agreement (DUA) with ATSDR to protect the confidentiality of data in accordance with the terms of the DUA and applicable laws. Applicants may use, alone or in conjunction with the ATSDR National ALS Registry, applicant-provided or third-party sourced ALS and case control registries in their research plans, as appropriate for their research proposals.

ATSDR National ALS Biorepository: ATSDR National ALS Biorepository biospecimens will not be provided to applicants for the RFA-TS-20-001 funding cycle and applicants should not

submit proposals that intend to use biospecimens from the ATSDR National ALS Biorepository for the RFA-TS-20-001 funding cycle. However, applicants may use applicant-provided or third-party sourced ALS biospecimens in their research plans, as appropriate for the research design. Applicants using applicant-provided or third-party sourced ALS biospecimens must include, as part of their research plan, use of a matched ALS epidemiological registry for identification and evaluation of ALS risk factors. The statistical power for the applicant-provided or third-party sourced ALS biospecimen repository must be sufficiently high to provide meaningful epidemiological analyses.