

# **I. OVERVIEW OF THE FUNDING OPPORTUNITY**

**Program Announcement for the Department of Defense**

**Defense Health Program**

**Congressionally Directed Medical Research Programs**

**Peer Reviewed Medical Research Program**

**Clinical Trial Award**

**Announcement Type: Initial**

**Funding Opportunity Number: W81XWH18PRMRPCTA**

**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), June 25, 2018
- **Invitation to Submit an Application:** July 2018
- **Application Submission Deadline:** 11:59 p.m. ET, September 27, 2018
- **End of Application Verification Period:** 5:00 p.m. ET, October 2, 2018
- **Peer Review:** November 2018
- **Programmatic Review:** January 2019

*This Program Announcement must be read in conjunction with the General Application Instructions, version 20180329. The General Applications 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.”*

Released May 4, 2018

DoD FY18 Peer Reviewed Medical Clinical Trial Award

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## **II. DETAILED INFORMATION ABOUT THE FUNDING OPPORTUNITY**

***New for 2018: Application submission by extramural organizations through Grants.gov requires use of the Workspace interface, which separates the application package into individual forms. Applicants must create a Workspace in Grants.gov, complete the required forms, and submit their application Workspace package.***

### **II.A. Program Description**

Applications to the Fiscal Year 2018 (FY18) Peer Reviewed Medical Research Program (PRMRP) 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 PRMRP was initiated in 1999 to provide support for military health-related research of exceptional scientific merit. Appropriations for the PRMRP from FY99 through FY17 totaled \$1.7 billion. The FY18 appropriation is \$330 million (M).

The vision of the FY18 PRMRP is to improve the health and well-being of all military Service members, Veterans, and beneficiaries. The PRMRP challenges the scientific and clinical communities to address at least one of the FY18 Topic Areas with original ideas that foster new directions along the entire spectrum of research and clinical care. The program seeks applications in laboratory, clinical, behavioral, epidemiologic, and other areas of research to advance knowledge in disease etiology, improve prevention, detection, diagnosis, treatment, and quality of life for those affected by a relevant disease or condition, and to develop and validate clinical care or public health guidelines.

#### **II.A.1. FY18 PRMRP Topic Areas**

All applications for PRMRP funding must specifically address at least one of the Topic Areas as directed by Congress and must be directly relevant to the healthcare needs of military Service members, Veterans, and/or beneficiaries. If the proposed research does not specifically address at least one of the FY18 PRMRP Topic Areas, the Government will administratively withdraw the application. The Government reserves the right to reassign the application's Topic Area if submitted under an inappropriate Topic Area. The FY18 PRMRP Topic Areas are listed below.

- Acute Lung Injury
- Antimicrobial Resistance
- Arthritis
- Burn Pit Exposure
- Cardiomyopathy
- Cerebellar Ataxia
- Chronic Migraine and Post-Traumatic Headache

- Chronic Pain Management
- Congenital Heart Disease
- Constrictive Bronchiolitis
- Diabetes
- Dystonia
- Eating Disorders
- Emerging Infectious Diseases
- Endometriosis
- Epidermolysis Bullosa
- Focal Segmental Glomerulosclerosis
- Fragile X
- Frontotemporal Degeneration
- Guillain-Barré Syndrome
- Hepatitis B and C
- Hereditary Angioedema
- Hydrocephalus
- Immunomonitoring of Intestinal Transplants
- Inflammatory Bowel Diseases
- Interstitial Cystitis
- Lung Injury
- Malaria
- Metals Toxicology
- Mitochondrial Disease
- Musculoskeletal Disorders
- Myotonic Dystrophy
- Non-Opioid Pain Management
- Nutrition Optimization
- Pancreatitis
- Pathogen-Inactivated Blood Products
- Post-Traumatic Osteoarthritis
- Pressure Ulcers
- Pulmonary Fibrosis
- Respiratory Health
- Rett Syndrome
- Rheumatoid Arthritis
- Scleroderma
- Sleep Disorders
- Spinal Muscular Atrophy
- Sustained-Release Drug Delivery
- Tinnitus
- Tissue Regeneration
- Tuberculosis
- Vaccine Development for Infectious Diseases
- Vascular Malformations
- Women's Heart Disease

Research relevant to one or more FY18 PRMRP Topic Areas may be considered for funding. ***Applicants should select the FY18 PRMRP Program Announcement most appropriate to the stage of the proposed research.*** Areas of Encouragement related to the FY18 PRMRP Topic

Areas have been identified by the Department of Defense (DoD), the Department of Veterans Affairs (VA), and other relevant stakeholders ([Appendix 2](#)). Applicants are urged to read and consider these Areas of Encouragement before preparing their applications. ***The information provided is not exhaustive, and applicants are not restricted to submitting applications that address an Area of Encouragement in this list.***

## **II.B. Award Information**

The PRMRP Clinical Trial Award supports the rapid implementation of clinical trials with the potential to have a significant impact on a disease or condition addressed in at least one of the Congressionally directed FY18 PRMRP Topic Areas. Clinical trials may be designed to evaluate promising new products, pharmacologic agents (drugs or biologics), devices, clinical guidance, and/or emerging approaches and technologies. Proposed projects may range from small proof-of-concept trials (e.g., pilot, first in human, Phase 0) to demonstrate feasibility or inform the design of more advanced trials, through large-scale trials to determine efficacy in relevant patient populations. All studies must be responsive to the healthcare needs of military Service members, Veterans, and/or beneficiaries; however, the use of military or Veteran populations is not required.

***Funding from this award mechanism must support a clinical trial.*** A clinical trial is defined as a prospective accrual of patients (human subjects) in whom an intervention (e.g., device, drug, biologic, surgical procedure, rehabilitative modality, behavioral intervention, or other) is tested for a measurable outcome with respect to safety, effectiveness, and/or efficacy. This outcome represents a direct effect on the subject of that intervention or interaction. The term “human subjects” is used in this Program Announcement to refer to individuals who will be recruited for or who will participate in the proposed clinical trial. For more information, a Human Subject Resource Document is provided at <https://ebrap.org/eBRAP/public/Program.htm>. Principal Investigators (PIs) seeking funding for a preclinical research project should consider one of the other FY18 PRMRP Program Announcements being offered.

If the proposed clinical trial involves the use of a drug that has not been approved by the U.S. Food and Drug Administration (FDA) for the proposed investigational use, then an Investigational New Drug (IND) application to the FDA that meets all requirements under the Code of Federal Regulations, Title 21, Part 312 (21 CFR 312) may be required.

If the proposed clinical trial involves the use of a device that has not been approved by the FDA for the proposed investigational use, then an Investigational Device Exemption (IDE) application that meets all requirements under 21 CFR 812 may be required.

***New for FY18: One of the following MUST be submitted in Attachment 13: Regulatory Strategy, with the full application by the application submission deadline:***

- 1) A copy of the FDA acknowledgment letter to include submission date and receipt date, and a statement that the FDA did not raise concerns and/or did not place the clinical trial on hold, or***

- 2) ***A copy of the FDA acknowledgment letter and meeting minutes (pre-IND/pre-IDE and/or Type C) that ascertain the FDA's concurrence to the proposed regulatory approach if a technical or a protocol amendment to an IND/IDE is necessary to complete the clinical trial, or***
- 3) ***A copy of the relevant national regulatory agency approval if the clinical trial will be conducted at an international site(s), or***
- 4) ***Evidence in writing from the IRB of record, or the FDA, or the international regulatory agency for clinical trials conducted at an international site(s) that the proposed investigational drug/agent/device is exempt or the proposed investigational device qualifies for an abbreviated IDE.***

For more information on IND applications, the FDA has provided guidance at <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm>.

The Government reserves the right to withdraw an application if an IND/IDE, IND/IDE amendment, and/or international regulatory approval is necessary but was not submitted with the Clinical Trial Award application by the submission deadline

Applications are not restricted to a predetermined cost limit. The requested budget must be justified and appropriate to the scope of the clinical trial proposed. Refer to [Section II.D.5, Funding Restrictions](#), for detailed funding information.

The following are important aspects of the Clinical Trial Award:

- The proposed intervention(s) to be tested should offer significant potential impact for individuals affected by the specified disease(s)/condition(s).
- Inclusion of preliminary data relevant to the proposed clinical trial is required.
- The proposed clinical trial must be based on sound scientific rationale that is established through logical reasoning and critical review and analysis of the literature.
- The application should describe the planned indication for the product label, if appropriate, and include an outline of the product development plan required to support that indication.
- The application should demonstrate availability of, and access to, a suitable patient population that will support a meaningful outcome for the study. The application should discuss how accrual goals will be achieved and how standards of care may impact the study population.
- The application should demonstrate documented availability of and access to the drug/compound, device, and/or other materials needed, as appropriate, for the proposed duration of the study. The quality and stability of the product should be documented and commensurate with current FDA manufacturing standards applicable to the type and phase of

product being developed (i.e., Quality System Regulation, Good Manufacturing Practices [GMP]).

- The proposed clinical trial design should include clearly defined objectives and appropriate endpoints/outcome measures, and comply with current Good Clinical Practice (GCP) guidelines.
- The application should include a clearly articulated statistical analysis plan, appropriate statistical expertise on the research team, and a power analysis reflecting sample size projections that will answer the objectives of the study.
- The application should include a clearly articulated data management plan and use of an appropriate database to safeguard and maintain the integrity of the data. If FDA regulated, the trial must use a 21CFR11-compliant database and appropriate data standards. For more on data standards, see <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM511237.pdf>.
- The application should include a clearly articulated safety management plan outlining how safety pharmacovigilance will be conducted, as applicable.
- The application should include a clearly articulated clinical monitoring plan outlining how the study will be monitored for GCP compliance.
- The application should include a study coordinator(s) who will guide the clinical protocol through the local Institutional Review Board (IRB) of record and other Federal agency regulatory approval processes, coordinate activities from all sites participating in the trial, and coordinate participant accrual.
- The application should include a Transition Plan (including potential funding and resources) showing how the product will progress to the next clinical trial phase and/or delivery to the market after the successful completion of the FY18 PRMRP Clinical Trial Award.
- The application should clearly demonstrate strong institutional support and if applicable, a commitment to serve as the FDA regulatory sponsor, ensuring all sponsor responsibilities described in 21 CFR 312, Subpart D, are fulfilled.
- Funded studies are required to register the study in the National Institutes of Health (NIH) clinical trials registry, [www.clinicaltrials.gov](http://www.clinicaltrials.gov), prior to initiation of the study. Refer to the General Application Instructions, Appendix 1, Section C, for further details.

**Military Relevance:** Relevance to the healthcare needs of military Service members, Veterans, and beneficiaries is a key feature of this award. Investigators are encouraged to consider the following characteristics as examples of how a project may demonstrate military relevance:

- Explanation of how the project addresses an aspect of the target disease/condition/technology that has direct relevance to military Service members, Veterans, and/or other military health system beneficiaries

- Description of how the knowledge, information, products, or technologies gained from the proposed research could be implemented in a dual-use capacity to benefit the civilian population and also address a military need
- Use of military or Veteran populations or datasets in the proposed research, if appropriate to the proposed research project
- Collaboration with DoD or VA investigators
- Involvement of military consultants (Army, Air Force) or specialty leaders (Navy, Marine Corps) to the Surgeons General in a relevant specialty area

PIs are encouraged to integrate and/or align their research projects with DoD and/or VA research laboratories and programs. Collaboration with a DoD or VA investigator is also encouraged. A list of websites that may be useful in identifying additional information about ongoing DoD and VA areas of research interest or potential opportunities for collaboration within the FY18 PRMRP Topic Areas can be found in [Appendix 3](#).

**Use of DoD or VA Resources:** If the proposed research involves access to active duty military patient populations and/or DoD resources or databases, the PI is responsible for demonstrating such access at the time of application submission and should develop a plan for maintaining access as needed throughout the proposed research. Access to target active duty military patient population(s) and/or DoD resource(s) or database(s) should be confirmed by including a letter of support, signed by the lowest-ranking person with approval authority.

If the proposed research involves access to VA patient populations, VA study resources and databases, and/or VA research space and equipment, VA PIs must have a plan for obtaining and maintaining access throughout the proposed research. Access to VA patients, resources, and/or VA research space should be confirmed by including 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. If appropriate, the application should identify the VA-affiliated non-profit corporation (NPC) as the applicant institution for VA PIs. If the VA NPC is not identified as the applicant institution for administering the funds, the application should 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.

Access to certain DoD or VA patient populations, resources, or databases may only be obtained by collaboration with a DoD or VA investigator who has a substantial role in the research and may not be available to a non-DoD or non-VA investigator if the resource is restricted to DoD or VA personnel. Investigators should be aware of which resources are available to them if the proposed research involves a non-DoD or non-VA investigator collaborating with the DoD and/or VA. If access cannot be confirmed at the time of application submission, the Government reserves the right to withdraw or revoke funding until the PI has demonstrated support for and access to the relevant population(s) and/or resource(s). Refer to [Section II.D.2.b.ii, Full Application Submission Components](#), for detailed information.

The types of awards made under the Program Announcement will be assistance agreements (grants or cooperative agreements). 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.

**Extramural Organizations:** An assistance agreement (grant or cooperative 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. 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.

**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 Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO), prior to research implementation. This administrative review requirement is in addition to the local IRB or Ethics Committee (EC) review. Local IRB/EC approval at the time of submission is *not* required. The HRPO is mandated to comply with specific laws and requirements governing all research involving human anatomical substances, human subjects, or human cadavers that is supported by the DoD. These laws and requirements will necessitate information in addition to that supplied to the IRB/EC. ***Allow a minimum of 2 to 3 months for HRPO regulatory review and approval processes.*** Additional time for regulatory reviews may be needed for clinical studies taking place in international settings. When possible, protocols should be written for research with human subjects and/or human anatomical substances that are specific to the DoD-supported effort outlined in the submitted application as a stand-alone study. Submission to HRPO of protocols involving more than the scope of work in the DoD-funded award will require HRPO review of the entire protocol (DoD and non-DoD funded). DoD human subjects protection requirements may be applied to non-DoD funded work and necessitate extensive revisions to the protocol. 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.

If the IRB determines that a trial presents greater than minimal risk to human subjects, the DoD requires an independent research monitor with expertise consistent with the nature of risk(s) identified within the research protocol. If applicable, refer to the General Application Instructions, Appendix 1, for more information on study reporting authorities and responsibilities of the research monitor.

**Multi-Institutional Clinical Trials:** If the proposed clinical trial is multi-institutional, plans for the multi-institutional structure governing the research protocol(s) should be outlined in the [Attachment 10: Study Personnel and Organization](#). The lead organization responsible for developing the master protocol and master consent form should be identified, and should be the single point of contact for regulatory submissions and requirements. A single IRB or EC pathway is strongly recommended whenever possible. The master protocol and consent form must be reviewed by HRPO prior to distribution to the additional sites for IRB/EC review. Communication and data transfer among the collaborating institutions, as well as how specimens and/or imaging products obtained during the study will be handled, should be included in the appropriate sections of the application. A separate intellectual and material property plan agreed upon by all participating institutions is also required for multi-institutional clinical trials.

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.

Awards will be made no later than September 30, 2019. For additional information refer to [Section II.F.1, Federal Award Notices](#).

## **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, Government, and research institutes.

**Intramural DoD Organization:** A DoD laboratory, DoD military treatment facility, and/or DoD activity embedded within a civilian medical center.

**Note:** Applications from an intramural DoD organization or from an extramural Federal organization may be submitted through a research foundation.

The USAMRAA makes awards to eligible organizations, not to individuals.

### **II.C.1.b. Principal Investigator**

PIs at or above the level of Assistant Professor (or equivalent) are eligible to submit applications.

An eligible Principal Investigator, 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 <http://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). As an exception, applicants may submit the research project described in their Clinical Trial Award application as part of an application to the FY18 PRMRP Focused Program Award (Funding Opportunity Number: W81XWH18PRMRPFPA); however, accepting multiple awards to support the same project will not be allowed).*

**Extramural Submission** is defined as an application submitted by an organization to Grants.gov.

**Intramural DoD Submission** is defined as an application submitted by a DoD organization to eBRAP.

## **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.

***Extramural Submissions:*** Pre-application content and forms must be accessed and submitted at [eBRAP.org](https://eBRAP.org). Full application packages must be accessed and submitted at Grants.gov.

***Intramural DoD Submissions:*** Pre-application content and forms and full application packages must be accessed and submitted at [eBRAP.org](https://eBRAP.org).

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* and *full application* as indicated below. The submission process should be started early to avoid missing deadlines. There are no grace periods.

**Pre-Application Submission:** All pre-applications for both extramural and intramural organizations must be submitted through eBRAP (<https://eBRAP.org/>).

**Full Application Submission:** Full applications must be submitted through the online portals as described below.

***Submitting Extramural Organizations:*** Full applications from extramural organizations must be submitted through a Grants.gov Workspace. Applications submitted by extramural organizations (e.g., research foundations) on behalf of intramural DoD or other Federal organizations or investigators will be considered extramural submissions. Applications from extramural organizations, including non-DoD Federal organizations, received through eBRAP will be withdrawn. See definitions in [Section II.C.1, Eligible Applicants](#).

***Submitting Intramural DoD Organizations:*** Intramural DoD organizations may submit full applications to either eBRAP or Grants.gov. Intramural DoD organizations that are unable to submit to Grants.gov should submit through eBRAP. Intramural DoD organizations with the capability to submit through Grants.gov may submit following the instructions for extramural submissions through Grants.gov or may submit to eBRAP.

***For Both Extramural and Intramural Applicants:*** A key feature of eBRAP is the ability of an organization's representatives and PIs to view and modify the full application submissions associated with them. 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. It is the applicant's responsibility to review all application components for accuracy as well as ensure proper ordering as specified in this Program Announcement.

*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](mailto: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, each submission is assigned a unique log number by eBRAP. 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](mailto: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.

PIs and organizations identified in the pre-application should be the same as those intended for the subsequent application submission. If any changes are necessary after submission of the pre-application, the PI must contact the CDMRP Help Desk at [help@eBRAP.org](mailto: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>. Note that the codes have recently been revised. Applicants are strongly encouraged to review and confirm the codes prior to making their selection.

Select up to two FY18 PRMRP Topic Areas addressed by the proposed research. If the proposed research project is aligned with more than one FY18 PRMRP Topic Area, select the topic area of highest relevance as the required first choice.

- **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 (R&R) 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 (R&R) 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.

[FY18 PRMRP 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](mailto:help@eBRAP.org) or 301-682-5507.

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 pre-application or application preparation, research, or other duties for submitted pre-applications or applications. For FY18, the identities of the peer review contractor and the programmatic review contractor may be found at the CDMRP website (<http://cdmrp.army.mil/about/2tierRevProcess>). Pre-applications or applications that include names of personnel from either of these companies will be administratively withdrawn unless plans to manage conflicts of interest (COIs) are provided and deemed appropriate by the Grants Officer. Refer to the General Application Instructions, Appendix 3, for detailed information.

- **Tab 4 – Conflicts of Interest**

List all individuals other than collaborators and key personnel who may have a COI in the review of the application (including those with whom the PI has a personal or professional relationship). Refer to the General Application Instructions, Appendix 3, Section C, for further information regarding COIs.

- **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 (four-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:

- **Topic Area:** Describe how the proposed project relates to at least one FY18 PRMRP Topic Area. If applicable, describe how the proposed research project addresses an FY18 PRMRP Area of Encouragement ([Appendix 2](#)).
- **Research Idea:** Describe the ideas and reasoning on which the proposed clinical trial is based; include relevant literature citations. Briefly describe the level of scientific evidence that supports the progression of this research to a clinical trial. Clearly specify which type (e.g., drug, device, biologic, behavioral) of clinical trial is being proposed and indicate the regulatory status, sponsor, and phase of trial and/or class of device, as appropriate.
- **Research Strategy:** Concisely state the project’s hypothesis and/or objectives, and specific aims. Briefly describe the patient population(s) to be recruited for the clinical trial and the experimental approach, including study design and endpoints/outcome measures. State the estimated budget needed to conduct the trial.
- **Personnel:** Briefly state the qualifications of the PI and key personnel to perform the clinical trial. Note any DoD- or VA-relevant collaborations.
- **Impact and Military Relevance:** Describe how the proposed work will have an impact on accelerating the movement of a promising intervention into clinical application. Explain how the project is relevant to the healthcare needs of military Service members, Veterans, and/or beneficiaries.
- **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 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 DHP and the PRMRP, pre-applications will be screened based on the following criteria:

- **Research Idea:** The degree to which the proposed clinical trial addresses an important question in one or more of the FY18 PRMRP Topic Areas. How well the rationale is supported, and how well the background provided indicates the research is ready to move into the phase of clinical trial proposed.
- **Research Strategy:** How well the specific aims, patient population, and proposed methodology will address the hypothesis and/or reach the desired objectives.
- **Personnel:** How the background and experience of the PI and other key personnel are appropriate to successfully complete the clinical trial.
- **Impact and Military Relevance:** The degree to which the proposed clinical trial, if successful, will improve patient care in the FY18 PRMRP Topic Area(s) addressed. How well the research will address a healthcare issue relevant to military Service members, Veterans, and/or beneficiaries.

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

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

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

Each application submission must include the completed full application package for this Program Announcement. The full application package is submitted by the Authorized

Organizational Representative through Grants.gov (<http://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 the 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.

**Table 1. Full Application Submission Guidelines**

Extramural Submissions	Intramural DoD Submissions
<b>Application Package Location</b>	
Download application package components for W81XWH18PRMRPCTA from Grants.gov ( <a href="http://www.grants.gov/">http://www.grants.gov/</a> ) and create a Grants.gov Workspace. The 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 W81XWH18PRMRPCTA from eBRAP ( <a href="https://ebrap.org/">https://ebrap.org/</a> ).
<b>Full Application Package Components</b>	
<b>SF424 (R&amp;R) Application for Federal Assistance Form:</b> Refer to the General Application Instructions, Section III.A.1, for detailed information.	<b>Tab 1 – Summary:</b> Provide a summary of the application information. <b>Tab 2 – Application Contacts:</b> This tab will be pre-populated by eBRAP; add Authorized Organizational Representative.

Extramural Submissions	Intramural DoD Submissions
<p>Descriptions of each required file can be found under Full Application Submission Components:</p> <ul style="list-style-type: none"> <li>• <a href="#">Attachments</a></li> <li>• <a href="#">Research &amp; Related Personal Data</a></li> <li>• <a href="#">Research &amp; Related Senior/Key Person Profile (Expanded)</a></li> <li>• <a href="#">Research &amp; Related Budget</a></li> <li>• <a href="#">Project/Performance Site Location(s) Form</a></li> <li>• <a href="#">R&amp;R Subaward Budget Attachment(s) Form</a> (if applicable)</li> </ul>	<p><b>Tab 3 – Full Application Files:</b> Upload files under each Application Component in eBRAP. Descriptions of each required file can be found under Full Application Submission Components:</p> <ul style="list-style-type: none"> <li>• <a href="#">Attachments</a></li> <li>• <a href="#">Key Personnel</a></li> <li>• <a href="#">Budget</a></li> <li>• <a href="#">Performance Sites</a></li> </ul> <p><b>Tab 4 – Application and Budget Data:</b> Review and edit proposed project start date, proposed end date, and budget data pre-populated from the Budget Form.</p>
<b>Application Package Submission</b>	
<p><b>Create a Grants.gov Workspace.</b> Add participants (investigators and Business Officials) to the Workspace, complete all required forms, and check for errors before submission.</p> <p><b>Submit a Grants.gov Workspace Package.</b> 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 <b>at least 24-48 hours prior to the close date</b> to allow time to correct any potential technical issues that may disrupt the application submission.</p> <p>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.</p>	<p><b>Submit package components to eBRAP (<a href="https://ebrap.org">https://ebrap.org</a>).</b></p> <p><b>Tab 5 – Submit/Request Approval Full Application:</b> 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.</p>
<b><u><a href="#">Application Verification Period</a></u></b>	
<p>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, <b>with the exception of the Project Narrative and Budget Form</b>, may be modified.</p>	<p>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</p>

Extramural Submissions	Intramural DoD Submissions
	<p>period, the full application package, <i>with the exception of the Project Narrative and Budget Form</i>, may be modified. 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.</p>
Further Information	
<p><b>Tracking a Grants.gov Workspace Package.</b>            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.</p>	<p>Refer to the General Application Instructions, Section IV, for further information regarding eBRAP requirements.</p>

Application viewing, modification, and verification in eBRAP are strongly recommended, but not required. *The Project Narrative and Budget cannot be changed after the application submission deadline.* Prior to the full application deadline, a corrected or modified full application package may be submitted. 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.

*Material submitted after the end of the application verification period, unless specifically requested by the Government, will not be forwarded for processing.*

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 (R&R) 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.

*The Project Narrative is NOT the formal clinical trial protocol. Instead, all essential elements of the proposed clinical trial necessary for scientific review must be included as directed in Attachment 1 (the Project Narrative) and Attachments 5-8 described below. Failure to submit these attachments as part of the application package will result in rejection of the entire application.*

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

Describe the proposed project in detail using the outline below.

- **Background:** Describe in detail the rationale for the study. Provide a literature review and describe the preliminary studies and/or preclinical data that led to the development of the proposed clinical trial. Provide a summary of other relevant ongoing, planned, or completed clinical trials and describe how the proposed study differs. Include a discussion of any current clinical use of the intervention under investigation, and/or details of its study in clinical trials for other indications (as applicable). The background section should clearly support the choice of study variables and should explain the basis for the study questions and/or study hypotheses. This section should establish the relevance of the study and explain the applicability of the proposed findings.

If the proposed clinical trial was initiated using other funding prior to this application, explain the history and background of the clinical trial and declare the source of prior funding. Specifically identify the portions of the study that will be supported with funds from this award.

- **Objectives/Specific Aims/Hypotheses:** Provide a description of the purpose and objectives of the study with detailed specific aims and/or study questions/hypotheses.

This information should agree with the primary aims and associated tasks described in the Statement of Work ([Attachment 4](#)).

- **Study Design:** Describe the type of study to be performed (e.g., treatment, prevention, diagnostic), the study phase or class (if applicable), and the study model (e.g., single group, parallel, crossover). Outline the proposed methodology in sufficient detail to show a clear course of action.
  - Identify the intervention to be tested and describe the projected results.
  - Define the primary and any secondary or interim endpoints/outcome measures, outline why they were chosen, and describe how and when they will be measured. Include a description of appropriate controls. Outline the timing and procedures planned during the follow-up period.
  - Describe the study population and the inclusion and exclusion criteria that will be used.
  - Describe the methods that will be used to recruit a sample of human subjects from the accessible population (e.g., convenience, simple random, stratified random).
  - Define each arm/study group of the proposed trial, if applicable. Describe the human subject-to-group assignment process (e.g., randomization, block randomization, stratified randomization, age-matched controls, alternating group, or other procedures). Explain the specific actions to accomplish the group assignment (e.g., computer assignment, use of table of random numbers).
  - Outline whether subjects, clinicians, data analysts, and/or others will be blinded during the study. Describe any other measures to be taken to reduce bias.
  - If using psychometric measures, describe their reliability and validity.
  - If using herbal medicines or nutritional supplements, describe the proposed measures to ensure consistency of dosing.
  - Describe potential problem areas and discuss alternative methods/approaches that may be employed to overcome them. Estimate the potential for subject loss to follow-up, and how such loss will be handled/mitigated.
- **Statistical Plan and Data Analysis:** Describe the statistical model and data analysis plan with respect to the study objectives. Specify the approximate number of human subjects to be enrolled. If multiple study sites are involved, state the approximate number to be enrolled at each site. Include a complete power analysis to demonstrate that the sample size is appropriate to meet the objectives of the study. If a subpopulation of a recruited sample population will be used for analysis, complete a statistical analysis to ensure appropriate power can be achieved within the subpopulation study. Ensure sufficient information is provided to allow thorough evaluation of all statistical calculations during review of the application.

- **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 publications are not publicly available, then copies of up to five published manuscripts may be included in Attachment 2. Extra items will not be reviewed.
- **Letters of Organizational Support:** Provide a letter (or letters, if applicable), signed by the Department Chair or appropriate organization official, confirming the laboratory space, equipment, and other resources available for the project. Letters of support not requested in the Program Announcement, 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 of Commitment (if applicable): If the proposed study involves use of a commercially produced investigational drug, device, or biologic, provide a letter of commitment from the commercial entity indicating availability of the product for the duration of the study, support for the proposed phase of research, and support for the indication to be tested.
- 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.
- Data and Research Resources Sharing Plan: Describe how data and resources generated during the performance of the project will be shared with and made available to the research community. 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.
- **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 patient 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 ACOS/R&D or Clinical Service Chief confirming access to VA patients, resources, and/or VA research space. For VA PIs, if the VA NPC 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.
- Letter of Commitment: If the proposed study includes a clinical trial and involves use of a commercially produced investigational drug, device, or biologic, provide a letter of commitment from the commercial entity indicating availability of the product for the duration of the trial, support for the proposed phase of research, and support for the indication to be tested.
- **Attachment 3: Technical and Lay Abstracts (two-page limit):** Start each document on a new page. Combine into one document and upload as “Abstract.pdf.” The technical and lay abstracts are used by all reviewers. Abstracts of all funded research projects will be posted publicly on the CDMRP website (<http://cdmrp.army.mil>). **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.

**Technical Abstract:** Technical abstracts should be written using the outline below. Programmatic reviewers typically do not have access to the full application and rely on the technical abstract for appropriate description of the project’s key aspects. Therefore,

clarity and completeness within the space limits of the technical abstract are highly important.

- **Background:** Present the ideas and rationale behind the proposed clinical trial.
- **Relevance to Topic Area:** State the relevance of the project to at least one FY18 PRMRP Topic Area. If applicable, describe how the proposed research project addresses an FY18 PRMRP Area of Encouragement ([Appendix 2](#)).
- **Hypothesis/Objective(s):** State the hypothesis to be tested and/or objective(s) to be reached.
- **Specific Aims:** State the specific aims of the study.
- **Study Design:** Briefly describe the study design including appropriate controls.
- **Clinical Impact:** Briefly describe how the proposed project will have an impact on research and patient care in the specified disease(s)/condition(s).
- **Military Relevance:** Describe the military relevance of the study.

**Lay Abstract:** Lay abstracts should be written using the outline below. *Do not duplicate the technical abstract.*

- Clearly describe the objectives and rationale for the proposed study and intervention in a manner readily understood by readers without a background in science or medicine.
- State the FY18 PRMRP Topic Area(s) addressed by the proposed research project. If applicable, describe how the proposed research project addresses an FY18 PRMRP Area of Encouragement ([Appendix 2](#)).
- Describe the ultimate applicability and impact of the research.
  - What types of patients will it help, and how will it help them?
  - What are the potential clinical applications and benefits?
- **Attachment 4: 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 Clinical Trial Award mechanism, use the SOW format example titled, “SOW for Clinical Research (Including Trials, Special Populations).” 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 projected or required for each task and at each site. Indicate quarterly enrollment targets. 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. If human anatomical substances (including cell lines) will be used, specify whether or not identifiable information is accessible to the research team by any means.
- If applicable, indicate timelines required for regulatory approvals relevant to human subjects research (e.g., IND or IDE applications) by the FDA or other Government agency.
- **Attachment 5: Impact Statement (two-page limit). Upload as “Impact.pdf.”**
  - Identify the volunteer population(s) that will participate in the proposed intervention, describe how they represent the target population that would benefit from the intervention, and describe the potential impact of the proposed clinical trial on the lives and health of individuals with regard to the FY18 PRMRP Topic Area(s).
  - ***Describe the short-term impact:*** Detail the anticipated outcomes that will be directly attributed to the results of the proposed clinical trial.
  - ***Describe the long-term impact:*** Explain the long-range vision for implementation of the intervention in the clinic or field, and describe the anticipated long-term benefits for the targeted population.
  - Describe any relevant controversies or treatment issues that will be addressed by the proposed clinical trial.
  - Describe any potential issues that might limit the impact of the proposed clinical trial.
  - Describe how the intervention represents an improvement over currently available interventions and/or standards of care.
- **Attachment 6: Military Relevance Statement (one-page limit): Upload as “MilRel.pdf.”**
  - Describe how the proposed study is responsive to the healthcare needs of military Service members, Veterans, and/or beneficiaries. Provide information about the incidence and/or prevalence of the disease or condition in the general population as well as in military Service members, Veterans, and/or beneficiaries.

- If active duty military, military families, and/or Veteran population(s) will be used in the proposed research project, describe the population(s) and the appropriateness of the population(s) for the proposed study. If a non-military population will be used for the proposed research project, explain how the population simulates the targeted population (i.e., military Service members, Veterans, and/or beneficiaries).
- If applicable, show how the proposed research project aligns with DoD and/or VA areas of research interests. Provide a description of how the knowledge or technology gained from the research could be implemented in a dual-use capacity to benefit the civilian population and address a military need, as appropriate.
- **Attachment 7: Intervention (no page limit): Upload as “Intervention.pdf.”** The Intervention attachment should include the components listed below.

- **Description of the Intervention:** Identify the intervention to be tested and describe the particular outcomes. As applicable, the description of the intervention should include the following components: complete name and composition, storage and handling information, source, dose, schedule, administration route, washout period, duration of the intervention, and concomitant medications allowed. Description of devices should include general concept of design, detailed operational instructions, any potential risks to users, and intended benefits. Other types of interventions should be fully described. Indicate who holds the intellectual property rights to the intervention, if applicable, and how the PI has obtained access to those rights for conduct of the clinical trial.

Summarize key preclinical pharmacological findings, dosage studies, and other clinical studies (if applicable) that examine the safety and stability (as appropriate) of the intervention.

- **Study Procedures:** Describe the interaction with the human subject to include the study intervention that he/she will experience. Provide sufficient detail in chronological order for a person uninvolved in the study to understand what the human subject will experience. Provide a schedule (e.g., flowchart or diagram) of study evaluations and follow-up procedures. Clearly delineate research procedures from routine clinical procedures. Discuss how compliance with current Good Laboratory Practices (GLP), GMP, and other regulatory considerations will be established, monitored, and maintained, as applicable.
- **Clinical Monitoring Plan:** Describe how the study will be conducted by and monitored for current ICH E6 (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) GCP compliance, by an independent clinical trial monitor (or clinical research associate). The monitoring plan should describe the types of monitoring visits to be conducted, the intervals (based on level of risk), how corrective actions will be reported to the Sponsor and PI, and how they will be corrected and prevented by the clinical trial site/PI.

- **Attachment 8: Human Subject Recruitment and Safety Procedures (no page limit): Upload as “HumSubProc.pdf.”** The Human Subject Recruitment and Safety Procedures attachment should include the components listed below.
  - **Study Population:** Describe the target population (to whom the study findings will be generalized) and the nature, approximate number, and pertinent demographic characteristics of the accessible population at the study site(s) (population from whom the sample will be recruited/drawn). Provide a table of anticipated enrollment counts at each study site. Demonstrate that the research team has access to the proposed study population at each site, and describe the efforts that will be made to achieve accrual goals. Furthermore, discuss past efforts in recruiting human subjects from the target population for previous clinical trials (if applicable). Address any potential barriers to accrual and plans for addressing unanticipated delays. Identify ongoing clinical trials that may compete for the same patient population and how they may impact enrollment progress. Provide justification related to the scientific goals of the proposed study for limiting inclusion of any group by age, race, ethnicity, or sex/gender. *For clinical trials proposing to include military personnel, refer to the General Application Instructions, Appendix 1, for more information.*
  - **Inclusion/Exclusion Criteria:** List the inclusion and exclusion criteria for the proposed clinical trial. Inclusion/exclusion criteria should take into consideration the specific risk profile of the studies to be conducted and the standard of care for that patient population. Provide detailed justification for exclusions.
 

*Inclusion of Women and Minorities in Study.* Consistent with the Belmont Report, “Ethical Principles and Guidelines for the Protection of Human Subjects,” and Congressional legislation, special attention is given to inclusion of women and/or minorities in studies funded or supported by the USAMRMC. This policy is intended to promote equity both in assuming the burdens and in receiving the benefits of human subjects research. Include an appropriate justification if women and/or minorities will be excluded from the clinical trial.
  - **Description of the Recruitment Process:** Explain methods for identification of potential human subjects (e.g., medical record review, obtaining sampling lists, healthcare provider identification).
    - Describe the recruitment process in detail. Address who will identify potential human subjects, who will recruit them, and what methods will be used to recruit them.
    - If human subjects will be compensated for participation in the study, include a detailed description of and justification for the compensation plan.
    - Describe the recruitment and advertisement materials. The recruitment materials should not be coercive or offer undue inducements and should accurately reflect the study.

- **Description of the Informed Consent Process:** Specifically describe the plan for obtaining informed consent from human subjects.
  - ***For the proposed study, provide a draft, in English, of the Informed Consent Form.***
  - Identify who is responsible for explaining the study, answering questions, and obtaining informed consent. Include a plan for ensuring that human subjects' questions will be addressed during the consent process and throughout the trial.
  - Include information regarding the timing and location of the consent process.
  - Address issues relevant to the mental capacity of the potential human subject (e.g., altered capacity due to administration of any mind-altering substances such as tranquilizers, conscious sedation or anesthesia, brain injury, stress/life situations, or human subject age), if applicable.
  - Address how privacy and time for decision making will be provided and whether or not the potential human subject will be allowed to discuss the study with anyone before making a decision.
  - Consider the need for obtaining ongoing consent or for re-assessing capacity over the course of a long-term study and describe any relevant procedures to assure continued consent.
  - Describe the plan for the consent of the individual's Legally Authorized Representative (LAR) to be obtained prior to the human subject's participation in the study. State law defines who may act as the LAR. The local IRB of record should be consulted for guidance regarding who can serve as LAR for research at the study site. Note: The PI must describe a clear intent to benefit for human subjects who cannot give their own consent to participate in the proposed clinical trial to be in compliance with Title 10 United States Code Section 980 (10 USC 980) (<http://www.gpo.gov/fdsys/pkg/USCODE-2011-title10/pdf/USCODE-2011-title10-subtitleA-partII-chap49-sec980.pdf>). If applicable, refer to the General Application Instructions, Appendix 1, for more information.
  - ***Assent.*** If minors or other populations that cannot provide informed consent are included in the proposed clinical trial, a plan to obtain assent (agreement) from those with capacity to provide it, or a justification for a waiver of assent, should be provided. PIs should consult with their local IRB to identify the conditions necessary for obtaining assent.
- **Screening Procedures:** List and describe any evaluations (e.g., laboratory procedures, history, or physical examination) that are required to determine eligibility/suitability for study participation and the diagnostic criteria for entry. Note that some screening procedures may require a separate consent or a two-stage consent process.

– **Risks/Benefits Assessment:**

- **Foreseeable risks:** Clearly identify all study risks, including potential safety concerns and adverse events. Study risks include any risks that the human subject is subjected to as a result of participation in the clinical trial. Consider psychological, legal, social, and economic risks as well as physical risks. If the risks are unknown, this should be stated. If applicable, any potential risk to the study personnel should be identified.
- **Risk management and emergency response:**
  - ❖ Describe how safety surveillance and reporting to the IRB and FDA (if applicable) will be managed and conducted.
  - ❖ Describe all safety measures to minimize and/or eliminate risks to human subjects and study personnel or to manage unpreventable risks. Include safeguards and planned responses such as dose reduction or stopping criteria based on toxicity grading scales or other predetermined alert values.
  - ❖ Discuss the overall plan for provision of emergency care or treatment for an adverse event for study-related injuries, to include who will be responsible for the cost of such care.
  - ❖ Address any special precautions to be taken by the human subjects before, during, and after the study (e.g., medication washout periods, dietary restrictions, hydration, fasting, pregnancy prevention).
  - ❖ Describe any special care (e.g., wound dressing assistance, transportation due to side effects of study intervention impairing ability to drive) or equipment (e.g., thermometers, telemedicine equipment) needed for human subjects enrolled in the study.
  - ❖ If the IRB determines that a trial presents greater than minimal risk to human subjects, the DoD requires an independent research monitor with expertise consistent with the nature of risk(s) identified within the research protocol. If applicable, refer to the General Application Instructions, Appendix 1, for more information on study reporting authorities and responsibilities of the research monitor.
- **Potential benefits:** Describe known and potential benefits of the study to the human subjects who will participate in the study. Articulate the importance of the knowledge to be gained as a result of the proposed research. Discuss why the potential risks to human subjects are reasonable in relation to the anticipated benefits to the human subjects and others that may be expected to result.
- **Attachment 9: Surveys, Questionnaires, and Other Data Collection Instruments, if applicable (no page limit): Upload as “Surveys.pdf.”** The Surveys, Questionnaires, and Other Data Collection Instruments attachment should include a copy of the most

recent version of surveys, questionnaires, data collection forms, rating scales, interview guides, or other instruments. For each instrument, describe how the information collected is related to the objectives of the study. Describe how and when the instrument(s) will be administered. Describe how the instrument(s) will be adapted to the subject population, if applicable.

- **Attachment 10: Study Personnel and Organization (no page limit):** Start each document on a new page. **Combine into one document and upload as “Personnel.pdf.”** The Study Personnel and Organization attachment should include the components listed below.
  - **Organizational Chart:** Provide an organizational chart that identifies key members of the study team and provides an outline of the governing structure for multi-institutional studies. Identify collaborating organizations, centers, and/or departments and name each person’s position on the project. Include any separate laboratory or testing centers. Identify the data and clinical coordinating center(s) and note any involvement from Contract Research Organizations, as appropriate. Identify and provide justification for the inclusion of international sites, as appropriate. If applicable, identify the FDA regulatory sponsor and any external consultants or other experts who will assist with FDA applications. While there is no specified format for this information, a table(s) or diagram is recommended. Note: This item may be made available for programmatic review.
  - **Study Personnel Description:** Briefly describe the roles of the individuals listed in the organizational chart on the project. Describe relevant experience and qualifications that demonstrate appropriate expertise for the given role, including previous interactions with the FDA, if applicable. An external research monitor (if applicable) and study coordinator(s) should be included.
  - **Study Management Plan:** Provide a plan for ensuring the standardization of procedures among staff and across sites (if applicable). If the proposed clinical trial is multi-institutional, clearly describe the multi-institutional structure governing the research protocol(s) across all participating institutions. Provide a regulatory submission plan for the master protocol and master consent form by the lead organization; include a single IRB/EC pathway whenever possible. If applicable, describe how communication and data transfer between the collaborating institutions will occur, as well as how data, specimens, and/or imaging products obtained during the study will be handled and shared.
- **Attachment 11: Data Management Plan (no page limit): Upload as “Data\_Manage.pdf.”** The Data Management Plan attachment should include the components listed below.
  - **Data Management:** Describe all methods used for data collection to include the following:
    - **Identifiers:** Describe the unique identifiers or specific code system to be used to identify human subjects, if applicable.

- **Confidentiality:**
  - ❖ Explain measures taken to protect the privacy of human subjects and maintain confidentiality of study data. Strategies to protect the privacy and confidentiality of study records, particularly those containing identifying information, should be addressed.
  - ❖ Address who will have access to study records, data, and specimens, including an acknowledgment that representatives of the DoD are eligible to review study records.
  - ❖ Address requirements for reporting sensitive information to state or local authorities.
- **Data capture, verification, and disposition:** Describe how data will be captured and verified. Describe where data (both electronic and hard copy) will be stored, who will keep the data, how the data will be stored, the process for locking the database at study completion, and the length of time data will be stored. Describe the proposed database, how it will be developed and validated, and its capability to safeguard and maintain the integrity of the data. Describe the database lock process. For FDA-regulated studies, compliance with 21 CFR 11 and appropriate data standards (such as those established by the Clinical Data Interchange Standards Consortium) are required.
- **Data reporting:** 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.
- **Sharing study results:** In cases where the human subject could possibly benefit medically or otherwise from the information, explain whether or not the results of screening and/or study participation will be shared with human subjects or their primary care provider, to include results from any screening or diagnostic tests performed as part of the study.
- **Laboratory Evaluations:**
  - **Specimens to be collected, schedule, and amount:** All specimens that will be collected for study purposes must be clearly stated. The collection schedule and amount of material collected must also be clearly described.
  - **Evaluations to be made:** Describe all evaluations that will be made for study purposes. Explain how the results of laboratory evaluations will be used to meet the objectives of the study (or to monitor safety of human subjects).
  - **Storage:** Describe specimen storage, to include location of storage, how long specimens will be stored, any special conditions required, labeling, and specimen disposition. Outline the plan to store specimens for future use to include

considerations for informed consent and providing human subjects with an opportunity to decline participation in the study.

- **Laboratories performing evaluations and special precautions:** Identify the laboratory performing each evaluation, the applicable quality standard, and any special precautions that should be taken in handling the samples. Special precautions that should be taken by the human subject before, during, or after the laboratory procedure should be clearly defined. If transport of samples is required, describe provisions for ensuring proper storage during transport.
- **Attachment 12: Transition Plan (three-page limit): Upload as “Transition.pdf.”**  
Describe/discuss the methods and strategies proposed to move the intervention to the next phase of development (clinical trials, commercialization, and/or delivery to the civilian or military market) after successful completion of the award. Applicants are encouraged to work with their organization’s Technology Transfer Office (or equivalent) to develop the transition plan. PIs are encouraged to explore developing relationships with industry and/or other funding agencies to facilitate moving the product into the next phase of development. The post-award transition plan should include the components listed below.
  - Details of the funding strategy to transition to the next level of development and/or commercialization (e.g., specific industry partners, specific funding opportunities to be applied for). Include a description of collaborations and other resources that will be used to provide continuity of development.
  - For Knowledge Products, a description of collaborations and other resources that will be used to provide continuity of development including proposed development or modification of clinical practice guidelines and recommendations, provider training materials, patient brochures, and other clinical support tools, scientific journal publications, models, simulations, and applications. A “Knowledge Product” is a non-materiel product that addresses an identified need, topic area, or capability gap, is based on current evidence and research, aims to transition into medical practice, training, tools, or to support materiel solutions (systems to develop, acquire, provide, and sustain medical solutions and capabilities), and educates or impacts behavior throughout the continuum of care, including primary prevention of negative outcomes.
  - A brief schedule and milestones for transitioning the intervention to the next phase of development (i.e., next-phase clinical trials, commercialization, delivery to the military or civilian market, incorporation into clinical practice, and/or approval by the FDA).
  - Ownership rights/access to the intellectual property necessary for the development and/or commercialization of products or technologies supported with this award and the Government’s ability to access such products or technologies in the future.
  - A risk analysis for cost, schedule, manufacturability, and sustainability.

- **Attachment 13: Regulatory Strategy (no page limit):** If submitting multiple documents, start each document on a new page. **Combine and upload as a single file named “Regulatory.pdf.”**

Describe the regulatory strategy using the following outline and provide supporting documentation as applicable.

- State the product/intervention name.

***For products/interventions that do not require regulation by the FDA or an international regulatory agency:***

- Describe the rationale for why the product/intervention is exempt from FDA oversight. Provide a copy of the confirmation in writing from the IRB of record, the FDA, or the international regulatory agency for clinical trials conducted at an international site(s) ***that the proposed investigational drug/agent/device is exempt or the proposed investigational device qualifies for an abbreviated IDE.***

***For products/interventions that require regulation by the FDA and/or an international regulatory agency:***

- State whether the product is FDA-approved, -licensed, or -cleared and marketed in the U.S.
- If the product is marketed in the U.S., state the product label indication. State whether the proposed research involves a change to the approved label indication for the route of administration, dosage level, and/or subject population. Indicate whether the proposed research involves a change that increases the risks associated with using the product. State whether the product is being promoted for an off-label use (where promotion involves the sale of a marketed product).
- Identify the regulatory sponsor. Include a signed sponsor commitment letter acknowledging the regulatory sponsor’s understanding of all sponsor responsibilities and commitment to oversee execution of the study.
- If an IND or IDE is required, provide a copy of the FDA acknowledgment letter to include submission date and receipt date. Provide an explanation of the status of the application (e.g., statement that the FDA did not raise concerns, past the critical 30-day period, pending response to questions raised by the FDA, on clinical hold).
- If a technical or a protocol amendment to an IND/IDE is necessary to complete the clinical trial, then provide a copy of the FDA acknowledgment letter and meeting minutes (pre-IND/pre-IDE and/or Type C) that ascertains the FDA’s concurrence to the proposed regulatory approach. Documents must demonstrate clear evidence that the proposed investigational drug or device will not require new IND/IDE submission pertaining to the indication and formulation to be used in the clinical trial.

- If the clinical trial will be conducted at an international site(s), provide equivalent information and supporting documentation relevant to the product/intervention and regulatory approval in the host country(ies).
- Provide a current status for manufacturing development (e.g., manufacturer’s name, GMP-compliant lots available, status of stability testing, etc.), non-clinical development (e.g., test facility name, status of pivotal GLP toxicology studies to support Phase I testing, etc.), and clinical development (e.g., clinical site name, safety profile, status of any completed or ongoing clinical trials).
- Describe the overall regulatory strategy and product development plan that will support the planned product indication. Include considerations for compliance with current GMP, GLP, and GCP guidelines.
- **Attachment 14: Representations** (extramural submissions only): Upload as “MandatoryReps.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 15: DoD Military Budget Form(s), 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 the DoD Military Budget Form, 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 and Related Budget form under subaward costs. Refer to the General Application Instructions, Section III.A.7, 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, 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.3, and for intramural submissions (via eBRAP), refer to the General Application Instructions, Section IV.A.2, 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 NIH Biographical Sketch may also be used. All biographical sketches should be submitted in the PDF format that is not editable.
- PI Previous/Current/Pending Support (no page limit): Upload as “Support\_LastName.pdf.”
- Key Personnel Biographical Sketches (five-page limit each): Upload as “Biosketch\_LastName.pdf.”
- Key Personnel Previous/Current/Pending Support (no page limit): Upload as “Support\_LastName.pdf.”

**Research & Related Budget:** 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.

**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.5, and for intramural submissions (via eBRAP), refer to the General Application Instructions, Section IV.A.4, for detailed information.

- **Extramural Applications Only**

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

- **Extramural Subaward:** Complete the Research & Related Subaward Budget Form through Grants.gov. (Refer to the General Application Instructions, Section III.A.6, 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 DoD Military Budget Form and upload to Grants.gov attachment form as Attachment 15. (Refer to the General Application Instructions, Section III.A.7, for detailed information.) Intramural DoD Collaborator(s) costs per year should be included on the Grants.gov Research and Related Budget form under subaward costs.

**DoD Military Budget Form:** A military facility collaborating in the performance of the project should be treated as a subaward for budget purposes. However, do not complete the

Grants.gov R&R Subaward Budget Attachment Form; instead, complete the DoD Military Budget Form (Attachment 15) to show all direct and indirect costs. 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.7, for detailed information.

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

Applicant organizations and all subrecipient organizations must have a DUNS number to submit applications to Grants.gov. The applicant organization must also be registered in the Entity Management functional area of the SAM with an “Active” status to submit applications through the Grants.gov portal. Verify the status of the applicant’s organization’s Entity registration in SAM well in advance of the application submission deadline. Allow 3 to 4 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.

### **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**

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 retrieved files against the specific Program Announcement requirements and discrepancies will be noted in both the email and in the “Full Application Files” tab in eBRAP. eBRAP does not confirm the accuracy of file content. It is the applicant’s responsibility to review all application components and ensure proper ordering as specified in the Program Announcement. ***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 Budget Form cannot be changed after the application submission deadline.

***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(s) 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 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 **4** years.

Applications are not restricted to a predetermined cost limit. The requested budget must be justified and appropriate to the scope of the clinical trial proposed.

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 using an indirect cost rate exceeding the organization's negotiated rate.

All direct and indirect costs of any subaward or contract must be included in the total direct costs of the primary award.

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

- Salary
- Research supplies
- Equipment
- Research-related subject costs
- Support for multidisciplinary collaborations, including travel
- Travel between collaborating organizations
- Travel costs for the PI to disseminate project results at one DoD-sponsored meeting to be specified by the program office during award negotiations (*i.e.*, the Military Health System Research Symposium)
- Travel costs for up to two investigators to travel to one scientific/technical meeting per year to present project outcomes from the PRMRP Clinical Trial Award

Awards made to extramural organizations will consist solely of assistance agreements (Cooperative Agreements and Grants). 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 fund 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.4, 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.4.*

*The CDMRP expects to allot approximately \$48M of the \$330M FY18 appropriation to fund approximately eight Clinical Trial Award applications, depending on the quality and number of applications received. Funding of applications received in response to this Program Announcement is contingent upon the availability of Federal funds for this program.*

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. The time is considered when establishing the award's period of performance. It is anticipated that awards made from this funding opportunity will be funded with FY18 funds, which will expire for use on September 30, 2024.

#### **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:

- **Clinical Impact**
  - To what degree the anticipated outcomes of the proposed clinical trial are to individuals affected by the specified disease/condition.
  - How well the sample population represents the targeted patient population that might benefit from the proposed intervention.
  - To what degree the potential outcomes of the proposed clinical trial will provide/improve short-term benefits for individuals.
  - How significantly the long-term benefits for implementation of the intervention may impact patient care and/or quality of life.

- **Research Strategy**

- How well the scientific rationale for clinically testing the intervention is supported by the preliminary data, critical review and analysis of the literature, and/or laboratory/preclinical evidence.
- How well the study aims, hypotheses and/or objective(s), experimental design, methods, data collection procedures, and analyses are designed to answer clearly the clinical objective(s).
- How well the inclusion and randomization criteria meet the needs of the proposed clinical trial.
- How well the exclusion criteria are justified.
- How well plans to collect specimens and conduct laboratory evaluations are addressed, if applicable.
- To what degree the data collection instruments (e.g., surveys, questionnaires), if applicable, are appropriate to the proposed study.

- **Intervention**

- Whether there is evidence of support, indicating availability of the intervention from its source, for the duration of the proposed clinical trial (if applicable).
- To what degree the intervention addresses the clinical need(s) described.
- How the intervention compares with currently available interventions and/or standards of care.
- To what degree preclinical and/or clinical evidence to support the safety of the intervention is provided.
- How well research procedures are clearly delineated from routine clinical procedures.
- Whether measures are described to ensure the consistency of dosing of active ingredients for nutritional supplements (if applicable).

- **Regulatory Strategy and Transition Plan**

- To what degree the regulatory strategy and development plan to support a new indication or product label change, if applicable, are appropriate and well described.
- Whether the application includes documentation that the study is exempt from FDA or other international agency regulation, or that IND or IDE approval (and/or international equivalent) has been obtained from the FDA and/or relevant international regulatory agency, as appropriate and is included in the Clinical Trial Award application submission.

- For investigator-sponsored regulatory exemptions (e.g., IND, IDE, or other international equivalent), whether there is evidence of appropriate institutional support, including capabilities to ensure monitoring as required by the FDA or relevant international regulatory agency.
  - Whether plans to comply with current GMP, GLP, and GCP guidelines are appropriate.
  - Whether the identified next level of development and/or commercialization is practical.
  - Whether the funding strategy described to bring the intervention to the next level of development (e.g., specific industry partners, specific funding opportunities to be applied for) is reasonable and achievable.
  - For Knowledge Products, whether the proposed collaborations and other resources for providing continuity of development, including proposed development or modification of clinical practice guidelines and recommendations, provider training materials, patient brochures, and other clinical support tools, scientific journal publications, models, simulations, and applications are established and/or achievable.
  - Whether the schedule and milestones for bringing the intervention to the next level of development (next-phase clinical trials, transition to industry, delivery to the market, incorporation into standard practice, and/or approval by the FDA) are achievable.
  - Whether the potential risk analysis for cost, schedule, manufacturability, and sustainability is realistic and reasonable.
  - How well the application identifies intellectual property ownership, demonstrates the appropriate access to all intellectual property rights necessary for development and commercialization, describes an appropriate intellectual and material property plan among participating organizations (if applicable), and addresses any impact of intellectual property issues on product development and subsequent Government access to products supported by this Program Announcement.
- **Recruitment, Accrual, and Feasibility**
    - How well the availability of human subjects for the clinical trial and the prospect of their participation is addressed.
    - Whether access to the proposed human subjects population is demonstrated.
    - The degree to which the recruitment, informed consent, screening, and retention processes for human subjects will meet the needs of the proposed clinical trial.
    - How well the application identifies possible delays (e.g., slow accrual, attrition) and presents adequate contingency plans to resolve them.
    - To what extent the proposed clinical trial might affect the daily lives of the individual human subjects participating in the study (e.g., Will human subjects still be able to take

their regular medications while participating in the clinical trial? Are human subjects required to stay overnight in a hospital?).

- **Statistical Analysis Plan**

- To what degree the statistical model and data analysis plan are suitable for the planned study.
- How the statistical plan, including sample size projections and power analysis, is adequate for the study and all proposed correlative studies.
- If applicable, whether the statistical plan compensates for the use of a subpopulation of a recruited sample population to ensure appropriate power can be achieved within the subpopulation study.

- **Ethical Considerations**

- Whether the population selected to participate in the trial stands to benefit from the knowledge gained.
- If applicable, how well the inclusion of international sites is justified.
- How well the level of risk to human subjects is minimized and whether the safety monitoring and reporting plan is appropriate for the level of risk.
- Whether a research monitor with expertise consistent with the nature of the potential risk(s) is identified, if applicable.
- How well the evidence shows that the procedures are consistent with sound research design and, when appropriate, that these procedures are already in use for diagnostic or treatment purposes.
- To what degree privacy and confidentiality issues are appropriately considered.
- To what degree the process for seeking informed consent is appropriate and whether safeguards are in place for vulnerable populations.

- **Personnel and Communication**

- Whether the composition of the study team (e.g., study coordinator, statistician) is appropriate.
- To what degree the study team's background and expertise are appropriate to accomplish the proposed work (e.g., statistical expertise, expertise in the disease, and expertise in conducting clinical trials).
- Whether the levels of effort of the study team members are appropriate for successful conduct of the proposed trial.

- How well the logistical aspects of the proposed clinical trial (e.g., communication plan, data transfer and management, standardization of procedures) meet the needs of the proposed clinical trial.
- For multi-site clinical trials, how well the lead site responsibilities and human research protections regulatory coordination are defined and planned for.

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

- **Environment**

- To what degree the scientific environment, clinical setting, and the accessibility of institutional resources support the clinical trial at each participating center or institution (including collaborative arrangements).
- Whether there is evidence for appropriate institutional commitment from each participating institution.

- **Budget**

- Whether the budget is 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 FY18 PRMRP, as evidenced by the following:
  - Adherence to the intent of the award mechanism
  - Military relevance
  - Program portfolio composition
  - Relative clinical impact

## **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 of applications against established criteria for determining technical merit. Each application is evaluated for its own merit, independent of other applications. The second tier is a programmatic review that makes recommendations for funding to the Commanding General, USAMRMC, on behalf of the DHA and the OASD(HA), based on technical merit, the relevance to the mission of the DHP and PRMRP, the specific intent of the award mechanism, and to other specified evaluation criteria in the Program Announcement. Programmatic review is a comparison-based process in which applications with scientific and technical merit compete in a common pool. *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 <http://cdmrp.army.mil/about/fundingprocess>.

All CDMRP review processes are conducted confidentially to maintain the integrity of the merit-based selection process. Panel members sign a statement that application and evaluation information will not be disclosed outside the panel. Violations of confidentiality can result in the dissolving of a panel(s) and other corrective actions. In addition, personnel at the applicant or collaborating organizations are prohibited from contacting persons involved in the review 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 (currently \$150,000) 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 (FAPIS).

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

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 (DoDGAR), 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 will be made no later than September 30, 2019. 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.

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 Organizations:*** Awards 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.

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

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

The organizational transfer of an award supporting a clinical trial is strongly discouraged and in most cases will not be allowed. Approval of a transfer request will be on a case-by-case basis at the discretion of the Grants Officer. An organizational transfer of an award will not be allowed in the last year of the (original) period of performance or any extension thereof.

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

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

If additional conference travel is proposed, prior to the rebudgeting and in advance of the incurrence of the travel costs, the Grants Officer should be consulted to determine the reasonableness of the expense in accordance with 2 CFR 200.407.

Applicable requirements in the DoDGAR found in 32 CFR, Chapter 1, 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 [USAMRAA General Research Terms and Conditions with Institutions of Higher Education, Hospitals, and Non-Profit Organizations](#): Addendum to the DoD R&D 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.

Quarterly technical progress reports will be required.

Award Chart: Complete the Award Chart template, a one-page PowerPoint file that must be downloaded from the CDMRP eBRAP System at <https://ebrap.org/eBRAP/public/Program.htm>, and submit to eBRAP at the time of award.

Award Expiration Transition Plan: An Award Expiration Transition Plan must be submitted with the final progress report. Use the one-page template titled, "Transition Plan," available on the on the eBRAP "Funding Opportunities & Forms" web page (<https://ebrap.org/eBRAP/public/Program.htm>) under the "Progress Report Formats" section.

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 Terms and Conditions (see General Application Instructions, Section III.A.4).

## **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](mailto: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](mailto: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 20180329f. The Program Announcement numeric version code will match the General Applications Instructions version code 20180329.

### **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.
- Submission of the same research project to different Funding Opportunities within the same program and fiscal year. Refer to [Section II.D, Application and Submission Information](#), for exceptions.
- Intervention (Attachment 7) is missing.
- Human Subject Recruitment and Safety Procedures (Attachment 8) is missing.
- Data Management Plan (Attachment 11) is missing.
- Regulatory Strategy (Attachment 13) 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 FY18 PRMRP 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 FY18 PRMRP Programmatic Panel members can be found at <http://cdmrp.army.mil/prmrp/panels/panels18>.*
- The application fails to conform to this Program Announcement description to the extent that appropriate review cannot be conducted.

- Inclusion of URLs, with the exception of links in References Cited and Publication and/or Patent Abstract sections.
- Page size is larger than 8.5 inches x 11.0 inches (approximately 21.59 cm x 27.94 cm).
- 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 FY18, the identities of the peer review contractor and the programmatic review contractor may be found at the CDMRP website (<http://cdmrp.army.mil/about/2tierRevProcess>). Applications that include names of personnel from either of these companies will be administratively withdrawn unless plans to manage COIs are provided and deemed appropriate by the Grants Officer. Refer to the General Application Instructions, Appendix 3, for detailed information.
- 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.
- The proposed research is not a clinical trial.
- For studies for which an IND or an IDE is not required/exempt, evidence in the form of formal communication from the FDA or the IRB of record to that effect is not provided.
- For studies requiring an IND or IDE, documentation of IND/IDE acknowledgement is not provided.
- For studies requiring an IND or IDE amendment, documentation of the FDA's concurrence to proposed regulatory approach is not provided.
- For studies with international sites, documentation of the relevant regulatory approval from the host country(ies) is not provided.
- The proposed research does not address at least one of the Congressionally directed FY18 PRMRP Topic Areas.
- An application submitted by a PI who does not meet the eligibility criteria will be withdrawn.

#### **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 (R&R) Application for Federal Assistance <b>(Extramural submissions only)</b>	Complete form as instructed.	
Summary (Tab 1) and Application Contacts (Tab 2) <b>(Intramural submissions only)</b>	Complete these 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 and Lay Abstracts: Upload as Attachment 3 with file name "Abstracts.pdf."	
	Statement of Work: Upload as Attachment 4 with file name "SOW.pdf."	
	Impact Statement: Upload as Attachment 5 with file name "Impact.pdf."	
	Military Relevance Statement: Upload as Attachment 6 with file name "MilRel.pdf."	
	Intervention: Upload as Attachment 7 with file name "Intervention.pdf."	
	Human Subject Recruitment and Safety Procedures: Upload as Attachment 8 with file name "HumSubProc.pdf."	
	Surveys, Questionnaires, and Other Data Collection Instruments: Upload as Attachment 9 with file name "Surveys.pdf."	
	Study Personnel and Organization: Upload as Attachment 10 with file name "Personnel.pdf."	
	Data Management Plan: Upload as Attachment 11 with file name "Data_Manage.pdf."	
	Transition Plan: Upload as Attachment 12 with file name "Transition.pdf."	
	Regulatory Strategy: Upload as Attachment 13 with file name "Regulatory.pdf."	
	Representations (Extramural submissions only): Upload as Attachment 14 with file name "MandatoryReps.pdf," if applicable.	
DoD Military Budget Form(s): Upload as Attachment 15 with file name "MFBudget.pdf," if applicable.		

<b>Application Components</b>	<b>Action</b>	<b>Completed</b>
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 ( <b>Extramural submissions only</b> )	Complete as instructed. Attach Budget Justification (BudgetJustification.pdf) to the appropriate field.	
Budget ( <b>Intramural submissions only</b> )	Complete the DoD Military Budget Form and justification.	
Project/Performance Site Location(s) Form	Complete form as instructed.	
R&R 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
CDMRP	Congressionally Directed Medical Research Programs
CFR	Code of Federal Regulations
COI	Conflict of Interest
DHA	Defense Health Agency
DHP	Defense Health Program
DoD	Department of Defense
DoDGAR	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	U.S. Department of Food and Drug Administration
FY	Fiscal Year
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HRPO	Human Research Protection Office
ICH E6	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
LAR	Legally Authorized Representative
M	Million
MIPR	Military Interdepartmental Purchase Request
NIH	National Institutes of Health
NPC	Non-Profit Corporation
OASD(HA)	Office of the Assistant Secretary of Defense for Health Affairs
OMB	Office of Management and Budget
ORCID	Open Researcher and Contributor ID, Inc.
ORP	Office of Research Protections
PI	Principal Investigator
PRMRP	Peer Reviewed Medical Research Program
RDT&E	Research, Development, Test, and Evaluation
SAM	System for Award Management
SOW	Statement of Work
STEM	Science, Technology, Engineering, Mathematics
USAMRAA	U.S. Army Medical Research Acquisition Activity
USAMRMC	U.S. Army Medical Research and Materiel Command
USC	United States Code
VA	Department of Veterans Affairs

## **APPENDIX 2: AREAS OF ENCOURAGEMENT**

Applications addressing any of the FY18 PRMRP Topic Areas are of interest to the program. *Any aspect of research relevant to one or more FY18 PRMRP Topic Areas may be considered for funding.* Areas of encouragement related to the FY18 PRMRP Topic Areas have been identified by the DoD, VA, and other relevant stakeholders. Applicants are urged to read and consider these areas of encouragement before preparing their applications. *The information provided is not exhaustive, and applicants are not restricted to submitting applications that address an area of encouragement in this list.*

### **Acute Lung Injury**

- Research on the etiology and prevention of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) caused by the host's (e.g., immune system's) responses to trauma, transfusion, burns, infection, hemorrhagic shock, inhalation, and/or oxygen exposure.
- Novel and/or innovative detection technologies or therapeutics to reduce the incidence and/or severity of ALI/ARDS and/or other lung injury secondary to trauma, transfusion, infection, burns, hemorrhagic shock, inhalation, and/or oxygen exposure.
- Strategies to stabilize and support the safe transport of patients with ALI/ARDS in order to optimize therapeutic interventions, particularly in operational scenarios requiring prolonged field care and/or longer transport times.
- Development of metrics to associate the long-term health outcomes of ALI/ARDS with physiological and physical performance.

### **Antimicrobial Resistance**

- Development of novel and/or innovative interventions, diagnostics, and treatment for multidrug-resistant pathogens, especially those that can be used in austere settings.
- Development of novel and/or innovative therapies that prevent and/or interrupt biofilm production in wound infections and infected hardware models.
- Development and testing of treatment protocols and/or diagnostic tests to limit prescribing antibiotics for conditions that are commonly viral in nature or conditions that would resolve themselves without antibiotic treatment (e.g., sinusitis, bronchitis, viral upper respiratory infections, and acute gastroenteritis).
- Development and evaluation of therapies to treat travelers' diarrhea to improve the time to clinical cure and minimize resistance acquisition.
- Development of gene editing tools (e.g., designer nucleases) that optimize treatment and raise the threshold for resistance of anti-infective agents.

### **Arthritis (other than Rheumatoid Arthritis or Post-Traumatic Osteoarthritis)**

- Research toward the development of clinical practice guidelines to prevent, identify, and treat arthritis.

- Research quantifying the impacts of obesity, weight loss, physical fitness (all components—cardiovascular, strength, flexibility, balance), and dietary factors on the development of or prevention/risk reduction of arthritis.
- Studies to examine using regenerative medicine techniques and therapies (including cell-based therapies) to prevent or treat osteoarthritis, including dose response information and the frequency and timing of application.
- Basic and translational research to identify treatments to mitigate and/or reverse osteoarthritis, particularly in the knee, hip, ankle, and shoulder.
- Identification and/or validation of biomarkers for early psoriatic arthritis.
- Research to establish activity recommendations for maximal joint life following joint repair, particularly in young patient populations.

### **Burn Pit Exposure**

- Research on the etiology and treatment of adverse health events related to military deployment to Iraq and Afghanistan that are associated with exposure to airborne hazards and open pit burning of solid waste and other materials.
- Toxicological studies to characterize emissions from open air burns, burn boxes, and incinerators and ascertain the toxicity and mechanisms of action of such chemicals and airborne environmental dust and mixtures, as well as interactions among pollutants and particulate materials.
- Identification and validation of biomarkers of both exposure to and health effects of burn pit combustion products, burning biomass and refuse, and geogenic dusts.
- Development and validation of instruments for assessing (including in real time) levels of exposure to airborne hazards for use in research and for occupational and environmental exposure monitoring.

### **Cardiomyopathy**

- Improve understanding of the pathophysiology of cardiomyopathies.
- Strategies to identify risk factors associated with the development of cardiomyopathy (i.e., genetic, lifestyle, exposure) in the civilian and/or military populations.
- Improve diagnosis and treatment of primary and secondary cardiomyopathies.
- Assess the multiple etiologies of cardiomyopathy (e.g., hypertension, ischemia, hemochromatosis, sleep apnea, radiation therapy, medications, smallpox vaccine, infections) in military Service members.

### **Cerebellar Ataxia**

- Research to improve understanding of all causes of cerebellar ataxia.
- Research to improve understanding of the association between nutrition and cerebellar ataxia.
- Research to better understand the role of physical rehabilitation/exercise in affecting postural disorders, balance and coordination in cerebellar ataxia patients.

- Research to identify therapeutic targets and novel therapeutic modalities including gene silencing/gene editing.

### **Chronic Migraine and Post-Traumatic Headache**

- Precision medicine research to investigate, develop, and validate biomarkers that are not only useful in diagnosing and monitoring traumatic brain injury patients with chronic migraine or post-traumatic headache, but can also identify individual responses to treatment.
- Epidemiological/natural history studies to characterize specific types of post-traumatic headache, the pathobiology of these headaches (such as the role of acute cortical spreading depression after injury as a risk factor for chronic headaches of a migrainous type) and the risk factors that might predispose people to certain types of post-traumatic headache.
- Research on the optimal approaches to effective management of acute and chronic pain management, and co-occurring psychological health disorders, for chronic migraine and post-traumatic headache, with a focus on assessing and eliminating adverse outcomes and decreasing polypharmacy.
- Evaluation of the use of mechanical stimulation and/or other non-pharmaceutical treatments to reduce acute and chronic migraines and headaches.
- Evaluation of the differences in etiology, diagnosis, treatment plan, and prevention of migraine headaches between men and women.

### **Chronic Pain Management**

- Develop and validate a user-friendly, objective pain measurement tool (e.g., instrument, questionnaire, scale) to assess the severity of pain and to inform pain management decisions.
- Development of tools to objectively assess and/or prevent pain chronification.
- Research to advance understanding of the impact of psychosocial factors and other types of comorbidities on pain chronification.
- Research on non-addictive and/or alternative methods to treat and manage chronic pain, particularly in complex patients (i.e., chronic, high-utilization, polypharmacy patients).
- Research to understand the mechanisms that sustain or resolve chronic pain.

### **Congenital Heart Disease**

- Development of approaches, including tissue engineering, that provide structural support, restore native activity, allow for tissue growth, and prevent the need for reoperation.
- Research to improve understanding of the causes of congenital heart defects, including genomic, proteomic, and metabolomic profiling.
- Research to design and implement disease-in-a-dish and/or microfluidic models with an established phenotype to increase the efficacy of finding novel and/or innovative drug targets, screen existing drugs, perform cardiotoxicity testing, and/or uncover pathogenesis.
- Research both on the risk of neurologic injury and on enhanced neuroprotection before, during, and after surgery for congenital heart disease.

- Population-based and outcomes-based research projects to assess the health outcomes of individuals with congenital heart disease across their life spans.

### **Constrictive Bronchiolitis**

- Research to understand the role of occupational and environmental exposures, including military-relevant volatile compounds, mineral and soil dusts, and other airborne particulates, in the etiology of constrictive bronchiolitis.
- Clinical assessments to determine the prevalence and severity of constrictive bronchiolitis and related respiratory diseases in previously deployed military Service members and/or Veterans.
- Development and testing of minimally invasive and non-invasive approaches for diagnosing constrictive bronchiolitis.
- Research to develop novel and/or innovative therapeutics to slow or reverse the progression of constrictive bronchiolitis.
- Development and/or validation of animal models for understanding mechanisms and etiology of constrictive bronchiolitis.

### **Diabetes**

- Research to better understand the heterogeneity of diabetes, including the identification of novel biomarkers.
- Identification and/or evaluation of interventions to reduce the development of diabetes among individuals meeting the clinical criteria for prediabetes.
- Research on interventions to prevent or treat diabetes complications, including diabetic retinopathy, nephropathy, neuropathy, and impaired wound healing.
- Research on the transplantation of allogenic or autologous pancreatic islet cells for long-term natural insulin production, including current good laboratory/clinical/manufacturing practices (as needed) for cell line development.
- Research to design and implement disease-in-a-dish and/or microfluidic models to model pancreatic islets to uncover pathogenesis and improve the efficiency of drug discovery.

### **Dystonia**

- Research to improve identification of delayed onset dystonia following traumatic brain injury.
- Research on the risk, incidence, and etiology of generalized dystonia, focal dystonia, multifocal dystonia, segmental dystonia, and/or hemidystonia.
- Research on interventions to prevent, slow the progression of, or treat dystonia.

### **Eating Disorders**

- Investigations into the prevalence, diagnosis, and treatment patterns of eating disorders in Service members and their families, including potential relationships with military-unique behaviors or conditions.

- Assessment of patterns of comorbidity between eating disorders and other mental health conditions, including an examination of whether eating disorders are more likely to precede or follow the development of other mental health conditions.
- Studies to identify the most effective treatments (and order of treatment) for patients with an eating disorder and a comorbid disorder.
- Research to advance the understanding of the biological, genetic, and environmental factors that influence eating disorders.
- Studies to elucidate and/or mitigate risk factors for the onset or recurrence of eating disorders, including the influence of social media.

### **Emerging Infectious Diseases**

- Development of biomarker-guided clinical management strategies for severe infectious disease in austere settings.
- Development of a rapid, specific, sensitive, and broadly applicable diagnostic methods for emerging pathogens including SARS, H1N1, Ebola, Zika, malaria, dengue, Chikungunya, and others.
- Development of risk assessment vector-borne diseases and novel strategies for vector control, including but not limited to novel insecticides, larvicide applications, and barrier methods. Target vectors include major disease dipteran (including but not limited to vectors such as mosquitoes and sand flies) and non-dipteran (including but not limited to reduviids and fleas) and other arthropods of military medical importance (e.g., ticks).
- Surveillance and modeling of epidemics and development of strategies to counter risks in emerging infectious diseases.
- Development of broad-acting detection systems to identify emerging members of a known viral family (e.g., a broad coronavirus panel that can detect Middle Eastern Respiratory Syndrome).

### **Endometriosis**

- Discovery and identification of new and/or validation of existing endometriosis-associated biomarkers for accurate, minimally invasive diagnosis.
- Research to elucidate the pathogenesis, evolution, pathophysiology, infertility, and pelvic pain associated with endometriosis.
- Development of novel treatments, including non-opioid pain therapies, or alternative therapies to alleviate symptoms and reduce secondary effects of endometriosis.
- Studies assessing the environmental etiology of endometriosis.

### **Epidermolysis Bullosa**

- Research to provide further insight into those cellular pathways that promote the development of squamous cell carcinomas in recessive dystrophic and junctional epidermolysis bullosa.

- Research, including clinical trials, focused on therapeutics (topical or systemic) or dressings that enhance wound healing in inherited epidermolysis bullosa.
- Research, including randomized controlled clinical trials, focused on systemic drugs that prevent, delay the onset, or modify the aggressiveness of squamous cell carcinoma in patients with recessive and junctional epidermolysis bullosa.
- Development of novel therapeutics to reduce epidermolysis bullosa symptoms, improve quality of life, or lead to a cure.

### **Focal Segmental Glomerulosclerosis**

- Research to improve understanding of the causes of primary and/or secondary focal segmental glomerulosclerosis, especially genetic mutations.
- Development of non-invasive methods to diagnose focal segmental glomerulosclerosis and its variants.
- Development of a curative therapy or treatments to delay or halt the progression of focal segmental glomerulosclerosis and/or prevent post-transplantation recurrence.
- Research to determine the efficacy of medications used off-label (outside the FDA-approved indication) to treat focal segmental glomerulosclerosis.

### **Fragile X**

- Development and evaluation of gene modification (e.g., gene editing or gene reactivation) therapeutics for the treatment of fragile X syndrome [including fragile X associated tremor/ataxia syndrome (FXTAS) and fragile X associated primary ovarian insufficiency (FXPOI)].
- Identification and validation of functional measures of the manifestations of fragile X syndrome (including FXTAS and FXPOI) across the life span.
- Research to advance the understanding of the pathophysiology/natural history or life course of fragile X syndrome (including FXTAS and FXPOI).
- Identification of novel targets and/or testing novel or existing therapeutics (e.g., repurposing drugs) for fragile X syndrome (including FXTAS and FXPOI).
- Research to establish the benefits of early diagnosis/early treatment of fragile X syndrome in patients and progeny.
- Development of a preclinical model that is representative of human fragile X syndrome.

### **Frontotemporal Degeneration**

- Basic research to establish in vivo and in vitro models for disease pathology, behavioral/cognitive symptoms, and motor dysfunction.
- Research to understand the neurological basis of deficits in social cognition and emotional regulation.
- Research to identify biomarkers and/or improve diagnostics for frontotemporal degeneration.

- Research to identify risk factors (e.g., gene networks, environmental factors).
- Development of evidence-based non-pharmacological and/or pharmacological treatments for behavioral, cognitive, speech, and/or motor dysfunctions of frontotemporal degeneration.

### **Guillain-Barré Syndrome**

- Research on the immune system cell types and molecular mechanisms responsible for the pathology of Guillain-Barré syndrome.
- Research to elucidate the characteristics of various exposures (e.g., viruses, bacteria, vaccinations, surgery, trauma) associated with Guillain-Barré syndrome and their effects on the immune system.
- Research to prevent or reduce the effects of residual weakness, relapse of muscle weakness, and other neurological and psychological symptoms of Guillain-Barré syndrome to improve patients' quality of life and increase their independence.
- Development of new treatments and refinement of existing treatments for Guillain-Barré syndrome.

### **Hepatitis B and C**

- Development of a vaccine against hepatitis C.
- Identification and reduction of hepatitis in blood products for transfusion.
- Research on strategies to reduce vertical (mother-to-child) transmission of hepatitis B virus and hepatitis C virus.
- Development of strategies for reliable, non-invasive, early detection of hepatitis-related liver disease and hepatocellular carcinoma.
- Research on strategies to promote reversal of liver fibrosis and/or assess the associated clinical and pathological outcomes.
- Clinical studies to evaluate combination or curative therapies for treatment of hepatitis B infection.

### **Hereditary Angioedema**

- Research toward development of a cure for hereditary angioedema.
- Development and/or validation of novel and/or innovative therapeutic strategies for the treatment and/or prevention of hereditary angioedema attacks.
- Research to improve early diagnosis of hereditary angioedema.
- Evaluation of existing, innovative, or novel therapeutics in pediatric hereditary angioedema patients.

### **Hydrocephalus**

- Research on the etiology, prevention, diagnosis, and treatment of post-traumatic hydrocephalus.

- Discovery or validation of novel and/or innovative therapies and therapeutic targets for the treatment of hydrocephalus and its sequelae, including therapies directed at myelin regeneration and repair.
- Development or validation of biomarkers and imaging techniques, particularly multimodal approaches, to aid in diagnosis, prognosis, and monitoring of therapeutic efficacy.
- Research on the prevention of shunt failure.
- Development or validation of improved hydrocephalus model systems.

### **Immunomonitoring of Intestinal Transplants**

- Studies to elucidate the role of the mucosal immune system, humoral, innate, and adaptive cellular immunity, other host-derived factors, or gut microbiota-derived factors in maintaining intestinal transplant viability and improving outcomes.
- Development and evaluation of evidence-based intestinal transplant strategies that focus on dampening the regional immune response against intestinal transplants or circumvent the induction of immunity against the transplant.
- Development and evaluation of implant-associated materials (e.g., scaffolds) with anti-inflammatory properties that protect the intestinal transplant from immune attack.
- Development and evaluation of strategies for inducing and maintaining populations of anti-inflammatory regulatory immune cell populations at the transplant site.
- Studies to improve immunomonitoring of recipient immune responses after intestinal transplantation, with a focus on prospective leukocyte profiling, to aid in diagnosis and treatment of immunological and immunosuppression-related complications.
- Development and/or validation of precise, real-time implanted monitoring devices to improve individualized patient outcomes after intestinal transplantation.

### **Inflammatory Bowel Diseases**

- Studies directed toward understanding how acute enteric infections may trigger chronic bowel diseases with acute and sub-acute inflammatory bowel disease, including genomic, microbiomic, immune mechanisms, and systems biology approaches.
- Studies to understand the interaction between acute/chronic stress and infection and the development of inflammatory bowel disease.
- Research to better characterize the association between the use of drugs, such as isotretinoin and long-term doxycycline, and the development of inflammatory bowel disease.
- Research on the role of diet in the development and progression of inflammatory bowel disease.
- Research on the influence of the microbiome on inflammatory bowel disease.
- Research on treatment strategies for patients with inflammatory bowel disease, including those who are refractory to standard care.

### **Interstitial Cystitis**

- Studies that define the risk, prevalence, and operational impact of interstitial cystitis among active duty personnel.
- Identification of biological markers for making a definitive diagnosis of interstitial cystitis.
- Evaluation and assessment of novel and/or innovative treatment options for interstitial cystitis patients, including intravesical therapy.
- Research on the etiology of interstitial cystitis to inform targeted therapy development.

### **Lung Injury**

- Studies to identify the prevalence and associated morbidity and mortality of blast overpressure lung injury.
- Improved methods for assessing lung injury due to chemical or physical (e.g., radiation) hazards and materials in occupational, operational, and training environments to improve surveillance, diagnosis, and prognosis.
- Improved methods for monitoring pulmonary exposure to chemical or physical agents that might cause lung injury.
- Identify pre-existing conditions that predispose an individual's susceptibility to lung injury resulting from environmental exposures (i.e., genetic predisposition).
- Preventive techniques, novel detection technologies, and therapeutics to reduce the incidence and/or severity of lung injury.

### **Malaria**

- Investigation of mechanisms of drug resistance in malaria, to include host and pathogen, region-specific resistance against drugs used for treatment and prophylaxis.
- Development of passive immunization approaches for the management of malaria.
- Development of malaria prophylactic regimens that encourage higher compliance and methods to monitor compliance in deployed Service members.
- Identification of novel and/or innovative malaria drug targets for blood and liver stage malaria parasites.
- Development of a vaccine that induces high levels of long-lived, broadly protective immunity against *Plasmodium falciparum* and/or *P. vivax*.

### **Metals Toxicology**

- Identification and validation of biomarkers to evaluate military Service members' acute exposure to toxic metals in an operational environment and predict potential consequent health risks and associated health outcomes.
- Retrospective studies to evaluate risks and exposure to military-relevant toxic metals among workers at industrial facilities.

- Research on the toxicity of metal combinations and the interaction between different metal components.
- Research on the toxicity of metal-based engineered nanomaterials, including those used in military applications.

### **Mitochondrial Disease**

- Identify and test non-invasive techniques and biomarkers to monitor mitochondrial function, aid in clinical diagnosis, and/or evaluate therapeutic efficacy.
- Development of improved tools and animal models to study primary mitochondrial disease and evaluate therapeutics.
- Research to better understand the pathology of primary mitochondrial diseases.
- Development of tools and methodologies to assess mitochondrial heteroplasmy on a cellular, tissue, and organ level.
- Research on novel and/or innovative treatments to alleviate symptoms or slow down the progression of mitochondrial diseases.

### **Musculoskeletal Disorders**

- Research to increase understanding, diagnosis, prevention, and/or treatments of chronic overuse musculoskeletal disorders.
- Research on measures (e.g., clinical biomarkers, novel/innovative interventions, therapeutics) to diagnose, predict, reduce the incidence of, or optimize health or return-to-duty outcomes in military training- and Service-related musculoskeletal disorders.
- Research on the validation and/or optimization of rehabilitation strategies for musculoskeletal disorders.
- Research to prevent, control, and/or optimize musculoskeletal health outcomes for work-related musculoskeletal disorders.
- Research on back pain treatment and/or management strategies to prevent surgery and recurrence of symptoms, identify factors that predict optimal treatment response for different patients, and encourage self-management.

### **Myotonic Dystrophy**

- Research on the role of epigenetic factors in the onset, progression, and/or severity of myotonic dystrophy in relevant animal models or patients.
- Research into the mechanisms of expanded CTG or CCTG repeat instability in somatic or germ line cells in myotonic dystrophy.
- Identification of biomarkers that can be detected through minimally invasive means to signal early changes in the progression of myotonic dystrophy.
- Development and/or testing of novel and/or innovative treatments, including those utilizing gene editing or silencing.

- Clinical research into the natural history of myotonic dystrophy, to understand disease progression and develop/validate clinical trial endpoint measures across the multiple organ systems involved in the disease.

### **Non-Opioid Pain Management**

- Development of non-opioid pain management therapies, including complementary and alternative medicine approaches.
- Research to increase understanding and prevention of the progression from acute pain to chronic pain.
- Research to identify and address biopsychosocial aspects of pain to reduce or eliminate the use of opioid pain medication(s).
- Research on pain management strategies for patients with limited access to skilled providers and resources, including battlefield, prolonged field, transport, and other resource-limited environments.
- Development of non-opioid pain medicine that can be given via inhalation or intramuscularly, submucosally, or intravenously on the battlefield to provide adequate relief of pain without affecting the cardiorespiratory systems.

### **Nutrition Optimization**

- Development and/or validation of nutrition-based strategies that mitigate the consequences of operational stressors on Service member health, readiness, and performance.
- Research on the impact of dietary supplements (vitamin supplements, probiotics, protein powders, etc.) on the physical and/or cognitive performance, including the readiness of military Service members.
- Development and/or validation of improved nutrition strategies for physical and/or cognitive performance enhancement and sustainment in the operational environment.
- Development of tools or devices to monitor nutritional intake at an individual level to promote a culture of wellness.
- Strategies to apply metabolomics to optimize nutrition, including improving Warfighter performance in training and operational environments.
- Research to optimize nutrition in resource-limited settings.

### **Pancreatitis**

- Development and testing of novel and/or innovative therapeutics for acute and/or chronic pancreatitis.
- Research on the basic biology and physiology of the pancreas to better understand the etiology and pathology of pancreatitis.
- Research to improve understanding and management of complications of pancreatitis.
- Retrospective studies to determine the risk and incidence of pancreatitis among former and current active duty personnel.

## **Pathogen-Inactivated Blood Products**

- Research on lyophilization of pathogen reduced/inactivated blood products and derivatives (platelets, plasma, red cells, cryoprecipitate, coagulation factors, etc.).
- Development and advancement of technology to improve the safety of blood products to include pathogen reduction/inactivation in whole blood for military/civilian blood donor centers and blood banks that meets the requirements for FDA licensure in support of domestic and global contingency/combat operations.
- Expansion and validation of the library of blood-borne pathogens that are reduced/inactivated to include emerging pathogens, genetically modified pathogens, and pathogen designed for biological warfare.
- Advancement in pathogen reduction technology to further improve the log-killed reduction for blood-borne pathogen of common interest (e.g., hepatitis B, Korean hemorrhagic fever virus, Bunyavirus, human immunodeficiency virus [HIV], Rift Valley fever, malaria, Babesia, Ebola, West Nile virus, dengue, chikungunya, Zika virus).
- Research studies, including clinical trials, to further characterize the effects of pathogen reduction technology in blood products (e.g., whole blood, platelets, plasma, cryoprecipitate).
- Development and validation of next generation technology and/or devices to reduce the production time for pathogen reduction/inactivation in whole blood.

## **Post-Traumatic Osteoarthritis**

- Research into cell-based approaches for treatment or prevention of post-traumatic osteoarthritis.
- Development or validation of novel and/or innovative approaches to restoring joint stability after injury.
- Studies to evaluate and develop best practices for multidisciplinary team approaches and treatment algorithms for post-traumatic osteoarthritis.
- Sustained release, intra-articular injectable steroidal, non-steroidal, or disease-modifying therapies that offer two or more months of symptomatic relief of pain and/or inflammation in a single injection.
- Research on therapies that target multiple phases of the cellular response pathways that are implicated in the development of post-traumatic osteoarthritis, including cell death, inflammation, matrix changes, and changes in catabolic and anabolic responses.

## **Pressure Ulcers**

- Novel strategies for the treatment (including mitigation of the advancement of stages) of pressure ulcers.
- Novel strategies for the prevention or early detection of pressure ulcers.
- Strategies to prevent or reduce the formation of pressure ulcers during long-range transport/aeromedical evacuation.

- Research on novel techniques for synthetic production, delivery, and adhesion methodologies leading to permanent closing of pressure ulcers. This might encompass synthetic fibers, novel tissue culture methodologies, growth factors, dermal printing, artificial skin, skin graft substitutes, regenerative medicine, etc.

### **Pulmonary Fibrosis**

- Identification of biomarkers of pulmonary injury or early predictors of interstitial lung disease.
- Development and/or validation of improved tools and animal models (excluding mice) to study pulmonary fibrosis and evaluate therapeutics.
- Research into the pathobiology and molecular mechanisms underlying the development and progression of pulmonary fibrosis.
- Retrospective studies to determine the risk and incidence of pulmonary fibrosis among military Service members, including Veterans.
- Development and/or testing of novel and/or innovative treatments, to include precision medicine approaches, to delay or modify the progression of pulmonary fibrosis.

### **Respiratory Health (excluding lung cancer and mesothelioma)**

- Research on the causes, treatment, and prevention of COPD, including identification and validation of biomarkers and disease phenotypes, as well as employing personalized medicine in clinical research and disease management.
- Research on the causes, treatment, and prevention of respiratory symptoms and ailments possibly associated with deployed and redeployed military personnel.
- Research to evaluate the impact of military service, primarily deployment, on the prevalence and severity of respiratory disease.
- Identification and/or validation of biochemical, physiological, or combined biomarkers for evaluating risk or extent of injury from either acute or long-term toxic occupational or environmental exposures.
- Research investigating exposure rates, detection, and treatment of diseases related to inhalation of mold and fungi, such as coccidioidomycosis from both indoor and outdoor sources.

### **Rett Syndrome**

- Identification and/or validation of novel and/or innovative biological targets for the treatment of Rett syndrome.
- Development and testing of interventions to improve the neurological symptoms of Rett syndrome.
- Research to understand the relationship between genetic mutations, physical traits, and symptoms in individuals with Rett syndrome.
- Research to understand Rett syndrome's commonalities with, and differences from, classic autism and regressive autism.

- Research on the pathobiology of MeCP2 and associated genes and proteins.

### **Rheumatoid Arthritis**

- Research to better understand the relationship between genetic risk and environmental triggers, such as infection or smoking, in developing rheumatoid arthritis.
- Studies that identify or validate biomarkers or personalized medicine strategies that allow for individualized medication choice based on the patient's underlying biology or disease state.
- Research on the long-term use of immunosuppressive and other therapies in patients with rheumatoid arthritis.
- Research to better characterize and understand the preclinical disease stage of rheumatoid arthritis for early diagnosis and treatment.
- Research on management of comorbidities, including biopsychosocial outcomes, for patients with rheumatoid arthritis.
- Research to establish activity recommendations following joint replacement for maximal joint life.

### **Scleroderma**

- Research on the molecular mechanisms and pathogenesis of scleroderma, including the identification of novel and/or innovative therapeutic targets.
- Development and/or validation of novel and/or innovative therapies for scleroderma.
- Identification and/or validation of biomarkers and other approaches for early diagnoses, monitoring disease progression, and/or assessment of treatment response.
- Epidemiologic studies investigating the impact of localized scleroderma (morphea) on duty performance, use of personal protective equipment, and deployability.

### **Sleep Disorders**

- Research on how the disruption of normal sleep and circadian rhythms adversely affects the physical and psychological health, safety, performance, and productivity of military personnel and civilian populations, including sex and gender differences.
- Identification and/or validation of non-CPAP-based treatment regimens that enhance compliance in military personnel (e.g., enhance readiness and deployability) and civilian populations.
- Research on the prevention and/or mitigation of sleep disorders that are associated with long aeromedical evacuation flights for both clinical team members and patients.
- Development and/or testing of non-pharmacological treatments for sleep disorders associated with long-term exposure to enclosed environments (e.g., aircraft, submarines, tanks).

### **Spinal Muscular Atrophy**

- Research into molecular and proteomic phenotyping the spinal muscular atrophy disease state.

- Research to determine mitochondrial involvement and astrocytic and other non-neuronal contributions to motor neuron vulnerability.
- Exploration of the form and function of SMN-depleted neuromuscular junctions at ultrastructural (e.g., dysregulation of endocytosis), transcriptomic, and proteomic levels, particularly the mildest SMN reduction that leads to consistent quantifiable motor neuron loss.
- Research to find non-SMN-altering spinal muscular atrophy modifying genes that may lead to identification of novel and/or innovative therapeutic targets or treatments.
- Research to further understand SMN gene regulation and post-transcriptional mechanisms leading to synergistic SMN-repleting approaches, as well as to determine whether boosting SMN induction maximizes efficacy.

### **Sustained-Release Drug Delivery**

- Development of technology that can provide long-term (for up to one week or more) sustained-release delivery of oral drugs. Potential applications of this technology could include long-term delivery of agents for post-traumatic stress, opiate dependence, low-dose pain control, allergies, attention deficit/hyperactivity disorder, chemoprophylaxis, and other conditions.
- Development of a delivery system (including novel GMP-grade biomaterials) that could accurately deliver prescription and non-prescription medications.
- Development of novel and/or innovative approaches for bioavailable and sustained-release oral formulations of existing broad-spectrum fungicidal, antimicrobial, antiparasitic, and antiviral medications.
- Development of a sustained release formulation of anti-tuberculosis drugs that would facilitate long-term treatment and reduce the emergence of resistance due to poor compliance.
- Research into techniques to provide sustained release of drugs in tissue repair applications, such as bone or nerve regeneration or vision restoration.

### **Tinnitus**

- Development and validation of objective tools/methods to diagnose and characterize tinnitus (e.g., imaging techniques to identify functional and structural changes in the brain, biomarkers of resiliency, and susceptibility to tinnitus).
- Research to understand the mechanisms of tinnitus, its relationship to noise-induced hearing loss, and progression to chronic tinnitus, with the focus on developing interventions.
- Research to understand and mitigate the negative impact of tinnitus on operational readiness of the military.
- Identification of novel and/or innovative therapies and/or devices for interventions to prevent, manage, and treat tinnitus, including behavioral approaches, new uses for existing drugs, nutritional and pharmaceutical strategies, and acoustic, electrical, and other stimulation technologies.

## **Tissue Regeneration**

- Development of novel therapies to repair neurosensory damage, maintain the distal end organ interface, or regenerate the neuromuscular junction for reinnervation of end organs during peripheral nerve regeneration.
- Development of novel therapies for regeneration of tendons and musculotendinous junctions.
- Development of novel therapies for regeneration of functional skeletal muscle, particularly stem cell-based approaches and treatments for volumetric muscle loss.
- Development and improvement of extended-time tissue preservation therapies and technologies for ischemia-reperfusion injury prevention and treatment.
- Research on novel approaches and therapies to understand mechanisms of immune rejection and obviate the need for chronic toxic immunosuppression in reconstructive transplantation and vascularized composite allotransplantation.
- Research into innovative methods for developing biocompatible scaffolds and stem cell therapies for manufacturing and production of tissues.

## **Tuberculosis**

- Development of a diagnostic assay that can be used at the point of care to rapidly and accurately diagnose tuberculosis to include multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis.
- Development of novel and/or innovative tuberculosis vaccines or optimization of current tuberculosis vaccines.
- Research to understand, diagnose, or treat multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis.

## **Vaccine Development for Infectious Diseases**

- Development of a therapeutic vaccine and/or other strategies for infectious diseases.
- Identification of correlate(s) of immunity against dengue, malaria, and other infectious agents and development of a surrogate test of protection.
- Development and fielding of vaccines to prevent U.S. Service members from becoming ill from endemic disease exposure during operational deployments. This includes, but is not limited to, Zika, dengue, chikungunya, hantavirus hemorrhagic fever with renal/pulmonary syndrome, rickettsioses, trypanosomiasis, leptospirosis, HIV, norovirus, Middle East Respiratory Syndrome, coronavirus, schistosomiasis, leishmaniasis, nipah, Lassa fever, and West Nile fever.
- Development of flexible vaccine technologies that can be used to rapidly respond to emerging and re-emerging infectious diseases threats.
- Evaluation of passive immunization strategies to use in conjunction with emerging infectious disease vaccinations.

### **Vascular Malformations**

- Studies into the natural history, genetics, and pathogenesis of vascular malformations.
- Research to improve methods to diagnose and manage vascular malformations.
- Research to discover or develop novel and/or innovative therapeutic targets and treatments to regress or prevent vascular malformations.
- Development of non-invasive or minimally invasive technologies or approaches for the control of internal bleeding, including cerebral arteriovenous malformations, associated with vascular malformations.
- Development of in vivo or in vitro models of vascular malformations for the purpose of identifying novel and/or innovative drug targets, screening existing drugs, and/or elucidating the pathogenesis of the disease.

### **Women's Heart Disease**

- Identification of gender-specific approaches to either develop novel diagnostics and treatments or increase the effectiveness of current practice to improve clinical care of women.
- Research on factors to predict and prevent the long-term impacts of gestational diabetes, gestational hypertension, and preeclampsia on the cardiovascular health of women.
- Research on trauma-induced cardiac arrest secondary to hemorrhage and polytrauma in the female population.
- Research focused on elucidating the potential relationship between post-traumatic stress disorder and women's heart disease.
- Studies to determine the risk and incidence of heart disease among current and/or former female Service members.

### APPENDIX 3: DOD AND VA WEBSITES

PIs are encouraged to integrate and/or align their research projects with Department of Defense (DoD) and/or Department of Veterans Affairs (VA) research laboratories and programs. Collaboration with DoD or VA investigators is also encouraged. Below is a list of websites that may be useful in identifying additional information about DoD and VA areas of research interest, ongoing research or potential opportunities for collaboration within the FY18 PRMRP Topic Areas.

Air Force Office of Scientific Research  
<http://www.wpafb.af.mil/afri/afosr/>

Air Force Research Laboratory  
<http://www.wpafb.af.mil/afri>

Armed Forces Radiobiology Research  
Institute  
<http://www.usuhs.edu/afri/>

Clinical and Rehabilitative Medicine  
Research Program  
<https://crmp.amedd.army.mil>

Combat Casualty Care Research Program  
<https://ccc.amedd.army.mil>

Congressionally Directed Medical  
Research Programs  
<http://cdmrp.army.mil>

Defense Advanced Research Projects  
Agency  
<https://www.darpa.mil/>

Defense Technical Information Center  
<http://www.dtic.mil>

Defense Threat Reduction Agency  
<http://www.dtra.mil/>

Military Health System Research  
Symposium  
<https://mhsrs.amedd.army.mil/SitePages/Home.aspx>

Military Infectious Diseases Research  
Program  
<https://midrp.amedd.army.mil>

Military Operational Medicine Research  
Program  
<https://momrp.amedd.army.mil>

Naval Health Research Center  
<http://www.med.navy.mil/sites/nhrc>

Navy and Marine Corps Public Health  
Center  
<http://www.nmcphc.med.navy.mil/>

Office of Naval Research  
<http://www.med.navy.mil/>

Office of the Under Secretary of Defense for  
Acquisition, Technology and Logistics  
<http://www.acq.osd.mil/>

Telemedicine and Advanced Technology  
Research Center  
<http://www.tatrc.org/>

Uniformed Services University of the Health  
Sciences  
<http://www.usuhs.edu/research>

U.S. Army Institute of Surgical Research  
<http://www.usaisr.amedd.army.mil/>

U.S. Army Medical Materiel Development  
Activity  
<http://www.usamma.army.mil/>

U.S. Army Medical Research Institute of  
Infectious Diseases  
<http://www.usamriid.army.mil/>

U.S. Army Medical Research and Materiel  
Command  
<http://mrmc.amedd.army.mil>

U.S. Army Research Institute of  
Environmental Medicine  
<http://www.usariem.army.mil/>

U.S. Army Research Laboratory  
<http://www.arl.army.mil>

### **Appendix 3 (Continued)**

U.S. Department of Defense Blast Injury  
Research Program

<https://blastinjuryresearch.amedd.army.mil/>

U.S. Department of Veterans Affairs, Office  
of Research and Development

<http://www.research.va.gov>

U.S. Naval Research Laboratory

<http://www.nrl.navy.mil>

Walter Reed Army Institute of Research

<http://www.wrair.army.mil/>