Program Announcement

for the

Defense Health Program

Defense Medical Research and Development Program

Department of Defense

Congressionally Directed Medical Research Programs

Peer Reviewed Orthopaedic Research Program

Clinical Trial Award

Funding Opportunity Number: W81XWH-14-PRORP-CTA

Catalog of Federal Domestic Assistance Number: 12.420

SUBMISSION AND REVIEW DATES AND TIMES

- **Pre-Application Deadline:** 5:00 p.m. Eastern time (ET), June 27, 2014
- **Invitation to Submit an Application:** August 2014
- **Application Submission Deadline:** 11:59 p.m. ET, October 24, 2014
- **End of Application Verification Period:** 5:00 p.m. ET, October 29, 2014
- **Peer Review:** December 2014
- **Programmatic Review:** February 2015

Change for Fiscal Year 2014: *The CDMRP eReceipt System has been replaced with the electronic Biomedical Research Application Portal (eBRAP). Principal Investigators and organizational representatives should register in eBRAP as soon as possible. All pre-applications must be submitted through eBRAP. In addition, applications submitted through Grants.gov will now be available for viewing, modification, and verification in eBRAP prior to the end of the application verification period.*

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

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I. FUNDING OPPORTUNITY DESCRIPTION

A. Program Description

Applications to the Fiscal Year 2014 (FY14) Peer Reviewed Orthopaedic Research Program (PRORP)) are being solicited for the Assistant Secretary of Defense for Health Affairs, Defense Health Program (DHP), by the U.S. Army Medical Research Acquisitions Activity (USAMRAA). The PRORP was initiated in 2009 to support research 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 FY13 totaled $218.5 million (M). The FY14 appropriation is $30M.

The FY14 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 musculoskeletal injuries sustained during combat or combat-related activities. It is expected that any research findings would also provide benefit to the general population. Applications involving multidisciplinary collaborations among academia, industry, the military services, the Department of Veterans Affairs (VA), and other federal Government agencies are highly encouraged.

B. FY14 PRORP Focus Areas

All applications must address at least one of the following FY14 PRORP Clinical Trial Award Focus Areas:

- Identify and reduce the secondary health effects (e.g., joint contracture, obesity, metabolic syndrome, poor bone health) that follow reduced mobility from traumatic neuromusculoskeletal injury, excluding spinal cord injuries. The focus should be on injuries sustained prior to the age of 45 and secondary health effects that develop within 5 years of injury.
- Physical or occupational therapy (PT/OT) interventions to establish optimal rehabilitation and examine the comparative effectiveness of different PT/OT regimes, such as studies that establish optimal strategies for weight bearing progression, gait training, and strengthening, and that prevent or treat post-traumatic joint stiffness and contracture in the ankle, knee, and/or elbow.
- Strategies to inhibit neuromas at surgical/amputation sites.
- The application of ***novel and/or innovative*** technologies and materials in prosthetic and orthotic device development toward the improvement or enhancement of:
    - Long-term socket performance, to include afferent and efferent user interface.
    - The fit of prosthetics, including the design and development of flexible socket suspension systems and incorporated interoperability of components to improve stability and usability.

- Socket performance (comfort, fit, moisture management, residual limb skin integrity, and durability). Novel upper extremity prosthetic sockets, including the design and development of flexible socket suspension systems, are highly encouraged.
- Myoelectric prosthetic durability (e.g., water resistance, waterproof components) to enhance the use of myoelectric prostheses in all military environments.

Studies that propose nominal or iterative advancements are not encouraged.

- Research toward osseointegration of upper extremity prostheses, including optimization of the skin-implant interface, prevention of infection, control strategies, and sensory feedback.
- Clinical trials to restore function after volumetric muscle loss, including physical therapy approaches.
- Research on treatment of non-battle orthopaedic injuries that impact unit readiness and reflect historical return to work rates less than 50% or longer than 6 months. Non-penetrating/non-ballistic injuries involving knee, shoulder, elbow, hip, or ankle will be considered, but funding will favor studies focusing on a single joint complex. Includes strategies for timing and effectiveness of treatment for multi-ligamentous knee injuries.

C. Award Information

The PRORP Clinical Trial Award is intended to support the rapid implementation of clinical trials with the potential to have a significant impact on military combat-related orthopaedic injuries, or non-battle injuries that significantly impact unit readiness and return-to-duty/work rates. The clinical trials may be designed to evaluate promising new products, pharmacologic agents (drugs or biologics), devices, clinical guidance, and/or emerging approaches and technologies. 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 researchers and clinicians is encouraged, and studies that include active duty military or Veteran participants as all or a portion of the study population will be given higher priority for funding during programmatic review.***

Proposed projects may range from small proof-of-concept trials to demonstrate feasibility or inform the design of more advanced trials (i.e., pilot, first in human, or Phase 0), through large-scale trials, to determine efficacy in relevant patient populations. Proof-of-concept trials should not request the maximum funding amount allowed under this Program Announcement/Funding Opportunity. All funding amounts requested should be well-justified and appropriate to the scope of work proposed.

Funding from this award mechanism must support a clinical trial. 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 exploratory information, safety, effectiveness, and/or efficacy. This outcome represents a direct effect on the human subject of that intervention or interaction. Clinical studies that seek to determine efficacy or effectiveness

of an intervention(s) without randomized assignment of patients to a study arm are allowed, if appropriate for the intervention to be tested. The term "human subjects" is used in this Program Announcement/Funding Opportunity to refer to individuals who will be recruited for or who will participate in the proposed clinical trial. For more information, a Human Subject Resource Document is provided at https://ebrap.org/eBRAP/public/Program Principal Investigators (PIs) seeking funding for a preclinical research project should consider one of the other FY14 PRORP award mechanisms/funding opportunities being offered.

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 ***prior to the application submission deadline.*** 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 ***prior to the application submission deadline***, or that the device is exempt from an 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 prior to the grant submission deadline, or if documented status of the IND or IDE has not been obtained within 6 months of the award date.

The following are important aspects of submission for the Clinical Trial Award:

- 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 with combat-related orthopaedic injuries or non-battle orthopaedic injuries that impact unit readiness and return-to-duty/work.
- Inclusion of preliminary data relevant to the proposed research project is required.
- The proposed research project must be based on sound scientific rationale that is established through logical reasoning and critical review and analysis of the literature.
- The application should describe the planned indication for the product label, if appropriate, and include an outline of the development plan required to support that indication.
- The application should demonstrate availability of, and access to, a suitable patient population in the numbers that will support a meaningful outcome for the study. The PI should discuss how accrual goals will be achieved and how standards of care may impact the study population.
- The application should demonstrate documented availability of and access to the drug/ compound, device, and/or other materials needed, as appropriate. 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 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, 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.
- The application should include a clearly articulated safety management plan, outlining how safety pharmacovigilance will be conducted as applicable.
- The application should include a clearly articulated clinical monitoring plan, outlining how the study will be monitored for GCP compliance.
- The application should include a study coordinator(s) who will guide the clinical protocol through the local Institutional Review Board (IRB) of record and other regulatory approval processes, coordinate activities from all sites participating in the trial, and coordinate participant accrual.
- The application should include a Transition Plan (including potential funding and resources) showing how the product will progress to the next phase of development after the successful completion of the PRORP Clinical Trial Award.
- The application should clearly demonstrate strong institutional support.
- The application should acknowledge the commitment to filing the study in the National Institutes of Health (NIH) clinical trials registry, www.clinicaltrials.gov.

Use of Human Subjects and Human Anatomical Substances: All Department of Defense (DoD)-funded research involving new and ongoing research with human subjects and human anatomical substances 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), in addition to the local IRB of record. Local IRB approval at the time of submission is NOT required. The HRPO is mandated to comply with specific laws and directives governing all research involving human subjects that is supported by the DoD. These laws and directives will require information in addition to that supplied to the IRB. Allow a minimum of 2-3 months for regulatory review and approval processes. Refer to the General Application Instructions, Appendix 6, for more information.

Use of Military and VA Populations: If the proposed research plan involves access to active duty military and/or VA patient populations or resources, the PI is responsible for establishing such access. If possible, access to target active duty military and/or VA patient populations/ resources should be confirmed at the time of application submission by inclusion of a letter of support, signed by the lowest ranking person with approval authority, for studies involving active duty military service members, Veterans, military and/or VA-controlled study materials, and military and/or VA databases. 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. Note that access to a Veteran population for clinical studies may only be obtained by either collaboration with a VA investigator where the VA investigator has a substantial role in the research, or by advertising to the general public.

Encouraged DoD Collaboration and Alignment: Military relevance is a key feature of this award. Therefore, PIs are strongly encouraged to collaborate, integrate, and/or align their projects with military and/or VA research laboratories and programs. Although not a comprehensive list, the following websites may be useful in identifying information about ongoing DoD areas of research interest:

Air Force Research Laboratory
http://www.wpafb.af.mil/afrl

Clinical and Rehabilitative Medicine Research Program
https://crmrp.amedd.army.mil

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

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

Defense Advanced Research Projects Agency
http://www.darpa.mil/

Defense Medical Research and Development Program
http://dmrdp.fhpr.osd.mil/home.aspx

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

Military Infectious Disease Research Program
https://midrp.amedd.army.mil

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

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

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

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

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

U.S. Army Medical Research Acquisition Activity
https://www.usamraa.army.mil/

U.S. Army Medical Research and Materiel Command
https://mrmc.amedd.army.mil

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

U.S. Department of Defense Blast Injury Research Program
https://blastinjuryresearch.amedd.army.mil/

U.S. Naval Research Laboratory
http://www.nrl.navy.mil

U.S. Department of Veterans Affairs, Office of Research and Development
http://www.research.va.gov

Walter Reed Army Institute of Research
http://wrair-www.army.mil

The Congressionally Directed Medical Research Programs (CDMRP) intends that data and research resources generated under awards funded by this Program Announcement/Funding Opportunity be made available to the research community (which includes both scientific and consumer advocacy communities) and to the public at large. For additional guidance, refer to the General Application Instructions, Appendix 4, Section L.

D. Eligibility Information

- PIs must be at or above the level of Assistant Professor (or equivalent)
- Cost sharing/matching is not an eligibility requirement.

- Eligible investigators must apply through an organization. Organizations eligible to apply include national, international, for-profit, non-profit, public, and private organizations.
- Refer to the General Application Instructions, Appendix 1, for general eligibility information.

E. Funding

- The maximum period of performance is **5** years.
- The maximum allowable total costs for the entire period of performance are **$4.0M.**
- All direct and indirect costs of any subaward (subgrant or subcontract) must be included in the total direct costs of the primary award.
- The applicant is encouraged to request less than the maximum allowable total cost limit, as appropriate to the scope of work proposed. Proof-of-concept trials should not request the maximum funding amount allowed under this Program Announcement/ Funding Opportunity.
- The applicant may request the entire maximum funding amount for a project that may have a period of performance less than the maximum **5** years.
- Regardless of the period of performance proposed, the applicant may not exceed the maximum allowable total costs. Indirect costs shall be proposed in accordance with the organization's negotiated rate agreement.

Refer to the General Application Instructions, Section II.C.4., for budget regulations and instructions for the Research & Related Budget. ***For all federal agencies or organizations collaborating with federal agencies, budget restrictions apply as are noted in Section II.C.4. of the General Application Instructions***.

For this award mechanism, direct costs:

Must be requested for:

- Travel costs of up to $1,800 for the PI to disseminate project results at one DoD-sponsored meeting to be specified by the CDMRP during the award performance period. These travel costs are in addition to those allowed for annual scientific/ technical meetings.

May be requested for (not all-inclusive):

- Salary
- Research supplies
- Equipment
- Research-related subject costs

- Travel between collaborating organizations
- Travel costs of up to $1,800 per year to attend scientific/technical meetings in addition to the required meeting described above

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

As required of all applicants to this Program Announcement/Funding Opportunity, if PIs from federal agencies submit applications, they must submit through Grants.gov. Therefore, federal applicants must be familiar with Grants.gov requirements, including the need for an active System for Award Management (SAM) registration and a Data Universal Numbering System (DUNS) number. Refer to Appendix 3 of the General Application Instructions for further information regarding Grants.gov requirements.

Awards to extramural organizations will consist solely of assistance agreements (Cooperative Agreements and Grants). Awards to intramural agencies and other federal agencies will be executed through the Military Interdepartmental Purchase Request (MIPR) or Funding Authorization Document (FAD) process. Direct transfer of funds from the recipient to a federal agency is not allowed except under very limited circumstances. Refer to the General Application Instructions, Section II.C.4. Research & Related Budget, for additional information on budget considerations for applications involving federal agencies.

The CDMRP expects to allot approximately $8.0M of the $30M FY14 appropriation to fund approximately two Clinical Trial Award applications, depending on the quality and number of applications received. Funding of applications received in response to this Program Announcement/Funding Opportunity is contingent upon the availability of federal funds for this program.

II. SUBMISSION INFORMATION

Submission is a two-step process requiring both (1) pre-application submission through the electronic Biomedical Research Application Portal (eBRAP) (https://eBRAP.org/) and (2) application submission through Grants.gov (http://www.grants.gov/).

New for FY14: ***The CDMRP has replaced its eReceipt System with eBRAP.*** Submission remains a two-step process requiring both pre-application and application submission.

PIs must be registered in eBRAP in order to submit a pre-application and receive notification of the status of a pre-application or application. A key feature of eBRAP is that an organization's

representatives and PIs are able to view and modify the Grants.gov application submissions associated with them, but only if the organization, Business Officials, and PIs are registered and affiliated to the organization in eBRAP (see *eBRAP User Guide* at *https://ebrap.org/eBRAP/public/UserGuide.pdf).* Upon completion of an organization's registration in eBRAP and approval by the CDMRP Help Desk, the organization name will be displayed in eBRAP to assist the organization's business officials and PIs as they register.

Note: Submission of either the pre-application to eBRAP or application to Grants.gov does not require registering an organization and affiliating its Business Officials and PIs in eBRAP; however, the ability to view and modify the Grants.gov application in eBRAP is contingent upon the registration and affiliation. ***Application viewing, modification, and verification in eBRAP is strongly recommended, but not required. The Project Narrative and Budget cannot be changed after the application submission deadline. Any other application component cannot be changed after the end of the application verification period.*** If verification is not completed by the end of the application verification period, the application will be reviewed as submitted through Grants.gov or may be subject to administrative rejection (see Section IV.A., Rejection).

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.

A. Where to Obtain the Application Package

To obtain the complete application package, including all required forms, perform a Grants.gov (http://www.grants.gov/) basic search using the Funding Opportunity Number: W81XWH-14-PRORP-CTA.

B. Pre-Application Submission and Content Form

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

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

A change in PI or organization after submission of the pre-application will be allowed only at the discretion of the US Army Medical Research Acquisition Activity (USAMRAA) Contracting/ Grants Officer.

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

- **Application Information – Tab 1**
- **Application Contacts – Tab 2**
    - It is recommended that PIs identify an Alternate Submitter in the event that assistance with pre-application submission is needed.
- **Collaborators and Conflicts of Interest (COI) – Tab 3**

  FY14 PRORP Steering Committee (SC) members should not be involved in any pre-application or application. For questions related to SC members and pre-applications or applications, refer to Section IV.C., Withdrawal, or contact the CDMRP Help Desk at help@eBRAP.org or 301-682-5507.
- **Required Files – Tab 4**

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

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

  The Preproposal Narrative should include the following:

    - **Focus Area:** Explain how the proposed work addresses at least one of the FY14 PRORP Clinical Trial Award Focus Areas.
    - **Research Idea:** Describe the ideas and reasoning on which the proposed clinical trial is based; include relevant literature citations. Briefly describe the level of scientific evidence that supports the progression of this research to a clinical trial. Clearly specify which type (e.g., drug, device, surgical) 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 objectives and specific aims. Briefly describe the patient population(s) to be recruited for the clinical trial and the experimental approach.
    - **Personnel:** Briefly state the qualifications of the PI and key personnel to perform the clinical trial.
    - **Military Benefit:** Describe how the proposed work will have an impact on accelerating the movement of a promising treatment for combat-related orthopaedic injuries, or non-battle orthopaedic injuries that impact unit readiness and return-to-duty/work, into a military clinical application.

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

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

- **Submit Pre-Application – Tab 5**

  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:** The degree to which the proposed clinical trial addresses the intent of the award mechanism and aligns with at least one of the FY14 PRORP Clinical Trial Award Focus Areas. How well the rationale is supported, and how well the background provided indicates the research is ready to move into a clinical trial.
  - **Research Strategy:** How well the specific aims, patient population, and proposed methodology will address the hypothesis and achieve the desired outcomes.
  - **Personnel:** How the background and experience of the PI and other key personnel are appropriate to successfully complete the clinical trial.
  - **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 traumatic orthopaedic injuries that impact unit readiness and return-to-duty/work.

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

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

C. Application Submission Content and Forms

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

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

New for FY14: ***Applications submitted through and validated by Grants.gov will be retrieved and processed by eBRAP to allow for review, modification, and verification.*** The PI and organizational representatives will receive an email request from eBRAP to review, modify, and verify the application submitted to Grants.gov. During this verification period, the PI may upload missing files (excluding those listed in Section IV.A., Rejection), replace files, and re-categorize files. These modifications must be completed by the end of the verification period.

Note: Changes to either the Project Narrative or Budget are not allowed in eBRAP; if such changes are required, the entire application package must be submitted through Grants.gov as a "Changed/Corrected Application" with the Previous Grants.gov Tracking ID ***prior to the application submission deadline (which occurs earlier than the end of the application verification period).***

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

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

2. **Attachments Form**

   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, etc.) used to describe the project. Inclusion of URLs that provide additional information to expand the Project Narrative and could confer an unfair competitive advantage is prohibited and will result in administrative withdrawal of the application.

     Describe the proposed project in detail using the outline below.

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

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

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

- **Study Design:** Describe the type of study 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.

  - Identify the intervention to be tested and describe the projected outcomes.
  - Define the study variables and describe how they will be measured. Include a description of appropriate controls and the endpoints to be tested.
  - 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).

- **Statistical Plan and Data Analysis:** Describe the statistical model and data analysis plan with respect to the study objectives. Specify the approximate number of human subjects to be enrolled. If multiple study sites are involved, state the approximate number to be enrolled at each site. Include a complete power analysis to demonstrate that the sample size is appropriate to meet the objectives of the study. If a subpopulation of a recruited sample population will be used for analysis, complete a statistical analysis to ensure appropriate power can be achieved within the subpopulation study.

- **Attachment 2: Supporting Documentation.** Start each document on a new page. Combine and upload as a single file named "Support.pdf." If documents are scanned to pdf, the lowest resolution (100 to 150 dpi) should be used. ***There are no***

page limits for any of these components unless otherwise noted. Include only those components described below; inclusion of items not requested may result in the removal of those items or administrative withdrawal of the application.

- References Cited: List the references cited (including URLs if available) in the Project Narrative using a standard reference format that includes the full citation (i.e., author[s], year published, title of reference, source of reference, volume, chapter, page numbers, and publisher, as appropriate).
- List of Abbreviations, Acronyms, and Symbols: Provide a list of abbreviations, acronyms, and symbols.
- Facilities, Existing Equipment, and Other Resources: Describe the facilities and equipment available for performance of the proposed project and any additional facilities or equipment proposed for acquisition at no cost to the award. Indicate whether or not Government-furnished facilities or equipment are proposed for use. If so, reference should be made to the original or present Government award under which the facilities or equipment items are now accountable. There is no form for this information.
- Publications and/or Patent Abstracts (five-document limit): Include relevant publication URLs and/or patent abstracts. If publications are not publicly available, then a copy/copies of the published manuscript(s) must be included in Attachment 2. Extra items will not be reviewed.
- Letters of Organizational Support: Provide a letter (or letters, if applicable), signed by the Department Chair or appropriate organization official, confirming the laboratory space, equipment, and other resources available for the project.
- Letters of Collaboration: Provide a signed letter from each collaborating individual or organization that will demonstrate that the PI has the support or resources necessary for the proposed work. 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.
- 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.
- Intellectual Property
  - Background and Proprietary Information: All software and data first produced under the award are subject to a federal purpose license in accordance with applicable DoD Grant and Agreement Regulations (DoDGAR) requirements. Provide a list of all background intellectual

property to be used in the project. Identify any proprietary information that will be provided to the Government and indicate whether the applicant will require a waiver of the federal purpose license.

  - Intellectual and Material Property Plan (if applicable): Provide a plan for resolving intellectual and material property issues among participating organizations.

- 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 4, Section L, for more information about the CDMRP expectations for making data and research resources publicly available.

- **Attachment 3: Technical Abstract (one-page limit):** Upload as "TechAbs.pdf."

  The technical abstract is used by all reviewers as a description of the project's key aspects. Therefore, clarity and completeness within the space limits of the technical abstract are highly important.

  Technical abstracts should be written using the outline below.

  - Background: State the FY14 PRORP Clinical Trial Award Focus Area(s) addressed by the proposed research. Present the ideas and reasoning behind the proposed work.
  - Objective/Hypothesis: State the objective/hypothesis to be tested. Provide evidence or rationale that supports the objective/hypothesis.
  - Specific Aims: State the specific aims of the study.
  - Study Design: Briefly describe the study design including appropriate controls.
  - Military Benefit: State briefly how the proposed project, if successful, will have an impact on combat-related orthopaedic injury research, unit readiness, return-to-duty/work, and/or patient care.

- **Attachment 4: Lay Abstract (one-page limit):** Upload as "LayAbs.pdf."

  Lay abstracts should be written using the following outline.

  - Describe the objectives and rationale for the application in a manner that will be ***readily understood by readers without a background in science or medicine***.
    - Do not duplicate the technical abstract.
  - Describe the ultimate applicability of the clinical research.
    - 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?
  - Briefly describe how the proposed project will benefit military populations and impact combat-related orthopaedic research and patient care.

- **Attachment 5: Statement of Work (SOW) (three-page limit):** Upload as "SOW.pdf." Refer to the General Application Instructions, Section II.C.2., for detailed guidance on creating the SOW.

  The suggested SOW format and examples specific to different types of research projects are available on the eBRAP "Program Announcement and Forms" web page (https://ebrap.org/eBRAP/public/Program.htm). For the Clinical Trial Award mechanism, use the SOW format example titled "SOW for Clinical Research (Including Trials, Special Populations)." The SOW must be in PDF format prior to attaching.

- **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.

  a. 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 (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 including those specific to recruitment from military and/or Veteran populations (if applicable). Provide plans for addressing unanticipated delays. Include justification of any age, race, ethnicity, or sex limitations provided.

  b. 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.

  c. Description of the Recruitment Process: Explain methods for identification of potential human subjects (e.g., medical record review, obtaining sampling lists, health care provider identification). ***Include a description of any considerations unique to recruitment from military or Veterans medical treatment facilities, 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.

- Include a detailed description of and justification for the compensation plan if the human subjects will be compensated for participation in the study.
- Describe the recruitment and advertisement materials. The recruitment materials should not be coercive or offer undue inducements and should accurately reflect the study.

d. Description of the Informed Consent Process: Specifically describe the plan for obtaining informed consent from human subjects.

- ***For the proposed study, provide a draft, in English, of the Informed Consent Form.***
- Identify who is responsible for explaining the study, answering questions, and obtaining informed consent. Include a plan for ensuring that human subjects' questions will be addressed during the consent process and throughout the trial.
- Include information regarding the timing and location of the consent process.
- Address issues relevant to the mental capacity of the potential human subject (e.g., altered capacity due to administration of any mind-altering substances such as tranquilizers, conscious sedation or anesthesia, brain injury, stress/life situations, or human subject age), if applicable.
- Address how privacy and time for decision making will be provided and whether or not the potential human subject will be allowed to discuss the study with anyone before making a decision.
- Consider the need for obtaining ongoing consent or for re-assessing capacity over the course of a long-term study and describe any relevant procedures to assure continued consent.
- Describe the plan for the consent of the individual's Legally Authorized Representative (LAR) to be obtained prior to the human subject's participation in the study. State law defines who may act as the LAR. The local IRB of record should be consulted for guidance regarding who can serve as LAR for research at the study site. Note: The PI must describe a clear intent to benefit for human subjects who cannot give their own consent to participate in the proposed clinical trial to be in compliance with Title 10 United States Code Section 980 (10 USC 980) (http://www.gpo.gov/fdsys/pkg/USCODE-2011-title10/pdf/USCODE-2011-title10-subtitleA-partII-chap49-sec980.pdf). If applicable, please refer to the General Application Instructions, Appendix 5, 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.

e. 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.

f. 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.
- **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.

a. Description of the Intervention: 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 detailed operational instructions, any potential risks to users, and intended benefits. Other types of interventions should be fully described.

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

b. 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.

c. 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) Good Clinical Practices (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.

a. 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 study 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 USAMRMC 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.

b. 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 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.

a. Organizational Chart: Provide an organizational chart identifying key members of the study team including institution/center/department and name each person's position on the project. A medical monitor (external to the study and not reimbursed by the study) and study coordinator(s) should be included. If applicable, include any external consultants or other experts who will assist with FDA applications. While there is no specified format for this information, a table(s) or diagram is recommended. Note: This item may be made available for programmatic review.

b. 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.

c. 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, plans for communication and data transfer between the collaborating institutions, as well as how data, specimens, and/or imaging

products obtained during the study will be handled, should be included. Provide a plan for real-time communication among collaborating institutions (if applicable).

- **Attachment 10: 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.

- **Attachment 11: Military Benefit Statement (one-page limit).** Upload as "MilBen.pdf."

  State explicitly how the proposed clinical trial, if successful, will accelerate the movement of the product, pharmacologic agent, device, clinical guidance, and/or emerging technology into clinical practice for 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. For applicants addressing the Focus Area on non-battle orthopaedic injuries, 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 have an impact. ***Although not all-inclusive***, these examples are intended to help PIs frame the impact 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

  Demonstrate how the proposed study is responsive to the health care needs of the military services and/or the U.S. 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 services and/or the U.S. Veteran population). Show how the proposed study complements ongoing DoD areas of orthopaedic research interest. Describe how the study design will replicate field conditions, if applicable.

- **Attachment 12: Transition Plan (one-page limit).** Upload as "Transition.pdf." Provide information on the methods and strategies proposed to move the product or knowledge outcomes to the next phase of clinical trials, commercialization, and/or delivery to the civilian or military market after successful completion of the award. The 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.
- Details of the funding strategy that will be used to bring the outcomes to the next level of development and/or commercialization (e.g., specific potential industry partners, specific funding opportunities to be applied for).
- For knowledge products, a description of how the knowledge will be further developed, disseminated, and incorporated into clinical care.
- A description of collaborations and other resources that will be used to provide continuity of development.
- A brief schedule and milestones for bringing the outcome(s) to the next phase of clinical trials, commercialization, and/or delivery to the military or civilian market, including when it can be anticipated to be transitioned to an industry partner or approved by the FDA, if applicable.
- A risk analysis for cost, schedule, manufacturability, and sustainability.
- A description of relevant product patents and intellectual property ownership, and their potential impact on product development and the Government's ability to access any products or technology supported with this award.

- **Attachment 13: IND/IDE Documentation:** If submitting multiple documents, start each document on a new page. Combine and upload as a single file named "IND-IDE.pdf."
  - 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. If an IND or IDE is required, it must be submitted to the FDA ***prior to the grant application submission deadline.***
  - If an IND or IDE application is required, indicate when it was submitted to the FDA and 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 an IND or IDE is not required for the proposed study, provide evidence in the form of communication from the FDA or the IRB of record to that effect.

3. **Research & Related Senior/Key Person Profile (Expanded):** Refer to the General Application Instructions, Section II.C.3., for detailed information.

   - PI Biographical Sketch (four-page limit): Upload as "Biosketch_LastName.pdf."
   - PI Previous/Current/Pending Support (no page limit): Upload as "Support_LastName.pdf."

- Key Personnel Biographical Sketches (four-page limit each): Upload as "Biosketch_LastName.pdf."
- Key Personnel Previous/Current/Pending Support (no page limit): Upload as "Support_LastName.pdf."

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

   - Budget Justification (no page limit): Upload as "BudgetJustification.pdf."

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

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

D. Verification of Grants.gov Application in eBRAP

For FY14, a new process has been initiated whereby organizational representatives and PIs can view their applications as submitted through Grants.gov and prior to peer review of the application. This will enable applicants to make modifications prior to scientific and programmatic evaluation of applications, provided the modifications are made by either the end of the application verification period or, for changes to the Project Narrative or Budget, by the application submission deadline.

After application submission to Grants.gov, eBRAP will retrieve and validate the application submission. eBRAP will notify the organizational representatives and PI via email and instruct them to log into eBRAP to review, modify, and verify the application. Files that fail eBRAP validation will be noted in both the email and in the Full Application Files tab. eBRAP does not validate the accuracy or completeness of content in the files. PIs are strongly encouraged to review all application components. If either the Project Narrative or the Budget fail eBRAP validation, an updated Grants.gov application package must be submitted via Grants.gov prior to the application submission deadline, which occurs earlier than the end of the application verification period. ***The Project Narrative and Budget cannot be changed after the application submission deadline. Any other application component cannot be changed after the end of the application verification period.***

E. Submission Dates and Times

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

F. Other Submission Requirements

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

All applications must be submitted through Grants.gov. Applicant organizations and all subrecipient organizations must have a DUNS number to submit applications to Grants.gov. The applicant organization must also be registered in the Entity Management functional area of the SAM with an "Active" status to submit applications through the Grants.gov portal. Refer to the General Application Instructions, Appendix 3, for information on Grants.gov requirements.

III. APPLICATION REVIEW INFORMATION

A. Application Review and Selection Process

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

All CDMRP review processes are conducted confidentially to maintain the integrity of the merit-based selection process. Panel members sign a non-disclosure 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.

B. Application Review Process

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

    - **Military Benefit and Clinical Impact**
        - How relevant the anticipated outcomes of the proposed clinical trial are to individuals with combat-related orthopaedic injuries, if applicable.
        - 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 work/duty, if applicable.
        - How well the sample 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 the short-term benefits for individuals with orthopaedic injuries.
- How significantly the long-term benefits for implementation of the intervention may impact patient care and/or quality of life.
- The degree to which the results of the proposed clinical trial will affect clinical practice for military service members with orthopaedic injuries.

- **Research Strategy**
  - How well the scientific rationale for testing the intervention is supported by the preliminary data, critical review and analysis of the literature, and/or laboratory/ preclinical evidence.
  - How well the study aims, hypotheses or objectives, experimental design, methods, data collection procedures, and analyses are designed to answer clearly the clinical objective.
  - How well the inclusion and randomization criteria meet the needs of the proposed clinical trial, as applicable.
  - How well the exclusion criteria are justified.
  - How well plans to collect specimens and conduct laboratory evaluations are addressed, if applicable.
- **Statistical Plan**
  - To what degree the statistical model and data analysis plan are suitable for the planned study.
  - How the statistical plan, including sample size projections and power analysis, is adequate for the study and all proposed correlative studies.
  - 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, if applicable.
- **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.
  - How the intervention compares with currently available interventions and/or standards of care.
  - To what degree the data collection instruments (e.g., surveys, questionnaires), if applicable, are appropriate to the proposed study.

- 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 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 GMP, GLP, 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 meeting entry criteria for the clinical trial and the prospect of their participation.
  - Whether the PI has demonstrated access to the proposed human subjects 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 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.
  - 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, and clinical studies).
  - How the levels of effort of the study team members are appropriate for successful conduct of the proposed trial.

- How well the logistical aspects of the proposed clinical trial (e.g., communication plan, data transfer and management, standardization of procedures) meet the needs of the proposed clinical trial.

- **Transition Plan**
  - Whether the funding strategy described to bring the outcome(s) to the next level of development (e.g., higher phase clinical trial, transition to industry, delivery to the market, incorporation into standard practice) is appropriate.
  - How the development plan to support a product label change, if applicable, is appropriate and well described.
  - Whether appropriate collaborations and other resources for providing continuity of development are established and/or well described.
  - How the schedule and milestones for bringing the outcome(s) to the next level of development (e.g., higher phase clinical trial, transition to industry, delivery to the market, incorporation into standard practice) are appropriate.
  - How well the potential risk analysis for cost, schedule, manufacturability, and sustainability is developed.
  - 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:

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

- **Budget**
  - Whether the budget is appropriate for the proposed research and within the limitations of this Program Announcement/Funding Opportunity.

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

2. **Programmatic Review:** To make funding recommendations, the following criteria are used by programmatic reviewers:

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

    b. **Relevance to the mission of the DHP and FY14 PRORP, as evidenced by the following:**

    - Adherence to the intent of the award mechanism
    - Program portfolio composition]
    - Programmatic relevance
    - Regulatory and development risk
    - Relative military benefit and clinical impact

C. Recipient Qualification

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

D. Application Review Dates

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

E. Notification of Application Review Results

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

IV. ADMINISTRATIVE ACTIONS

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

A. Rejection

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

- Preproposal Narrative exceeds page limit.
- Preproposal Narrative is missing.

The following will result in administrative rejection of the application:

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

- Submission of the same research project to different funding opportunities within the same program and fiscal year.
- Human Subject Recruitment and Safety Procedures (Attachment 6) is missing.
- Intervention (Attachment 7) is missing.
- Data Management (Attachment 8) is missing.

B. Modification

- Pages exceeding the specific limits will be removed prior to review for all documents other than the Preproposal Narrative and Project Narrative.
- Documents not requested will be removed.
- Following application submission to Grants.gov, the PI will receive an email request from eBRAP to review, modify, and verify the application submitted to Grants.gov. During this verification period, the PI may upload missing documents (excluding those listed in Section IV.A., Rejection), replace files, and re-categorize files. These modifications must be completed by the end of the application verification period; otherwise, the application will be reviewed as submitted.

C. Withdrawal

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

- A FY14 PRORP Steering Committee (SC) 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 FY14 PRORP SC members can be found at http://cdmrp.army.mil/prorp/panels/panel14.
- The application fails to conform to this Program Announcement/Funding Opportunity description to the extent that appropriate review cannot be conducted.
- Total costs as shown on the Research & Related Budget exceed the maximum allowed by this Program Announcement/Funding Opportunity.
- Inclusion of URLs, with the exception of links in References Cited and Publication and/or Patent Abstract sections.
- Page size is larger than 8.5 inches x 11.0 inches (approximately 21.59 cm x 27.94 cm).
- Inclusion of any employee of CDMRP review contractors in applications for funding without adequate plans to mitigate conflicts of interest. Refer to the General Application Instructions, Section II.B., for detailed information.
- Personnel from applicant or collaborating organizations are found to have contacted persons involved in the review process to gain protected evaluation information or to influence the evaluation process.
- The PI does not meet the eligibility criteria.
- The proposed research is not a clinical trial.
- IND/IDE application has not been submitted to the FDA, if applicable.

D. Withhold

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

V. AWARD ADMINISTRATION INFORMATION

A. Award Notice

Awards will be made no later than September 30, 2015. Refer to the General Application Instructions, Appendix 4, for additional award administration information.

B. Administrative Requirements

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

C. National Policy Requirements

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

D. Reporting

Refer to the General Application Instructions, Appendix 4, Section J, for general information on reporting requirements.

Quarterly technical progress reports and quad charts will be required.

E. Award Transfers

The institution 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.
Refer to the General Application Instructions, Appendix 4, Section M, for general information on organization or PI changes.

VI. AGENCY CONTACTS

A. CDMRP Help Desk

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

Phone: 301-682-5507

Email: help@eBRAP.org

B. Grants.gov Contact Center

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

Phone: 800-518-4726

Email: support@grants.gov

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

VII. APPLICATION SUBMISSION CHECKLIST

Grants.gov Application Components	Action	Completed
SF-424 (R&R) Application for Federal Assistance	Complete form as instructed.	
Attachments Form	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."	
	Surveys, Questionnaires, and Other Data Collection Instructions: Upload as Attachment 10 with file name "Surveys.pdf," if applicable.	
	Military Benefit Statement: Upload as Attachment 11 with file name "MilBen.pdf."	
	Transition Plan: Upload as Attachment 12 with file name "Transition.pdf."	
	IND/IDE Documentation: Upload as Attachment 13 with file name "IND-IDE.pdf."	
Research & Related Senior/Key Person Profile (Expanded)	Attach PI Biographical Sketch (Biosketch_LastName.pdf) to the appropriate field.	
	Attach PI Previous/Current/Pending Support (Support_LastName.pdf) to the appropriate field.	
	Attach Biographical Sketch (Biosketch_LastName.pdf) for each senior/key person to the appropriate field.	
	Attach Previous/Current/Pending (Support_LastName.pdf) for each senior/key person to the appropriate field.	
Research & Related Budget	Complete as instructed. Attach Budget Justification (BudgetJustification.pdf) to the appropriate field.	
Project/Performance Site Location(s) Form	Complete form as instructed.	
R & R Subaward Budget Attachment(s) Form	Complete form as instructed.	