Program Announcement

for the

Defense Health Program

Department of Defense

Congressionally Directed Medical Research Programs

Amyotrophic Lateral Sclerosis Research Program

Therapeutic Development Award

Funding Opportunity Number: W81XWH-15-ALSRP-TDA

Catalog of Federal Domestic Assistance Number: 12.420

SUBMISSION AND REVIEW DATES AND TIMES

- **Pre-Application Deadline:** 5:00 p.m. Eastern time (ET), May 11, 2015
- **Invitation to Submit an Application:** July 2015
- **Application Submission Deadline:** 11:59 p.m. ET, August 20, 2015
- **End of Application Verification Period:** 5:00 p.m. ET, August 25, 2015
- **Peer Review:** October 2015
- **Programmatic Review:** December 2015

The CDMRP eReceipt System has been replaced with the electronic Biomedical Research Application Portal (eBRAP). Principal Investigators and organizational representatives should register in eBRAP as soon as possible. All pre-applications must be submitted through eBRAP. In addition, applications submitted through Grants.gov will now be available for viewing, modification, and verification in eBRAP prior to the end of the application verification period.

This Program Announcement/Funding Opportunity is one of two documents with instructions to prepare and submit an application for this funding opportunity. The second document, the General Application Instructions, is available for downloading from Grants.gov.

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I. FUNDING OPPORTUNITY DESCRIPTION

A. Program Description

Applications to the Fiscal Year 2015 (FY15) Amyotrophic Lateral Sclerosis Research Program (ALSRP) are being solicited for the Defense Health Agency, Research, Development, and Acquisition (DHA RDA) Directorate, by the U.S. Army Medical Research Acquisition Activity (USAMRAA). As directed by the Office of the Assistant Secretary of Defense for Health Affairs, the DHA RDA Directorate manages and executes the Defense Health Program (DHP) Research, Development, Test, and Evaluation (RDT&E) appropriation. The executing agent for this Program Announcement/Funding Opportunity is the Congressionally Directed Medical Research Programs (CDMRP). The ALSRP was initiated in 2007 to provide support for research of exceptional scientific merit aimed at the preclinical assessment of therapeutics for amyotrophic lateral sclerosis (ALS). Appropriations for the ALSRP from FY07 through FY14 totaled $46.9 million (M). The FY15 appropriation is $7.5M.

The goal of the ALSRP is to fund innovative preclinical research in order to develop new treatments and contribute to a cure for ALS.

B. Award Information

The ALSRP Therapeutic Development Award mechanism was first offered in FY07. Since then, 168 Therapeutic Development Award applications have been received, and 16 have been recommended for funding.

The Therapeutic Development Award supports the preclinical development of therapeutic leads for ALS. The proposed studies are expected to be empirical in nature and product-driven.

New for FY15: The maximum period of performance is 2 years. The Therapeutic Development Award no longer supports development of model or screening systems or the conduct of screening. Those activities are now supported under the ALSRP FY15 Therapeutic Idea Award mechanism.

Applications must clearly identify a lead molecule, or limited group of lead molecules, possessing demonstrated biological activity on a pathway relevant to ALS disease onset and/or progression.

The FY15 Therapeutic Development Award supports a wide range of post-discovery development activities ranging from post-discovery validation right up to IND submission. Supported activities must begin with lead compounds in hand and can include (1) secondary validation of leads obtained from screening or by other means to demonstrate target selectivity and mechanism of action, (2) optimization of potency and pharmacological properties and development of structure-activity maps via synthesis and testing of derivatives and sister compounds, (3) studies of formulation and stability, and/or (4) development of GMP production methods, (5) collection of data needed for Food and Drug Administration (FDA) Investigational New Drug (IND) applications to include compound characterization, absorption, distribution, metabolism, excretion (ADME) studies, and dose/response and toxicology studies.

Validation of existing biomarkers and development of them as markers for mechanism-specific drug activity and/or clinical progression, in parallel with therapeutic lead validation and development, is also of interest.

Applications must include **preliminary data** relevant to the phase(s) of the preclinical development process covered by the proposed research, including the following:

- Background data supporting the putative mechanism of action as a viable therapeutic approach.
- A specific lead molecule or a limited group of specifically identified lead molecules.
- Proof of identity and purity.
- If appropriate to the proposed phase of development:
    - Availability of primary and secondary in vitro bioactivity assays for optimization or structure-activity relationship studies.
    - Identification of appropriate preclinical animal models.
    - Availability of appropriate target engagement and selectivity assays to measure desirable activity at the intended target and to assess process-related artifacts and the potential for undesirable activities at related but unintended targets.

The application should include a clear statistical plan of analysis, if appropriate. Applicants must clearly and explicitly articulate a plan for bringing the candidate molecule(s) or compound(s) to the next level of development.

If a therapeutic agent(s) or model(s) that is the subject of a Therapeutic Development Award application was initially developed under an ALSRP Therapeutic Idea Award, the applicant should describe the role of the Therapeutic Idea Award in that development.

Investigators interested in basic research focused on ALS drug and target discovery should consider the FY15 ALSRP Therapeutic Idea Award, which does not require preliminary data (http://cdmrp.army.mil/funding/alsrp).

Collaborations: The preclinical drug development process may require resources beyond those available at single institutions. Therefore, applications proposing collaborations, including biotechnology/pharmaceutical industry partnerships, are encouraged.

- Collaborations should be dedicated to a single, preclinical development project rather than a set of independent subprojects.
- Letters confirming/supporting the collaboration are required.
- If the collaboration is multi-organizational, participating organizations should ensure the success of the collaboration by resolving potential intellectual and material property issues and by removing organizational barriers that might interfere with achieving high levels of cooperation.

- The proposed means to resolve intellectual property issues must be delineated in an Intellectual and Material Property Plan to be included with the application (see Section II.C.2, Attachment 2, Intellectual Property Plan).

Applications Involving Industry: Applications originating from or collaborating with the biotechnology/pharmaceutical industry are encouraged. Biotechnology or pharmaceutical companies who apply for the Therapeutic Development Award, as an individual applicant or as part of a collaboration, are encouraged to leverage their own resources to complement the funding provided by this award.

Research Involving Human Anatomical Substances, Human Subjects, or Human Cadavers: This award is intended for preclinical studies. The use of human substances and specimens is restricted to existing pathological or diagnostic samples and specimens. **Clinical trials are not permitted under this Program Announcement/Funding Opportunity.**

If human-derived substances are obtained from a public source or if the materials are deidentified, they may qualify as exempt under Title 32, Code of Federal Regulations, Part 219, Section 101(b) (32 CFR 219.101[b]). A Human Research Protection Office (HRPO) Submission Form for Research Involving Use of Data/Specimens will be requested if an application proposing the use of exempt materials is recommended for funding. Additional information regarding this research may be found on the U.S. Army Medical Research and Materiel Command (USAMRMC) HRPO website (http://mrmc.amedd.army.mil/index.cfm?pageid=research_protections.orp_faq) and under Regulatory Information and Forms at https://ebrap.org/eBRAP/public/Program

For research involving the use of cadaveric specimens, refer to the General Application Instructions, Appendix 5, for additional Army requirements.

Department of Defense (DoD)-funded research involving new and ongoing research with human anatomical substances, or human subjects must be reviewed and approved by the USAMRMC Office of Research Protections (ORP), and HRPO, in addition to the local Institutional Review Board (IRB) of record. Local IRB approval at the time of submission is not required. The HRPO is mandated to comply with specific laws and requirements governing all research involving human anatomical substances that is supported by the DoD. These laws and requirements will necessitate information in addition to that supplied to the IRB. Allow a minimum of 2 to 3 months for HRPO regulatory review and approval processes. Refer to the General Application Instructions, Appendix 5, and the Human Subject Resource Document available on the eBRAP "Funding Opportunities & Forms" web page (https://ebrap.org/eBRAP/public/Program.htm) for additional information.

Research Involving Animals: All DoD-funded research involving new and ongoing research with animals must be reviewed and approved by the USAMRMC ORP Animal Care and Use Review Office (ACURO), in addition to the local Institutional Animal Care and Use Committee (IACUC) of record. IACUC approval at the time of submission is not required. Specific documents relating to the use of animals in the proposed research will be requested if the application is selected for funding. The ACURO must review and approve all animal use prior to the start of working with animals. PIs must submit the institutional animal use protocol,

IACUC approval of that protocol, and a version of the animal use appendix titled "Research Involving Animals." ***Allow at least 2 to 3 months for regulatory review and approval processes for animal studies.*** Refer to General Application Instructions, Appendix 5, for additional information.

Standards for Preclinical Study Design: All projects should adhere to a core set of standards for rigorous study design and reporting to maximize the reproducibility and translational potential of preclinical research. The standards are described in Landis, S. C., et al. A call for transparent reporting to optimize the predictive value of preclinical research. *Nature* 2012, 490: 187-191 (www.nature.com/nature/journal/v490/n7419/full/nature11556.html). Projects that include research on animal models are required to submit Attachment 8, Animal Research Plan, as part of the application package to describe how these standards will be addressed. Applicants should consult the ARRIVE (Animal Research: Reporting *In Vivo* Experiments) guidelines to ensure relevant aspects of rigorous animal research are adequately planned for and, ultimately, reported. The ARRIVE guidelines can be found at http://www.elsevier.com/__data/promis_misc/622936arrive_guidelines.pdf.

The CDMRP intends that information, data, and research resources generated under awards funded by this Program Announcement/Funding Opportunity be made available to the research community (which includes both scientific and consumer advocacy communities) and to the public at large. For additional guidance, refer to the General Application Instructions, Appendix 3, Section L.

C. Eligibility Information

- Independent investigators at all academic levels (or equivalent) are eligible to submit applications.
- Cost sharing/matching is not an eligibility requirement.
- Eligible investigators must apply through an organization. Organizations eligible to apply include national, international, for-profit, nonprofit, public, and private organizations.
- Refer to the General Application Instructions, Appendix 1, for general eligibility information.

D. Funding

- The maximum period of performance is **2** years.
- The anticipated direct costs budgeted for the entire period of performance will not exceed $**1,000,000**. Associated indirect costs can be budgeted in accordance with the organization's negotiated rate. No budget will be approved by the Government exceeding $**1,000,000** direct costs or using an indirect rate exceeding the organization's negotiated rate.

- All direct and indirect costs of any subaward (subgrant or subcontract) must be included in the total direct costs of the primary award.
- The applicant may request the entire maximum funding amount for a project that may have a period of performance less than the maximum **2** years.

Refer to the General Application Instructions, Section II.C.5., for budget regulations and instructions for the Research & Related Budget. ***For all Federal agencies or organizations collaborating with Federal agencies, budget restrictions apply as are noted in Section II.C.5. of the General Application Instructions***.

For this award mechanism, direct costs may be requested for (not all-inclusive):

- Salary
- Research supplies
- Equipment (Note: Cost sharing is encouraged for large equipment purchases)
- Consultation with scientific and/or technical experts (e.g., statisticians, editors)
- Travel between collaborating organizations
- Travel costs to attend scientific/technical meetings

Intramural (DoD), other Federal agency, and extramural investigators are encouraged to apply to this Program Announcement/Funding Opportunity. An intramural investigator is defined as a DoD military or civilian employee working within a DoD laboratory or medical treatment facility, or working in a DoD activity embedded within a civilian medical center. Intramural applicants and collaborators are reminded to coordinate receipt and commitment of funds through their respective resource managers. It is permissible for an intramural investigator to be named as a collaborator on an application submitted by an extramural investigator. ***In such cases, the extramural investigator must include a letter from the intramural collaborator's Commander or Commanding Officer that authorizes the involvement of the intramural collaborator.***

As required of all applicants to this Program Announcement/Funding Opportunity, if PIs from Federal agencies submit applications, they must submit through Grants.gov. Therefore, Federal applicants must be familiar with Grants.gov requirements, including the need for an active System for Award Management (SAM) registration and a Data Universal Numbering System (DUNS) number. Refer to Section II.A. of the General Application Instructions for further information regarding Grants.gov requirements.

Awards to extramural organizations will consist solely of assistance agreements (Cooperative Agreements and Grants). Awards to intramural agencies and other Federal agencies may be executed through a direct fund transfer (e.g., the Military Interdepartmental Purchase Request [MIPR] or Funding Authorization Document [FAD] process). Direct transfer of funds from the recipient to a Federal agency is not allowed except under very limited circumstances. Refer to the General Application Instructions, Section II.C.5. Research & Related Budget, for additional information on budget considerations for applications involving Federal agencies.

The CDMRP expects to allot approximately $3.2M of the $7.5M FY15 appropriation to fund approximately 2 Therapeutic Development Award applications, depending on the quality and number of applications received. Funding of applications received in response to this Program Announcement/Funding Opportunity is contingent upon the availability of Federal funds for this program.

II. SUBMISSION INFORMATION

Submission of applications that are essentially identical or propose essentially the same research project to different funding opportunities within the same program and fiscal year is prohibited and will result in administrative withdrawal of the duplicative application.

Submission is a two-step process requiring both (1) pre-application submission through the electronic Biomedical Research Application Portal (eBRAP) (https://eBRAP.org/) and (2) application submission through Grants.gov (http://www.grants.gov/). Refer to the General Application Instructions, Section II.A., for registration and submission requirements for eBRAP and Grants.gov.

eBRAP is a multifunctional web-based system that allows PIs to submit their pre-applications electronically through a secure connection, to view and edit the content of their pre-applications and full applications, to receive communications from the CDMRP, and to submit documentation during award negotiations and period of performance. A key feature of eBRAP is the ability of an organization's representatives and PIs to view and modify the Grants.gov application submissions associated with them. eBRAP will validate Grants.gov application files against the specific Program Announcement/Funding Opportunity requirements and discrepancies will be noted in an email to the PI and in the Full Application Files tab in eBRAP. It is the applicant's responsibility to review all application components for accuracy as well as ensure proper ordering as specified in this Program Announcement/Funding Opportunity.

PIs should ensure that their name and email address are the same as the name and email address that will be provided on the SF-424 Form of the Grants.gov application package submitted to Grants.gov. The organization, Business Officials, PI(s), and eBRAP log number named in the full application submitted to Grants.gov must match those named in the pre-application in eBRAP.

Application viewing, modification, and verification in eBRAP is strongly recommended, but not required. The Project Narrative and Budget cannot be changed after the application submission deadline. Any other application component cannot be changed after the end of the verification period.

A. Where to Obtain the Grants.gov Application Package

To obtain the Grants.gov application package, including all required forms, perform a basic search using the Funding Opportunity Number W81XWH-15-ALSRP-TDA in Grants.gov (http://www.grants.gov/).

B. Pre-Application Submission and Content Form

All pre-application components must be submitted by the PI through eBRAP (https://eBRAP.org/). Because the invitation to submit an application is based on the contents of the pre-application, investigators should not change the title or research objectives after the pre-application is submitted.

PIs and organizations identified in the pre-application should be the same as those intended for the subsequent application submission. If any changes are necessary after submission of the pre-application, the PI must contact the CDMRP Help Desk at help@eBRAP.org or 301-682-5507.

The pre-application consists of the following components, which are organized in eBRAP by separate tabs (refer to the General Application Instructions, Section II.B., for additional information on pre-application submission):

- **Application Information – Tab 1**
- **Application Contacts – Tab 2**
    - Enter contact information for the PI. Enter the organization's Business Official responsible for sponsored program administration (the "person to be contacted on matters involving this application" in Block 5 of the Grants.gov SF-424 form). The Business Official must either be selected from the eBRAP list or invited in order for the pre-application to be submitted.
    - It is recommended that PIs identify an Alternate Submitter in the event that assistance with pre-application submission is needed.
- **Collaborators and Key Personnel – Tab 3**
    - Enter the name, organization, and role of all collaborators and key personnel associated with the application.
    - FY15 ASLRP Integration Panel (IP) members should not be involved in any pre-application or application. For questions related to IP members and pre-applications or applications, refer to Section IV.C., Withdrawal, or contact the CDMRP Help Desk at help@eBRAP.org or 301-682-5507.
- **Conflicts of Interest (COIs) – Tab 4**
    - List all individuals other than collaborators and key personnel who may have a COI in the review of the application (including those with whom the PI has a personal or professional relationship).
- **Pre-Application Files – Tab 5**

  Note: Upload document(s) as individual PDF files unless otherwise noted. eBRAP will not allow a file to be uploaded if the number of pages exceeds the limit specified below.

  Preproposal Narrative (three-page limit): The Preproposal Narrative page limit applies to text and non-text elements (e.g., figures, tables, graphs, photographs, diagrams, chemical structures, drawings, etc.) used to describe the project. Inclusion of

URLs that provide additional information to expand the Preproposal Narrative and could confer an unfair competitive advantage is prohibited and may result in administrative withdrawal of the pre-application.

The Preproposal Narrative should include the following:

- **Research Strategy and Objectives**: Concisely state the project's objectives and specific aims. Identify the specific lead molecule(s) on which the proposed development work will be based. Briefly describe the putative therapeutic mechanism of action and summarize existing data demonstrating biological activity. Describe how the action of drug candidates on a specific mechanistic target(s) will be discerned and/or how clinical progression will be determined. Describe the outcome(s) of the proposed project and potential for FDA IND submission.
- **Impact:** Describe how the project will make an important contribution to ALS therapeutic development. Describe in general terms how the outcomes of the project, if successful, will be translated to the clinic and made available to ALS patients.
- **Personnel:** Briefly state the qualifications of the PI, collaborators (if applicable), and key personnel to perform the described research project.

Pre-Application Supporting Documentation: The items to be included as supporting documentation for the pre-application ***must be uploaded as individual documents*** and are limited to:

- References Cited (one-page limit): List the references cited (including URLs if available) in the Preproposal Narrative using a standard reference format that includes the full citation (i.e., author[s], year published, title of reference, source of reference, volume, chapter, page numbers, and publisher, as appropriate).
- List of Abbreviations, Acronyms, and Symbols: Provide a list of abbreviations, acronyms, and symbols used in the Preproposal Narrative.
- Key Personnel Biographical Sketches (five-page limit per individual).

- **Submit Pre-Application – Tab 6**
  - This tab must be completed for the pre-application to be accepted and processed.

Pre-Application Screening

- **Pre-Application Screening Criteria**

  To determine the technical merits of the pre-application and the relevance to the mission of the DHP and the ALSRP, pre-applications will be screened based on the following criteria:

  - **Research Strategy and Objectives:** How well the scientific rationale supports the project objectives and feasibility. How well the proposed research adheres to the intent of the mechanism. Whether the pre-application identifies a specific lead compound (or limited group of specific lead compounds). To what extent the preliminary data supports the idea that the candidate compound(s) represents a potential, viable therapeutic against ALS. If proposed, how appropriate the

proposed biomarkers will be for assessing drug action on a specific mechanistic target(s) or clinical progression. To what extent the proposed work will move the candidate molecule(s) significantly closer to an IND submission.

- **Impact:** Whether the project will make an important contribution to development of clinical therapeutics for ALS. Whether the general steps for clinical translation of the projected outcomes of the project are adequately described.
- **Personnel:** How appropriate the qualifications of the PI and key personnel are for performing the proposed research project.

- **Notification of Pre-Application Screening Results**

  Following the pre-application screening, PIs will be notified as to whether or not they are invited to submit applications; however, they will not receive feedback (e.g., a critique of strengths and weaknesses) on their pre-application. The estimated timeframe for notification of invitation to submit an application is indicated on the title page of this Program Announcement/Funding Opportunity.

C. Application Submission Content and Forms

Full applications will not be accepted unless the PI has received notification of invitation.

The CDMRP cannot make allowances/exceptions to its policies for submission problems encountered by the applicant organization using system-to-system interfaces with Grants.gov.

Each application submission must include the completed Grants.gov application package provided in Grants.gov for this Program Announcement/Funding Opportunity. The Grants.gov application package is submitted by the Authorized Organizational Representative through the Grants.gov portal (http://www.grants.gov/).

Note: The Project Narrative and Budget Form cannot be changed after the application submission deadline. If either the Project Narrative or the budget fails eBRAP validation or if the Project Narrative or Budget Form needs to be modified, an updated Grants.gov application package must be submitted via Grants.gov as a "Changed/Corrected Application" with the previous Grants.gov Tracking ID ***prior to the application submission deadline***.

Grants.gov application package components: For the Therapeutic Development Award, the Grants.gov application package includes the following components (refer to the General Application Instructions, Section II.C., for additional information on application submission):

1. **SF-424 (R&R) Application for Federal Assistance Form:** Refer to the General Application Instructions, Section II.C., for detailed information.

2. **Attachments Form**

   Each attachment to the Grants.gov application forms must be uploaded as an individual PDF file in accordance with the formatting guidelines listed in Appendix 2 of the General Application Instructions. For all attachments, ensure that the file names are consistent with the guidance. Grants.gov will reject attachments with file names longer

than 50 characters or incorrect file names that contain characters other than the following: A-Z, a-z, 0-9, underscore, hyphen, space, and period. In addition, Grants.gov has file size limits that may apply in some circumstances. Individual attachments may not exceed 20 MB and the file size for the entire Grants.gov application package may not exceed 200 MB.

- **Attachment 1: Project Narrative (20-page limit):** Upload as "ProjectNarrative.pdf." The page limit of the Project Narrative applies to text and non-text elements (e.g., figures, tables, graphs, photographs, diagrams, chemical structures, drawings, etc.) used to describe the project. Inclusion of URLs that provide additional information to expand the Project Narrative and could confer an unfair competitive advantage is prohibited and may result in administrative withdrawal of the application.

  Describe the proposed project in detail using the outline below. The project narrative must include preliminary data relevant to the phase(s) of the preclinical development process addressed by the proposed research.

  - **Background:** Present data showing that the proposed therapeutic is a feasible candidate for advanced preclinical development. Describe the ideas and reasoning behind the proposed work. Cite relevant literature. The following data are required:
    - Background data supporting the putative mechanism of action as a viable therapeutic approach;
    - The chemical (or biological) identities of the lead molecules(s);
    - Proof of identity and purity of the lead(s) (For small molecules, typically >95% by NMR, LC-MS, melting point, etc., with no single impurity >0.5%. For biologics, often by HPLC, LC-MS, immunochemistry, nucleotide or amino acid sequence analysis, etc.);
    - For any proposed biomarker development or validation, present the rationale and existing evidence indicating that the proposed biomarkers will reflect disease progression or action of candidate therapeutics on specific mechanistic targets.
  - **Objectives and Specific Aims:** Concisely explain the project's objectives and specific aims and their rationale. Show how the specific aims will support the proposed outcome(s) of the study/project.
  - **Research Strategy:** Describe the study design, methods, models and analyses, including statistical analyses, where applicable, in sufficient detail for assessment of the application. Address planned statistical analyses for animal studies in Attachment 8, Animal Research Plan. Address potential problem areas and present alternative methods and approaches.

    If appropriate to the proposed phase of development:

    - Availability of primary and secondary in vitro bioactivity assays for optimization or structure-activity relationship studies.

- Identification of appropriate preclinical animal models.
- Availability of appropriate target engagement and selectivity assays to measure desirable activity at the intended target and to assess artifacts and the potential for undesirable activities at related but unintended targets.
- Outline the chemical synthetic pathway for modification of lead compounds and/or formulation of potential delivery systems.

- **Attachment 2: Supporting Documentation.** Start each document on a new page. Combine and upload as a single file named "Support.pdf." If documents are scanned to pdf, the lowest resolution (100 to 150 dpi) should be used. ***There are no page limits for any of these components unless otherwise noted. Include only those components described below; inclusion of items not requested will be removed or may result in administrative withdrawal of the application.***
  - References Cited: List the references cited (including URLs if available) in the Project Narrative using a standard reference format that includes the full citation (i.e., author[s], year published, title of reference, source of reference, volume, chapter, page numbers, and publisher, as appropriate).
  - List of Abbreviations, Acronyms, and Symbols: Provide a list of abbreviations, acronyms, and symbols.
  - Facilities, Existing Equipment, and Other Resources: Describe the facilities and equipment available for performance of the proposed project and any additional facilities or equipment proposed for acquisition at no cost to the award. Indicate whether or not Government-furnished facilities or equipment are proposed for use. If so, reference should be made to the original or present Government award under which the facilities or equipment items are now accountable. There is no form for this information.
  - Publications and/or Patent Abstracts: Include a list of relevant publication URLs and/or patent abstracts. If publications are not publicly available, then copies of up to five published manuscripts may be included in Attachment 2. Extra items will not be reviewed.
  - Letters of Organizational Support: Provide a letter (or letters, if applicable), signed by the Department Chair or appropriate organization official, confirming the laboratory space, equipment, and other resources available for the project. Letters of support not requested in the Program Announcement/Funding Opportunity, such as those from members of Congress, do not impact application review or funding decisions.
  - Letters of Collaboration: Provide a signed letter from each collaborating individual or organization that will demonstrate that the PI has the support or resources necessary for the proposed work.
  - Intellectual Property
    - Background and Proprietary Information: All software and data first produced under the award are subject to a Federal purpose license in

accordance with applicable DoD Grant and Agreement Regulations (DoDGAR) requirements. Provide a list of all background intellectual property to be used in the project or provide a statement that none will be used. If applicable, state and identify the proprietary information that will be provided to the Government and indicate whether the applicant will require a waiver of the Federal purpose license.

- Intellectual and Material Property Plan (if applicable): Provide a plan for resolving intellectual and material property issues among participating organizations.
- Commercialization Strategy (if applicable): Describe the commercialization plan. The plan should include intellectual property, market size, financial analysis, strengths and weaknesses, barriers to the market, competitors, and management team. Discuss the significance of this development effort, when it can be anticipated, and the potential commercial use for the technology being developed

- Data and Research Resources Sharing Plan: Describe how data and resources generated during the performance of the project will be shared with the research community. Refer to the General Application Instructions, Appendix 3, Section L for more information about the CDMRP expectations for making data and research resources publicly available.

- **Attachment 3: Technical Abstract (one-page limit): Upload as "TechAbs.pdf."** Use only characters available on a standard QWERTY keyboard. Spell out all Greek letters, other non-English letters, and symbols. Graphics are not allowed.

  The technical abstract is used by all reviewers. Of particular importance, programmatic reviewers typically do not have access to the full application and therefore rely on the technical abstract for appropriate description of the project's key aspects. Therefore, clarity and completeness within the space limits of the technical abstract are highly important.

  Use the outline below:

  - Background: Present the ideas and reasoning behind the proposed work.
  - Objective/Hypothesis: State the objectives/hypothesis(es) to be tested. Provide evidence or rationale that supports the objectives/hypothesis(es).
  - Product: Describe the product to be developed.
  - Specific Aims: State the specific aims of the study.
  - Study Design: Briefly describe the study design including appropriate controls.
  - Impact: Summarize briefly how the proposed project will impact the development of therapeutics for ALS.

- **Attachment 4: Lay Abstract (one-page limit): Upload as "LayAbs.pdf."** Use only characters available on a standard QWERTY keyboard. Spell out all Greek letters, other non-English letters, and symbols. Graphics are not allowed.

  Do not duplicate the technical abstract. The lay abstract is used by all reviewers. Describe the scientific objective and rationale for the proposed project in a manner that will be readily understood by readers without scientific or medical backgrounds.

  Describe the ultimate applicability of the research.

  - What type of ALS patients will it help and how will it help them?
  - What are the potential clinical applications, benefits, and risks?
  - What is the projected time it may take to achieve a patient-related outcome?
  - What are the likely contributions of this study in advancing the development of therapeutics for ALS?

- **Attachment 5: Statement of Work (SOW) (three-page limit): Upload as "SOW.pdf."** The suggested SOW format and examples specific to different types of research projects are available on the eBRAP "Funding Opportunities & Forms" web page (https://ebrap.org/eBRAP/public/Program.htm). For the Therapeutic Development Award mechanism, use the SOW format example titled "SOW for Advanced Tech Development Research." The SOW must be in PDF format prior to attaching. Refer to the General Application Instructions, Section II.C.3., for detailed guidance on creating the SOW.

- **Attachment 6: Impact Statement (one-page limit): Upload as "Impact.pdf."** Explain how the expected results of the study will make an important contribution to ALS therapeutic development. Describe the potential impact of the product on patients' lives.

- **Attachment 7: Transition Plan (one-page limit): Upload as "Transition.pdf."** Describe potential methods and strategies to move the product to the next phase of development/clinical trials after successful completion of the award. The transition plan should include the following components:

  - Outline a funding strategy that could be used to bring the therapy to the next phase of development/clinical trials.
  - Describe collaborations and other resources that could be used to provide continuity of development.
  - Provide a brief schedule and milestones for bringing the therapy to the next phase of development/clinical trials.

- **Attachment 8: Animal Research Plan (three-page limit), if applicable: Upload as "AnimalPlan.pdf."** When the proposed study involves animals, the applicant is required to submit a summary describing the animal research that will be conducted. Applicants should not submit a verbatim replica of the protocol(s) to be

submitted to the IACUC as the Animal Research Plan. The Animal Research Plan should address the following points for each proposed animal study:

- Briefly describe the research objective(s) of the animal study. Explain how and why the animal species, strain, and model(s) being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.
- Summarize the procedures to be conducted. Describe how the study will be controlled.
- Describe the randomization and blinding procedures for the study, and any other measures to be taken to minimize the effects of subjective bias during animal treatment and assessment of results. If randomization and/or blinding will not be utilized, provide justification.
- Provide a sample size estimate for each study arm and the method by which it was derived, including power analysis calculations.
- Describe how data will be handled, including rules for stopping data collection, criteria for inclusion and exclusion of data, how outliers will be defined and handled, statistical methods for data analysis, and identification of the primary endpoint(s).

- **Attachment 9: Collaboration Plan (one-page limit), if applicable: Upload as "Collaboration.pdf."** If a collaborative project is proposed, the applicant must submit a summary of the structure and intent of the collaboration(s). ***Note: Some of the items in the Collaboration Plan may be made available for programmatic review:***
  - Describe the role of each collaborator as part of a working relationship;
  - Explain why the work should be done together rather than through separate efforts;
  - Describe the expertise and resources (physical and process resources or intellectual properties) that each collaborator will bring to the effort and how they are best suited to carry out the proposed research.

- **Attachment 10: Collaborating DoD Military Facility Budget Form(s), if applicable:** Upload as "MFBudget.pdf." If a Military Facility (military health system facility, research laboratory, treatment facility, dental treatment facility, or a DoD activity embedded with a civilian medical center) will be a collaborator in performance of the project, complete the Collaborating DoD Military Facility Budget Form (available for download on the eBRAP "Funding Opportunities & Forms" web page), including a budget justification, for each Military Facility as instructed. Refer to the General Application Instructions, Section II.C.8., for detailed information.

3. **Research & Related Senior/Key Person Profile (Expanded):** Refer to the General Application Instructions, Section II.C.4., for detailed information. ***Note: Some of the items in this attachment may be made available for programmatic review***.

- PI Biographical Sketch (five-page limit): Upload as "Biosketch_LastName.pdf." The suggested biographical sketch format is available on the "Funding Opportunities & Forms" web page (https://ebrap.org/eBRAP/public/Program.htm) in eBRAP. The five-page National Institutes of Health Biographical Sketch may also be used.
- PI Previous/Current/Pending Support (no page limit): Upload as "Support_LastName.pdf."
- Key Personnel Biographical Sketches (five-page limit each): Upload as "Biosketch_LastName.pdf."
- Key Personnel Previous/Current/Pending Support (no page limit): Upload as "Support_LastName.pdf."

4. **Research & Related Budget:** Refer to the General Application Instructions, Section II.C.5., for detailed information.

   - Budget Justification (no page limit): Upload as "BudgetJustification.pdf." The budget justification for the entire period of performance must be uploaded to the Research & Related Budget after completion of the budget for Period 1.

5. **Project/Performance Site Location(s) Form:** Refer to the General Application Instructions, Section II.C.6., for detailed information.

6. **R & R Subaward Budget Attachment(s) Form (if applicable):** Refer to the General Application Instructions, Section II.C.7., for detailed information.

D. Applicant Verification of Grants.gov Submission in eBRAP

Prior to the end of the application verification period, PIs and organizational representatives can review and modify in eBRAP certain components of an application submitted to Grants.gov. Following retrieval and processing of the Grants.gov application, eBRAP will notify the organizational representatives and PI by email to log into eBRAP to review, modify, and verify the Grants.gov application submission. eBRAP will validate retrieved files against the specific Program Announcement/Funding Opportunity requirements and discrepancies will be noted in both the email and in the Full Application Files tab in eBRAP. eBRAP does not confirm the accuracy of file content. It is the applicant's responsibility to review all application components and ensure proper ordering as specified in the Program Announcement/Funding Opportunity. ***If either the Project Narrative or the budget fails eBRAP validation, an updated Grants.gov application package must be submitted via Grants.gov as a "Changed/Corrected Application" with the previous Grants.gov Tracking ID prior to the application submission deadline.*** The Project Narrative and Budget Form cannot be changed after the application submission deadline.

E. Submission Dates and Times

All submission dates and times are indicated on the title page of this Program Announcement/ Funding Opportunity. Pre-application and application submissions are required. Failure to meet either of these deadlines will result in application rejection.

F. Other Submission Requirements

Refer to the General Application Instructions, Appendix 2, for detailed formatting guidelines.

All applications must be submitted through Grants.gov. Applicant organizations and all subrecipient organizations must have a DUNS number to submit applications to Grants.gov. The applicant organization must also be registered in the Entity Management functional area of the SAM with an "Active" status to submit applications through the Grants.gov portal. Refer to the General Application Instructions, Section II.A., for information on Grants.gov registration requirements.

III. APPLICATION REVIEW INFORMATION

A. Application Review and Selection Process

All applicants are evaluated by scientists, clinicians, and consumer advocates using a two-tier review process. The first tier is peer review of applications against established criteria for determining technical merit. The second tier is a programmatic review that makes recommendations for funding to the DHA RDA Directorate and the Office of the Assistant Secretary of Defense for Health Affairs, based on (a) technical merit and (b) the relevance to the mission of the DHP and ALSRP, and to the specific intent of the award mechanism. The highest-scoring applications from the first tier of review are not automatically recommended for funding. Additional information about the two-tier process used by the CDMRP can be found at http://cdmrp.army.mil/about/fundingprocess.

All CDMRP review processes are conducted confidentially to maintain the integrity of the merit-based selection process. Panel members sign a nondisclosure statement that application and evaluation information will not be disclosed outside the panel. Violations of confidentiality can result in the dissolving of a panel(s) and other corrective actions. In addition, personnel at the applicant or collaborating organizations are prohibited from contacting persons involved in the review process to gain protected evaluation information or to influence the evaluation process. Violations of these prohibitions will result in the administrative withdrawal of the organization's application. Violations by panel members or applicants that compromise the confidentiality of the review process may also result in suspension or debarment from Federal awards. Furthermore, the unauthorized disclosure of confidential information of one party to another third party is a crime in accordance with Title 18 United States Code 1905.

B. Application Review Process

1. **Peer Review:** To determine technical merit, all applications will be evaluated according to the following **scored** criteria, which are of **equal importance**:

    - **Background (preliminary data are required)**
        - How strongly the presented background data demonstrates that the proposed therapeutic approach is ready for advanced preclinical development;

- How well the presentation of background data support the putative mechanism of action as a viable therapeutic approach;
- Is/are the lead molecule(s) specifically identified;
- How well the data presented demonstrate proof of identity and purity of the lead(s) (For small molecules, typically >95% by NMR, LC-MS, melting point, etc., with no single impurity >0.5%. For biologics, often by HPLC, LC-MS, immunochemistry, amino acid analysis, etc.);
- For any proposed development or validation of existing biomarkers: How well the rationale and background data support the hypothesis that the proposed biomarkers will reflect disease progression or action of candidate therapeutics on specific mechanistic targets.

- **Objectives and Specific Aims**
  - How well the project's objectives and specific aims are developed and extent to which they support the proposed outcome.
- **Research Strategy**
  - How well the experimental design, methods, and analyses including statistical analyses support the study outcomes;
  - The extent to which the study is product-driven;
  - The extent to which the preclinical models described in the proposal are appropriate and well developed.
  - How well the applicant identifies potential problems and addresses alternative approaches.

  If appropriate to the proposed phase of development:
  - How appropriate, available, and well developed the described primary and secondary in vitro bioactivity assays are for optimization or structure-activity relationship studies;
  - How appropriate, available, and well developed the described target engagement and selectivity and assays are for measurement of desirable activity at the intended target, for assessing artifacts, and for assessing the potential for undesirable activities at related but unintended targets;
  - How feasible are the outlined chemical synthetic pathways for modification of lead compounds or the formulation of potential delivery systems and are they based on rational design.

  For studies involving animal research:
  - How well the animal study (or studies) is designed to achieve the objectives, including the relevance of model and endpoints/outcome measures to be used;
  - The extent to which the study (or studies) is designed to achieve reproducible and rigorous results, including controls, sample size estimation, blinding, randomization, and data handling;

For research involving collaborations:

- The degree to which the proposed working relationship described in the Collaboration Plan suggests effective communication and appropriate working relationships between partners;
- How well described the contribution of resources or property from collaborating partners is described and the extent to which this contribution may be expected to facilitate successful attainment of project objectives.

- **Impact and Translational Potential**
  - The extent to which this study might be expected to impact the development of therapeutics for ALS (applications should be assessed for both long and short term impact);
  - How and to what extent the therapeutic(s) will have a potential impact on patients' lives, and the quality and feasibility of the Transition Plan.
- **Personnel**
  - How appropriate research team members' backgrounds and expertise are for development of the proposed product and conduct of the proposed research;
  - How appropriate the proposed levels of effort are for the successful development of the proposed product.

In addition, the following unscored criteria will also contribute to the overall evaluation of the application:

- **Environment**
  - The appropriateness of the scientific environment for the proposed research;
  - Whether the research requirements are supported adequately by the availability of and accessibility to facilities and resources (including collaborative arrangements);
  - The quality and extent of organizational support, including the ability to support the therapy for the next level of clinical trials/development;
  - If multi-organizational, the quality and completeness of the Intellectual and Material Property Plan.
- **Budget**
  - Whether the budget is appropriate for the proposed research and within the limitations of this Program Announcement/Funding Opportunity.
- **Application Presentation**

  To what extent the writing, clarity, and presentation of the application components influence the review.

2. **Programmatic Review:** To make funding recommendations and select the application(s) that, individually or collectively, will best achieve the program objectives, the following **equally considered** criteria are used by programmatic reviewers:

   a. **Ratings and evaluations of the peer reviewers**

   b. **Relevance to the mission of the DHP and FY15 ALSRP, as evidenced by the following:**

      - Program portfolio composition
      - Adherence to the intent of the award mechanism
      - Programmatic relevance
      - Relative impact

C. Recipient Qualification

For general information on required qualifications for award recipients, refer to the General Application Instructions, Appendix 1.

D. Application Review Dates

All application review dates and times are indicated on the title page of this Program Announcement/Funding Opportunity.

E. Notification of Application Review Results

Each PI and organization will receive email notification of posting of the funding recommendation in eBRAP. Each PI will receive a peer review summary statement on the strengths and weaknesses of the application.

IV. ADMINISTRATIVE ACTIONS

After receipt of pre-applications from eBRAP or applications from Grants.gov, the following administrative actions may occur:

A. Rejection

The following will result in administrative rejection of the pre-application:

- Preproposal Narrative is missing.

The following will result in administrative rejection of the application:

- Submission of an application for which a letter of invitation was not received.
- Project Narrative is missing.
- Project Narrative exceeds page limit.

- Budget is missing.
- Submission of the same research project to different Funding Opportunities within the same program and fiscal year.

B. Modification

- Pages exceeding the specific limits will be removed prior to review for all documents other than the Project Narrative.
- Documents not requested will be removed.

C. Withdrawal

The following may result in administrative withdrawal of the pre-application or full application:

- A FY15 ALSRP IP member is named as being involved in the research proposed or is found to have assisted in the pre-application or application processes including, but not limited to, concept design, application development, budget preparation, and the development of any supporting documentation. A list of the FY15 ALSRP IP members can be found at http://cdmrp.army.mil/alsrp/panels/panels15.
- The application fails to conform to this Program Announcement/Funding Opportunity description to the extent that appropriate review cannot be conducted.
- Inclusion of URLs, with the exception of links in References Cited and Publication and/or Patent Abstract sections.
- Page size is larger than 8.5 inches x 11.0 inches (approximately 21.59 cm x 27.94 cm).
- Inclusion of any employee of CDMRP review contractors in applications for funding without adequate plans to mitigate conflicts of interest. Refer to the General Application Instructions, Section II.B., for detailed information.
- Personnel from applicant or collaborating organizations are found to have contacted persons involved in the review process to gain protected evaluation information or to influence the evaluation process.
- The PI does not meet the eligibility criteria.
- The application is or includes a clinical trial.

D. Withhold

Applications that appear to involve research misconduct will be administratively withheld from further consideration pending institutional investigation. The institution will be required to provide the findings of the investigation to the USAMRAA Grants Officer for a determination of the final disposition of the application.

V. AWARD ADMINISTRATION INFORMATION

A. Award Notice

Awards will be made no later than September 30, 2016. Refer to the General Application Instructions, Appendix 3, for additional award administration information.

Any assistance instrument awarded under this Program Announcement/Funding Opportunity will be governed by the award terms and conditions, which conform to DoD's implementation of the Office of Management and Budget (OMB) circulars applicable to financial assistance. Terms and conditions of new awards made after December 26, 2014 may include revisions to reflect DoD implementation of new OMB guidance in the Code of Federal Regulations, Title 2, Part 200, "Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards" (2 CFR part 200).

B. Administrative Requirements

Refer to the General Application Instructions, Appendix 3 for general information regarding administrative requirements.

C. National Policy Requirements

Refer to the General Application Instructions, Appendix 4 for general information regarding national policy requirements.

D. Reporting

Refer to the General Application Instructions, Appendix 3, Section J, for general information on reporting requirements. .

E. Award Transfers

Changes in PI are not allowed, except under extenuating circumstances that will be evaluated on a case-by-case basis and at the discretion of the Grants Officer.

Refer to the General Application Instructions, Appendix 3, Section M, for general information on organization or PI changes.

VI. AGENCY CONTACTS

A. CDMRP Help Desk

Questions related to Program Announcement/Funding Opportunity content or submission requirements as well as questions related to the submission of the pre-application through eBRAP should be directed to the CDMRP Help Desk, which is available Monday through Friday from 8:00 a.m. to 5:00 p.m. ET. Response times may vary depending upon the volume of inquiries.

Phone: 301-682-5507

Email: help@eBRAP.org

B. Grants.gov Contact Center

Questions related to application submission through Grants.gov portal should be directed to the Grants.gov Contact Center, which is available 24 hours a day, 7 days a week (closed on U.S. Federal holidays). Note that the CDMRP Help Desk is unable to provide technical assistance with Grants.gov submission.

Phone: 800-518-4726

Email: support@grants.gov

Sign up on Grants.gov for "send me change notification emails" by following the link on the Synopsis page for the Program Announcement/Funding Opportunity or by responding to the prompt provided by Grants.gov when first downloading the Grants.gov application package. If the Grants.gov application package is updated or changed, the original version of the application package may not be accepted by Grants.gov.

VII. APPLICATION SUBMISSION CHECKLIST

Grants.gov Application Components	Upload Order	Action	Completed
SF-424 (R&R) Application for Federal Assistance		Complete form as instructed.	
Attachments Form	1	Project Narrative: Upload as Attachment 1 with file name "ProjectNarrative.pdf."	
	2	Supporting Documentation: Upload as Attachment 2 with file name "Support.pdf."	
	3	Technical Abstract: Upload as Attachment 3 with file name "TechAbs.pdf."	
	4	Lay Abstract: Upload as Attachment 4 with file name "LayAbs.pdf."	
	5	Statement of Work: Upload as Attachment 5 with file name "SOW.pdf."	
	6	Impact/Transition Statement: Upload as Attachment 6 with file name "Impact.pdf."	
	7	Innovation Statement: Upload as Attachment 7 with file name "Innovation.pdf."	
	8	Animal Research Plan: Upload as Attachment 8 with file name "AnimalPlan.pdf" if applicable.	
	9	Collaboration Plan: Upload as Attachment 9 with file name "CollaborationPlan.pdf" if applicable.	
	10	Collaborating DoD Military Facility Budget Form(s): Upload as Attachment 10 with file name "MFBudget.pdf," if applicable.	
Research & Related Senior/Key Person Profile (Expanded)		Attach PI Biographical Sketch (Biosketch_LastName.pdf) to the appropriate field.	
		Attach PI Previous/Current/Pending Support (Support_LastName.pdf) to the appropriate field.	
		Attach Biographical Sketch (Biosketch_LastName.pdf) for each senior/key person to the appropriate field.	
		Attach Previous/Current/Pending (Support_LastName.pdf) for each senior/key person to the appropriate field.	
Research & Related Budget		Complete as instructed. Attach Budget Justification (BudgetJustification.pdf) to the appropriate field.	
Project/Performance Site Location(s) Form		Complete form as instructed.	
R & R Subaward Budget Attachment(s) Form		Complete form as instructed.	
Confidential Letters of Recommendation		Confirm upload to eBRAP.	