Image Description: Centers for Disease Control

Centers for Disease Control

Agency for Toxic Substances and Disease Registry Extramural Research Program Office

Identify and Characterize Potential Environmental Risk Factors for Amyotrophic Lateral Sclerosis (ALS) and Evaluate Their Impact on ALS Disease Incidence and Progression

RFA-TS-17-001

Application Due Date: 04/28/2017

Identify and Characterize Potential Environmental Risk Factors for Amyotrophic Lateral Sclerosis (ALS) and Evaluate Their Impact on ALS Disease Incidence and Progression

RFA-TS-17-001

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Part 1. Overview Information

Participating Organization(s)

Centers for Disease Control

Components of Participating Organizations

Agency for Toxic Substances and Disease Registry Extramural Research Program Office (ATSDR ERPO)
Agency for Toxic Substances and Disease Registry (ATSDR)

Funding Opportunity Announcement (FOA) Title

Identify and Characterize Potential Environmental Risk Factors for Amyotrophic Lateral Sclerosis (ALS) and Evaluate Their Impact on ALS Disease Incidence and Progression

Activity Code

Applications in response to this FOA will be funded using the R01 activity code.

Funding Opportunity Announcement Type

New

Funding Opportunity Announcement Number

RFA-TS-17-001

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

93.061

Category of Funding Activity:

Health

FOA Purpose

The Agency for Toxic Substances and Disease Registry (ATSDR) is soliciting investigator-initiated research that will identify and characterize environmental toxicants in human biological samples that may be potential environmental risk factors for Amyotrophic Lateral Sclerosis (ALS). Applications are also sought that will evaluate the impact of environmental toxicants on the development and progression of ALS, including gene-environment interactions. Information gleaned from this investigator-initiated research will provide a greater understanding of the possible link between exposures to environmental toxicants and the etiology of ALS.

The purpose of Amendment 1 to this FOA is to provide additional clarifying information based on questions received from potential applicants prior to and during the Pre-Application Conference Call held on February 13, 2017. A summary of the questions and answers can be found in ***Section VIII. Other Information*** of the amended FOA.

The purpose of Amendment 2 to this FOA is to edit the Eligibility Section of the FOA and to modify the application due date.

Key Dates

Publication Date: **To receive notification of any changes to RFA-TS-17-001, 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: 03/06/2017

Letters of Intent are requested by March 6, 2017. Letters of Intent are optional.

Application Due Date: **04/28/2017**

Applications are due April 28, 2017

On-time submission requires that electronic applications be error-free and made available to CDC for processing from eRA Commons on or before the deadline date. Applications must be submitted to and validated successfully by Grants.gov/eRA Commons no later than 5:00 PM U.S. Eastern Time. Note: HHS/CDC grant submission procedures do not provide a period of time beyond the application due date 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: **06/21/2017**

Estimated date is June 21, 2017. The actual review may occur in June or July 2017.

Secondary Review: **07/12/2017**

Estimated date is July 12, 2017. The actual review may occur in July or August 2017.

Estimated Start Date: **09/30/2017**

Estimated start date is September 30, 2017

Expiration Date: **05/30/2017**

Due Dates for E.O. 12372: Executive Order 12372 does not apply to this program.

Required Application Instructions

It is critical that applicants follow the instructions in the SF 424 (R&R) Application Guide except where instructed to do otherwise in this FOA. Conformance to all requirements (both in the Application Guide and the FOA) is required and strictly enforced. Applicants must read and follow all application instructions in the Application Guide as well as any program-specific instructions noted in Section IV. When the program-specific instructions deviate from those in the Application Guide, follow the program-specific instructions.

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.

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.

Purpose: ATSDR is soliciting investigator-initiated research that will identify and characterize environmental toxicants in human biological samples that may be potential environmental risk factors for Amyotrophic Lateral Sclerosis (ALS). Applications are also sought that will evaluate the impact of environmental toxicants on the development and progression of ALS, including gene-environment interactions. Information gleaned from this investigator-initiated research will provide a greater understanding of the possible link between exposures to environmental toxicants and the etiology of ALS.

Research FOA RFA-TS-17-001 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 FOA will be a research grant.

Funds Available and Anticipated Number of Awards

ATSDR intends to commit up to $2,500,000 in FY17 to fund up to five applications for this FOA. The awards issued under this FOA 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 anticipated that the size and duration of each award may also vary. The total amount awarded will depend upon the number, quality, duration and cost of the applications received.

Budget and Project Period

The total award for the first year of funding will not exceed $2,500,000 (including direct and indirect costs). Each budget period will be twelve months. The maximum award amount, per award and including direct and indirect costs, will be $500,000 for the first 12-month budget period.

The project period will be up to three years, anticipated for September 30, 2017 to September 29, 2020. **An applicant is expected to request a project period of three years but may request a project period of no less than two years in order to complete the proposed research plan**. The maximum total funding, including direct and indirect costs, for an award with a three year project period is expected to be up to $1,500,000 per award.

Applicants must specifically describe the level of annual funding and project period requested.

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. 1 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 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 FOA. Only one application per principal investigator will be funded under this FOA. Additionally, applicant institutions submitting applications with essentially the same proposed research to two or more CDC FOAs will

not be funded under more than one FOA.

Application Type. NEW

Special Date(s). A pre-application teleconference call will be conducted on February 13, 2017 to address questions from prospective applicants regarding FOA RFA-TS-17-001, Identify and Characterize Potential Environmental Risk Factors for Amyotrophic Lateral Sclerosis (ALS) and Evaluate Their Impact on ALS Disease Incidence and Progression. The call will begin at 2:00PM Eastern and end at 3:00PM Eastern, or sooner if all questions are addressed. Questions and answers from the discussion will be included in an amended FOA approximately 3 weeks after the call.

Participant Access Information

- **Call Date: February 13, 2017**
- Call Start Time: 2:00 PM Eastern
- Call End Time: 3:00 PM Eastern
- Call Leader: Marcienne Wright, PhD, Scientific Program Official
- Toll-Free Number: 1-877-201-5465
- Conference ID: 14914695

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

Hearing Impaired. Telecommunications for the hearing impaired are available at: TTY: (770) 488-2783.

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]

1. Background and Purpose

Background:

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, 2016). 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 (Wang 2016; Al-Chalabi, 2013; Wingo, 2011).

Research suggests that associations may exist between exposure to organophosphates (e.g. pesticides), heavy metals, or other persistent environmental toxicants and the incidence and progression of ALS (reviewed in Sutedja, 2009; Su, 2016; Yu, 2014; Morahan, 2007). However the specific environmental toxicants and the etiologic role(s) they play in the development and progression of ALS, including the existence and influence of gene-environment interactions that may promote genetic susceptibility to ALS, are not well defined (Al-Chalabi, 2013; Clerc, 2016). Additional research using human-based epidemiological, molecular, and/or computational approaches is needed to better elucidate if and how exposure to organophosphates, heavy metals, or other persistent environmental toxicants can precipitate ALS, whether these environmental toxicants play a causal or contributory role in the development and progression of ALS, to what degree initial

exposure or exposure over time these environmental toxicants influence the development and progression of ALS, and the key biological pathways and genes that these environmental toxicants may act on in persons with ALS.

The uncertainty about the incidence and prevalence of ALS, as well as the lack of knowledge about the etiology of the disease, 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, including environmental and occupational, 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.

The use of biological sample repositories ("biorepositories") has advanced our understanding of environmental determinants and mediators of diseases, and the underlying gene-environment interactions involved in disease incidence and progression. In 2014, NCEH/ATSDR coordinated an ALS pilot feasibility study to identify the best way to collect and store biological samples from persons with ALS. In the fall of 2016, ATSDR launched the **National ALS Biorepository.** The National ALS Biorepository stores biological samples from in-home collection (e.g., blood, hair, or saliva) and postmortem collection (e.g., brain, bone, spinal cord, cerebrospinal fluid, muscle, and skin). Specimens from the National ALS Biorepository are collected from a geographically representative sample of persons with ALS who are self-enrolled in the Registry. Samples from the National ALS Biorepository are paired with completed risk factor data from the National ALS Registry, including demographic and other environmental and occupational data currently being provided by persons with ALS.

National ALS Biorepository samples and **National ALS Registry** data are available for researchers to examine potential exposures to environmental toxicants and their relationship to demographic, environmental, and occupational data in order to better understand the etiologic role(s) environmental, genetic, and epigenetic risk factors play in the development and progression of various forms of ALS.

Purpose:

The purpose of this funding opportunity announcement (FOA) is to solicit investigator-initiated research that will identify and characterize environmental toxicants (e.g., organophosphates, heavy metals, and other persistent environmental chemicals) in biological samples that may be potential environmental risk factors for amyotrophic lateral sclerosis (ALS). Funds are available to conduct evaluation on the influence of environmental toxicants on the development and progression of ALS, including potential gene-environment interactions. Information gleaned from this investigator-initiated research will provide a greater understanding of the possible link between exposures to environmental toxicants and the etiology of ALS. The intended results expected as a consequence of research funded under this announcement are listed in more detail in the Objectives/Outcomes section of this document.

Objectives:

The applicant shall address all of the following objectives:

a) Identify and characterize the composition and concentrations of organophosphate metabolites (or associated biomarkers), heavy metals, or other persistent environmental toxicants in biological samples of persons with ALS.

b) Evaluate environmental toxicant associated linkage(s) between analyzed human biological samples

and sample-matched ALS epidemiological data, including environmental, demographic, occupational, behavioral and familial risk factors, etc.

c) Examine the functional relationship between environmental toxicants in human biological samples and key biological pathways or genes associated with the development and/or progression of ALS.

Research funded under this FOA is expected to produce outcomes that will advance our understanding of whether correlates exist between environmental toxicant (or relevant biomarker) concentrations in human biological samples and the incidence of ALS; whether linkages between environmental toxicant exposures and other demographic risk factors for ALS disease risk and/or progression can be identified; whether gene-environment interactions contribute to the development and progression of ALS, and, if so, the mechanism(s) by which these interactions may influence genetic susceptibility to ALS.

References:

1. 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
2. Rowland LP et al. Amyotrophic lateral sclerosis. NEJM 2001. 344(22):1688-1700 (2001).
3. 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. Neurotoxicity 2016. http://dx.doi.org/10.1016/j.neuro.2016.06.015
4. Al-Chalabi A and Hardiman O. The epidemiology of ALS: a conspiracy of genes, environment, and time. Nature Rev Neurology 2013. 9:617-628
5. Wingo T, Cutler D, Yarab N et al. The heritability of amyotropic lateral sclerosis in a clinically ascertained United States research registry. PLoS One. 2011. 6(11):e27985
6. Sutedja N, Veldink JH, Fischer K et al. Exposure to chemicals and metals and risk of amyotrophic lateral sclerosis: A systematic review. Amyotrophic Lateral Sclerosis. 2009.10: 302–309
7. Su FC, Goutman S, Chernyak S, et al. Association of environmental toxins with amyotropic lateral sclerosis. JAMA Neurol. 2016. 73(7):803-11
8. Yu Y, Su FC, Callahan BC et al. Environmental risk factors and amyotropic lateral sclerosis (ALS): a case control study of ALS in Michigan. PLoS One. 2014. 9(6):e1011186
9. Morahan JM, Yu B, Trent RJ et al. Genetic susceptibility to environmental toxicants in ALS. Am J Med Genet B Neuropsychiatr Genet. 2007. 144B(7):885-890
10. Clerc P, Lipnick S, and Willet C. A look in to the future of ALS research. Drug Discov Today. 2016. 21(6):939-949
11. 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.
12. Talbot EO, Malek AM, and Lacomis D. The epidemiology of amyotrophic lateral sclerosis. Hand Clin Neurol 2016. 138:225-238.
13. Chio A, Logrosino G, Traynor BJ, et al. Global epidemiology of amyotrophic lateral sclerosis: a systematic review of the published literature. Neuroepidemiology 2013. 41:118–30.
14. Roelofs-Iverson RA, Mulder DW, Elveback LR, et al. ALS and heavy metals: a pilot case-control study. Neurology 1984. 34:393–5.
15. Carlesi C, Pasquali L, Piazza S, et al. Strategies for clinical approach to neurodegeneration in amyotrophic lateral sclerosis. Arch Ital Biol 2011;149:151–67.
16. Wang MD, Gomes J, Cashman NR, Little J, Krewski D. A meta-analysis of observational studies of the association between chronic occupational exposure to lead and amyotrophic lateral sclerosis. J Occup Environ Med 2014;56:1235–42.
17. 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.
18. Oskarsson B, Horton DK, Mitsumoto H. Potential environmental factors in amyotrophic lateral

sclerosis. Neurol Clin 2015. 33:877–88.
19. Beard JD, Kamel F. Military service, deployments, and exposures in relation to amyotrophic lateral sclerosis etiology and survival. Epidemiol Rev 2015;37:55–70.
20. Kaye WE, Sanchez M, Wu J. Feasibility of creating a national ALS registry using administrative data in the United States. Amyotroph Lateral Scler Frontotemporal Degener 2014;15:433–9.

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 FOA directly supports the United States Department of Health and Human Services (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 FOA 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

ALS is a progressive and often fatal neuromuscular disease that affects almost 16,000 people, and their families, in the United States. Yet, little is known about the incidence, prevalence, or etiology of the disease, including the role that environmental toxicants play in the development or progression of various forms of ALS. This research will expand our current understanding of the potential environmental risk factors for ALS.

Relevant Work

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. ATSDR 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) and the second National ALS registry Report in August 2016 (covering 2012-2013).

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; Bryan, L; et. al.; Prevalence of Amyotrophic Lateral Sclerosis — United States, 2012–2013. MMWR August 5, 2016; 65 (8); 1-12

3. 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

4. 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.

5. 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 role that environmental risk factors may have on ALS etiology. There is interest in learning if and how exposure to environmental toxicants influence the development and progression of ALS. The identification and characterization of organophosphates (e.g. pesticides), heavy metals, and other persistent environmental toxicants in biological samples of persons with ALS will advance our understanding of whether environmental toxicants cause and/or contribute to ALS, and if environmental toxicants interact with susceptibility genes and biological pathways associated with ALS. Information produced from this research will help ATSDR better understand if there are specific environmental risk factors and environment-gene interactions that may or may not increase the likelihood and/or progression of ALS.

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. 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 blood and body fluid and tissue samples; 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 may result in the identification of human ALS susceptibility genes and key biological pathways impacted by environmental exposures.

Biological sample selection and analysis: For human biological sample analysis, investigators are encouraged to use standardized and recognized practices (e.g., College of American Pathology) to ensure sample integrity and quality assurance. While variability may exist in the selection of biological samples, investigators should attempt to conduct analyses with large uniform sample sizes. Where appropriate, a control group should be identified to sample for comparison purposes.

ALS case control studies and epidemiological datasets: Prospective or retrospective case-control studies may be considered and analyses of existing ALS epidemiological datasets 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.

Biological samples and ALS epidemiological data may be provided by the applicant and/or may be requested from the National ALS Biorepository and National ALS Registry. For evaluation of environmental toxicant-associated linkage(s) between analyzed human biological samples and ALS epidemiological data (FOA Objective B), the ALS epidemiological data must be sample-matched to the biological samples being evaluated. The applicant is required to address, in the application's research plan: a) the *availability* and *quality* of biological samples and ALS epidemiological data research resources proposed for evaluation, b) a justification for the use of the specific biological sample and ALS epidemiological data resources, c) an attestation that the biological samples and ALS epidemiological data are sample-matched, and d) limitations in the analysis of the specific biological samples and ALS epidemiological data proposed for evaluation.

Although it is not required for consideration of funding under this announcement, applicants are encouraged to include the National ALS Biorepository samples and National ALS Registry enrollees, as appropriate, in their research plans. The National ALS Biorepository and National ALS Registry tools for researcher access can be found at wwwn.cdc.gov/als/ALSRegistryResearchApplicationInfo.aspx**.** Applicants should be aware that for institutions awarded a grant under FOA RFA-TS-17-001, the principal investigator and key personnel requesting access to the National ALS Biorepository and 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.

- Funds are available for environmental toxicant risk factor research on ALS that uses human biological

samples from an ALS biorepository and data from a sample-matched human ALS registry. **Applications proposing studies outside of the stated focus area of this FOA (e.g., research on non-ALS diseases, etc.) will be considered nonresponsive.**

- While applicants may include specific aims comparing environmental toxicant-mediated etiology of ALS to the etiology of other non-ALS neuromuscular diseases, **applications proposing research which focuses *primarily* on non-ALS neuromuscular diseases will be considered nonresponsive.**
- While applicants may evaluate similarities between human ALS and neuromuscular diseases in non-human species, **applications proposing research which focuses *primarily* on ALS or ALS-like neuromuscular diseases in non-human species will be considered nonresponsive.**
- While applicants may identify non-environmental risk factor correlates to the development and progression of ALS in biological samples, **applications proposing research which focuses *primarily* on non-environmental risk factors (e.g. electric shock, physical injuries, infectious agents, etc.) in the development or progression of ALS will be considered nonresponsive.**

Objectives/Outcomes

The applicant shall address all of the following objectives:

a) Identify and characterize the composition and concentrations of organophosphate metabolites (or associated biomarkers), heavy metals, or other persistent environmental toxicants in biological samples of persons with ALS.

b) Evaluate environmental toxicant associated linkage(s) between analyzed human biological samples and sample-matched ALS epidemiological data, including environmental, demographic, occupational, behavioral and familial risk factors, etc.

c) Examine the functional relationship between environmental toxicants in human biological samples and key biological pathways or genes associated with the development and/or progression of ALS.

Research funded under this FOA is expected to produce outcomes that will advance our understanding of whether correlates exist between environmental toxicant (or relevant biomarker) concentrations in human biological samples and the incidence of ALS; whether linkages between environmental toxicant exposures and other demographic risk factors for ALS disease risk and/or progression can be identified; whether gene-environment interactions contribute to the development and progression of ALS, and, if so, the mechanism(s) by which these interactions may influence genetic susceptibility to ALS.

Target Population

This FOA supports the conduct of research that will benefit all ALS patients. Although it is not required for consideration of funding under this announcement, applicants are encouraged to include the National ALS Biorepository samples and National ALS Registry enrollees, as appropriate, in their research plans. The applicant is encouraged to consider submitting an application to use samples from the **National ALS Biorepository** and data from the **National ALS Registry**. The National ALS Biorepository and National ALS Registry tools for researcher access can be found at wwwn.cdc.gov/als/ALSRegistryResearchApplicationInfo.aspx.

Collaboration/Partnerships

Applicant researchers are expected to develop collaborations pertinent to the proposed research plan. Documentation of effective and well-defined working relationships with any organization and/or outside entity expected to participate in the proposed research that will ensure implementation and sustainability of the proposed activities should be included in the application. These relationships should be evidenced by letters of support or memoranda of understanding or agreement detailing the nature and extent of the involvement from the performing organization and outside entities.

Evaluation/Performance Measurement

Applicants should include analytic plans that describe the research design and hypotheses, data collection measures, and methods to evaluate the effectiveness of the proposed research strategy to address the hypotheses within the project period. Outcomes to be evaluated should be clearly specified.

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. This must be reflected in the grantee's budget in their application submitted in response to this FOA.

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 FOA are contingent on the availability of funds and submission of a sufficient number of meritorious applications.

Award Ceiling: $500,000 Per Budget Period

Award Floor: $350,000 Per Budget Period

Total Project Period Length: 3 year(s)

Throughout the project period, 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 FOA.

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:

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" when submitting via www.grants.gov.
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

2. Foreign Organizations

Foreign Organizations are not eligible to apply.

Foreign components of U.S. Organizations are not eligible to apply.

For this announcement, applicants may not include collaborators or consultants from foreign institutions. All applicable federal laws and policies apply.

3. Special Eligibility Requirements

NONE

N/A

4. Justification for Less than Maximum Competition

N/A

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."

- Funds are available for environmental toxicant risk factor research on ALS that uses human biological samples from an ALS biorepository and data from a sample-matched human ALS registry. **Applications proposing studies outside of the stated focus area of this FOA (e.g., research on non-ALS diseases, etc.) will be considered nonresponsive.**
- While applicants may include specific aims comparing environmental toxicant-mediated etiology of ALS to the etiology of other non-ALS neuromuscular diseases, **applications proposing research which focuses *primarily* on non-ALS neuromuscular diseases will be considered nonresponsive.**
- While applicants may evaluate similarities between human ALS and neuromuscular diseases in non-human species, **applications proposing research which focuses *primarily* on ALS or ALS-like neuromuscular diseases in non-human species will be considered nonresponsive.**
- While applicants may identify non-environmental risk factor correlates to the development and progression of ALS in biological samples, **applications proposing research which focuses *primarily* on non-environmental risk factors (e.g. electric shock, physical injuries, infectious agents, etc.) in the development or progression of ALS will be considered nonresponsive.**

The biosketch for the PI, co-PI, or Co-Investigator must include documentation of expertise, experience, and knowledge related to research studies using large datasets; evaluating ALS epidemiologic demographic risk factors; characterizing toxicants, metals and/or their biomarkers in biological samples; and evaluating gene-enviroment interactions. Expertise is illustrated by evidence of at least one peer-reviewed publication or 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-Principal 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 review.**

The Letters of Support Section must include documentation of effective and well-defined working

relationships between the grantee institution and any organizations or outside entities expected to participate in the proposed research that will ensure implementation and sustainability of the proposed activities. This should be evidenced by letters of support or memoranda of understanding or agreement detailing the nature and extent of the involvement from the grantee organization and outside entities. **Applications that do not meet this requirement will be considered non-responsive and will not be forwarded for 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/#1.
- 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 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 registration process at least four (4) weeks prior to the application due date.

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 1-866-705-5711Image Description: Image Description: (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 grantee 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 grantee 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,(http://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf), applications received in response to the same funding opportunity announcement 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 FOA 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. Eligible applicant organizations may submit more than one application to this FOA, 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

Applicants must download the SF424 (R&R) application package associated with this funding opportunity from www.Grants.gov.

If access to the Internet is not available or if the applicant encounters difficulty accessing the forms on-line, contact the HHS/CDC Office of Grants Services (OGS) Technical Information Management Section (TIMS) staff at (770) 488-2700Image Description: or ogstims@cdc.gov for further instructions. Hours: Monday - Friday, 7am – 4:30pm U.S. Eastern Time. CDC Telecommunications for the hearing impaired or disabled is available at: TTY 1-888-232-6348Image Description: .

2. Content and Form of Application Submission

It is critical that applicants follow the instructions in the SF424 (R&R) Application Guide http://grants.nih.gov/grants/how-to-apply-application-guide.htm and here: http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general-forms-d.pdf, except where instructed in this Funding Opportunity Announcement to do otherwise. Conformance to the requirements in the Application Guide is required and strictly enforced. Applications that are out of compliance with these instructions may be delayed or not accepted for review.

The forms package associated with this FOA includes all applicable components, mandatory and optional. Please note that some components marked optional in the application package are required for submission of applications for this FOA. Follow the instructions in the SF 424 (R&R) Application Guide to ensure you complete all appropriate “optional” components.

In conjunction with the SF424 (R&R) components, CDC grants applicants should also complete and submit additional components titled “PHS398.” Note the PHS398 should include assurances and certifications,

additional data required by the agency for a complete application. While these are not identical to the PHS398 application form pages, the PHS398 reference is used to distinguish these additional data requirements from the data collected in the SF424 (R&R) components. A complete application to CDC will include SF424 (R&R) and PHS398 components. These forms can be downloaded from http://grants.nih.gov/grants/forms.htm

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 in Grants.gov under "Other Attachment Forms." The document should be labeled: "Report on Programmatic, Budgetary, and Commitment Overlap."

3. Letter of Intent

Due Date for Letter of Intent: **03/06/2017**

Letters of Intent are optional but requested.

Due Date for Letter of Intent: March 6, 2017

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 funding opportunity announcement (FOA):

The letter of intent should be sent to:

Oscar Tarragó, MD, MPH

Scientific Review Officer

National Center for Injury Prevention and Control

Centers for Disease Control and Prevention (CDC)

4770 Buford Hwy, NE, Mailstop F-63

Atlanta, GA 30341

Telephone: 770-488-3492

Email: NCIPC_ERPO@cdc.gov

4. Required and Optional Components

A complete application has many components, both required and optional. The forms package associated with this FOA in Grants.gov includes all applicable components for this FOA, required and optional.

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 16 components. Not all 16 components of the Research Plan apply to all Funding Opportunity Announcements (FOAs). Specifically, some of the following 16 components are for Resubmissions or Revisions only. See the SF 424 (R&R) Application Guide http://grants.nih.gov/grants/how-to-apply-application-guide.htm and here: http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general-forms-d.pdf for additional information. Please attach applicable sections of the following Research Plan components as directed in Part 2, Section 1 (Funding Opportunity Announcement Description).

Follow the page limits stated in the SF 424 (R&R) unless otherwise specified in the FOA. As applicable to and specified in the FOA, 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 FOA.

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 timeline.

4. Inclusion Enrollment Report (Renewal and Revision applications ONLY)

5. Progress Report Publication List (for Continuation ONLY)

Human Subjects Section

6. Protection of Human Subjects

7. Inclusion of Women and Minorities

8. Targeted/Planned Enrollment Table (for New Application ONLY)

9. Inclusion of Children

Other Research Plan Sections

10. Vertebrate Animals

11. Select Agent Research

12. Multiple PD/PI Leadership Plan.

13. Consortium/Contractual Arrangements

14. Letters of Support

15. Resource Sharing Plan(s)

16. Appendix

Component 4 (Inclusion Enrollment Report) applies only to Renewal and Revision applications for clinical research. Clinical research is that which is conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies). Follow the page limits in the SF 424 (R&R) Application Guide unless otherwise specified in the FOA. All instructions in the SF424 (R&R) Application Guide http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general-forms-d.pdf must be followed along with any additional instructions provided in the FOA.

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:
• Descriptions of the data to be produced in the proposed project
• How access will be provided to the data (including provisions for protection of privacy, confidentiality, security, intellectual property, or other rights)
• 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
• Plans for archival and long-term preservation of the data, or explaining why long-term preservation and access cannot be justified
Examples of DMPs may be found here: University of California https://dmp.cdlib.org/, or USGS, http://www.usgs.gov/datamanagement/plan/dmplans.php

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 FOA must be followed. For this specific FOA, 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.

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 http://grants.nih.gov/grants/how-to-apply-application-guide/forms-d/general-forms-d.pdf.

9. Submission Dates & Times

Part I. Overview Information contains information about Key Dates. Applicants are encouraged to submit in advance of the deadline to ensure they have time to make any application corrections that might be necessary for successful submission.
Organizations must submit applications via Grants.gov (https://www.grants.gov), the online portal to find and apply for grants across all Federal agencies. The eRA Commons systems retrieve the application from Grants.gov and check the application against CDC business rules. If no errors are found, the application will be assembled in the eRA Commons for viewing by the applicant before moving on for further CDC processing.
If errors are found, the applicant will be notified in the eRA Commons. They must make required changes to the local copy of their application and submit again through Grants.gov.
Applicants are responsible for viewing their application in the eRA Commons to ensure accurate and

successful submission.
Once you can see your application in the Commons, be sure to review it carefully as this is what the reviewer will see. Applicants must then complete the submission process by tracking the status of the application in the eRA Commons (http:// grants.nih. gov/grants /guide/url_redirect .htm? id=11123).
Information on the submission process is provided in the SF424 (R&R) Application Guide.
Note: HHS/CDC grant submission procedures do not provide a period of time beyond the grant application due date 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).
The application package is not complete until it has passed the Grants.gov/eRA Commons validation process. This process and email notifications of receipt, validation or rejection may take two (2) business days.
Applicants are strongly encouraged to allocate additional time prior to the submission deadline to submit their applications and to correct errors identified in the validation process. Applicants are encouraged also to check the status of their application submission to determine if the application packages are complete and error-free. Applicants who encounter system errors when submitting their applications must attempt to resolve them by contacting the Grants.gov Contact Center
(1-800-518-4726Image Description: Image Description: ; support@grants.gov). If the system errors cannot be resolved, applicants must contact TIMS at
770-488-2700Image Description: Image Description: ; ogstims@cdc.gov for guidance at least 3 calendar days before the deadline date.
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. This validation process may take as long as two (2) business days. A third and final e-mail message is generated once the applicant's application package has passed validation and the grantor has confirmed receipt of the application.

Unsuccessful Submissions: If an application submission was unsuccessful, ***the applicant*** must:
1. Track his/her submission and verify the submission status (tracking should be done initially regardless of rejection or success).
    a. If the status states "***rejected***," do #2a or #2b.
2. Check his/her emails from both Grants.gov and eRA Commons for rejection notices.
    a. If the deadline has passed, he/she should email the Grant Management Specialist listed in the FOA (pgotim@cdc.gov) explaining why the submission failed. b. If there is time before the deadline, he/she should correct the problem(s) and resubmit as soon as possible.

Due Date for Applications: **04/28/2017**

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)

This initiative is not subject to intergovernmental review (http:// www. whitehouse.gov/ omb/ grants_spoc).

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.
For more information on expanded authority and pre-award costs, go to:
http://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).
Awardees 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: http://www.cdc.gov/grants/additionalrequirements/index.html for revised AR-25.

12. Other Submission Requirements and Information

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/ Electronic Receipt /avoiding errors.htm or http:// grants. nih.gov/grants/ Electronic Receipt/submit app.htm
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?

Will successful completion of the proposed activities significantly advance our current knowledge of the impact of environmental toxicants and environment-gene interactions on ALS etiology, including whether environmental toxicants increase the likelihood and/or progression of ALS?

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 conducting:

- empirical research on ALS epidemiologic demographic risk factors, including the use of case-controlled studies and the use of large datasets?
- analysis of organophosphate metabolites (or associated biomarkers), heavy metals, or other persistent environmental toxicants in human blood and body fluid and/or tissue samples?
- molecular, histological or computational research on phenotypic biological effects (e.g., biochemical, genetic, epigenetic, or physiological) that identifies and characterizes gene-environment interactions?

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 FOA?

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 FOA?

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

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 applicant address in the application's research plan:

- the availability and quality of biological samples and ALS epidemiological data research resources proposed for evaluation,
- a justification for the use of the specific biological sample and ALS epidemiological data resources,
- an attestation that the biological samples and ALS epidemiological data are sample-matched, and
- limitations in the analysis of the specific biological samples and ALS epidemiological data proposed for evaluation?

Does the applicant propose a study with adequate sample size to test the proposed hypotheses?

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?

Do the proposed studies 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 project documented in the application by letters of support or memoranda of understanding that include detailed information about the nature of existing relationships?

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 (http://www.cdc.gov/grants/additionalrequirements/index.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 (http:// www.cdc.gov /maso Policy /Policy_women.pdf and http:// www.gpo.gov /fdsys /pkg /FR-1995-09-15 /pdf/95-22950.pdf #page=1) and the policy on the Inclusion of Persons Under 21 in Research (http:// 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 five points: 1) proposed use of the animals, and species, strains, ages, sex, and numbers to be used; 2) justifications for the use of animals and for the appropriateness of the species and numbers proposed; 3) adequacy of veterinary care; 4) procedures for limiting discomfort, distress, pain and injury to that which is unavoidable in the conduct of scientifically sound research including the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices; and 5) methods of euthanasia and reason for selection if not consistent with the AVMA Guidelines on Euthanasia. For additional information on review of the Vertebrate Animals section, please refer to the Worksheet for Review of the Vertebrate Animal Section (http://grants.nih.gov/grants/guide/url_redirect.htm?id=11150).

Biohazards

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

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.

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: http://www.cdc.gov/grants/additionalrequirements/index.html
New additional requirement: CDC requires awardees 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 funding opportunity announcement 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:
• Type of data to be produced in the proposed project;
• Mechanisms for providing access to and sharing of the data (including provisions for the protection of privacy, confidentiality, security, intellectual property, or other rights);
• 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.
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

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 FOA. Following initial peer review, recommended applications will receive a second level of review. The following will be considered in making funding decisions:

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

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 Awardee 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 funding opportunity announcement.

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 FOA 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 (http://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.

Awardees 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

All HHS/CDC grant and cooperative agreement awards include the HHS Grants Policy Statement as part of the NoA. For these terms of award, see the HHS Grants Policy Statement Part II: Terms and Conditions of Award (http://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf).

Awardees must comply with the administrative requirements (AR) outlined in 45 Code of Federal Regulations (CFR) Part 75, as appropriate, as well as any additional requirements included in the FOA. Specific requirements that apply to this FOA are the following:

AR-1: Human Subjects Requirements

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

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: Release and Sharing of Data

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: Distinguishing Public Health Research and Public Health Nonresearch

AR-32: FY 2012 Enacted General Provisions

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

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))/Homepage.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 FOA:

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:http://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 http://www.cdc.gov/grants/additionalrequirements/index.html outlines the components of a DMP and provides additional information for investigators regarding the requirements for data accessibility, storage, and preservation.

4. Cooperative Agreement Terms and Conditions

N/A

5. Reporting

Awardees will be required to submit the Non-Competing Continuation Grant Progress Report (PHS 2590) annually 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 awardees 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 awardees of Federal grants to report information about first-tier subawards and executive compensation under Federal assistance awards issued in FY2011 or later. All awardees of applicable 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 (http://www.hhs.gov/sites/default/files/grants/grants/policies-regulations/hhsgps107.pdf).

Technical Review Statement Response Requirements

Grantees 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. Grantees 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.

Annual Report Requirements

Grantees will be required to electronically submit an Annual Report due within 90 days following the end of each budget period. The Annual Report should include at a minimum:

- A description of the completion status of each Specific Aim and/or research objective(s) or milestone(s) for the budget period.
- A complete list of the publications and presentations planned or completed to date - including status (e.g., published [include reference], in review, under development).
- A description of any changes made in the IRB.
- A description of any changes made in the Data Management Plan.

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**, (use form PHS 2590, posted on the HHS/CDC website, www.grants.gov and at http:// grants.nih.gov/grants/ funding/2590/ 2590.htm, **is due 90 to 120 days prior to the end of the current budget period.** 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 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 project period.**

B. Content of Reports

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

- Description of Progress during Annual Budget Period: Current Budget Period Progress reported on the PHS 2590 (http:// grants1.nih.gov/ grants/funding/ 2590/2590.htm) http:// grants.nih.gov/grants/ funding/2590/2590.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:

The frequency of other progress reporting and reporting format will be agreed on between the awardee and CDC.

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. **All CDC Financial Expenditure data due on/after October 1, 2012 must be submitted using the FFR via the eFSR/FFR system in the eRA Commons.** All Federal Reporting in the Payment Management System is unchanged. All new submissions should be prepared and submitted as FFRs.
CDC's implementation of the FFR retains a financial reporting period that coincides with the budget period of a particular project. However, **the due date for annual FFRs will be 90 days after the end of the calendar quarter in which the budget period ends**. Note that this is a change in due dates of annual FFRs and may provide up to 60 additional days to report, depending upon when the budget period end date falls within a calendar quarter. For example, if the budget period ends 1/30/2012, the annual FFR is due 6/30/2012 (90 days after the end of the calendar quarter of 3/31/2012). Due dates of final reports will remain unchanged. The due date for final FFRs will continue to be 90 days after the project period end date.
Grantees must submit closeout reports in a timely manner. Unless the Grants Management Officer (GMO) of the awarding Institute or Center approves an extension, grantees 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 grantees are now available at http:// grants.nih.gov/ grants/forms.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://era.nih.gov/registration_accounts.cfm
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/ registration/ registration Instructions. jsp 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: http:// era.nih.gov/ commons /index.cfm.
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 project period. 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: 800-518-4726Image Description:
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: 301-402-7469Image Description: or 866-504-9552Image Description: (Toll Free)
TTY: 301-451-5939Image Description:
Email: commons@od.nih.gov
Hours: Monday - Friday, 7am - 8pm U.S. Eastern Time

CDC Technical Information Management Section (TIMS)
Telephone 770-488-2700Image Description:
Email: ogstims@cdc.gov
Hours: Monday - Friday, 7am – 4:30pm U.S. Eastern Time

Scientific/Research Contact(s)

Marcienne Wright, PhD

Scientific Program Official

National Center for Injury Prevention and Control

Centers for Disease Control and Prevention (CDC)

Telephone: 770-488-4850

Email: marcienne.wright@cdc.hhs.gov

Peer Review Contact(s)

Oscar Tarragó, MD, MPH

Scientific Review Officer

National Center for Injury Prevention and Control

Centers for Disease Control and Prevention (CDC)

4770 Buford Hwy, NE, Mailstop F-63

Atlanta, GA 30341

Telephone: 770-488-3492

Email: NCIPC_ERPO@cdc.gov

Financial/Grants Management Contact(s)

Kerwin Lawrence

Grants Management Specialist

Office of Grants Services

Telephone: 770-488-1120

Email: mpx7@cdc.gov

Section VIII. Other Information

Other CDC funding opportunity announcements 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 FOA must be responsive to the specific requirements and objectives of this FOA and must be submitted as a new application through www.grants.gov. Application documents included in an application to a previous FOA may be submitted as part of this application process. Please read the current FOA carefully to make sure that what is submitted is consistent with the intent of this FOA, 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 FOA.

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

Successful grantees will be permitted expanded authorities in the administration of this award as provided for in the Code of Federal Regulations, Title 2, Subtitle A, Chapter II, Part 200, Subpart D, §200.308(d)(4). Specific authorities granted will be detailed in the official Notice of Award document.

Amendment 1 to RFA-TS17-001

Q & A received before and during the RFA-TS17-001 Pre-Application Conference Call

held on 2/13/2017 at 2:00 PM Eastern Time

Q1. Can the principal investigator/project director employ a graduate student research assistant as a member of the research team personnel to support the specific research project for FOA RFA-TS-17-001?

A1. Yes. In accordance with the HHS Grant Policy Statement, tuition remission and other forms of compensation paid as, or in lieu of, wages to students (including fellows) under research grants are allowable, provided the following conditions are met:

1. The individual is performing activities necessary to the grant.

2. Tuition remission and other forms of compensation are consistently provided, in accordance with established institutional policy, to students performing similar activities conducted in non-sponsored as well as in sponsored activities.

3. During the academic period, the student is enrolled in an advanced degree program at a recipient or affiliated institution and the activities of the student in relation to the federally sponsored research project are related to the degree program.

4. The tuition or other payments are reasonable compensation for the work performed and are conditioned explicitly upon the performance of necessary work.

5. It is the institution's practice to similarly compensate students in non-sponsored as well as sponsored activities.

Q2: Would a proposal focused on cyanobacterial toxins from harmful algal blooms be considered responsive to Notice of Funding Opportunity RFA-TS-17-001?

A2: Per *Section I. Funding Opportunity Description 1. Background and Purpose*: The applicant shall address all of the following objectives:

a) Identify and characterize the composition and concentrations of organophosphate metabolites (or associated biomarkers), heavy metals, or other persistent environmental toxicants in biological samples

of persons with ALS.

b) Evaluate environmental toxicant associated linkage(s) between analyzed human biological samples and sample-matched ALS epidemiological data, including environmental, demographic, occupational, behavioral and familial risk factors, etc.

c) Examine the functional relationship between environmental toxicants in human biological samples and key biological pathways or genes associated with the development and/or progression of ALS.

Provided that the analysis of cyanobacterial toxins occurs from biological samples of persons with ALS, the study evaluating cyanobacterial toxins will be responsive to the FOA. A study evaluating cyanobacterial toxins in harmful algal blooms will be non-responsive to the FOA.

Q3. What kind of biological sample resources are available in the National ALS Biorepository?

A3. The National ALS Biorepository stores biological samples from in-home collection (e.g., blood, hair, and urine) from 330 patients and postmortem collection (e.g., brain, bone, spinal cord, cerebrospinal fluid, muscle, and skin) from 21 patients. Specimens from the National ALS Biorepository are collected from a geographically representative sample of persons with ALS who are self-enrolled in the Registry. Samples from the National ALS Biorepository are paired with completed risk factor data from the National ALS Registry, including demographic and other environmental and occupational data currently being provided by persons with ALS.

Q4. What Biorepository-matched demographic or epidemiologic data is available in the National ALS Registry?

A4. The National ALS Registry contains self-reported patient responses to the following questions:

1. Demographics
2. Employment history
3. Military service
4. Alcohol/smoking history
5. Exercise history
6. Family history: ALS/Alzheimer's/Parkinson's
7. ALSFRS symptom questions
8. History: pesticides/herbicides
9. Occupational chemical exposures
10. Non-occupational herbicide/pesticide exposures
11. History: Non-occupational chemical exposures
12. Menstruation/pregnancy history
13. History: caffeine
14. History: Head injury
15. Health insurance
16. Symptoms

Q5. How do I apply for access to the National ALS Biorepository and National ALS Registry?

A5. ATSDR has developed an online tool for researchers to request samples from the National ALS Biorepository. The directions and system platform for joining the National ALS Registry **as a researcher** can be accessed at wwwn.cdc.gov/als/ALSRegistryResearchApplicationInfo.aspx. The application must include information about:

- who is conducting the study
- who is sponsoring the study
- the study objectives and procedures
- Institutional Review Board (IRB) approved recruitment materials, and
- proof of IRB approval (e.g., an IRB approval letter)

Q6. Will I have to sign a Data Use Agreement with ATSDR in order to access the National ALS Biorepository and National ALS Registry?

A6. Yes. You will need to sign an ATSDR ALS Data Use Agreement, a Material Transfer Agreement, and a Researcher Agreement to request specimens and registry data.

Q7. What information will the ATSDR ALS Data Use Agreement include?

A7. The data use agreement establishes the basic terms and conditions for the sharing, protection, and use of aggregate data from the National ALS Registry and National ALS Biorepository, including ensuring, to the extent possible, that use of the data will be limited to approved research or public health purposes and that individually identifiable records of any person or establishment included in the National ALS Registry and National ALS Biorepository is not released.

Q8. How will the privacy requirements of the ATSDR ALS Data Use Agreement impact my ability to share the results of my research as required by the RFA's Data Management Plan?

A8. *Section IV. Application and Submission Information 5. PHS 398 Research Plan Component* of the FOA requires that applicants who plan to collect public health data submit a Data Management Plan (DMP) as a part 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 should include:

- Descriptions of the data to be produced in the proposed project
- How access will be provided to the data (including provisions for protection of privacy, confidentiality, security, intellectual property, or other rights)
- 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
- Plans for archival and long-term preservation of the data, or explaining why long-term preservation and access cannot be justified

You can provide, in your DMP, a justification as to why you cannot share raw ALS Registry or Biorepository data in keeping with the terms of the ATSDR ALS DUA. **However you will be required to share any secondary data/outcomes that your team develops as a result of using the National ALS Registry and National ALS Biorepository.** You should speak to that intent to share your secondary data/outcomes in your DMP in keeping with the FOA and AR-25 requirements. Additionally, you should provide in your DMP clear directions to potential users of the National ALS Registry and National ALS Biorepository on how to access the National ALS Registry and National ALS Biorepository and instructions on how to submit an application to the National ALS Registry and National ALS Biorepository holder in

order to access that dataset.

Q9. How soon after I apply for researcher access to the National ALS Biorepository and National ALS Registry will the data be made available to me?

A9. After an application has been received by ATSDR, ATSDR will review the application for completeness and relevance to National ALS Biorepository and National ALS Registry participants. It will then be evaluated by an ALS subject matter expert panel external to CDC. All members of the subject matter expert panel will be required to sign a conflict of interest form and non-disclosure agreement form to protect an applicant's proprietary research information. ATSDR will not approve access for applications that do not have Institutional Review Board approval or, if applicable, an FDA IND or IDE number for an investigational test article.

The ATSDR approval process may take up to 60 business days from the receipt of a complete application. Additional requirements (e.g., signing a Material Transfer Agreement) will need to be completed before data and/or specimens are transferred. ATSDR estimates that it may take up to one month to fill the order after approval by the review panel.

Q10. When should I apply for researcher access to the National ALS Biorepository and National ALS Registry?

A10. The ATSDR National ALS Biorepository and National ALS Registry accepts applications for access from qualified researchers at any time.For the purposes of RFA-TS-17-001, the grantee PI should apply for access as soon as the grantee institution receives a formal Notice of Grant Award.

Q11. What is the cost to access and use the National ALS Registry?

A11. There is no cost to use the National ALS Registry.

Q12. What is the cost to access and use the National ALS Biorepository?

A12. There is a fee associated with access to and use of the National ALS Biorepository. The total cost to access and use samples from the National ALS Biorepository will depend on the applicant's specific research plan. For example, it is provisionally anticipated that the cost to access one sample per patient from the National ALS Biorepository (n =330 patients), including sample processing, shipping, and quality control monitoring is expected to cost roughly $1000 USD.

Anticipated costs to access and use the National ALS Biorepository (and/or any other biospecimen bank requiring a fee for access and use), should be included in the detailed budget and budget justification section of Standard Form-424 (Research and Related) [SF-424(R&R)] of the application.

Q13. Will new samples and data be added to the National ALS Biorepository and National ALS Registry during my project period? Will I be able to access samples and data that are added to these repositories after I start my project?

A13. New specimens are scheduled to be collected beginning in February 2017. Given the requirements for ATSDR accessioning of new samples (e.g., processing and genotyping), samples may not be ready for request until early 2018.

NOTE: Applicants are encouraged by ATSDR staff to carefully review the Responsiveness Criteria and the

Data Management Plan requirements listed in FOA RFA-TS-17-001 while preparing their proposals.