I. OVERVIEW OF THE FUNDING OPPORTUNITY

Program Announcement for the Department of Defense

Defense Health Program

Congressionally Directed Medical Research Programs

Peer Reviewed Orthopaedic Research Program

Integrated Clinical Trial Award

Announcement Type: Initial

Funding Opportunity Number: W81XWH-17-PRORP-ICTA

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), July 12, 2017
- **Invitation to Submit an Application:** August 16, 2017
- **Application Submission Deadline:** 11:59 p.m. ET, September 27, 2017
- **End of Application Verification Period:** 5:00 p.m. ET, October 3, 2017
- **Peer Review:** November 2017
- **Programmatic Review:** January 2018

This Program Announcement must be read in conjunction with the General Application Instructions version 20170516. 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."

TABLE OF CONTENTS

II. DETAILED INFORMATION ABOUT THE FUNDING OPPORTUNITY

II.A. Program Description

Applications to the Fiscal Year 2017 (FY17) Peer Reviewed Orthopaedic Research Program (PRORP)) 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 PRORP was initiated in 2009 to provide support for research of exceptional scientific merit focused on optimizing recovery and restoration of function for military personnel with orthopaedic injuries sustained in combat or combat-related duties. Appropriations for the PRORP from FY09 through FY16 totaled $308.5 million (M). The FY17 appropriation is $30M.

The FY17 PRORP challenges the scientific community to address the most significant gaps in care for the leading burden of injury and loss of fitness for military duty by funding innovative, high-impact, clinically relevant research to advance optimal treatment and rehabilitation from neuromusculoskeletal injuries (excluding spinal cord injuries) sustained during combat or combat-related activities. It is expected that any research findings would also benefit the general population. Applications involving multidisciplinary collaborations among academia, industry, the military Services, the Department of Veterans Affairs (VA), and other Federal agencies are highly encouraged.

II.A.1. FY17 PRORP Focus Areas

All applications must integrate at least two (minimum of one from the Surgical Care category and one from the Rehabilitation category) and a maximum of four of the following FY17 PRORP Focus Areas into a cohesive project. Selection of the appropriate Focus Areas is the responsibility of the applicant. Studies that combine Focus Areas synergistically and propose significant advancements are particularly encouraged. Applications addressing only one Focus Area should consider applying for the FY17 PRORP Clinical Trial Award (Funding Opportunity Number: W81XWH-17-PRORP-CTA) mechanism, which can be accessed at http://cdmrp.army.mil/funding/default.shtml.

Surgical Care Focus Areas:

- Peripheral Nerve Injuries: Treatment strategies to improve outcomes from segmental peripheral nerve defects of motor and mixed (motor and sensory) peripheral nerve damage from crush or complete injury.

- Prevention of Heterotopic Ossification: Techniques to retard or prevent the development of human post-traumatic heterotopic ossification in the upper extremity.

- Volumetric Muscle Loss: Techniques to regenerate functional, innervated muscle units in treatment of volumetric muscle loss.

- Extremity Fractures: Strategies to optimize patient outcomes after extremity fracture (i.e., time to begin rehabilitation, weight-bearing strategy, etc.).

- Pelvic Ring Injuries: Treatment strategies to improve outcomes of complex pelvic ring injuries.

- Compartment Syndrome: Strategies to improve current diagnoses for compartment syndrome.

- Gaps in Clinical Practice Guidelines: Address gaps in current orthopaedic clinical practice guidelines (CPGs) and recommendations (http://www.usaisr.amedd.army.mil/cpgs.html). Applications under this Focus Area must specify which orthopaedically relevant CPG the application is intended to support. Applicants should also highlight the expected impact of their research on orthopaedic clinical practice.

- Surgical Techniques to Optimize Gait: Validate surgical techniques to optimize gait efficiency and outcomes for patients with amputation or limb salvage.

- Soft Tissue Trauma: Strategies to develop and/or identify musculoskeletal extremity soft tissue trauma treatments optimizing return to duty, work, or reintegration.

- Osteoarthritis: Treatment strategies involving large animal studies, clinical research, or clinical trials to improve outcomes of osteoarthritis and/or post-traumatic osteoarthritis.

Rehabilitation Focus Areas:

- Post-Operative Pain Management: Develop and/or validate strategies for post-operative pain management following orthopaedic trauma that minimize or eliminate opioid use. The primary outcome measures should relate to rehabilitation endpoints and not focus solely on pain scores.

- Prosthetic and/or Orthotic Device Function: Development and optimization of novel, innovative technologies to improve prosthetic and/or orthotic device function and durability, including intuitive efferent (motor) and afferent (sensory) user interfaces and considerations for interoperability.

- Secondary Physical Health Effects: Techniques or technologies that improve prediction, identification, and reduction of secondary physical health effects (e.g., obesity, arthrosis, osteoporosis, cardiovascular disease) following severe/high-energy traumatic neuromusculoskeletal non-spinal cord injury. The focus should be on injuries sustained between the ages of 18-50 and secondary physical health effects that develop within 5 years of injury.

- Physical or Occupational Therapy: Development and/or validation of optimal physical or occupational therapy treatment strategies and sequence of progression throughout the

rehabilitation continuum to maximize functional outcomes following severe neuromusculoskeletal injury, excluding the central nervous system. Examples include optimal timing, frequency, duration, and intensity of rehabilitation interventions.

- Barriers to Successful Therapy Outcomes: Identify, quantify, and stratify confounding treatable factors (e.g., pain, sleep, nutrition, compliance) that inhibit or delay optimal orthopaedic rehabilitation outcomes.

- Rehabilitation Outcomes: Development and/or validation of standardized measures to objectively assess and improve rehabilitation outcomes, including multi-extremity trauma and/or psychosocial resiliency and reintegration, following neuromusculoskeletal injury.

- Osteoarthritis: Development and/or validation of optimal physical or occupational therapy treatment strategies to improve outcomes of osteoarthritis and/or post-traumatic osteoarthritis.

II.B. Award Information

The PRORP Integrated Clinical Trial Award (ICTA) supports the rapid implementation of an interdisciplinary clinical trial that integrates both surgical and rehabilitation strategies and has the potential to have a major impact on the treatment of combat-related orthopaedic injuries and/or the treatment of non-battle injuries that significantly impact unit readiness and return-to-duty/-work rates.

Projects that follow patients across the continuum of care are highly encouraged. The projects should include both surgical and rehabilitation strategies that create a cohesive project. Surgical strategies are reconstruction and repair and/or application of biologics, pharmaceuticals, and devices for the purpose of restoration of native architecture, composition, and function of traumatically injured tissues. Rehabilitative strategies are those that restore function following injury or illness, with the goal of optimal health and independence. Projects should integrate principles and approaches from surgical and rehabilitative strategies, beyond what each approach would result in alone, with the goal of optimizing form, function, and independence for those who have sustained traumatic orthopaedic injuries. Care should be taken to avoid or account for confounding factors in the analyses.

Required Qualified Collaborator(s): The ICTA supports collaborative interdisciplinary research between/among physical therapists, occupational therapists, prosthetists, surgeons, and other orthopaedic care providers. To encourage meaningful and productive multidisciplinary collaborations, ***the project must include at least one investigator with orthopaedic rehabilitation expertise and at least one clinician who specializes in orthopaedic or trauma care.*** A clinician is defined as an individual who is credentialed (possesses the necessary degrees, licenses, and other certifications) and practicing as a care provider in a relevant capacity. Biographical sketches should include appropriate documentation of credentials. It is the responsibility of the Principal Investigator (PI) and the collaborating investigator(s) to describe how their combined expertise will better address the research question, why the work should be performed through collaboration rather than through separate efforts, and how the research design will create a reciprocal flow of ideas and information between the multiple

disciplines represented. The proposed collaboration should involve substantial contributions from each of the key collaborators identified, with evidence of significant intellectual input from each key collaborator into the design of the project. The PI must submit a Qualified Collaborator Statement that clearly describes the proposed collaborator(s), the collaboration, and addresses how each of the criteria below are met. Use Attachment 9: Study Personnel and Organization to provide this statement. In addition, each collaborator must provide a letter of collaboration describing his/her involvement in the proposed work. Use Attachment 2 to provide this documentation (see Section II.D.2.b.ii, Full Application Submission Components, Attachment 2: Supporting Documentation).

The following criteria must be met for the required Qualified Collaborator(s):

- A Qualified Collaborator must be an investigator with orthopaedic rehabilitation expertise or a clinician who specializes in orthopaedic or trauma care.

- The Qualified Collaborator(s) must significantly contribute to the project such that the proposed work could not be accomplished without his/her involvement. This is expected to include both intellectual input and research resources (e.g., supplies, reagents, equipment, personnel, services, tissue samples, or access to patients or populations).

- The Qualified Collaborator(s) and PI must each contribute a minimum of a 5% level of effort to the project. Contribution of the Qualified Collaborator(s) and PI should be reflected in the application budget.

All applications are required to articulate the relevance of the proposed project to military and/or Veteran populations affected by orthopaedic injury. ***Collaboration with military and VA researchers and/or clinicians is encouraged. Studies that include active duty military or Veteran participants as all or a portion of the study population are encouraged.***

Preclinical animal research is not allowed under the FY17 PRORP ICTA. Funding from this award mechanism must support one cohesive clinical trial and may not be used for preclinical research studies. A clinical trial is defined as a prospective accrual of human subjects where an intervention (e.g., device, drug, biologic, surgical procedure, rehabilitative modality, behavioral intervention, or other) is tested on a human subject for a measurable outcome with respect to safety, effectiveness, and/or efficacy. This outcome represents a direct effect on the human 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 on how to distinguish clinical research from clinical trials, a Human Subject Resource Document is provided at https://ebrap.org/eBRAP/public/Program.htm. PIs seeking funding for a preclinical research project should consider one of the other FY17 PRORP award mechanisms, which can be accessed at http://cdmrp.army.mil/funding/default.

If the 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 and must be submitted to the FDA

within 6 months of the award date. If the investigational product is a device, evidence that an Investigational Device Exemption (IDE) application that meets all requirements under 21 CFR 812 has been submitted to the FDA within 6 months of the award date, or that the device is exempt from an IDE, or qualifies for an abbreviated IDE, is required. The Government reserves the right to withdraw funding if an IND or IDE is necessary but has not been submitted to the FDA within 6 months of the award date, or if documented status of the IND or IDE has not been obtained within 12 months of the award date.

The following are important aspects of submission for the ICTA:

- The proposed clinical trial is expected to begin no later than 12 months after the award date, or 18 months for FDA-regulated studies.

- The proposed intervention to be tested should offer significant potential impact for military personnel and Veterans with combat-related orthopaedic injuries or non-battle orthopaedic injuries that impact unit readiness and return to duty/work.

- 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. Likewise, it should include an outline of the development plan and regulatory strategy 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 applicant should discuss how accrual goals will be achieved and how standards of care may impact the study enrollment.

- The application should demonstrate documented availability of, and access to, the drug/ compound, device, and/or other materials needed, as appropriate. The quality of the product should be commensurate with FDA manufacturing standards applicable to the type and phase of product being developed (i.e., Quality System Regulation, Good Manufacturing Practices).

- The application should demonstrate the study team has experience interacting with the FDA, to include previous FDA submissions, if applicable.

- The proposed clinical trial design should include clearly defined and appropriate endpoints, and follow 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 clearly 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. For FDA-regulated studies, compliance with 21 CFR 11 is required.

- The application should include a clearly articulated safety management plan outlining how safety and 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.

- For studies determined to be greater than minimal risk to human subjects by the local IRB of record, the Department of Defense (DoD) requires an independent research monitor with expertise consistent with the nature of risk(s) identified within the research project. If applicable, refer to the General Application Instructions, Appendix 6, for more information on study reporting authorities and responsibilities of the research monitor.

- 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 FY17 PRORP ICTA.

- The application should clearly demonstrate strong institutional support (refer to Section II.D.2.b.ii, Full Application Submission Components, Attachment 2: Supporting Documentation).

- Funded studies are required to file the study in the National Institutes of Health (NIH) clinical trials registry, http://www.clinicaltrials.gov/. Refer to the General Application Instructions, Appendix 6, Section C, for further details.

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 9: 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 Ethics Committee (EC) pathway is strongly recommended whenever possible. The master protocol and consent form must be reviewed by Human Research Protection Office (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.

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 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. Organizations are encouraged to consider use of site personnel familiar with local/host nation regulatory review requirements. 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. Submission to HRPO of protocols covering more than the scope of work in the DoD-funded award will require HRPO review of the entire protocol as DoD-supported research and may include extensive modifications to meet DoD human subjects protection requirements. 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.

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, 2018. 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 academia, biotechnology companies, foundations, Government, and research institutes. *Extramural Submission: Application submitted by a non-DoD organization to Grants.gov.*

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

Note: Applications from an intramural organization or from an extramural non-DoD 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:

The PI must be an independent investigator at or above the level of Assistant Professor (or equivalent).

It is expected that the expertise of the PI and Qualified Collaborator(s) will be complementary covering orthopaedic rehabilitation as well as orthopaedic or trauma care. One investigator must be a clinician with the appropriate expertise.

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

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

II.C.2. Cost Sharing

Cost sharing/matching is not an eligibility requirement.

II.C.3. Other

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

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

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

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

II.D. Application and Submission Information

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

Extramural Submission is defined as an application submitted by a non-DoD organization to Grants.gov.

Intramural Submission is defined as an application submission by a DoD organization for an intramural investigator, who is a DoD military or civilian employee working within a DoD laboratory or military treatment facility, or working in a DoD activity embedded within a civilian medical center.

II.D.1. Address to Request Application Package

Submitting Extramural and Intramural Organizations: Pre-application content and forms can be accessed at eBRAP (https://eBRAP.org).

Submitting Extramural Organizations: Full application packages can be accessed at Grants.gov.

Submitting Intramural Organizations: Full application packages can be accessed at 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/).

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.

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 Grants.gov. 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.

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. Applications from extramural organizations, including non-DoD Federal organizations, received through eBRAP will be withdrawn. See definitions in Section II.C.1, Eligible Applicants.

eBRAP allows intramural organizations to submit full applications following pre-application submission.

For both Extramural and Intramural submissions: 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 application submission process. Inconsistencies may delay application processing and limit or negate the ability to view, modify, and verify the application in eBRAP. If any changes need to be made, the applicant should contact the CDMRP Help Desk at help@eBRAP.org or 301-682-5507 prior to the application 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 will be needed 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 may result in delays in processing.**

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

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

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

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

- **Tab 1 – Application Information**

- **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.

  FY17 PRORP Programmatic Panel members should not be involved in any pre-application or application. For questions related to Panel members and pre-applications or applications, refer to Section II.H.2.c, Withdrawal, or contact the CDMRP Help Desk at help@eBRAP.org or 301-682-5507.

  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 FY17, 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 (three-page limit):** The Preproposal Narrative page limit applies to text and non-text elements (e.g., figures, tables, graphs, photographs, diagrams, chemical structures, drawings) used to describe the project. Inclusion of URLs that provide additional information to expand the Preproposal Narrative and could confer an unfair competitive advantage is prohibited and may result in administrative withdrawal of the pre-application.

    The Preproposal Narrative should include the following:

    - **Alignment with Focus Area:** Explain how the proposed work is interdisciplinary and addresses two to four of the FY17 PRORP Focus Areas (at least one must be from the Surgical Care category and at least one must be from the Rehabilitation category).

    - **Research Idea:** Identify the intervention to be tested and describe the projected outcomes. Describe the ideas and reasoning on which the proposed clinical trial is based; include relevant literature citations. Briefly describe the preliminary scientific evidence that supports the progression of this research into the phase of clinical trial proposed. Clearly specify which type (e.g., prospective, randomized, controlled) of clinical trial is being proposed and indicate the phase of trial and/or class of device and regulatory status, 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. Include a description of the target patient population and controls, as appropriate. Outline the measures that will be attempted, if necessary, to increase subject throughput and subsequent enrollment.

    - **Impact:** Describe how the proposed work will have an impact on accelerating the movement of a promising treatment into clinical application. Address the project's relevance to patients who have sustained traumatic orthopaedic injuries.

- **Military Benefit:** Explain how the project will benefit military Service members and/or Veterans who have sustained combat-related orthopaedic injuries or non-battle orthopaedic injuries that impact unit readiness and return to duty/work. State explicitly how the proposed work may have an immediate and/or long-term impact on patient care and/or restoration of function for those who have sustained combat-related or non-battle orthopaedic injuries that affect readiness or return to return to duty/work.

- **Personnel:** Briefly state the qualifications of the PI, Qualified Collaborator(s), and other key personnel to perform the clinical trial (detailed key personnel biographical sketches [six pages per individual] are allowed as part of pre-application supporting documentation, as described below). Note any DoD or VA collaborations.

- **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 (six-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.

  - **Quad Chart: Upload as "QuadChart.pdf."** The Quad Chart template is a one-page PowerPoint file that must be downloaded from eBRAP at https://ebrap.org/eBRAP/public/Program.htm in the "Generic Forms for Application Submission" section, then completed and saved as a PDF file.

- **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 PRORP, pre-applications will be screened based on the following criteria:

- **Research Idea:** How well the rationale is supported, and how well the background provided indicates the research is ready to move into a clinical trial. The degree to which the proposed

clinical trial addresses the intent of the award mechanism, is interdisciplinary, and aligns with two to four of the FY17 PRORP Focus Areas (at least one of which is from the Surgical Care category and one of which is from the Rehabilitation category).

- **Research Strategy:** How well the specific aims, patient population, and proposed methodology will achieve the desired outcomes. The degree to which the clinical volume or measures to increase volume and enrollment are likely to provide an adequately powered study.

- **Impact:** The extent to which the study will make important contributions to patient care and/or restoration of function for those who have sustained traumatic orthopaedic injuries.

- **Military Benefit:** The degree to which the proposed clinical trial, if successful, will improve and/or innovate clinical care for military Service members and Veterans who have sustained combat-related orthopaedic injuries or non-battle orthopaedic injuries that impact unit readiness and return to duty/work.

- **Personnel:** How the background and experience of the PI, Qualified Collaborator(s), and other key personnel are appropriate to successfully complete the clinical trial.

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 time frame 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.

All contributors and administrators to the application must use matching compatible versions of Adobe software when editing and preparing application components. The use of different software versions will result in corruption of the submitted file. Refer to the General Application Instructions, Section III, for details on compatible Adobe software.

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, including non-DoD Federal agencies, must submit full applications through Grants.gov. Submissions of extramural applications through eBRAP may be withdrawn.

Table 1. Full Application Submission Guidelines

Extramural Submissions	Intramural DoD Submissions
Application Package Location	
Download application package components for W81XWH-17-PRORP-ICTA from Grants.gov (https://www.grants.gov).	Download application package components for W81XWH-17-PRORP-ICTA from eBRAP (https://ebrap.org).
Full Application Package Components	
SF424 (R&R) Application for Federal Assistance Form: Refer to the General Application Instructions, Section III.A.1, for detailed information.	**Tab 1 – Summary:** Provide a summary of the application information. **Tab 2 – Application Contacts:** This tab will be pre-populated by eBRAP; add Authorized Organizational Representative.
Descriptions of each required file can be found under Full Application Submission Components: • Attachments • Research & Related Senior/Key Person Profile (Expanded) • Research & Related Budget • Project/Performance Site Location(s) Form • R&R Subaward Budget Attachment(s) Form (if applicable)	**Tab 3 – Full Application Files:** Upload files under each Application Component in eBRAP. Descriptions of each required file can be found under Full Application Submission Components: • Attachments • Key Personnel • Budget • Performance Sites **Tab 4 – Application and Budget Data:** Review and edit proposed project start date, proposed end date, and budget data pre-populated from the Budget Form.

Extramural Submissions	Intramural DoD Submissions
Application Package Submission	
Submit package components to Grants.gov (http://www.grants.gov). If either the Project Narrative or the budget fails eBRAP validation or if the Project Narrative or the budget need 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.	**Submit package components to eBRAP (https://ebrap.org).** **Tab 5 – Submit/Request Approval Full Application:** After all components are uploaded and prior to the full application submission deadline, enter your password in the space provided "Enter Your Password Here" and press the "Submit Full Application" button. eBRAP will notify your Resource Manager/Comptroller or equivalent Business Official by email to log into eBRAP to review and to approve prior to the application submission deadline.
Application Verification Period	
The full application package submitted to Grants.gov may be viewed and modified in eBRAP until the end of the application verification period. During the application verification period, the full application package, ***with the exception of the Project Narrative and Budget Form,*** may be modified.	After eBRAP has processed the full application, the organizational Resource Manager/Comptroller or equivalent Business Official and PI(s) will receive an email notification of this status and will be able to view and modify application components in eBRAP. During the application verification period, the full application package, ***with the exception of the Project Narrative and Budget Form,*** may be modified.
Further Information	
Refer to Section III of the General Application Instructions for further information regarding Grants.gov requirements.	Refer to Section IV of the General Application Instructions for further information regarding eBRAP requirements.

The organization's Business Official or Authorized Organization Representative (or Resource Manager/Comptroller) should approve/verify the full application submission prior to the application verification deadline.

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. 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 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 6-8 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, noting potential challenges and alternative solutions where appropriate.

    – **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 interdisciplinary approach and the applicability of the proposed findings to the relevant FY17 PRORP Focus Areas.

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 study questions/hypotheses.

- **Study Design:** Describe the scope (pilot, Phase 0, Phase 1, etc.) and type of clinical trial to be performed (e.g., prospective, randomized, controlled) and outline the proposed methodology in sufficient detail to show a clear course of action. Describe potential challenges and alternative strategies where appropriate.

  - State the intervention to be tested and describe the projected outcomes.

  - Define the study variables (e.g., active drug, dose-response), outline why they were chosen, and describe how they will be measured. Include a description of appropriate controls and the endpoints to be tested.

  - Describe the study population and 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).

  - Describe the human subject-to-group assignment process (e.g., randomization, block randomization, stratified randomization, age-matched controls, alternating group, or other procedures), if applicable. Explain the specific actions to accomplish the group assignment (e.g., computer assignment, use of table of random numbers).

  - If using psychometric measures, describe their reliability and validity.

- **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. Describe analytical techniques for managing multiple sites and care providers contributing patients to the study, if applicable. 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. All interim analyses (formal or informal, pre-planned or ad hoc) should be addressed in full.

- **Access to Target Population/Enrollment Strategy:** Describe access to the target population for the proposed study. Based on clinical volume reported in pre-application and updated for this submission (number of patients per month for last 12 months), state the projected quarterly enrollment for each study site (as appropriate), and provide a contingency plan, including a threshold at which the plan will be implemented, to be executed if enrollment fails to meet expectations.

- **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. Any additional material viewed as an extension of the Project Narrative will be removed or may result in administrative withdrawal of the application.

  There are no page limits for any of these components unless otherwise noted. Include only those components described below; inclusion of items not requested will 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.

  - Current Quad Chart: Provide a current Quad Chart. If no changes have been made to the project, the same Quad Chart submitted with the pre-application may be used.

  - Letters of Organizational Support (one-page limit per letter is recommended): 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 Confirming Access to Military or VA Patient Populations or Resources (if applicable): If the proposed research plan involves access to active duty military and/or VA patient populations or resources, include a letter of support, signed by the lowest ranking person with approval authority, confirming such access. If access cannot be confirmed at the time of application submission, the Government reserves the right to withhold or revoke funding until the PI has demonstrated support for and access to the relevant population(s) and/or resources.

- Letters of Collaboration (if applicable; one-page limit per letter is recommended): 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; one-page limit per letter is recommended): 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 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.

  - Should the applicant intend to use, in the performance of this program, pre-existing, legally protected and perfected intangible property and for which no Federal funds had been used in the development of said property, the applicant must:

    - Clearly identify all such property;

    - Identify the cost to the Federal government for use or license of such property, if applicable; or

    - Provide a statement that no property meeting this definition will be used on this project.

- Data and Research Resources Sharing Plan: Describe how data and resources generated during the performance of the project will be shared with the research

community. Refer to the General Application Instructions, Appendix 2, Section K, for more information about the CDMRP expectations for making data and research resources publicly available.

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

  Technical abstracts should be written using the outline below. Abstracts of all funded research projects will be posted on the CDMRP website (http://cdmrp.army.mil); therefore, proprietary or confidential information should not be included.

  - **Background:** State the FY17 PRORP Focus Areas addressed by the proposed research. Present the ideas and rationale behind the proposed clinical trial.
  - **Objective/Hypothesis:** State the objective to be reached/hypothesis to be tested.
  - **Specific Aims:** State the specific aims of the study.
  - **Study Design:** Briefly describe the study design including appropriate controls.
  - **Military Benefit and Clinical Impact:** State briefly how the proposed project, if successful, will have an immediate and/or long-term impact on optimizing recovery and restoration of function for Service members and/or Veterans with orthopaedic injuries sustained in combat or combat-related activities, as well as their family members, caregivers, and the general public. Briefly describe how the proposed project will have an impact on patient care for those who have sustained combat related or non-battle orthopaedic injuries that affect readiness or return to duty/work.

- **Attachment 4: Lay Abstract (one-page limit):** Upload as "LayAbs.pdf." The lay abstract is used by all reviewers. Abstracts of all funded research projects will be posted publicly. ***Do not include proprietary or confidential information***. Use only characters available on a standard QWERTY keyboard. Spell out all Greek letters, other non-English letters, and symbols. Graphics are not allowed.

  - Clearly describe the objectives and rationale for the proposed study in a manner readily understood by readers without a background in science or medicine. ***Do not duplicate the technical abstract.*** Abstracts of all funded research projects will be posted on the CDMRP website (http://cdmrp.army.mil); therefore, proprietary or confidential information should *not* be included.
  - Describe the ultimate applicability and impact of the research.
    - Which of the FY17 PRORP Focus Areas will be addressed?
    - What types of patients will it help and how will it help them?

- What are the potential clinical applications, benefits, and risks?
- What is the projected timeline it may take to achieve the expected patient-related outcome?

– Describe how the proposed project will benefit Service members and/or Veterans who sustained combat related or non-battle orthopaedic injuries that affect readiness or return to duty/work. Also describe benefits to their families, caregivers, and the general public, as applicable.

○ **Attachment 5: Statement of Work (SOW) (three-page limit):** Upload as "SOW.pdf." The suggested SOW format and examples specific to different types of research projects are available on the eBRAP "Funding Opportunities & Forms" web page (https://ebrap.org/eBRAP/public/Program.htm). For the ICTA 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 (animal or human) and/or human anatomical samples projected or required for each task and at each site. Refer to Appendix 1 of the General Application Instructions for additional information regarding regulatory requirements.

Briefly state the methods to be used.

For studies with prospective accrual of human subjects, indicate quarterly enrollment targets.

If applicable, 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 and IDE applications) by the FDA or other Government agency.

- **Attachment 6: 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). Demonstrate that the research team has access to the proposed study population. 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. Include justification of any age, race, ethnicity, or sex limitations provided. ***For clinical trials proposing to include military personnel, please refer to the General Application Instructions, Appendix 6, 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). Include a description of any considerations unique to recruitment from military treatment facilities or VA medical centers, if applicable.

    - 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 clinical trial, 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, please refer to the General Application Instructions, Appendix 6, 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. Please note that some screening procedures may require a separate consent or a two-stage consent process. Informed consent must be obtained prior to initiation of any procedures for the purpose of determining eligibility.

- **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, please refer to the General Application Instructions, Appendix 6, 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 subject, a specific community, or society.

- **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 the conduct of the clinical trial.

Summarize key preclinical pharmacological findings, dosage studies, and other clinical studies (if applicable) that examine the safety 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. Discuss how compliance with Good Laboratory Practices (GLP), Good Manufacturing Practices (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 ICH E6 (International Conference on Harmonisation 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: Data Management (no page limit):** Upload as "Data_Manage.pdf." The Data Management 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. For FDA-regulated studies, compliance with 21 CFR 11 is required.

- **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.

  - **Labs performing evaluations and special precautions:** Identify the laboratory performing each evaluation, as well as 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 9: 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. Identify the data and clinical coordinating center(s) and note any involvement from Contract Research Organizations, 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. 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. 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.

- **Qualified Collaborator Statement:** Provide a statement that identifies the Qualified Collaborator(s) and addresses all criteria, as described in Section II.B, Award Information. It should be clear that the success of the project depends on the unique skills and contributions of both the PI and the Qualified Collaborator(s).

- **Attachment 10: Military Benefit and Clinical Impact Statement (two-page limit).** Upload as "MilBenClinImpact.pdf."

  - State explicitly how the proposed clinical trial, if successful, will accelerate the movement of the product, pharmacologic agent, device, procedure, clinical guidance, and/or emerging technology into clinical practice for those who sustained combat-related orthopaedic injuries. Further, describe the impact of this study on the lives of individuals recovering from combat-related orthopaedic injuries, including, but not limited to, how the expected results of the proposed work will contribute to the goal of decreasing the clinical impact of these injuries. When applicable, also describe the impact of the study on unit readiness and return-to-duty/-work capabilities. The following are examples of ways in which proposed studies, if successful, may demonstrate military benefit. Although not all-inclusive, these examples are intended to help PIs frame the military relevance of the proposed research:

    - Has the potential to change the standard of care for military orthopaedic injuries

    - Proposes new paradigms or challenges existing paradigms in patient care of military orthopaedic injuries

        - Contributes to development or validation of evidence-based policy or guidelines for patient evaluation and care of military orthopaedic injuries

    - Demonstrate how the proposed study is responsive to the healthcare needs of the military Services members and/or the Veteran population. If active duty military or Veteran population(s) will be used in the proposed research project, describe the population(s), the appropriateness of the population(s) for the proposed study, and the feasibility of using the population(s). 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 and/or the Veteran population). Show how the proposed study complements ongoing DoD areas of orthopaedic research interest, if applicable. Describe how the study design will replicate field conditions, if applicable.

    - Describe the potential impact of the proposed clinical trial on the outcomes of these individuals with regard to the FY17 PRORP Focus Areas addressed in the application.

    - 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, if applicable.

- **Attachment 11: Transition Plan and Regulatory Strategy (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.

    - The planned indication for the product label, if appropriate, and an outline of the development plan required to support that indication.

    - Describe in detail the FDA regulatory strategy, to include considerations for compliance with GMP, GLP, and GCP (if appropriate).

- Details of the funding strategy to transition to the next level of development and/or commercialization (e.g., partners, internal/external funding opportunities to be applied for).

- 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 CPGs 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 (next-phase clinical trials, commercialization, delivery to the military or civilian market, incorporation into clinical practice, and/or approval by the FDA). Include identification of the FDA regulatory strategy (if appropriate).

- 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 12: IND/IDE Documentation (no-page limit):** If submitting multiple documents, start each document on a new page. Combine and upload as a single file named "IND-IDE.pdf."

  - Complete the IND/IDE Documentation Form, which is available for download on the Full Announcement page for this Program Announcement/Funding Opportunity on Grants.gov.

  - State whether the trial requires regulation by the FDA. If FDA regulation is required, describe the planned indication for the proposed product and whether an IND/IDE is necessary. Identify the IND/IDE sponsor. If an IND or IDE is required, it must be submitted to the FDA ***within 6 months of the award date.***

  - If an IND or IDE has already been obtained for the investigational drug or device pertaining to the indication to be studied, provide evidence in the form of formal communication (e.g., letterhead correspondence) from the FDA.

  - If an IND or IDE application has been submitted, provide an explanation of the status of the IND or IDE application (e.g., past the critical 30-day period, pending response to questions raised by the Agency, on clinical hold). Provide a summary of previous meetings with the FDA on development of this product, if appropriate. A copy of the Agency meeting minutes should be included if available. Provide copies of

communications from the FDA relevant to the most recent status of the IND or IDE application.

- If the IND or IDE application is not yet submitted, provide evidence that an IND or IDE will be submitted ***within 6 months of award date.*** Examples include results and minutes of a pre-IND or pre-IDE meeting with the FDA, a pre-IND/pre-IDE meeting request to the FDA, or other communication with the FDA. Provide the anticipated date of IND/IDE submission.

- If an IND or IDE is not required for the proposed study, or if it qualifies for an abbreviated IDE, provide evidence in the form of formal communication (e.g., letterhead correspondence) from the FDA or the IRB of record to that effect. Devices qualifying for an abbreviated IDE must comply with the abbreviated IDE requirements but do not require the submission of an IDE application to the FDA.

- Identify any consultants or experts who will assist in the regulatory application, if applicable, and include a copy of any curricula vitae or biographical sketches in the Key Personnel Biographical Sketches section of the application.

- **Attachment 13: 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 14: DoD Military Budget Form(s), if applicable:** Upload as "MFBudget.pdf." If a military facility (military health system facility, research laboratory, treatment facility, dental treatment facility, or a DoD activity embedded with a civilian medical center) will be a collaborator in performance of the project, complete the 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 –**

  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 (six-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 portable document format (pdf) that is not editable.

- PI Previous/Current/Pending Support (no page limit): Upload as "Support_LastName.pdf."
- Key Personnel Biographical Sketches (six-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.)
  - **Intramural DoD Collaborator(s):** Complete the DoD Military Budget Form and upload to Grants.gov as Attachment 14. (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.

II.D.3. Dun and Bradstreet 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 by 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 Section III of the General Application Instructions 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

Prior to the end of the application verification period, PIs and organizational representatives can review and modify in eBRAP certain components of a submitted application. 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.

II.D.5. Funding Restrictions

The maximum period of performance is **4** years.

The anticipated total costs budgeted for the entire period of performance will not exceed **$4.5M**. If indirect cost rates have been negotiated, indirect costs are to be budgeted in accordance with the organization's negotiated rate. No budget will be approved by the Government exceeding **$4.5M** total costs or 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.

The applicant may request the entire maximum funding amount for a project that may have a period of performance less than the maximum **4** years.

For this award mechanism, direct costs must be requested for:

- Travel costs for the PI(s) to disseminate project results at one DoD PRORP In-Progress Review (IPR) meeting in Year 3. For planning purposes, it should be assumed that the meeting will be held in the National Capital Area. These travel costs are in addition to those allowed for annual scientific/technical meetings.

May be requested for (not all-inclusive):

- Salary
- Research supplies and equipment
- Research-related subject costs
- Clinical research costs
- Support for multidisciplinary collaborations, including travel
- Travel costs for up to three investigator(s) to travel to two scientific/technical meeting(s) per year in addition to the required IPR meeting described above.

Shall not be requested for:

- Preclinical research costs

Extramural (non-Federal) awards 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. Intragovernmental only 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 Section III.A.4, of the General Application Instructions***.

The CDMRP expects to allot approximately $4.5M of the $30M FY17 of the FY17 PRORP appropriation(s) to fund approximately one ICTA application, 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.

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:

- **Military Benefit and Clinical Impact**
    - How well the proposed clinical trial addresses two to four of the FY17 PRORP Focus Areas (at least one of which is from the Surgical Care category and one of which is from the Rehabilitation category).
    - How relevant the anticipated outcomes of the proposed clinical trial are to individuals with orthopaedic injuries.
    - How well the project addresses a critical issue in treatment of non-battle orthopaedic injuries that impact unit readiness and the ability to return to duty/work, if applicable.
    - To what extent the practical application of the proposed intervention will have a long-term benefit for individuals with combat-related orthopaedic injuries and impact patient care and/or quality of life.
    - How well the proposed study population represents the targeted patient population that might benefit from the proposed intervention.
    - How the potential outcomes of the proposed clinical trial will provide/improve short-term benefits for individuals with orthopaedic injuries.
    - To what degree the intervention represents an improvement over currently available interventions and/or standards of care.
- **Research Strategy**
    - How well the scientific rationale for the proposed clinical trial 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 objectives, experimental design, methods, data collection procedures, and analyses are designed to address the clinical objective.
    - How well the proposed study integrates both surgical and rehabilitation strategies.

- 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.

- **Statistical Plan**
  - To what degree the statistical model and data analysis plan are suitable for the planned study.
  - Whether 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.
  - How well the proposal accounts for the possibility of limited clinical enrollment (beyond anticipated attrition).

- **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.
  - To what degree the PI has provided preclinical and/or clinical evidence to support the safety of the intervention.
  - To what degree the regulatory strategy is well-described and feasible including:
    - Whether a member of the study team holds the IND/IDE for the indication proposed or whether the timeline proposed for obtaining the IND/IDE, abbreviated IDE, or exemption is appropriate (if applicable).
    - For investigator-sponsored INDs, whether there is evidence of appropriate institutional support, including capabilities to ensure monitoring as required by the FDA.
    - Whether plans to comply with GMPs, GLPs, and GCP guidelines are appropriate.

- Whether measures are described to ensure the consistency of dosing of active ingredients for nutritional supplements (if applicable).

- **Recruitment, Accrual, and Feasibility**

  - How well the PI addresses the availability of human subjects for the clinical trial and the prospect of their participation.

  - Whether the PI has demonstrated access to the proposed human subject population.

  - 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 current clinical volume and proposed measures to increase volume ensure adequate study enrollment.

  - 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?)

- **Ethical Considerations**

  - How the level of risk to human subjects is minimized, and how the safety monitoring and reporting plan is appropriate for the level of risk.

  - 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.

  - Whether a research monitor with expertise consistent with the nature of the potential risk(s) is identified, if applicable.

  - To what degree privacy 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, expertise in clinical studies).

- To what extent the levels of effort 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.

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

- **Transition Plan and Regulatory Strategy**

  - Whether the identified next level of development and/or commercialization is realistic.

  - Whether the funding strategy described to bring the intervention to the next level of development (e.g., higher phase clinical trial, transition to industry, delivery to the market, incorporation into standard practice) is reasonable and realistic.

  - How the regulatory strategy and development plan to support a product label change, if applicable, are appropriate and well described.

  - Whether the proposed collaborations and other resources for providing continuity of development, including proposed development or modification of CPGs and recommendations, provider training materials, patient brochures, and other clinical support tools, scientific journal publications, models, simulations, and applications are established and/or achievable.

  - How the schedule and milestones for bringing the intervention to the next level of development (e.g., higher phase clinical trial, 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, describes any 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/Funding Opportunity.

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

- **Budget**

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

- Whether the budget is appropriate for the proposed research.

- **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.

- **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 FY17 PRORP, as evidenced by the following:

  - Adherence to the intent of the award mechanism

  - Program portfolio composition

  - Regulatory and developmental risk

  - Relative military relevance and 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 PRORP, 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.shtml.

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 process to gain protected evaluation information or to influence the evaluation process. Violations of these prohibitions will result in the administrative withdrawal of the organization's application. Violations by panel members or applicants that compromise the confidentiality of the review process may also result in suspension or debarment from Federal awards. Furthermore, the unauthorized disclosure of confidential information of one party to another third party is a crime in accordance with 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 (FAPIIS).

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

The Federal awarding agency will consider any comments by the applicant, in addition to other information in the designated integrity and performance system, in making a judgment about the applicant's integrity, business ethics and record of performance under Federal awards when determining a recipient's qualification prior to award, according to the qualification standards of the Department of Defense Grant and Agreement Regulations (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, 2018. Refer to the General Application Instructions, Appendix 2, for additional award administration information.

Awards are made to organizations, not to individual PIs. 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 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). 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.

After email notification of application review results through the 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 documents.

Intramural 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 managers (RM).

After email notification of application review results through the 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. Award Transfers

The organization 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.

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

II.F.2. Administrative and National Policy Requirements

Applicable requirements in the 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 for Institutions of Higher Education, Hospitals, and Non-Profit Organizations 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. Annual progress reports as well as a final progress report will be required.

Quarterly technical progress reports, quad charts, and in-person presentations will be required.

Awards resulting from this Program Announcement will incorporate additional reporting requirements related to recipient integrity and performance matters. Recipient organizations that have Federal contract, grant, and cooperative agreement awards with a cumulative total value greater than $10,000,000 are required to provide information to FAPIIS about certain civil, criminal, and administrative proceedings that reached final disposition within the most recent 5-year period and that were connected with performance of a Federal award. Recipients are required to disclose semiannually information about criminal, civil, and administrative proceedings as specified in the applicable Terms and Conditions. The applicable Terms and Conditions for institutions of higher education, hospitals, and nonprofit organizations is available in OAR Article I, Section B, in the July 2016 R&D General Terms and Conditions. The applicable Terms and Conditions for for-profit organizations is available in Section 34 of the February 2017 USAMRAA General Research Terms and Conditions with For-Profit Organizations.

II.G. Federal Awarding Agency Contacts

II.G.1. CDMRP Help Desk

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

Phone: 301-682-5507

Email: help@eBRAP.org

II.G.2. Grants.gov Contact Center

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

Phone: 800-518-4726; International 1-606-545-5035

Email: support@grants.gov

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

II.H. Other Information

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

Questions related to this Program Announcement should refer to the Program name, the Program Announcement name, and the Program Announcement version code 20170516b. The Program Announcement numeric version code will match the General Applications Instructions version code 20170516.

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 is missing.
- Budget is missing.

- Human Subject Recruitment and Safety Procedures (Attachment 6) is missing.
- Intervention (Attachment 7) is missing.
- Data Management (Attachment 8) 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 FY17 PRORP 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 FY17 PRORP Programmatic Panel members can be found at http://cdmrp.army.mil/prorp/panels/panels17***.
- 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 FY17, 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 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.
- Applications may be administratively withdrawn from further consideration if the applicant cannot demonstrate access to the relevant study population or resources.
- The invited application does not propose the same research project described in the pre-application.
- The proposed research is not a clinical trial.
- The proposed project includes preclinical research.
- Project Narrative exceeds page limit
- Submission of the same research project to different Funding Opportunities within the same program and fiscal year.

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 **(Extramural submissions only)**	Complete form as instructed.	
Summary (Tab 1) and Application Contacts (Tab 2) **(Intramural submissions only)**	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 Abstract: Upload as Attachment 3 with file name "TechAbs.pdf."	
	Lay Abstract: Upload as Attachment 4 with file name "LayAbs.pdf."	
	Statement of Work: Upload as Attachment 5 with file name "SOW.pdf."	
	Human Subject Recruitment and Safety Procedures: Upload as Attachment 6 with file name "HumSubProc.pdf."	
	Intervention: Upload as Attachment 7 with file name "Intervention.pdf."	
	Data Management: Upload as Attachment 8 with file name "Data_Manage.pdf."	
	Study Personnel and Organization: Upload as Attachment 9 with file name "Personnel.pdf."	
	Military Benefit and Clinical Impact Statement: Upload as Attachment 10 with file name "MilBenClinImpact.pdf."	
	Transition Plan and Regulatory Strategy: Upload as Attachment 11 with file name "Transition.pdf."	
	IND/IDE Documentation: Upload as Attachment 13 with file name "IND-IDE.pdf."	
	Surveys, Questionnaires, and Other Data Collection Instruments: Upload as Attachment 13 with file name "Surveys.pdf," if applicable.	
	DoD Military Budget Form(s): Upload as Attachment 14 with file name "MFBudget.pdf," if applicable.	

Application Components	Action	Completed
Research & Related Senior/Key Person Profile (Expanded)	Attach PI Biographical Sketch (Biosketch_LastName.pdf) to the appropriate field.	
	Attach PI Previous/Current/Pending Support (Support_LastName.pdf) to the appropriate field.	
	Attach Biographical Sketch (Biosketch_LastName.pdf) for each senior/key person to the appropriate field.	
	Attach Previous/Current/Pending (Support_LastName.pdf) for each senior/key person to the appropriate field.	
Research & Related Budget **(Extramural submissions only)**	Complete as instructed. Attach Budget Justification (BudgetJustification.pdf) to the appropriate field.	
Budget **(Intramural submissions only)**	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

ACURO	Animal Care and Use Review Office
CDMRP	Congressionally Directed Medical Research Programs
CFR	Code of Federal Regulations
COI	Conflict of Interest
CPG	Clinical Practice Guidelines
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. Food and Drug Administration
FY	Fiscal Year
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HRPO	Human Research Protection Office
IACUC	Institutional Animal Care and Use Committee
ICH E6	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICTA	Integrated Clinical Trial Award
IRB	Institutional Review Board
LAR	Legally Authorized Representative
M	Million
MIPR	Military Interdepartmental Purchase Request
NIH	National Institutes of Health
OASD(HA)	Office of the Assistant Secretary of Defense for Health Affairs
ORCID	Open Researcher and Contributor ID, Inc.
ORP	Office of Research Protections
PRORP	Peer Reviewed Orthopaedic Research Program
PI	Principal Investigator
RDT&E	Research, Development, Test, and Evaluation
RM	Resource Manager
SAM	System for Award Management
SOW	Statement of Work
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