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: Initial

Funding Opportunity Number: HT9425-23-ALSRP-TIA

**Assistance Listing 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 13, 2023

- **Invitation to Submit an Application:** June 2023

- **Application Submission Deadline:** 11:59 p.m. ET, July 13, 2023

- **End of Application Verification Period:** 5:00 p.m. ET, July 18, 2023

- **Peer Review:** September 2023

- **Programmatic Review:** November 2023

This program announcement must be read in conjunction with the General Application Instructions, version 800. 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."

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II. DETAILED INFORMATION ABOUT THE FUNDING OPPORTUNITY

II.A. Program Description

Applications to the Fiscal Year 2023 (FY23) Amyotrophic Lateral Sclerosis Research Program (ALSRP) are being solicited by the U.S. Army Medical Research Acquisition Activity (USAMRAA) using delegated authority provided by United States Code, Title 10, Section 4001 (10 USC 4001). The execution management agent for this program announcement is the Congressionally Directed Medical Research Programs (CDMRP) at the U.S. Army Medical Research and Development Command (USAMRDC). The ALSRP was initiated in 2007 to provide support for research of exceptional scientific merit. Appropriations for the ALSRP from FY07 through FY22 totaled $189.4 million (M). The FY23 appropriation is $40.0M.

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

II.B. Award Information

The FY23 ALSRP Therapeutic Idea Award supports the initial exploration of innovative, high-risk, high-gain ideas aimed at Amyotrophic Lateral Sclerosis (ALS) drug or treatment discovery. The studies supported by this award mechanism are expected to be hypothesis-driven and generate preliminary data for future avenues of therapeutic investigation. 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. Applications may demonstrate the ability to achieve interpretable results in the absence of preliminary data supporting the hypothesis. 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. Research with high impact should pioneer transformative research that could lay the foundation for a new direction in the field of ALS therapeutic development. Projects should strive to produce the type and amount of data needed to apply for the next stage, i.e., ALSRP Therapeutic Development Award or other mechanisms for ALS therapeutic advancement.

The Therapeutic Idea Award encourages applications submitted by early-career investigators as well as applications that include meaningful and productive collaborations between/among 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.

Biomarker Option: The FY23 ALSRP Therapeutic Idea Award 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 apart from 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 effectiveness of the therapeutic development process. For further description, see Section II.D.2.b.ii, Full Application Submission Components, Attachment 9, Biomarker Statement.

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

- National Institute of Neurological Disorders and Stroke (NINDS) Biomarker Program.
  https://www.ninds.nih.gov/current-research/focus-tools-topics/focus-biomarkers-research

- U.S. Food and Drug Administration (FDA) Biomarker Qualification Program.
  https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program

- FDA Guidance Document – "Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry." September 2019. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/amyotrophic-lateral-sclerosis-developing-drugs-treatment-guidance-industry

- Verber NS, Shepheard SR, Sassani M, et al. 2019. Biomarkers in motor neuron disease: A state of the art review. *Frontiers in Neurology* 10:291.
  https://www.frontiersin.org/articles/10.3389/fneur.2019.00291/full

- 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

- 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

Clinical trials are not allowed under this award mechanism. A clinical trial is defined as a research study in which one or more human subjects are prospectively assigned to one or more

interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes. However, identification of treatment approaches using biological correlates of disease activity and progression in preexisting, de-identified human specimens from well-characterized, adequately controlled, and sufficiently powered patient cohorts is permitted and is encouraged. Examples of acceptable sources for preexisting biosamples or datasets include controlled clinical trials, observational studies, publicly available biorepositories, and registries (e.g., Centers for Disease Control and Prevention 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.health.mil/alsrp/resources/ALSRPresources). Other resources may be used, provided they have an adequate description of repository parameters and mechanisms for broad access. *All clinical specimens must exist at the time of application submission; collection of new specimens will not be supported.*

Applicants seeking support for the development of products beyond drug or treatment discovery should consider the FY23 ALSRP Therapeutic Development Award (Funding Opportunity Number HT9425-23-ALSRP-TDA), which supports advanced preclinical development activities (https://cdmrp.health.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, but is not limited to, 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 FY23 ALSRP Therapeutic Idea Award should not exceed **$600,000**.

The anticipated direct costs budgeted for the entire period of performance for an FY23 Therapeutic Idea Award – Biomarker Option should not exceed **$750,000**. Refer to Section II.D.5, Funding Restrictions, for detailed funding information.

Awards will be made no later than September 30, 2024. For additional information refer to Section II.F.1, Federal Award Notices.

The CDMRP expects to allot approximately $10.6M 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 FY23 funding opportunity will be funded with FY23 funds, which will expire for use on September 30, 2029.

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 SC Landis et al., 2012, A call for transparent reporting to optimize the predictive value of preclinical research, *Nature* 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 8, Animal Research Plan, as part of the application package to describe how these standards will be addressed. Applicants should consult the ARRIVE guidelines 2.0 (Animal Research: Reporting *In Vivo* Experiments) to ensure relevant aspects of rigorous animal research are adequately planned for and, ultimately, reported. The ARRIVE guidelines 2.0 can be found at https://arriveguidelines.org/arrive-guidelines.

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. *Amyotrophic Lateral Sclerosis* 11(1-2):38-45. https://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. *Amyotrophic Lateral Sclerosis* 9(1):4-15. https://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. *Amyotrophic Lateral Sclerosis* 8(4):217-223. https://dx.doi.org/10.1080/17482960701292837

Research Involving Animals: All research funded by the FY23 ALSRP Therapeutic Idea Award involving new and ongoing research with animals must be reviewed and approved by the USAMRDC Office of Human and Animal Research Oversight (OHARO) 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.

Research Involving Human Data, Human Anatomical Substances, Human Subjects, or Human Cadavers: All DOD-funded research involving new and ongoing research with human data, human anatomical substances, human subjects, or human cadavers must be reviewed and approved by the USAMRDC OHARO, Office of Human Research Oversight (OHRO), 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 application submission is *not* required; however local IRB/EC approval is necessary prior to OHRO review. Allow up to 3 months to complete the OHRO regulatory review and approval process following submission of *all required and complete* documents to the OHRO. Refer to the General Application Instructions, Appendix 1, and the OHARO web page https://mrdc.health.mil/index.cfm/collaborate/research_protections/hrpo for additional information.

Use of DOD or Department of Veterans Affairs (VA) Resources: If the proposed research involves access to active-duty military or veteran patient populations and/or DOD or VA 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.

II.C. Eligibility Information

II.C.1. Eligible Applicants

II.C.1.a. Organization: All organizations, including foreign organizations, foreign public entities, and 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 organizations 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: An 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.*

The 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) on an application.

Early-career investigators (defined as independent, non-mentored investigators within 10 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 strongly 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.

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).

II.D.1. eBRAP and Grants.gov

The electronic Biomedical Research Application Portal (eBRAP) (https://ebrap.org) is a secure web-based system that allows PIs to submit their pre-applications, view and verify extramural full applications submitted to Grants.gov (https://grants.gov), receive communications from the CDMRP, and submit documentation during award negotiations and throughout the period of performance. eBRAP also allows intramural organizations to submit full applications following pre-application submission.

Grants.gov is a federal system required to be utilized by agencies to receive and process extramural grant applications. Full applications may only be submitted to Grants.gov after submission of a pre-application through eBRAP.

Contact information for the eBRAP Help Desk and the Grants.gov Contact Center can be found in [Section II.G, Federal Awarding Agency Contacts](#).

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.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 eBRAP 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 eBRAP 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 applicant must contact the eBRAP 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.

When starting the pre-application, PIs should ensure that they have selected the appropriate application category in eBRAP:

- TIA – Therapeutic Idea Award

- TIA-BO – Therapeutic Idea Award – Biomarker Option

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.

  [FY23 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 eBRAP 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 (uniform resource locators) 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:

    – **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. Innovative uses or investigations of previously developed resources are acceptable.

    – **Impact:** State explicitly how the proposed work will have an impact on the development of therapeutics for ALS and on patient populations. Outline, in general terms, the next steps to transition the study outcomes to therapeutic application(s).

    – **Research Strategy and Feasibility:** Explain the rationale for selecting the specific target(s) for investigation. Concisely state the project's objectives and specific aims. Describe how the proposed experiments demonstrate the testability of the hypothesis. Describe the "high-risk/high-reward" nature of the

testable hypothesis to be investigated. If animal models are to be used, describe the selected model and its relevance to the hypothesis. Explain the feasibility of the study leading to a therapy for ALS.

  – **For Pre-Applications Submitted Under the Biomarker Option:** Describe the biomarker category and intended use in ALS therapeutic development, including regulatory considerations for use in ALS clinical trials.

○ **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 Prepoposal 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 Prepoposal Narrative.

  – **Key Personnel Biographical Sketches (five-page limit per individual):** *All biographical sketches should be uploaded as a single combined file.* Biographical sketches should be used to 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 Defense Health Program (DHP) and the ALSRP, pre-applications will be screened based on the following criteria:

○ **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.

○ **Research Strategy and Feasibility:** How well the scientific rationale supports the project objectives, specific aims, and feasibility. The degree to which the proposed experiments demonstrate the testability of the hypothesis.

- o **For Pre-Applications Submitted Under the Biomarker Option:** To what extent the biomarker category and intended use in ALS therapeutic development, including regulatory considerations for use in ALS clinical trials, is described.

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

  Following the pre-application screening, PIs will be notified as to whether 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 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://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 the Project Narrative.

Table 1. Full Application Submission Guidelines

Extramural Submissions	Intramural DOD Submissions
Application Package Location	
Download application package components for HT9425-23-ALSRP-TIA from Grants.gov (https://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 HT9425-23-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 • 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. ***Do not password***

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 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. ***Do not password protect any files of the application package, including the Project Narrative.***	***protect any files of the application package, including the Project Narrative.***
[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 megabytes (MB), and the file size for the entire full application package may not exceed 200 MB.

    ○ **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.

        – **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. For hypothesis-generating research that may be high-risk, clearly describe the potential gain and anticipated advancements in ALS therapeutic development.

        – **Scientific Rationale:** Present the scientific rationale behind the proposed work. Explain how the novel idea is supported by sound logical reasoning and strong scientific rationale. Cite relevant, published literature and, if applicable, any preliminary data (preliminary data are not required). 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.

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

- **Research Strategy and Feasibility:** Describe the experimental design, methods, and analyses including appropriate controls in sufficient detail for analysis. 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 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. Address potential problem areas and present alternative methods and approaches. As the Therapeutic Idea Award is designed to be a "high-risk/high-reward" mechanism, hypotheses may prove incorrect, but the proposed experiments must be feasible and designed to adequately test the hypotheses.

- **Next Steps:** Describe the next steps to transition the study outcomes into further therapeutic application(s) including how the project will produce the type and amount of data needed to apply for the next stage, i.e., ALSRP Therapeutic Development Award or other mechanisms to advance ALS therapeutic advancement.

- **Biomarker Option:** For applications submitting under the Biomarker Option, clearly state the biomarker category and 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 ALS therapeutic. Describe potential regulatory considerations for use in ALS clinical trials. ***Additional details of the marker effort should be provided in [Attachment 9, Biomarker 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 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 demonstrating 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.

- **Intellectual Property:** Information can be found in the 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.

- **Data Management Plan (two-page limit):** Describe the data management plan in accordance with Section 3.c, Enclosure 3, DoD Instruction 3200.12.

  - For Extramural Applications: Refer to General Application Instructions, Section III.A.2, Attachments Form, Attachment 2, Supporting Documentation, for more detailed information.

  - For Intramural Applications: Refer to General Application Instructions, Section IV.A.1, Application Component – Attachments, Attachment 2, Supporting Documentation, for more detailed information.

- **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.

The technical abstract should be structured in accordance with the outline below:

- **Background:** Present the scientific rationale 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***. ***Do not duplicate the technical abstract.*** Use only characters available on a standard QWERTY keyboard. Spell out all Greek letters, other non-English letters, and symbols. Graphics are not allowed.

Provide background information necessary for readers ***without scientific or medical training*** to readily understand the rationale and feasibility of the proposed research project. The lay abstract should also clearly describe the scientific objective the project is designed to achieve. The lay abstract should be structured in accordance with the outline below:

- – 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 (three-page limit): Upload as "SOW.pdf".** The suggested Statement of Work (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). Recommended strategies for assembling the SOW can be found at https://ebrap.org/eBRAP/public/Program.htm.

For the FY23 ALSRP Therapeutic Idea Award mechanism, refer to the "***Suggested SOW Strategy Generic Research***" document for guidance on preparing the SOW and use the blank SOW format titled "Suggested SOW 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.

○ **Attachment 6: Impact Statement (one-page limit): Upload as "Impact.pdf".** Describe how the proposed work will impact development of therapeutics for ALS. Articulate a pathway to making a clinical impact for individuals with, or at risk for, ALS. Specifically highlight how the research will achieve the following by the end of the performance period:

- – Advance the development of a groundbreaking ALS therapeutic, including for specific subset populations.

- – Show potential for application in the clinic and ultimate impact on ALS patient populations.

- – Advance biomarkers with the potential for meaningful treatment outcomes in parallel with the main therapeutic development effort (if applicable).

○ **Attachment 7: 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.health.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 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: Biomarker Statement (no page limit): Required for all applications submitting under the Biomarker Option. Upload as "Biomarker.pdf".** Preliminary biomarker characterization must address qualification criteria described in relevant ALS biomarker literature. See Section II.B, Award Information, for more information on 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. Explain how the biomarker characterization addresses 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 eventual clinical trials of the proposed novel therapeutic, including regulatory considerations.

○ **Attachment 10: 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 11: 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, using "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 1681[a] 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".

  – For extramural submissions, refer to the General Application Instructions, Section III.A.4, for detailed information.

  – For intramural submissions, refer to the General Application Instructions, Section IV.A.3, for detailed information.

- 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".

  – For extramural submissions, refer to the General Application Instructions, Section III.A.4, for detailed information.

  – For intramural submissions, refer to the General Application Instructions, Section IV.A.3, for detailed information.

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 11](#). (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. Unique Entity Identifier (UEI) and System for Award Management (SAM)

The applicant organization must be registered as an entity in SAM (https://www.sam.gov/SAM/) and receive confirmation of an "Active" status before submitting an application through Grants.gov. *As of April 2022, all federal awards including, but not limited to, contracts, grants, and cooperative agreements will use the UEI generated through SAM.gov.* Refer to the General Application Instructions, Section III, for further information regarding Grants.gov requirements.

II.D.4. Submission Dates and Times

All submission dates and times are indicated in [Section I, Overview of the Funding Opportunity](#). 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 application's direct costs budgeted for the entire period of performance should 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.

Application Submissions to the Therapeutic Idea Award – Biomarker Option: The anticipated direct costs budgeted for the entire period of performance will not exceed **$750,000**. 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 **$750,000** direct costs or using an indirect cost rate exceeding the organization's negotiated rate. *A Therapeutic Idea Award – Biomarker Option application that does not meet the criteria specified for that option may be funded at the lower maximum direct costs of $600,000, 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):

- Costs for one investigator to travel to one scientific/technical meeting per year. The intent of travel costs to scientific/technical meetings is to present project information from the FY23 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 listed in decreasing order of importance.

- **Innovation**

  ○ How well the research 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.

  ○ If the project represents hypothesis-generating research that may be high-risk, how well the potential gain and anticipated advancements in ALS therapeutic development are described. Innovative uses or investigations of previously developed resources are acceptable.

- **Impact**

  ○ To what extent the research will make a significant contribution toward the development of groundbreaking therapeutics for ALS, including for specific subset populations.

- ○ How well the next steps for further therapeutic development are articulated, including how the project will produce the type and amount of data needed to apply for the next stage, i.e., ALSRP Therapeutic Development Award or other mechanisms for ALS therapeutic advancement.

- ○ How well the potential impact of the therapeutic on ALS patient populations is described.

- **Research Strategy and Feasibility**

  - ○ How well the scientific rationale supports the project and its feasibility, as demonstrated by a critical review and analysis of the literature and/or by logical reasoning.

  - ○ Whether the proposed experiments and analysis are well integrated and likely to generate conclusive answers to the proposed hypotheses, whether positive or negative. As the Therapeutic Idea Award is designed to be a "high-risk/high-reward" mechanism, hypotheses may prove incorrect, but the proposed experiments must be designed to adequately test the hypotheses.

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

  - ○ How well the potential challenges and alternative strategies are identified.

  - ○ If applicable, whether the ALS model group size is described and the method by which it was derived, including power analysis calculations.

  - ○ If applicable, whether the proposed ALS animal model(s), endpoints/measures, and data analyses, including statistical methods, are appropriate and whether the study design incorporates existing ALS model use guidelines.

- **Biomarker Statement** *(for applications submitted to the Biomarker Option only)***:**

  - ○ 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 demonstrate target engagement, help refine individual patient or patient subgroup selection, and/or clarify biological impact of a potential therapeutic.

  - ○ How well the application describes the extent to which the biomarker results will be used to steer the development process.

  - ○ How easily and reliably the biomarker(s) could be implemented in eventual clinical trials of the proposed novel therapeutic.

- **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.

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.

- **Budget**

  ○ Whether the **direct** costs exceed the allowable direct 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 FY23 ALSRP, as evidenced by the following:

  - Adherence to the intent of the award mechanism.

  - Relative innovation and impact.

  - Program portfolio composition.

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. ***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.*** Additional information about the two-tier process used by the CDMRP can be found at https://cdmrp.health.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 200.1, 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 FY23 funds are anticipated to be made no later than September 30, 2024. 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 the 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 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.A.5.

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 and the USAMRAA General Research Terms and Conditions: Addendum to the DoD R&D General Terms and Conditions for further information.

Certification Regarding Disclosure of Funding Sources. The proposing entity must comply with Section 223(a) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021, which requires that the PI and all key personnel:

- Certify that the current and pending support provided on the application is current, accurate, and complete;

- Agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award; and

- Have been made aware of the requirements under Section 223(a)(1) of this Act.

False, fictitious, or fraudulent statements or claims may result in criminal, civil, or administrative penalties (18 USC 1001).

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.

The Award Terms and Conditions will specify if additional and/or more frequent reporting is required.

Awards resulting from this program announcement may entail 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 $10M 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. These 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. eBRAP 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 eBRAP Help Desk, which is available Monday through Friday from 8:00 a.m. to 5:00 p.m. ET (closed on most U.S. federal holidays). 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 eBRAP 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 800c. The program announcement numeric version code will match the General Application Instructions version code 800.

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 FY23 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 FY23 ALSRP Programmatic Panel members can be found at https://cdmrp.health.mil/alsrp/panels/panels23.***

- 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 FY23, the identities of the peer review contractor and the programmatic review contractor may be found at the CDMRP website (https://cdmrp.health.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.

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"	
	Impact Statement: Upload as Attachment 6 with file name "Impact.pdf"	
	Data and Research Resources Sharing Plan: Upload as Attachment 7 with file name "Sharing.pdf"	
	Animal Research Plan: Upload as Attachment 8 with file name "AnimalPlan.pdf" if applicable	
	Biomarker Statement: Upload as Attachment 9 with file name "Biomarker.pdf" if applicable	
	Representations (extramural submissions only): Upload as Attachment 10 with file name "RequiredReps.pdf"	
	Suggested Collaborating DOD Military Facility Budget Format: Upload as Attachment 11 with file name "MFBudget.pdf" if applicable	
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	

Application Components	Action	Completed
	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
ALS	Amyotrophic Lateral Sclerosis
ALSRP	Amyotrophic Lateral Sclerosis Research Program
ARRIVE	Animal Research: Reporting *In Vivo* Experiments
CDMRP	Congressionally Directed Medical Research Programs
CFR	Code of Federal Regulations
DHP	Defense Health Program
DOD	Department of Defense
DoDGARs	Department of Defense Grant and Agreement Regulations
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	U.S. Food and Drug Administration
FY	Fiscal Year
IACUC	Institutional Animal Care and Use Committee
IRB	Institutional Review Board
M	Million
MB	Megabytes
MIPR	Military Interdepartmental Purchase Request
NINDS	National Institute of Neurological Disorders and Stroke
OHARO	Office of Human and Animal Research Oversight (previously Office of Research Protections)
OHRO	Office of Human Research Oversight (previously Human Research Protection Office)
ORCID	Open Researcher and Contributor ID, Inc.
PDF	Portable Document Format
PI	Principal Investigator
SAM	System for Award Management
SOW	Statement of Work
STEM	Science, Technology, Engineering, and/or Mathematics
TIA	Therapeutic Idea Award
TIA-BO	Therapeutic Idea Award – Biomarker Option
URL	Uniform Resource Locator

UEI	Unique Entity Identifier
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