I. OVERVIEW OF THE FUNDING OPPORTUNITY

Program Announcement for the Department of Defense

Defense Health Program

Congressionally Directed Medical Research Programs

Amyotrophic Lateral Sclerosis Research Program

Therapeutic Idea Award

Announcement Type: Modification

Funding Opportunity Number: W81XWH-20-ALSRP-TIA

Catalog of Federal Domestic Assistance Number: 12.420 Military Medical
Research and Development

SUBMISSION AND REVIEW DATES AND TIMES

- **Pre-Application Submission Deadline:** 5:00 p.m. Eastern time (ET), April 15, 2020

- **Invitation to Submit an Application:** May 2020

- **Application Submission Deadline:** 11:59 p.m. ET, July 30, 2020

- **End of Application Verification Period:** 5:00 p.m. ET, August 4, 2020

- **Peer Review:** September 2020

- **Programmatic Review:** November 2020

This Program Announcement must be read in conjunction with the General Application Instructions, version 501. The General Application Instructions document is available for downloading from the Grants.gov funding opportunity announcement by selecting the "Package" tab, clicking "Preview," and then selecting "Download Instructions."

TABLE OF CONTENTS

II. DETAILED INFORMATION ABOUT THE FUNDING OPPORTUNITY

II.A. Program Description

Applications to the Fiscal Year 2020 (FY20) Amyotrophic Lateral Sclerosis Research Program (ALSRP) are being solicited for the Defense Health Agency (DHA) J9, Research and Development Directorate, by the U.S. Army Medical Research Acquisition Activity (USAMRAA) using delegated authority provided by United States Code, Title 10, Section 2358 (10 USC 2358). As directed by the Office of the Assistant Secretary of Defense for Health Affairs (OASD[HA]), the DHA manages the Defense Health Program (DHP) Research, Development, Test, and Evaluation (RDT&E) appropriation. The execution management agent for this Program Announcement 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 FY19 totaled $89.4 million (M). The FY20 appropriation is $20M.

The proposed research must be relevant to active duty Service members, Veterans, military beneficiaries, and/or the American public.

II.B. Award Information

The FY20 ALSRP Therapeutic Idea Award supports hypothesis-driven therapeutic development and is designed to promote new ideas aimed at drug or treatment discovery that are still in the early stages of development. Development and/or modification of preclinical model systems or the application of high-throughput screens to define or assess lead compounds for ALS treatment may also be proposed. All research projects should include a well-formulated, testable hypothesis based on strong scientific rationale that holds translational potential to improve ALS treatment and/or advance a novel treatment modality. Preliminary data are not required. While the inclusion of preliminary data is not prohibited, the strength of the application should not rely on preliminary data, but on the innovative approach.

Projects that focus primarily on investigating the pathophysiology of ALS, without consideration of therapeutic development, are not within the scope of this Funding Opportunity.

Innovation and impact are important aspects of the Therapeutic Idea Award. Research deemed innovative may introduce a new paradigm, challenge current paradigms, introduce novel concepts or technologies, or exhibit other uniquely creative qualities that may lead to potential therapeutics for ALS. Impact may be near-term or long-term, but must be significant and move beyond an incremental advancement.

The Therapeutic Idea Award encourages applications submitted by early career investigators as well as applications that include meaningful and productive collaborations between investigators. Applicants from outside the ALS research field are encouraged to include collaborators with the

necessary relevant expertise, such as experience with ALS model systems, endpoints, and pathogenic findings.

Identification of treatment approaches using biological correlates of disease activity and progression in pre-existing, de-identified human specimens from well-characterized, adequately controlled, and sufficiently powered patient cohorts is encouraged. Examples of acceptable sources for pre-existing biosamples or datasets include controlled clinical trials, observational studies, publicly available biorepositories, and registries (e.g., Centers for Disease Control and Prevention [CDC] National ALS Registry and/or Biorepository; https://www.cdc.gov/als/Default.html). Active duty military and/or Veteran patient populations or resources should be considered. A list of suitable resources can be found on the ALSRP web page (https://cdmrp.army.mil/alsrp/resources/ALSRPresources). Other resources may be used, provided a letter of support adequately describes the relevant repository parameters and mechanisms for broad access to data and samples. **All specimens must exist at the time of application submission; collection of new specimens will not be supported**.

Therapeutically Relevant Biomarker Option: The FY20 ALSRP Therapeutic Idea Award Therapeutically Relevant Biomarker Option encourages applicants to include the development of biomarker(s) in parallel with the main proposed Therapeutic Idea Award research effort. Additional funding, as described in Section II.D.5, Funding Restrictions, is being offered for the co-development of biomarkers that will enhance the drug development process. Efforts may include development of target engagement biomarkers, objective pharmacodynamic biomarkers to measure the biological effect of an investigational therapeutic, or predictive/cohort-selective biomarkers that indicate whether a specific therapy will be effective in an individual patient or patient subgroup. Development of markers for the purposes of diagnosis, prognosis, or measurement of disease progression without consideration of the therapeutic development process will not be supported.

To apply for this option, applicants must clearly describe the marker and its potential to improve the efficacy of the therapeutic development process. For further description, see Section II.D.2.b.ii, Full Application Submission Components. Before preparing the Therapeutically Relevant Biomarker Statement, applicants are encouraged to review the draft guidance issued by the FDA, "Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment," as well as the patient-focused document developed by the ALS community, "Drug Development for Amyotrophic Lateral Sclerosis Guidance for Industry," which provides direction beyond the FDA guidance and includes the community consensus on key therapeutic development topics.

For further information on biomarker types, qualifications, and use in ALS clinical trials, it is recommended that applicants consult the following resources:

- van den Berg LH, Sorenson E, Gronseth G, et al. 2019. Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials. *Neurology 92*(14):e1610-e1623. https://n.neurology.org/content/92/14/e1610

- Biomarker Qualification: Evidentiary Framework. US FDA Draft Guidance for Industry. 2018. https://www.regulations.gov/contentStreamer?documentId=FDA-2018-D-4267-0002&attachmentNumber=1&contentType=pdf

- Benatar M, Boylan K, Jeromin A, et al. 2016. ALS biomarkers for therapy development: state of the field and future directions. *Muscle Nerve* 53(2):169-182. https://doi.org/10.1002/mus.24979

Applicants seeking support for the development of products beyond drug or treatment discovery should consider the FY20 ALSRP Therapeutic Development Award (Funding Opportunity Number: W81XWH-20-ALSRP-TDA), which supports advanced preclinical development activities (https://cdmrp.army.mil/funding/alsrp).

The types of awards made under the Program Announcement will be assistance agreements. An assistance agreement is appropriate when the Federal Government transfers a "thing of value" to a "state, local government," or "other recipient" to carry out a public purpose of support or stimulation authorized by a law of the United States instead of acquiring property or service for the direct benefit and use of the U.S. Government. An assistance agreement can take the form of a grant or cooperative agreement. The level of involvement on the part of the Department of Defense (DoD) during project performance is the key factor in determining whether to award a grant or cooperative agreement. If "no substantial involvement" on the part of the funding agency is anticipated, a grant award will be made (31 USC 6304). Conversely, if substantial involvement on the part of the funding agency is anticipated, a cooperative agreement will be made (31 USC 6305), and the award will identify the specific substantial involvement. Substantial involvement may include collaboration, participation, or intervention in the research to be performed under the award. The award type, along with the start date, will be determined during the negotiation process.

The anticipated direct costs budgeted for the entire period of performance for an FY20 ALSRP Therapeutic Idea Award will not exceed **$500,000**. The anticipated direct costs budgeted for the entire period of performance for an FY20 ALSRP Therapeutic Idea Award with the Therapeutically Relevant Biomarker Option will not exceed **$600,000**. Refer to Section II.D.5, Funding Restrictions, for detailed funding information.

Awards will be made no later than September 30, 2021. For additional information refer to Section II.F.1, Federal Award Notices.

The CDMRP expects to allot approximately $12.8M to fund approximately 16 Therapeutic Idea Award applications. Funding of applications received is contingent upon the availability of Federal funds for this program as well as the number of applications received, the quality and merit of the applications as evaluated by scientific and programmatic review, and the requirements of the Government. Funds to be obligated on any award resulting from this funding opportunity will be available for use for a limited time period based on the fiscal year of the funds. It is anticipated that awards made from this FY20 funding opportunity will be funded with FY20 funds, which will expire for use on September 30, 2026.

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 SC, 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). While these

standards are written for preclinical studies, the basic principles of randomization, blinding, sample-size estimation, and data handling derive from well-established best practices in clinical studies. Projects that include research on animal models are required to submit Attachment 10, 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.

Guidelines for the Use of ALS Animal Models: Many factors must be considered in the design of studies using animal models of ALS. A number of investigators and organizations have published guidelines and recommendations for the design of ALS animal model studies. Applicants are strongly encouraged to become familiar with the concepts presented in the articles listed below and to incorporate recommendations contained therein in their study designs. While most of the recommendations pertain to the SOD1-G93A transgenic mouse model, many general concepts for using animal models for ALS research are also described, including the following:

- Ludolph AC, Bendotti C, Blaugrund E, et al. 2010. Guidelines for preclinical animal research in ALS/MND: A consensus meeting. *Amyotroph Lateral Scler Frontotemporal Degener* 11(1-2):38-45. http://dx.doi.org/10.3109/17482960903545334

- Scott S, Kranz JE, Cole J, et al. 2008. Design, power, and interpretation of studies in the standard murine model of ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 9(1):4-15. http://dx.doi.org/10.1080/17482960701856300

- Ludolph AC, Bendotti C, Blaugrund E, et al. 2007. Guidelines for the preclinical *in vivo* evaluation of pharmacological active drugs for ALS/MND: Report on the 142nd ENMC International Workshop. *Amyotroph Lateral Scler Frontotemporal Degener* 8(4):217-223. http://dx.doi.org/10.1080/17482960701292837

The CDMRP intends that information, data, and research resources generated under awards funded by this Program Announcement 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 2, Section K.

Research Involving Human Anatomical Substances, Human Subjects, or Human Cadavers: All DoD-funded research involving new and ongoing research with human anatomical substances, human subjects, or human cadavers must be reviewed and approved by the U.S. Army Medical Research and Development Command (USAMRDC) Office of Research Protections (ORP), Human Research Protection Office (HRPO), prior to research implementation. This administrative review requirement is in addition to the local Institutional Review Board (IRB) or Ethics Committee (EC) review. Local IRB/EC approval at the time of submission is *not* required. ***Allow a minimum of 2 to 3 months for HRPO regulatory review and approval processes***. Refer to the General Application Instructions, Appendix 1, and the Human Subject Resource Document available on the electronic Biomedical Research Application Portal (eBRAP) "Funding Opportunities & Forms" web page (https://ebrap.org/eBRAP/public/Program.htm) for additional information.

Use of DoD or Department of Veterans Affairs (VA) Resources: If the proposed research involves access to active duty military patient populations and/or DoD resources or databases, the application must describe the access at the time of submission and include a plan for maintaining access as needed throughout the proposed research. Refer to Section II.D.2.b.ii, Full Application Submission Components, for detailed information. Refer to the General Application Instructions, Appendix 1, for additional information.

Research Involving Animals: All DoD-funded research involving new and ongoing research with animals must be reviewed and approved by the USAMRDC 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. ***Allow at least 3 to 4 months for ACURO regulatory review and approval processes for animal studies.*** Refer to the General Application Instructions, Appendix 1, for additional information.

II.C. Eligibility Information

II.C.1. Eligible Applicants

II.C.1.a. Organization: All organizations, including international organizations, are eligible to apply.

Government Agencies Within the United States: Local, state, and Federal Government agencies are eligible to the extent that applications do not overlap with their fully funded internal programs. Such agencies are required to explain how their applications do not overlap with their internal programs.

As applications for this Program Announcement may be submitted by extramural and intramural organizations, these terms are defined below.

Extramural Organization: An eligible non-DoD organization. Examples of extramural organizations include academic institutions, biotechnology companies, foundations, Federal Government organization other than the DoD, and research institutes.

Intramural DoD Organization: A DoD laboratory, DoD military treatment facility, and/or DoD activity embedded within a civilian medical center. ***Intramural Submission: Application submitted by a DoD organization for an intramural investigator working within a DoD laboratory or Military Treatment Facility or in a DoD activity embedded within a civilian medical center.***

USAMRAA makes awards to eligible organizations, not to individuals.

II.C.1.b. Principal Investigator

Independent investigators at all academic levels (or equivalent) are eligible to be named as Principal Investigator (PI).

Early career investigators (defined as independent, non-mentored investigators within 5 years of their last training position e.g., postdoctoral fellowship, medical residency, clinical fellowship as of the application submission deadline) are encouraged to apply.

An eligible PI, regardless of ethnicity, nationality, or citizenship status, must be employed by, or affiliated with, an eligible organization.

The CDMRP encourages all PIs to participate in a digital identifier initiative through Open Researcher and Contributor ID, Inc. (ORCID). Registration for a unique ORCID identifier can be done online at https://orcid.org/.

II.C.2. Cost Sharing

Cost sharing/matching is not an eligibility requirement.

II.C.3. Other

Organizations must be able to access **.gov** and **.mil** websites in order to fulfill the financial and technical deliverable requirements of the award and submit invoices for payment.

There are no limitations on the number of applications for which an investigator may be named as a PI.

For general information on required qualifications for award recipients, refer to the General Application Instructions, Appendix 3.

Refer to Section II.H.2, Administrative Actions, for a list of administrative actions that may be taken if a pre-application or application does not meet the administrative, eligibility, or ethical requirements defined in this Program Announcement.

II.D. Application and 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(s).

Extramural Submission:

- Pre-application content and forms must be accessed and submitted at eBRAP.org.

- Full application packages must be accessed and submitted at Grants.gov.

Intramural DoD Submission:

- Pre-application content and forms must be accessed and submitted at eBRAP.org.

- Full application packages must be accessed and submitted at eBRAP.org.

Note: Applications from an intramural DoD organization or from an extramural Federal Government organization may be submitted to Grants.gov through a research foundation.

II.D.1. Address to Request Application Package

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.

Contact information for the CDMRP Help Desk and the Grants.gov Contact Center can be found in Section II.G, Federal Awarding Agency Contacts.

II.D.2. Content and Form of the Application Submission

Submission is a two-step process requiring both *pre-application* (eBRAP.org) and *full application* (eBRAP.org or Grants.gov) as indicated below. The submission process should be started early to avoid missing deadlines. There are no grace periods. Full application submission guidelines differ for extramural (Grants.gov) and intramural (eBRAP.org) organizations (refer to Table 1. Full Application Guidelines).

The application title, eBRAP log number, and all information for the PI, Business Official(s), performing organization, and contracting organization must be consistent throughout the entire pre-application and full application submission process. Inconsistencies may delay application processing and limit or negate the ability to view, modify, and verify the application in eBRAP. If any changes need to be made, the applicant should contact the CDMRP Help Desk at help@eBRAP.org or 301-682-5507 prior to the application submission deadline.

II.D.2.a. Step 1: Pre-Application Submission Content

During the pre-application process, eBRAP assigns each submission a unique log number. This unique eBRAP log number is required during the full application submission process.

To begin the pre-application process, first select whether the submitting organization is extramural or intramural, then confirm your selection or cancel. **Incorrect selection of extramural or intramural submission type will delay processing.**

If an error has been made in the selection of extramural versus intramural and the pre-application submission deadline has passed, the PI or Business Official must contact the CDMRP Help Desk at help@eBRAP.org or 301-682-5507 to request a change in designation.

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.

The applicant organization and associated PI 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.

PIs with an ORCID identifier should enter that information in the appropriate field in the "My Profile" tab in the "Account Information" section of eBRAP.

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):

- **Tab 1 – Application Information**

  Submission of application information includes assignment of primary and secondary research classification codes, which may be found at https://ebrap.org/eBRAP/public/Program.htm. Applicants are strongly encouraged to review and confirm the codes prior to making their selection.

- **Tab 2 – Application Contacts**

  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 SF424 Research & Related Form). The Business Official must be either selected from the eBRAP list or invited in order for the pre-application to be submitted.

  Select the performing organization (site at which the PI will perform the proposed work) and the contracting organization (organization submitting on behalf of the PI, which corresponds to Block 5 on the Grants.gov SF424 Research & Related Form), and click on "Add Organizations to this Pre-application." The organization(s) must be either selected from the eBRAP drop-down 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.

- **Tab 3 – Collaborators and Key Personnel**

  Enter the name, organization, and role of all collaborators and key personnel associated with the application.

  FY20 ALSRP Programmatic Panel members should not be involved in any pre-application or application. For questions related to panel members and pre-applications or applications, refer to Section II.H.2.c, Withdrawal, or contact the CDMRP Help Desk at help@eBRAP.org or 301-682-5507.

- **Tab 4 – Conflicts of Interest**

  List all individuals other than collaborators and key personnel who may have a conflict of interest in the review of the application (including those with whom the PI has a personal or professional relationship).

- **Tab 5 – Pre-Application Files**

  Note: Upload documents 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) 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 Feasibility:** Concisely state the project's objectives and specific aims. State the ideas and reasoning on which the proposed work is based. Explain the rationale for selecting the specific target(s) for investigation and the feasibility of the study leading to a therapy for ALS.

  - **Innovation:** Describe how the project may introduce a new paradigm, challenge current paradigms, introduce novel concepts or agents, or exhibit other uniquely creative qualities that may lead to potential therapeutics for ALS.

  - **Impact:** State explicitly how the proposed work will have an impact on the development of therapeutics for ALS. Outline, in general terms, steps to transition the study outcomes to therapeutic application.

  - **For pre-applications submitted under the Therapeutically Relevant Biomarker Option:** Describe how the proposed marker will demonstrate target engagement, predicts whether the proposed treatment will be effective in an individual patient or patient subgroup, and/or clarify biological impact of a potential therapeutic. Given the early nature of Therapeutic Idea Award projects, preliminary biomarker characterization that considers qualification criteria described in relevant ALS biomarker literature should be discussed.

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

  - **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, reference title, and reference source, including 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):** *All biographical sketches should be uploaded as a single combined file.* Biographical sketches, including those for early career investigators and collaborators, should demonstrate background and expertise through education, positions, publications, and previous work accomplished.

- **Tab 6 – Submit Pre-Application**

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 Feasibility:** How well the scientific rationale supports the project objectives, specific aims, and feasibility.

  ○ **Innovation:** How well the project introduces a new paradigm, challenges current paradigms, introduces novel concepts or agents, or exhibits other uniquely creative qualities that may lead to potential therapeutics for ALS.

  ○ **Impact:** Whether the proposed work will have an impact on the development of therapeutics for ALS. Evidence of an outline for transition of study outcomes to therapeutic application.

  ○ **Personnel:** How appropriate the qualifications of the PI and key personnel are for performing the proposed research project. Early career investigators and collaborative proposals are encouraged. If the applicant is from outside the ALS research field, whether the proposal includes collaborators with the necessary relevant expertise, such as experience with ALS model systems, endpoints, and pathogenic findings.

  ○ **For pre-applications submitted under the Therapeutically Relevant Biomarker Option:** To what extent the proposed biomarker(s) will indicate target engagement, the biological effect of the potential therapeutic for which it is being developed, and/or predicts whether a specific therapeutic will be effective in an individual patient or patient subgroup. How well the preliminary biomarker characterization considers qualification criteria described in relevant ALS biomarker literature.

- **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 detailed feedback (e.g., a formal critique of strengths and weaknesses) on their pre-application. The estimated timeframe for notification of invitation to submit an application is indicated in Section I, Overview of the Funding Opportunity. Invitations to submit a full application are based on the Pre-Application Screening Criteria listed above.

II.D.2.b. Step 2: Full Application Submission Content

Applications will not be accepted unless notification of invitation has been received.

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 full application package for this Program Announcement. The full application package is submitted by the Authorized Organizational Representative through Grants.gov (https://www.grants.gov/) for extramural organizations or through eBRAP (https://ebrap.org/) for intramural organizations. See Table 1 below for more specific guidelines.

II.D.2.b.i. Full Application Guidelines

Extramural organizations must submit full applications through Grants.gov. Applicants must create a Grants.gov Workspace for submission, which allows the application components to be completed online and routed through the applicant organization for review prior to submission. Applicants may choose to download and save individual PDF forms rather than filling out webforms in Workspace. A compatible version of Adobe Reader **must** be used to view, complete, and submit an application package consisting of PDF forms. If more than one person is entering text into an application package, the ***same version*** of Adobe Reader software should be used by each person. Check the version number of the Adobe software on each user's computer to make sure the versions match. Using different versions of Adobe Reader may cause submission and/or save errors – even if each version is individually compatible with Grants.gov. Refer to the General Application Instructions, Section III, and the "Apply For Grants" page of Grants.gov (https://www.grants.gov/web/grants/applicants/apply-for-grants.html) for further information about the Grants.gov Workspace submission process. Submissions of extramural applications through eBRAP may be withdrawn.

Do not password protect any files of the application package, including Project Narrative.

Table 1. Full Application Submission Guidelines

Extramural Submissions	Intramural DoD Submissions
Application Package Location	
Download application package components for W81XWH-20-ALSRP-TIA from Grants.gov (https://www.grants.gov) and create a Grants.gov Workspace. Workspace allows online completion of the application components and routing of the application package through the applicant organization for review prior to submission.	Download application package components for W81XWH-20-ALSRP-TIA from eBRAP (https://ebrap.org).
Full Application Package Components	
SF424 Research & Related Application for Federal Assistance Form: Refer to the General Application Instructions, Section III.A.1, for detailed information.	**Tab 1 – Summary:** Provide a summary of the application information. **Tab 2 – Application Contacts:** This tab will be pre-populated by eBRAP; add Authorized Organizational Representative.
Descriptions of each required file can be found under Full Application Submission Components: • Attachments • Research & Related Personal Data • Research & Related Senior/Key Person Profile (Expanded) • Research & Related Budget • Project/Performance Site Location(s) Form • *(if applicable)* Research & Related Subaward Budget Attachment(s) Form	**Tab 3 – Full Application Files:** Upload files under each Application Component in eBRAP. Descriptions of each required file can be found under Full Application Submission Components: • Attachments • Key Personnel • Budget • Performance Sites **Tab 4 – Application and Budget Data:** Review and edit proposed project start date, proposed end date, and budget data pre-populated from the Budget Form.
Application Package Submission	
Create a Grants.gov Workspace. Add participants (investigators and Business Officials) to Workspace, complete all required forms, and check for errors before submission. **Submit a Grants.gov Workspace Package.** An application may be submitted through Workspace by clicking the "Sign and Submit" button on the "Manage Workspace" page, under the "Forms" tab. Grants.gov recommends submission of the application package **at least 24-48 hours prior to the close date** to allow time	**Submit package components to eBRAP (https://ebrap.org).** **Tab 5 – Submit/Request Approval Full Application:** After all components are uploaded and prior to the full application submission deadline, enter your password in the space provided next to "Enter Your Password Here" and press the "Submit Full Application" button. eBRAP will notify your Resource Manager/ Comptroller/Task Area Manager or equivalent Business Official by email.

Extramural Submissions	Intramural DoD Submissions
to correct any potential technical issues that may disrupt the application submission. **Note:** If either the Project Narrative or the budget fails eBRAP validation or if the Project Narrative or the budget 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.	
[Application Verification Period](#)	
The full application package submitted to Grants.gov may be viewed and modified in eBRAP until the end of the application verification period. During the application verification period, the full application package may be modified *with the exception of the Project Narrative and Research & Related Budget Form*.	After eBRAP has processed the full application, the organizational Resource Manager/Comptroller/ Task Area Manager or equivalent Business Official and PI will receive email notification of this status and will be able to view and modify application components in eBRAP. During the application verification period, the full application package may be modified *with the exception of the Project Narrative and Research & Related Budget Form*. Your Resource Manager/ Comptroller/Task Area Manager or equivalent Business Official should log into eBRAP to review and to approve prior to the application verification deadline.
Further Information	
Tracking a Grants.gov Workspace Package. After successfully submitting a Workspace package, a Grants.gov Tracking Number is automatically assigned to the package. The number will be listed on the "Confirmation" page that is generated after submission. Refer to the General Application Instructions, Section III, for further information regarding Grants.gov requirements.	Refer to the General Application Instructions, Section IV, for further information regarding eBRAP requirements.

The full application package must be submitted using the unique eBRAP log number to avoid delays in application processing.

II.D.2.b.ii. Full Application Submission Components

- **Extramural Applications Only**

  SF424 Research & Related Application for Federal Assistance Form: Refer to the General Application Instructions, Section III.A.1, for detailed information.

- **Extramural and Intramural Applications**

  Attachments:

  Each attachment to the full application components must be uploaded as an individual file in the format specified and in accordance with the formatting guidelines listed in the General Application Instructions, Appendix 4.

  For all attachments, ensure that the file names are consistent with the guidance. Attachments will be rejected if the file names are longer than 50 characters or have incorrect file names that contain characters other than the following: A-Z, a-z, 0-9, underscore, hyphen, space, and period. In addition, there are file size limits that may apply in some circumstances. Individual attachments may not exceed 20 MB, and the file size for the entire full application package may not exceed 200 MB. *It is important to include the attachment name as a header on each page of the attachment files.*

  ○ **Attachment 1: Project Narrative (12-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) 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.

    The Project Narrative should be structured in accordance with the outline below. If necessary, additional subheadings may be used.

    – **Background:** Present the ideas and reasoning behind the proposed work. Explain the rationale for believing that the specific targets chosen for investigation will lead to a therapy and how feasibility is enhanced by exploitation of pathways known to be involved in ALS onset or progression. Cite relevant literature, published data, or other ALS-relevant preliminary data (if applicable).

    – **Hypothesis or Objective:** State the hypothesis(es) to be tested or the objective(s) to be reached.

    – **Specific Aims:** Concisely explain the project's specific aims to be funded by this award.

    – **Research Strategy:** Describe the experimental design, methods, and analyses including appropriate controls in sufficient detail for analysis. Describe the statistical

plan, if appropriate, for the proposed research. Address potential problem areas and present alternative methods and approaches.

As appropriate, address the following:

- Describe features of any screening assays or preclinical models to be developed and/or modified that render them particularly suitable for identification and/or assessment of therapeutic agents.

- Explain how the proposed tools or models are suited to, and will be used for, preclinical testing or development of therapeutics, as opposed to basic pathophysiology research.

- If applicable, how well the animal study (or studies) considers the guidelines for working with ALS animal models and is designed to achieve the objectives, including the relevance of the model and endpoints/outcome measures to be used.

- For applications submitting under the Therapeutically Relevant Biomarker Option, describe how the proposed marker will demonstrate target engagement, help refine individual patient or patient subgroup selection, and/or clarify biological impact of a potential therapeutic. Given the early nature of Therapeutic Idea Award projects, preliminary biomarker characterization that considers qualification criteria described in relevant ALS biomarker literature should be discussed. *Additional details of the marker effort should be provided in* [Attachment 6: Therapeutically Relevant Marker Statement](#).

○ **Attachment 2: Supporting Documentation: Combine and upload as a single file named "Support.pdf".** Start each document on a new page. If documents are scanned to PDF, the lowest resolution (100 to 150 dpi) should be used. The Supporting Documentation attachment should not include additional information such as figures, tables, graphs, photographs, diagrams, chemical structures, or drawings. These items should be included in the Project Narrative.

There are no page limits for any of these components unless otherwise noted. Include only those components described below; inclusion of items not requested or viewed as an extension of the Project Narrative will result in the removal of those items 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 Patents:** Include a list of relevant publication URLs and/or patent abstracts. If articles 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, such as those from members of Congress, do not impact application review or funding decisions.

- **Letters of Collaboration (if applicable):** 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. If an investigator at an intramural organization is named as a collaborator on an application submitted through an extramural organization, the application must include a letter from the collaborator's Commander or Commanding Officer at the intramural organization that authorizes the collaborator's involvement.

- **Letters Confirming Access to Population(s) or Resource(s), e.g., Human Anatomical Substances, Databases (if applicable):** Provide a letter of support signed by the appropriate institution official who has the authority to confirm access to the proposed population(s) or resource(s) necessary to carry out the study. If access cannot be confirmed at the time of application submission, the Government reserves the right to withhold or revoke funding until the PI has demonstrated support for and access to the relevant population(s) and/or resource(s).

- **Intellectual Property:** Information can be found in Code of Federal Regulations, Title 2, Part 200.315 (2 CFR 200.315), "Intangible Property."

  - 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.

- **Use of DoD Resources (if applicable):** Provide a letter of support signed by the lowest-ranking person with approval authority confirming access to active duty military populations and/or DoD resources or databases.

- **Use of VA Resources (if applicable):** Provide a letter of support from the VA Facility Director(s) or individual designated by the VA Facility Director(s), such as the Associate Chief of Staff for Research and Development (ACOS/R&D) or Clinical Service Chief, confirming access to VA patients, resources, and/or VA research space. For VA PIs, if the VA non-profit corporation is not identified as the applicant institution for administering the funds, include a letter from the VA ACOS/R&D confirming this arrangement and identifying the institution that will administer the funds associated with the proposed research.

○ **Attachment 3: Technical Abstract (one-page limit): Upload as "TechAbs.pdf".** The technical abstract is used by all reviewers. Abstracts of all funded research projects will be posted publicly. ***Do not include proprietary or confidential information.*** Use only characters available on a standard QWERTY keyboard. Spell out all Greek letters, other non-English letters, and symbols. Graphics are not allowed.

  Use the outline below:

  - Background: Present the ideas and reasoning behind the work including a scientific rationale for the choice of therapeutic target(s) being studied.

  - Objective/Hypothesis: State the objective to be reached/hypothesis to be tested.

  - Specific Aims: State the specific aims of the study.

  - Study Design: Briefly describe the study design including appropriate controls.

  - Innovation: Summarize briefly the innovative aspects of the proposed project.

  - 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".** The lay abstract is used by all reviewers. Abstracts of all funded research projects will be posted publicly. ***Do not include proprietary or confidential information***. 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. Provide background information necessary for readers without scientific or medical training to readily understand the rationale and feasibility of the proposed research project. It should also clearly describe the scientific objective the project is designed to achieve.

- 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?

- If the research is too basic for clinical applicability, describe the interim outcomes.

- 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 Idea Award mechanism, use the SOW format example titled, "SOW (Statement of Work) Generic Format." The SOW must be in PDF format prior to attaching.

The SOW should include a list of major tasks that support the proposed specific aims, followed by a series of subtasks outlined related to the major tasks and milestones within the period of performance. The SOW should describe only the work for which funding is being requested by this application and, as applicable, should also:

- Include the name(s) of the key personnel and contact information for each study site/subaward site.

- Indicate the number (and type, if applicable) of research subjects (animal or human) and/or human anatomical samples projected or required for each task and at each site. Refer to the General Application Instructions, Appendix 1, for additional information regarding regulatory requirements.

- Identify cell line(s) and commercial or organizational source(s) to be used.

○ **Attachment 6: Therapeutically Relevant Biomarker Statement** *(required for all applications submitting under the Therapeutically Relevant Biomarker Option)* **(no page limit): Upload as "TherapeuticRelevance.pdf".** Biomarker reporting is often specific to the biology of a given therapeutic. Appropriate markers should be developed at the same time as the treatment approach itself. Preliminary biomarker characterization must consider qualification criteria described in relevant ALS biomarker literature.

Provide the following information:

- **Biomarker(s) Description:** Describe the marker(s) and the theoretical or empirical basis for its potential utility. Markers may reference levels of analytes in fluids or samples, radiologically measured parameters, event time frames, or any other objectively measured values used to reach a single interpretation. Specify the aspect

of the marker that is measured and the form in which it is used for biological interpretation.

- **Purpose in ALS Drug Development:** Describe how the proposed marker(s) will demonstrate target engagement, help refine individual patient or patient subgroup selection, and/or clarify biological impact of a potential therapeutic. Describe the extent to which the marker results will be used to steer the development process. Describe how the preliminary biomarker characterization considers qualification criteria described in relevant ALS biomarker literature. The inclusion of a decision-tree diagram that explicitly illustrates the application of the marker(s) and includes the actions that would be taken based on the marker results is recommended. Describe how easily and reliably the biomarker may be implemented in various clinical settings.

○ **Attachment 7: Impact Statement (one-page limit): Upload as "Impact.pdf".** Describe the ultimate vision for how the proposed work, if successful, will impact the development of therapeutics for ALS in the short- and/or long-term. Articulate the pathway to making a clinical impact for individuals with, or at risk for, ALS. Outline future steps and identify current or potential collaborations for transition of study outcomes to therapeutic application.

○ **Attachment 8: Innovation Statement (one-page limit): Upload as "Innovation.pdf".**

- Summarize how the proposed study is innovative. Describe how the proposed research project introduces a new paradigm, challenges existing paradigms, or looks at existing problems or issues from a new perspective.

- If the proposed research project is high-risk, explain the potential gain and how anticipated outcomes will further the development of therapeutics for ALS.

○ **Attachment 9: Data and Research Resources Sharing Plan (one-page limit): Upload as "Sharing.pdf".** Describe how data and resources generated during the performance of the project will be shared with the research community. Describe whether the proposed plan for data sharing includes existing publicly available curated ALS repositories/data platforms or other resources with relevant repository parameters and mechanisms for broad access to data and samples and whether the plan describes organizational and technical capabilities sufficient to share project data in a timely manner. A list of suitable resources can be found on the ALSRP web page (https://cdmrp.army.mil/alsrp/resources/ALSRPresources). Refer to the General Application Instructions, Appendix 2, Section K, for more information about the CDMRP expectations for making data and research resources publicly available. Include plans for making raw data available in appropriate publicly accessible ALS databases at the time of publication or at the time of conclusion of the funding. The Government reserves the right to identify repositories for submission of data for archive. Any costs associated with submission will be addressed during award negotiations.

- ○ **Attachment 10: 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).

    – Describe how data will be reported and how it will be assured that the documentation will support a regulatory filing with the FDA, if applicable.

- ○ **Attachment 11: 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):

    – Describe the specific role(s) of each collaborator in the proposed project.

    – Explain why the work should be done together rather than through isolated 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 12: Representations, if applicable (extramural submissions only): Upload as "RequiredReps.pdf".** All extramural applicants must complete and submit the Required Representations template available on eBRAP (https://ebrap.org/eBRAP/public/Program.htm). For more information, see the General Application Instructions, Appendix 5, Section B, Representations.

- ○ **Attachment 13: Suggested Collaborating DoD Military Facility Budget Format, if applicable: Upload as "MFBudget.pdf".** If a military facility (Military Health System facility, research laboratory, medical 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 a separate budget, "Suggested Collaborating DoD Military Facility Budget Format," available for download on the eBRAP "Funding Opportunities & Forms" web page https://ebrap.org/eBRAP/public/Program.htm), including a budget justification, for each military facility as instructed. The costs per year should be included on the Grants.gov Research & Related Budget Form under subaward costs. Refer to the General Application Instructions, Section III.A.8, for detailed information.

- **Extramural and Intramural Applications**

  To evaluate compliance with Title IX of the Education Amendments of 1972 (20 USC A§1681 et seq.), the DoD is collecting certain demographic and career information to be able to assess the success rates of women who are proposed for key roles in applications in science, technology, engineering, and/or mathematics (STEM) disciplines. To enable this assessment, each application must include the following forms completed as indicated.

  Research & Related Personal Data: For extramural submissions (via Grants.gov), refer to the General Application Instructions, Section III.A.3, and for intramural submissions (via eBRAP), refer to the General Application Instructions, Section IV.A.2, for detailed information.

  Research & Related Senior/Key Person Profile (Expanded): For extramural submissions (via Grants.gov), refer to the General Application Instructions, Section III.A.4, and for intramural submissions (via eBRAP), refer to the General Application Instructions, Section IV.A.3, for detailed information.

  - ○ 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 National Institutes of Health Biographical Sketch may also be used. All biographical sketches should be submitted in uneditable PDF format.

  - ○ 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".

    – Include biographical sketches for collaborators, if applicable.

  - ○ Key Personnel Previous/Current/Pending Support (no page limit): Upload as "Support_LastName.pdf".

Research & Related Budget: For extramural submissions (via Grants.gov), refer to the General Application Instructions, Section III.A.5, and for intramural submissions (via eBRAP), refer to the General Application Instructions, Section IV.A.4, 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.

Project/Performance Site Location(s) Form: For extramural submissions (via Grants.gov), refer to the General Application Instructions, Section III.A.6, and for intramural submissions (via eBRAP), refer to the General Application Instructions, Section IV.A.5, for detailed information.

- **Extramural Applications Only**

    Research & Related Subaward Budget Attachment(s) Form (if applicable): Refer to the General Application Instructions, Section III.A.7, for detailed information.

    - ○ **Extramural Subaward:** Complete the Research & Related Subaward Budget Form through Grants.gov. (Refer to the General Application Instructions, Section III.A.7, for detailed information.) Verify subaward budget(s) and budget justification forms are present in eBRAP during the application verification period. If these components are missing, upload them to eBRAP before the end of the application verification period.

    - ○ **Intramural DoD Collaborator(s):** Complete the "Suggested Collaborating DoD Military Facility Budget Format" and upload to Grants.gov attachment form as **Attachment 13**. (Refer to the General Application Instructions, Section IV.A.4, for detailed information.) Each Intramural DoD Collaborator should include costs per year on the Grants.gov Research & Related Budget Form under subaward costs.

II.D.3. Dun and Bradstreet Data Universal Numbering System (DUNS) Number and System for Award Management (SAM)

Applicant organizations and all sub-recipient 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. Verify the status of the applicant organization's Entity registration in SAM well in advance of the application submission deadline. Allow several weeks to complete the entire SAM registration process. If an applicant has not fully complied with the requirements at the time the Federal awarding agency is ready to make a Federal award, the Federal awarding agency may determine that the applicant is not qualified to receive a Federal award and use that determination as a basis for making a Federal award to another applicant. Refer to the General Application Instructions, Section III, for further information regarding Grants.gov requirements.

Announcement of Transition to SAM-Generated Unique Entity Identifier (UEI): Through December 2020, a transition from DUNS to the SAM-generated UEI will occur. Refer to the

General Application Instructions, Section III.1, DUNS Number, for more information on the transition and timing.

II.D.4. Submission Dates and Times

All submission dates and times are indicated in <u>Section I, Overview of the Funding Opportunity</u>. Pre-application and application submissions are required. The pre-application and application submission process should be started early to avoid missing deadlines. There are no grace periods. Failure to meet either of these deadlines will result in submission rejection.

Applicant Verification of Full Application Submission in eBRAP

For Both Extramural and Intramural Applicants: eBRAP allows an organization's representatives and PIs to view and modify the full application submissions associated with them. Following retrieval and processing of the full application, eBRAP will notify the organizational representatives and PI by email to log into eBRAP to review, modify, and verify the full application submission. eBRAP will validate full application files against the specific Program Announcement requirements, and discrepancies will be noted in an email to the PI and in the "Full Application Files" tab in eBRAP. eBRAP does not confirm the accuracy of file content Application viewing, modification, and verification in eBRAP are strongly recommended, but not required. It is the applicant's responsibility to review all application components and ensure proper ordering as specified in the Program Announcement. ***If either the Project Narrative or the budget fails eBRAP validation or needs to be modified, an updated full application package must be submitted prior to the application submission deadline. The Project Narrative and Research & Related Budget Form cannot be changed after the application submission deadline.*** Other application components may be changed until the end of the application verification period. Verify that subaward budget(s) and budget justification forms are present in eBRAP during the application verification period. If these components are missing, upload them to eBRAP before the end of the application verification period. After the end of the application verification period, the full application cannot be modified.

Extramural Submission: The full application package submitted to Grants.gov may be viewed and modified in eBRAP until the end of the application verification period. During the application verification period, the full application package, ***with the exception of the Project Narrative and Budget Form,*** may be modified.

Intramural DoD Submission: After eBRAP has processed the full application, the organizational Resource Manager/Comptroller/Task Area Manager or equivalent Business Official and PI will receive email notification of the status and will be able to view and modify application components in eBRAP. During the application verification period, the full application package, ***with the exception of the Project Narrative and Budget Form***, may be modified. The Resource Manager/Comptroller/Task Area Manager or equivalent Business Official should log into eBRAP to review and to approve the application package prior to the application verification deadline.

For All Submissions: Verify that subaward budget(s) with budget justification are present in eBRAP during the application verification period. If these components are missing, upload them to eBRAP before the end of the application verification period.

II.D.5. Funding Restrictions

The maximum period of performance is **2** years.

Application submissions to the standard Therapeutic Idea Award: The anticipated direct costs budgeted for the entire period of performance will not exceed **$500,000**. If indirect cost rates have been negotiated, indirect costs are to be budgeted in accordance with the organization's negotiated rate. No budget will be approved by the Government exceeding **$500,000** direct costs or using an indirect cost rate exceeding the organization's negotiated rate.

Application submissions to the Therapeutic Development Award with the Therapeutically Relevant Biomarker Option: The anticipated direct costs budgeted for the entire period of performance will not exceed **$600,000**. If indirect cost rates have been negotiated, indirect costs are to be budgeted in accordance with the organization's negotiated rate. No budget will be approved by the Government exceeding **$600,000** direct costs or using an indirect cost rate exceeding the organization's negotiated rate. *A Therapeutic Idea Award application including Therapeutically Relevant Biomarker Option that does not meet the criteria specified for that option may be funded at the lower maximum direct costs of $500,000, i.e., at the level of the standard Therapeutic Idea Award, as described above.*

All direct and indirect costs of any subaward or contract 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.

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

- Salary

- Research supplies

- Clinical research costs

- Support for multidisciplinary collaborations, including travel

- Travel costs for one investigator to travel to two scientific/technical meetings per year. The intent of travel costs to scientific/technical meetings is to present project information from the FY20 ALSRP Therapeutic Idea Award.

For extramural awards with an intragovernmental component, direct transfer of funds from an extramural award recipient to a DoD or other Federal agency is not allowed except under very limited circumstances. Funding to intramural DoD and other Federal agencies will be managed through a direct funds transfer. Intramural applicants are responsible for coordinating through

their agency's procedures the use of contractual or assistance funding awards or other appropriate agreements to support extramural collaborators.

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

II.D.6. Other Submission Requirements

Refer to the General Application Instructions, Appendix 4, for detailed formatting guidelines.

II.E. Application Review Information

II.E.1. Criteria

II.E.1.a. Peer Review

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

- **Research Strategy and Feasibility**

  ○ The degree to which the scientific rationale supports the project and its feasibility, as demonstrated by a critical review and analysis of the literature, published data, ALS-relevant preliminary data (if applicable), and/or logical reasoning.

  ○ The extent to which the feasibility of the proposed work is enhanced by exploitation of pathways known to be involved in ALS onset or progression.

  ○ How well the hypotheses or objectives, aims, experimental design, methods, and analyses are developed and integrated into the project.

  ○ Whether the application acknowledges potential problems and describes alternative approaches to address those problems.

  ○ Whether the proposed ALS animal model, if applicable, is appropriate and how well existing animal model guidelines are incorporated into the study design.

  ○ If applicable, whether data will be appropriately reported and documented to support a regulatory filing with the FDA.

  ○ As appropriate:

    – How well features of screening assays or preclinical models to be developed and/or modified that render them particularly suitable for identification and/or assessment of therapeutic agents are described.

– Whether the proposed tools or models are suited to, and will be used for, preclinical testing or development of therapeutics, as opposed to basic pathophysiology research.

For applications submitted to the Therapeutically Relevant Biomarker Option:

○ How well the preliminary biomarker characterization considers qualification criteria described in relevant ALS biomarker literature.

○ How well theoretical arguments and/or empirical data support the utility of the proposed biomarker.

○ To what extent the proposed biomarker(s) indicates target engagement, the biological effect of the potential therapeutic for which it is being developed, and/or predicts whether a specific therapeutic will be effective in an individual patient or patient subgroup.

○ The extent to which the use of the proposed biomarker will steer and enhance the therapeutic development process.

○ How well the application describes the aspect(s) of the biomarker being measured and the form in which it will be used for biological interpretation.

○ How easily and reliably this biomarker might be implemented in various clinical settings.

- **Data and Research Resources Sharing Plan**

  ○ Whether the proposed plan for data sharing includes existing publicly available curated ALS repositories/data platforms or other resources with relevant repository parameters and mechanisms for broad access to data and samples.

  ○ Whether the plan describes organizational and technical capabilities sufficient to share project data in a timely manner.

- **Innovation**

  ○ How well the research proposes new paradigms or challenges existing paradigms in one or more of the following ways: concept or question, research methods or technologies, or adaptations of existing methods or technologies that will lead to new therapies for ALS.

  ○ If the proposed research is high-risk, how well the potential gain and anticipated significant advancement in ALS therapeutic development is described.

- **Impact**

  Assuming the objectives/goals of the proposed research project are realized:

  ○ How the research, if successful, will make a significant contribution toward the development of therapeutics for ALS in the short- and/or long-term.

  ○ How well future steps are outlined and whether current or potential collaborations for transition of study outcomes to therapeutic application are described.

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

- **Personnel**

    - The extent to which the background, expertise, and levels of effort of the PI and key personnel will contribute to the success of the proposed project.

    - If early career investigators or applicants from outside the ALS research field are named as PI, whether collaborators with the necessary relevant expertise, such as experience with ALS model systems, endpoints, and pathogenic findings, are included as part of the research team.

    - How appropriate the levels of effort are for successful conduct of the proposed work.

    For research involving collaborations:

    - How well each collaborating individual's contribution is described.

    - The degree to which the proposed working relationship described in the Collaboration Plan contributes to successful attainment of project objectives.

- **Budget**

    - Whether the **direct** maximum costs are equal to or less than the allowable direct maximum costs as published in the Program Announcement.

    - Whether the budget is appropriate for the proposed research.

- **Environment**

    - Whether the scientific environment is appropriate for the proposed research.

    - Whether the research requirements are supported by the availability of and accessibility to facilities and resources (including collaborative arrangements).

    - Whether the quality and extent of organizational support are appropriate for the proposed research.

- **Application Presentation**

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

II.E.1.b. Programmatic Review

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

- Ratings and evaluations of the peer reviewers

- Relevance to the mission of the DHP and FY20 ALSRP, as evidenced by the following:

    ○ Program portfolio composition

    ○ Relative impact and innovation

    ○ Adherence to the intent of the award mechanism

II.E.2. Application Review and Selection Process

All applications are evaluated by scientists, clinicians, and consumers in a two-tier review process. The first tier is **peer review**, the evaluation of applications against established criteria to determine technical merit, where each application is assessed for its own merit, independent of other applications. The second tier is **programmatic review**, a comparison-based process in which applications with high scientific and technical merit are further evaluated for programmatic relevance. Final recommendations for funding are made to the Commanding General, USAMRDC, on behalf of the DHA and the OASD(HA). ***The highest-scoring applications from the first tier of review are not automatically recommended for funding. Funding recommendations depend on various factors as described in*** [***Section II.E.1.b, Programmatic Review***](Section II.E.1.b, Programmatic Review)***.*** Additional information about the two-tier process used by the CDMRP can be found at https://cdmrp.army.mil/about/2tierRevProcess. An information paper describing the funding recommendations and review process for the award mechanisms for the ALSRP will be provided to the PI and posted on the CDMRP website.

All CDMRP review processes are conducted confidentially to maintain the integrity of the merit-based selection process. Panel members sign a statement declaring 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 and approval 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 and approval 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 18 USC 1905.

II.E.3. Integrity and Performance Information

Prior to making an assistance agreement award where the Federal share is expected to exceed the simplified acquisition threshold, as defined in 2 CFR 200.88, over the period of performance, the Federal awarding agency is required to review and consider any information about the applicant that is available in the Federal Awardee Performance and Integrity Information System (FAPIIS).

An applicant organization may review FAPIIS, accessible through SAM, and submit comments to FAPIIS on any information about the organization that a Federal awarding agency previously entered and is currently available in FAPIIS.

The Federal awarding agency will consider any comments by the applicant, in addition to other information in the designated integrity and performance system, in making a judgment about the applicant's integrity, business ethics, and record of performance under Federal awards when determining a recipient's qualification prior to award, according to the qualification standards of the Department of Defense Grant and Agreement Regulations (DoDGARs), Section 22.415.

II.E.4. Anticipated Announcement and Federal Award Dates

All application review dates and times are indicated in [Section I, Overview of the Funding Opportunity](#).

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.

II.F. Federal Award Administration Information

II.F.1. Federal Award Notices

Awards supported with FY20 funds are anticipated to be made no later than September 30, 2021. Refer to the General Application Instructions, Appendix 2, for additional award administration information.

After email notification of application review results through eBRAP, and if selected for funding, a representative from USAMRAA will contact the Business Official authorized to negotiate on behalf of the PI's organization.

Pre-award costs: An institution of higher education, hospital, or other non-profit organization may, at its own risk and without the Government's prior approval, incur obligations and expenditures to cover costs up to 90 days before the beginning date of the initial budget period of a new award. Refer to the General Application Instructions, Section III.B.

Only an appointed USAMRAA Grants Officer may obligate the Government to the expenditure of funds. No commitment on the part of the Government should be inferred from discussions with any other individual. **The award document signed by the Grants Officer is the official authorizing document.**

Federal Government Organizations: Funding made to Federal Government organizations (to include intramural DoD organizations) will be executed through the Military Interdepartmental Purchase Request (MIPR) or Funding Authorization Document (FAD) process. Transfer of funds is contingent upon appropriate safety and administrative approvals. Intramural applicants and collaborators are reminded to coordinate receipt and commitment of funds through their respective Resource Manager/Task Area Manager/Comptroller or equivalent Business Official.

II.F.1.a. PI Changes and Award Transfers

Unless otherwise restricted, changes in PI or organization will be allowed at the discretion of the USAMRAA Grants Officer, provided the intent of the award mechanism is met.

An organizational transfer of an award will not be allowed in the last year of the (original) period of performance or any extension thereof.

Refer to the General Application Instructions, Appendix 2, Section B, for general information on organization or PI changes.

II.F.2. Administrative and National Policy Requirements

Applicable requirements in the DoDGARs found in 32 CFR, Chapter I, Subchapter C, and 2 CFR, Chapter XI, apply to grants and cooperative agreements resulting from this Program Announcement.

Refer to the General Application Instructions, Appendix 2, for general information regarding administrative requirements.

Refer to the General Application Instructions, Appendix 5, for general information regarding national policy requirements.

Refer to full text of the latest DoD R&D General Terms and Conditions; the General Research Terms and Conditions with Institutions of Higher Education, Hospitals, and Non-Profit Organizations: Addendum to the DoD R&D General Terms and Conditions; and the USAMRAA General Research Terms and Conditions with For-Profit Organizations for further information.

II.F.3. Reporting

Refer to the General Application Instructions, Appendix 2, Section A, for general information on reporting requirements. ***If there are technical reporting requirement delinquencies for any existing USAMRAA-sponsored awards at the applicant organization, no new awards will be issued to the applicant organization until all delinquent reports have been submitted.***

Annual progress reports as well as a final progress report will be required.

Awards resulting from this Program Announcement will incorporate additional reporting requirements related to recipient integrity and performance matters. Recipient organizations that have Federal contract, grant, and cooperative agreement awards with a cumulative total value greater than $10,000,000 are required to provide information to FAPIIS about certain civil, criminal, and administrative proceedings that reached final disposition within the most recent 5-year period and that were connected with performance of a Federal award. Recipients are required to disclose, semiannually, information about criminal, civil, and administrative proceedings as specified in the applicable Representations (see General Application Instructions, Appendix 5, Section B).

II.G. Federal Awarding Agency Contacts

II.G.1. CDMRP Help Desk

Questions related to Program Announcement content or submission requirements as well as questions related to the pre-application or intramural application submission 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

II.G.2. Grants.gov Contact Center

Questions related to extramural 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; International 1-606-545-5035

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 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.

II.H. Other Information

II.H.1. Program Announcement and General Application Instructions Versions

Questions related to this Program Announcement should refer to the Program name, the Program Announcement name, and the Program Announcement version code 501a. The Program Announcement numeric version code will match the General Application Instructions version code 501.

II.H.2. Administrative Actions

After receipt of pre-applications or applications, the following administrative actions may occur:

II.H.2.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 exceeds page limit.

- Project Narrative is missing.

- Budget is missing.

II.H.2.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.

II.H.2.c. Withdrawal

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

- An FY20 ALSRP Programmatic Panel 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 FY20 ALSRP Programmatic Panel members can be found at https://cdmrp.army.mil/alsrp/panels/panels20*.

- The application fails to conform to this Program Announcement description.

- 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).

- To preserve the integrity of its peer and programmatic review processes, the CDMRP discourages inclusion of any employee of its review contractors having any role in the preparation, research, or other duties for submitted applications. For FY20, the identities of the peer review contractor and the programmatic review contractor may be found at the CDMRP website (https://cdmrp.army.mil/about/2tierRevProcess). Applications that include names of personnel from either of these companies may be administratively withdrawn.

- Personnel from applicant or collaborating organizations are found to have contacted persons involved in the review or approval process to gain protected evaluation information or to influence the evaluation process.

- Applications from extramural organizations, including non-DoD Federal agencies, received through eBRAP may be withdrawn.

- Applications submitted by an intramural DoD organization may be withdrawn if the intramural organization cannot coordinate the use of contractual, assistance, or other appropriate agreements to provide funds to extramural collaborators.

- Submission of the same research project to different funding opportunities within the same program and fiscal year.

- The invited application proposes a different research project than that described in the pre-application.

- A clinical trial is proposed.

- The PI does not meet the eligibility criteria.

- The applicant fails to demonstrate access to the relevant study population or resources.

II.H.2.d. Withhold

Applications that appear to involve research misconduct will be administratively withheld from further consideration pending organizational investigation. The organization 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.

II.H.3. Application Submission Checklist

Application Components	Action	Completed
SF424 Research & Related Application for Federal Assistance **(extramural submissions only)**	Complete form as instructed	
Summary (Tab 1) and Application Contacts (Tab 2) **(intramural submissions only)**	Complete tabs as instructed	
Attachments	Project Narrative: Upload as Attachment 1 with file name "ProjectNarrative.pdf"	
	Supporting Documentation: Upload as Attachment 2 with file name "Support.pdf"	
	Technical Abstract: Upload as Attachment 3 with file name "TechAbs.pdf"	
	Lay Abstract: Upload as Attachment 4 with file name "LayAbs.pdf"	
	Statement of Work: Upload as Attachment 5 with file name "SOW.pdf"	
	Therapeutically Relevant Biomarker Statement: Upload as Attachment 6 with file name "TherapeuticRelevance.pdf" if applicable	
	Impact Statement: Upload as Attachment 7 with file name "Impact.pdf"	
	Innovation Statement: Upload as Attachment 8 with file name "Innovation.pdf"	
	Data and Research Resources Sharing Plan: Upload as Attachment 9 with file name "Sharing.pdf"	
	Animal Research Plan: Upload as Attachment 10 with file name "AnimalPlan.pdf" if applicable	
	Collaboration Plan: Upload as Attachment 11 with file name "Collaboration.pdf" if applicable	
	Representations (extramural submissions only): Upload as Attachment 12 with file name "RequiredReps.pdf" if applicable	
	Suggested DoD Collaborating Military Facility Budget Format: Upload as Attachment 13 with file name "MFBudget.pdf" if applicable	

Application Components	Action	Completed
Research & Related Personal Data	Complete form as instructed	
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 **(extramural submissions only)**	Complete as instructed. Attach Budget Justification (BudgetJustification.pdf) to the appropriate field	
Budget **(intramural submissions only)**	Suggested DoD Military Budget Format, including justification	
Project/Performance Site Location(s) Form	Complete form as instructed	
Research & Related Subaward Budget Attachment(s) Form, if applicable	Complete form as instructed	

APPENDIX 1: ACRONYM LIST

ACOS/R&D	Associate Chief of Staff for Research and Development
ACURO	Animal Care and Use Review Office
ADME	Absorption, Distribution, Metabolism, and Excretion
ALS	Amyotrophic Lateral Sclerosis
ALSRP	Amyotrophic Lateral Sclerosis Research Program
CDC	Centers for Disease Control and Prevention
CDMRP	Congressionally Directed Medical Research Programs
CFR	Code of Federal Regulations
DHA	Defense Health Agency
DHP	Defense Health Program
DoD	Department of Defense
DoDGARs	Department of Defense Grant and Agreement Regulations
DUNS	Data Universal Numbering System
eBRAP	Electronic Biomedical Research Application Portal
EC	Ethics Committee
ET	Eastern Time
FAD	Funding Authorization Document
FAPIIS	Federal Awardee Performance and Integrity Information System
FDA	Food and Drug Administration
FY	Fiscal Year
HRPO	Human Research Protection Office
IACUC	Institutional Animal Care and Use Committee
IRB	Institutional Review Board
M	Million
MIPR	Military Interdepartmental Purchase Request
NPC	Non-Profit Corporation
OASD(HA)	Office of the Assistant Secretary of Defense for Health Affairs
ORCID	Open Researcher and Contributor ID, Inc.
ORP	Office of Research Protections
PI	Principal Investigator
RDT&E	Research, Development, Test, and Evaluation
SAM	System for Award Management
SOW	Statement of Work
STEM	Science, Technology, Engineering, and/or Mathematics
TDA	Therapeutic Development Award
TIA	Therapeutic Idea Award
UEI	Unique Entity Identifier

URL	Uniform Resource Locator
USAMRAA	U.S. Army Medical Research Acquisition Activity
USAMRDC	U.S. Army Medical Research and Development Command
USC	United States Code
VA	Department of Veterans Affairs