Program Announcement

for the

Department of Defense

Defense Health Program

Congressionally Directed Medical Research Programs

Gulf War Illness Research Program

Innovative Treatment Evaluation Award

Funding Opportunity Number: W81XWH-15-GWIRP-ITEA

Catalog of Federal Domestic Assistance Number: 12.420

SUBMISSION AND REVIEW DATES AND TIMES

- **Pre-Application Deadline:** 5:00 p.m. Eastern time (ET), August 13, 2015
- **Invitation to Submit an Application:** September 2015
- **Application Submission Deadline:** 11:59 p.m. ET, October 29, 2015
- **End of Application Verification Period:** 5:00 p.m. ET, November 3, 2015
- **Peer Review:** January 2016
- **Programmatic Review:** March 2016

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 2015 (FY15) Gulf War Illness Research Program (GWIRP) are being solicited for the Defense Health Agency, Research, Development, and Acquisition (DHA RDA) Directorate, by the U.S. Army Medical Research Acquisition Activity (USAMRAA). As directed by the Office of the Assistant Secretary of Defense for Health Affairs, the DHA RDA Directorate manages and executes the Defense Health Program (DHP) Research, Development, Test, and Evaluation (RDT&E) appropriation. The executing agent for this Program Announcement/Funding Opportunity is the Congressionally Directed Medical Research Programs (CDMRP). The GWIRP was initiated in 2006 to provide support for research of exceptional scientific merit to study the health effects of deployment to the 1990-1991 Persian Gulf War on U.S. Warfighters. Appropriations for the GWIRP from FY06 through FY14 totaled $89 million (M). The FY15 appropriation is $20M.

The GWIRP challenges the scientific community to design high-impact research that will improve the health and lives of Veterans who have Gulf War illness (GWI). GWI is characterized by multiple diverse symptoms that typically include chronic headache, widespread pain, cognitive difficulties, debilitating fatigue, gastrointestinal problems, respiratory symptoms, sleep problems, and other abnormalities that are not explained by established medical diagnoses or standard laboratory tests.

The population of Veterans affected by GWI is a subset of the nearly 700,000 who served during the Gulf War. Specifically, these Gulf War Veterans were deployed to the theatre of operations in Southwest Asia, including Iraq, Kuwait, and Saudi Arabia. Studies indicate that approximately 25% to 30% (or 175,000 to 210,000) of Gulf War Veterans continue to experience symptoms associated with their deployment as described above.

The GWIRP will focus on innovative projects that have the potential to make a significant impact on finding treatments for GWI. While such projects may include identification of objective indicators of pathology that distinguish ill from healthy Gulf War Veterans or studies to understand the underlying pathobiology of GWI, projects should exhibit clear translational potential to lead to treatments for Veterans with GWI.

For FY15, the GWIRP will include an additional focus on patterns of health and disease in Gulf War Veterans that will be supported by the new Gulf War Illness Epidemiology Research Award (GWIERA). For information about the GWIERA (Opportunity Number W81XWH-15-GWIRPGWIERA), see http://cdmrp.army.mil/funding/gwirp. The GWIRP encourages high-risk/ high-reward research; however, all projects must demonstrate solid judgment and sound rationale.

B. Award Information

The FY15 GWIRP is offering two award mechanisms to evaluate potential interventions for GWI: the Innovative Treatment Evaluation Award and the Clinical Trial Award.

The Innovative Treatment Evaluation Award, described in this Program Announcement, supports the initial evaluation of a treatment or intervention in early phase or pilot clinical trials (Phase 0, I, or I/II), and does not require preliminary data. These trials will hereafter collectively be referred to as "pilot clinical trials." In contrast, the Clinical Trial Award is intended to support larger, more definitive (Phase II-III, U.S. Food and Drug Administration [FDA] device class I III) clinical trials. (For information about the Clinical Trial Award, see http://cdmrp.army.mil/funding/gwirp.)

The Innovative Treatment Evaluation Award mechanism was first offered in FY08. Since then, 42 Innovative Treatment Evaluation Award applications have been received, and 15 have been recommended for funding.

The Innovative Treatment Evaluation Award mechanism supports the early systematic evaluation of innovative interventions with the potential to impact the health and lives of Veterans with GWI. The results of preliminary studies funded by this award should have the potential to provide clinical proof-of-principle data and support future development of broader efficacy studies of the proposed interventions.

Innovation is an important component of the Innovative Treatment Evaluation Award. An application may demonstrate innovation not only by investigating a novel therapeutic approach for GWI, but also by studying a treatment that may have been utilized for other chronic multisymptom illnesses, but has not yet been studied in Veterans with GWI. For example, a pharmacological treatment or nutritional supplement suggested by previous research to be beneficial for fibromyalgia or chronic fatigue syndrome could be evaluated in Veterans with GWI under the Innovative Treatment Evaluation Award. However, the focus of the research must be clearly on GWI (and Veterans of the 1990-1991 Gulf War) and not on another disease process or Veteran cohort.

Given the emphasis on innovation in the Innovative Treatment Evaluation Award, applications are not required to include preliminary data. If preliminary data are provided, the data do not necessarily have to come from the GWI research field. Whether or not preliminary data are included in the application, the proposed research project should be based on sound scientific rationale that is established through logical reasoning and critical review and analysis of the literature. Trials of treatments or interventions for which considerable preliminary and/or preclinical data have been developed should be proposed under the Clinical Trial Award (see http://cdmrp.army.mil/gwirp/default).

This award mechanism is designed to evaluate a broad scope of treatment approaches with potential for application to GWI. Treatment approaches may include pharmacologic or other physiological interventions, including conventional, alternative, or complementary (combination of alternative and conventional) approaches. A variety of experimental and non-experimental study designs are acceptable under this award mechanism. The proposed study design will depend on the specific treatment or intervention to be assessed, resources available to clinical investigators, and the level of evidence currently available to support the proposed treatment for GWI. Examples of potential prospective designs may include systematic case series, prospective outcome evaluation studies, small-scale randomized trials, a combination of these, or other innovative prospective methods. Also of interest are interventions based on biological

alterations identified in Veterans with GWI. All studies involving interventions, regardless of design, are considered clinical trials.

The Innovative Treatment Evaluation Award supports execution of clinical trials with the potential to have a significant impact on the health and lives of Veterans with GWI. Health outcomes of interest should include improvements in overall functional status or in symptom complexes (e.g., cognitive function, musculoskeletal/pain symptoms, gastrointestinal symptoms, fatigue, respiratory problems, skin abnormalities, sleep difficulties and others) individually and/or as they may interact with each other.

Applications proposing studies whose principal focus is on the treatment of psychiatric conditions, including post-traumatic stress disorder (PTSD), will be administratively withdrawn and will not be funded under this Program Announcement/Funding Opportunity.

While Gulf War Veterans are affected by amyotrophic lateral sclerosis (ALS, also called Lou Gehrig's disease) at twice the rate of Veterans who did not serve in the Gulf War, the GWIRP will not accept applications focusing on ALS research. However, applications that focus on GWI symptomatology may include GW Veterans with ALS if the latter disorder is included in the study's GWI case definition. [For those interested in pursuing ALS-focused studies, the office of the Congressionally Directed Medical Research Programs (CDMRP) offers a separate ALS research program (see http://cdmrp.army.mil/alsrp)].

Applications Involving Industry: Applications involving the biotechnology/pharmaceutical industry are encouraged whether as Single or Initiating Principal Investigators (PIs) or as collaborators. Biotechnology or pharmaceutical companies who apply for the Innovative Treatment Evaluation Award, as an individual applicant or as part of a collaboration, are encouraged to leverage their own resources to complement the funding provided by this award.

GWI Case Definitions for Clinical Research: In 2014, the Institute of Medicine (IOM) released the report "Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Reexamined" (available online at http://www.iom.edu/Reports/2014/Chronic-Multisymptom-Illness-in-Gulf-War-Veterans-Case-Definitions-Reexamined.aspx). In this report, the IOM recommends the use of both the Centers for Disease Control and Prevention (CDC) definition of GWI and the Kansas definition for GWI. Therefore, applicants may construct a definition of subgroups or symptom clusters as appropriate to the specific treatment, intervention or trial design; however, all cases and controls must additionally be scored and analyzed according to both the CDC and the Kansas definitions for GWI for comparative purposes. Any project-specific case definition must recognize the multisymptom nature of GWI.

Note: The 2014 report of the Research Advisory Committee on Gulf War Veterans' illnesses, "Gulf War Illness and the Health of Gulf War Veterans: Research Update and Recommendations, 2009-2013," provides information on GWI, including case definitions and research on epidemiology, etiology, pathobiology, and treatment. The report can be found online at http://www.bu.edu/sph/files/2014/04/RAC2014.pdf.

Funding from this award mechanism must support a pilot 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 exploratory information, safety, effectiveness, and/or efficacy. This outcome represents a direct effect on the human subject of that intervention or interaction. PIs seeking funding for a preclinical research project should consider one of the other award mechanisms/funding opportunities being offered. 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

If the clinical trial involves the use of a drug that has not been approved by the FDA for the proposed investigational use, evidence that an Investigational New Drug (IND) exemption application that meets all requirements under the Code of Federal Regulations, Title 21, Part 312 (21 CFR 312) has been submitted or will be submitted to the FDA ***within 60 days of award*** is required. 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 or will be submitted to the FDA ***within 60 days of award***, or that the device is exempt from an IDE, is required. The Government reserves the right to withdraw funding if the IND or IDE application has not been submitted to the FDA within 60 days of the Department of Defense (DoD) award date or if the 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 Innovative Treatment Evaluation Award:

- The proposed pilot 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 Veterans with GWI.
- 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 and ***the application must identify the pathobiological mechanism being targeted.***
- 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.
- PIs must demonstrate availability of and access to a suitable Gulf War Veteran population that will support a meaningful outcome for the study. PIs are encouraged to collaborate with an investigator who has demonstrated access to a population of Gulf War Veterans, particularly investigators within the U.S. Department of Veterans Affairs (VA).
- 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 [GMP]).

- 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.
- The application should include a clearly articulated safety management plan, outlining how safety pharmacovigilance will be conducted as applicable.
- The application should include a clearly articulated clinical monitoring plan, outlining how the study will be monitored for GCP compliance.
- The application should include a study coordinator(s) who will guide the clinical protocol through the local Institutional Review Board (IRB) of record and other Federal agency regulatory approval processes, coordinate activities from all sites participating in the trial, and coordinate participant accrual.
- The application should include a Transition Plan (including potential funding and resources) showing how the product will progress to the next clinical trial phase and/or delivery to Veterans suffering from GWI after the successful completion of the GWIRP Innovative Treatment Evaluation 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 clinical trials registry, www.clinicaltrials.gov.

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), in addition to the local Institutional Review Board (IRB) of record. Local IRB 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. ***Allow a minimum of 2 to 3 months for HRPO regulatory review and approval processes***. The HRPO reviews and approves the participation of each site in the clinical trial. Refer to the General Application Instructions, Appendix 5, and the Human Subject Resource Document available on the eBRAP "Funding Opportunities & Forms" web page (https://ebrap.org/eBRAP/public/Program.htm) for additional information.

The CDMRP intends that information, 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 3, Section L.

C. Eligibility Information

- Independent investigators at any academic level (or equivalent) are eligible to apply
- Cost sharing/matching is not an eligibility requirement.
- Eligible investigators must apply through an organization. Organizations eligible to apply include national, international, for-profit, nonprofit, public, and private organizations.
- Refer to the General Application Instructions, Appendix 1, for general eligibility information.

D. Funding

- The maximum period of performance is **3** years.
- The anticipated direct costs budgeted for the entire period of performance will not exceed **$700,000**. Associated indirect costs can be budgeted in accordance with the organization's negotiated rate. No budget will be approved by the Government exceeding **$700,000** direct costs or using an indirect rate exceeding the organization's negotiated rate.
- 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 may request the entire maximum funding amount for a project that may have a period of performance less than the maximum **3** years.

Refer to the General Application Instructions, Section II.C.5., 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.5. of the General Application Instructions***.

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

- Travel costs for the PI(s) to disseminate project results at one DoD military-related meeting. 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-related subject costs
- Veteran subject reimbursement and compensation
- Clinical research costs
- Support for multidisciplinary collaborations

- Travel between collaborating organizations
- Travel costs 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 Section II.A. 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 may be executed through a direct fund transfer (e.g., 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.5. Research & Related Budget, for additional information on budget considerations for applications involving Federal agencies.

The CDMRP expects to allot approximately $3.4M of the $20M FY15 GWIRP appropriation to fund approximately three Innovative Treatment Evaluation 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 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.

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/). Refer to the General Application Instructions, Section II.A. for registration and submission requirements for eBRAP and Grants.gov.

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. A key feature of eBRAP is the ability of an organization's representatives and PIs to view and modify the Grants.gov application submissions associated with them. eBRAP will validate Grants.gov application files against the specific Program Announcement/Funding Opportunity 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/Funding Opportunity.

PIs should ensure that their name and email address are the same as the name and email address that will be provided on the SF-424 Form of the Grants.gov application package submitted to Grants.gov. The organization, Business Officials, PI(s), and eBRAP log number named in the full application submitted to Grants.gov must match those named in the pre-application in eBRAP.

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.

A. Where to Obtain the Grants.gov Application Package

To obtain the Grants.gov application package, including all required forms, perform a basic search using the Funding Opportunity Number W81XWH-15-GWIRP-ITEA in Grants.gov (http://www.grants.gov/).

B. Pre-Application Submission Content

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):

- **Application Information – Tab 1**
- **Application Contacts – Tab 2**
    - 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 SF-424 Form). The Business Official must either be selected from the eBRAP 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.

- **Collaborators and Key Personnel – Tab 3**
  - Enter the name, organization, and role of all collaborators and key personnel associated with the application.
  - FY15 GWIRP Integration Panel (IP) members should not be involved in any pre-application or application. For questions related to IP 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.
- **Conflicts of Interest (COIs) – Tab 4**
  - 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).
- **Pre-Application Files – Tab 5**

  Note: 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:

  - **Research Idea:** State the ideas and reasoning on which the proposed intervention is based. Explain the mechanistic rationale of the treatment. Describe how the rationale and any preliminary data support the research.
  - **Research Strategy:** Concisely state the project's objectives and specific aims. Describe the published case definition of GWI to be used in the proposed project. Clearly specify the intervention to be tested, and indicate the phase of the trial and/or class of device, as appropriate.
  - **Impact:** State how the proposed project will accelerate the movement of a promising treatment for GWI into clinical application. Describe how the results of the proposed pilot clinical trial will, if successful, lead to future large-scale clinical trials.
  - **Innovation:** Describe how the proposed intervention is new or unstudied in the population of Veterans with GWI.

- **Personnel:** Briefly state the qualifications of the PI and key personnel to perform the proposed research project. Describe the composition of the clinical team. Provide details on how the team (including investigator(s), study coordinator, statistician) possesses the appropriate expertise in conducting clinical trials.

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 (five-page limit per individual).

- **Submit Pre-Application – Tab 6**
  - 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 GWIRP, pre-applications will be screened based on the following criteria:

  - **Research Idea:** How the proposed intervention is based on ideas and reasoning that appropriately support the study.
  - **Research Strategy:** How well the specific aims support the research idea. If applicable, whether there is sufficient justification for any case definition to be used other than the Kansas or CDC case definitions in the proposed clinical research. Whether the phase of the proposed clinical trial is appropriate for the Innovative Treatment Evaluation Award mechanism.
  - **Impact:** How the research describes a potentially effective treatment or intervention for GWI. How the proposed clinical trial will, if successful, lead to future large-scale clinical trials.
  - **Innovation:** How the research is innovative in bringing a new or unstudied treatment or intervention to the population of Gulf War Veterans.
  - **Personnel:** How the qualifications of the PI(s) and research team are appropriate to perform the proposed research project.

- **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. Full Application Submission Content

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

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

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

Note: The Project Narrative and Budget Form cannot be changed after the application submission deadline. If either the Project Narrative or the budget fails eBRAP validation or if the Project Narrative or Budget Form needs to be modified, an updated Grants.gov application package must be submitted via Grants.gov as a "Changed/Corrected Application" with the previous Grants.gov Tracking ID ***prior to the application submission deadline***.

Grants.gov application package components: For the Innovative Treatment Evaluation 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**

   Each attachment to the Grants.gov application forms must be uploaded as an individual PDF file in accordance with the formatting guidelines listed in Appendix 2 of the General Application Instructions. For all attachments, ensure that the file names are consistent with the guidance. Grants.gov will reject attachments with file names 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, Grants.gov has file size limits that may apply in some circumstances. Individual attachments may not exceed 20 MB and the file size for the entire Grants.gov 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 (12-page limit): Upload as "ProjectNarrative.pdf."** The page limit of the Project Narrative applies to text and non-text elements (e.g., figures, tables, graphs, photographs, diagrams, chemical structures, drawings, 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 may result in administrative withdrawal of the application.

  Describe the proposed project in detail using the outline below.

  - **Background:** Describe in detail the rationale for the study, including a description of the pathobiological mechanism being targeted by the proposed intervention. Provide a literature review and describe any 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 also establish the relevance of the study for Veterans with GWI and explain the applicability of the proposed findings.

    If the proposed pilot 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.

  - **Clinical Trial:** Provide detailed plans for initiating and conducting the clinical trial during the course of the award. 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.

    - All subjects and controls must be scored at least according to both CDC and Kansas case definitions for GWI for the purpose of comparative analysis. If any additional case definition other that the CDC or Kansas definition is to be used, describe this definition and explain the rationale behind its inception and use.
    - Identify the intervention to be tested and describe the projected outcomes.
    - Define the study variables, 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 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 including the expected effects of inclusion/exclusion criteria. 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 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 Patent Abstracts: Include a list of relevant publication URLs and/or patent abstracts. If publications are not publicly available, then copies of up to five published manuscripts may be included in Attachment 2. Extra items will not be reviewed.

  - Letters of Organizational Support: Provide a letter (or letters, if applicable), signed by the Department Chair or appropriate organization official, confirming the laboratory space, equipment, and other resources available for the project. Letters of support not requested in the Program Announcement/Funding Opportunity, such as those from members of Congress, do not impact application review or funding decisions.

- Letters of Collaboration (if applicable): Provide a signed letter from each collaborating individual or organization that will demonstrate that the PI has;
  - Availability of, access to, and quality control for all critical reagents.
  - Availability of and access to the appropriate Veteran population(s).

  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.
- In the letter(s) describe the expertise and resources (physical and process resources or intellectual properties) that each collaborator will bring to the effort and how they are best suited to carry out the proposed research.
- Intellectual Property
  - Background and Proprietary Information: All software and data first produced under the award are subject to a Federal purpose license. Provide a list of all background intellectual property to be used in the project or provide a statement that none will be used. If applicable, state and identify the 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.
- GMP (if applicable): Provide information regarding the resources available to aid in the development of sufficient quantities of the drug or reagent under GMP.
- 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 3, 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."** Use only characters available on a standard QWERTY keyboard. Spell out all Greek letters, other non-English letters, and symbols. Graphics are not allowed.

  The technical abstract is used by all reviewers. The programmatic reviewers may not have access to the full application and may rely on the technical abstract for appropriate description of the project's key aspects. Therefore, clarity and completeness within the space limits of the technical abstract are highly important.

  Technical abstracts should be structured as follows:

  - Background: Present the ideas and rationale behind the proposed work.

- Objective/Hypothesis: State the objective/hypothesis to be tested. Provide evidence that supports the objective/hypothesis.
- Specific Aims: State the specific aims of the study.
- Study Design: Briefly describe the study design including the intervention to be tested, the study population, outcome measures, and appropriate controls.
- Clinical Impact: Briefly describe how the proposed project will have an impact on Veterans with GWI.

- **Attachment 4: Lay Abstract (one-page limit): Upload as "LayAbs.pdf."** Use only characters available on a standard QWERTY keyboard. Spell out all Greek letters, other non-English letters, and symbols. Graphics are not allowed.

  Lay abstracts should be written using the outline below. ***Do not duplicate the technical abstract.*** Minimize use of acronyms and abbreviations. The lay abstract is an important component of the application review process because it outlines issues of particular interest to the consumer advocate community.]

  - Describe the scientific objective and rationale for the proposed project in a manner that will be readily understood by readers without scientific or medical backgrounds. Identify the specific pathobiological mechanism to be targeted.
  - Do not duplicate the technical abstract.
  - Describe the ultimate applicability and impact of the research.
    - What types of patients will it help, and how will it help them?
    - What are the potential clinical applications, benefits, and risks?
    - What is the projected time it may take to achieve a patient-related outcome?
    - What are the likely contributions of this study in advancing treatment for GWI?

- **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 Innovative Treatment Evaluation Award mechanism, use the SOW format example titled "SOW for Clinical Research." The SOW must be in PDF format prior to attaching. Refer to the General Application Instructions, Section II.C.3., for detailed guidance on creating the SOW.

  The GWIRP strongly encourages timely dissemination of the results of GWIRP-sponsored research as a product of the research program. Timely dissemination is critical to improvement of the lives of Veterans with GWI, the advancement of the field, and the continued success of the program. Therefore, SOWs submitted to the GWIRP must include at least one task or aim focused on preparation and submission of publications. This task or aim must be scheduled to commence at least 6 months prior to the end of the award's period of performance.

- **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 Gulf War Veteran 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.

  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. Indicate how the proposed inclusion and exclusion criteria might impact the similarity between the study population and the eventual target population for the treatment.

  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).

  - 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. Note: PIs are urged to consider including reimbursement for travel and accommodations and/or other appropriate expenses for Gulf War Veterans participating in clinical trials.
  - Describe the recruitment and advertisement materials. The recruitment materials should not be coercive or offer undue inducements and should accurately reflect the study.
  - Provide a letter of support from the lowest ranking person with approval authority for studies involving Veterans, VA- or military-controlled study materials, and/or VA or military databases (e.g., Defense Manpower Data

Center Data Request System) if applicable. PIs whose applications will require obtaining and/or using Veterans' data from VA or military databases should confirm the ability to meet database requirements prior to application submission.

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.
    - For a trial in which the IRB determines there is greater than minimal risk to human subjects, the DoD requires an independent research monitor with expertise consonant with the nature of risk(s) identified within the research protocol. If applicable, please refer to the General Application Instructions, Appendix 5, 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.

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), 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) 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 how the privacy of human subjects and confidentiality of study data will be protected. 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.

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 including location of storage, length of storage, labeling, specimen disposition and any special conditions required. Outline the plan to store specimens for future use to include considerations for informed consent while providing human subjects 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.

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. Name the individuals who will provide statistical and bioethical expertise. If these are to be provided through institutional resources rather than named team members, then indicate the institutional resources that will be used.

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). Describe how statistical and bioethical issues will be managed in the study organization: Describe how emergent statistical or ethical issues would be raised and resolved.

- **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: Impact and Innovation Statement (two-page limit). Upload as "ImpAndInn.pdf."**
  - **Impact**
    - Identify the Gulf War Veteran population(s) that will participate in the proposed intervention, describe how they represent the target population that would benefit from the intervention, and describe the potential impact of the proposed clinical trial on the outcomes of Veterans with GWI.
    - 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 Veterans with GWI.
  - **Innovation**
    - State how the clinical trial demonstrates innovation in bringing a new or unstudied treatment or intervention to the population of Veterans with GWI. Innovation may include adapting treatments for a related disorder, such as fibromyalgia or chronic fatigue syndrome, for application to Veterans with GWI.

- **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 or delivery to Veterans with GWI (e.g., specific potential industry partners, specific funding opportunities to be applied for).
- A description of collaborations and other resources that will be used to provide continuity of development. If an industry applicant, partner, or collaborator is involved, indicate any resources the industrial entity will be leveraging in this investigation.
- A risk analysis for cost, schedule, manufacturability, and sustainability.

- **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."**
  - 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.
  - 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 60 days of award. 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, provide evidence in the form of communication from the FDA or the IRB of record to that effect.

- **Attachment 14: Outcomes Statement, if applicable (one-page limit): Upload as "Outcomes.pdf."** List all prior research projects/awards relating to GWI, including resulting publications, abstracts, patents or other tangible outcomes. Only research and outcomes directly relevant to GWI should be listed. Note: This item will be made available for programmatic review.

- **Attachment 15: Collaborating DoD Military Facility 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 Collaborating DoD Military Facility Budget Form (available for download on the eBRAP "Funding Opportunities & Forms" web page), including a budget justification, for each Military Facility as instructed. Refer to the General Application Instructions, Section II.C.8., for detailed information.

3. **Research & Related Senior/Key Person Profile (Expanded):** Refer to the General Application Instructions, Section II.C.4., for detailed information.

   - PI Biographical Sketch (five-page limit): Upload as "Biosketch_LastName.pdf." The suggested biographical sketch format is available on the "Funding Opportunities & Forms" web page (https://ebrap.org/eBRAP/public/Program.htm) in eBRAP. The five-page National Institutes of Health Biographical Sketch may also be used.
   - PI Previous/Current/Pending Support (no page limit): Upload as "Support_LastName.pdf."
   - Key Personnel Biographical Sketches (five-page limit each): Upload as "Biosketch_LastName.pdf."
   - Key Personnel Previous/Current/Pending Support (no page limit): Upload as "Support_LastName.pdf."

4. **Research & Related Budget:** Refer to the General Application Instructions, Section II.C.5., 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.

5. **Project/Performance Site Location(s) Form:** Refer to the General Application Instructions, Section II.C.6., for detailed information.

6. **R & R Subaward Budget Attachment(s) Form (if applicable):** Refer to the General Application Instructions, Section II.C.7., for detailed information.

D. Applicant Verification of Grants.gov 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 an application submitted to Grants.gov. Following retrieval and processing of the Grants.gov application, eBRAP will notify the organizational representatives and PI by email to log into eBRAP to review, modify, and verify the Grants.gov application submission. eBRAP will validate retrieved files against the specific Program Announcement/Funding Opportunity 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/Funding Opportunity. ***If either the Project Narrative or the budget fails eBRAP validation, 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.*** The Project Narrative and Budget Form cannot be changed after the application submission deadline.

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, Section II.A., for information on Grants.gov registration 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 DHA RDA Directorate and the Office of the Assistant Secretary of Defense for Health Affairs, based on (a) technical merit and (b) the relevance to the mission of the DHP, the GWIRP, 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 nondisclosure 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 Title 18 United States Code 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:

   - **Clinical Impact**
     - Whether the proposed pilot clinical trial will introduce a new, promising treatment for GWI.
     - How relevant the anticipated outcomes of the proposed clinical trial are to Veterans with GWI. If a multi-armed trial comparing different interventions is proposed, how relevant each proposed arm is to GWI.
     - How the potential outcomes of the proposed clinical trial will provide/improve short-term benefits for ill Gulf War Veterans.
     - How significantly the long-term benefits of the intervention may impact treatment of GWI and quality of life for Veterans with GWI.
   - **Innovation**
     - How the proposed treatment is new or unstudied in Veterans with GWI.
     - If applicable, how the research demonstrates innovation by adapting treatments used for a related disorder, such as fibromyalgia or chronic fatigue syndrome, for application to Veterans with GWI.
   - **Research Strategy**
     - How well the scientific rationale for testing the intervention including the description of the pathobiological mechanism being targeted is supported by the preliminary data, critical review and analysis of the literature, and/or laboratory/preclinical evidence.
     - How the type of clinical trial (e.g., prospective, randomized, controlled) proposed is appropriate to meet the project's objectives.
     - 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 exclusion criteria and the randomization method meet the needs of the proposed clinical trial in terms of the pathobiology and symptomology of GWI and overall research strategy.
     - If the application proposes use of a case definition or other than CDC and Kansas case definitions, how well that case definition is described and justified.
     - If applicable, how well plans to collect specimens and conduct laboratory evaluations are addressed in terms of technical/methodological, operational, and logistical considerations.

- 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.
  - How adequate is the statistical plan for the study and all proposed correlative studies, including the randomization methods, sample size projections, power analysis, and the impact of inclusion and exclusion criteria on the study.
  - How well the sample population represents the targeted patient population in a statistical sense taking into account the stated inclusion and exclusion criteria
  - 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.
- **Intervention**
  - To what degree the intervention addresses the needs of Veterans with GWI. For a clinical trial with multiple arms, the applicability of each intervention for GWI.
  - 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.
  - 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 and Accrual**
  - How well the PI addresses the availability of Gulf War Veterans for the clinical trial and the prospect of their participation.
  - Whether the PI has demonstrated access to the proposed Gulf War Veteran population and whether the PI has provided a letter from an appropriate authority showing approved access to Gulf War Veterans or use of data from Veterans.
  - The degree to which the recruitment, informed consent, screening, and retention processes for human subjects will meet the scientific and operational 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? Will there be reimbursement for expenses, e.g., travel and accommodations?).

- **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.
  - To what degree privacy issues are appropriately considered.
  - To what degree the process for recruitment and seeking informed consent are appropriate with respect to subject protections and whether safeguards are in place for vulnerable populations.
  - To what extent are proposed sample collection and laboratory evaluations planned to coincide with standard clinical care and to otherwise minimize risk, discomfort, and inconvenience to study subjects.
  - The adequacy of integration of bioethical expertise in the project.
- **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, schedule, and milestones described are appropriate to bring the outcome(s) to the next level of clinical trials or to Veterans with GWI.
  - 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 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).

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

- **Budget**
  - Whether the budget is appropriate for the proposed research and within the limitations of this Program Announcement/Funding Opportunity.
- **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.
  - If applicable, to what degree the intellectual and material property plan is appropriate.
- **Application Presentation**
  - To what extent the writing, clarity, and presentation of the application components influence the review.

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

   a. Ratings and evaluations of the peer reviewers

   b. Relevance to the mission of the DHP and FY15 GWIRP, as evidenced by the following:

   - Adherence to the intent of the award mechanism
   - Program portfolio composition
   - Programmatic relevance
   - Relative impact and innovation
   - Relative outcomes from the PI's previous GWI-related research, if applicable.

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 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 Project Narrative.
- Documents not requested will be removed.

C. Withdrawal

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

- A FY15 GWIRP IP 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 FY15 GWIRP IP members can be found at http://cdmrp.army.mil/gwirp/panels/panels15.

- The application fails to conform to this Program Announcement/Funding Opportunity 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).
- 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 invited application does not propose the same research project described in the pre-application.
- The proposed research is not a clinical trial.
- The application fails to conform to this Program Announcement/Funding Opportunity description to the extent that appropriate review cannot be conducted.
- The application describes research focusing on ALS. (Applications that focus on GWI symptomatology may include Gulf War Veterans with ALS if the latter disorder is included in the study's GWI case definition.)
- The application describes research whose principal focus is on psychiatric disease or psychological stress as the primary cause of GWI.
- An application submitted by a PI who does not meet the eligibility criteria will be withdrawn.

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, 2016. Refer to the General Application Instructions, Appendix 3, for additional award administration information.

Any assistance instrument awarded under this Program Announcement/Funding Opportunity will be governed by the award terms and conditions, which conform to DoD's implementation of the Office of Management and Budget (OMB) circulars applicable to financial assistance. Terms and conditions of new awards made after December 26, 2014 may include revisions to reflect DoD implementation of new OMB guidance in the Code of Federal Regulations, Title 2, Part 200, "Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards" (2 CFR part 200).

B. Administrative Requirements

Refer to the General Application Instructions, Appendix 3, for general information regarding administrative requirements.

C. National Policy Requirements

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

D. Reporting

Refer to the General Application Instructions, Appendix 3, Section I, for general information on reporting requirements.

Quarterly technical progress reports 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 3, 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 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.

VII. APPLICATION SUBMISSION CHECKLIST

Grants.gov Application Components	Upload Order	Action	Completed
SF-424 (R&R) Application for Federal Assistance		Complete form as instructed.	
Attachments Form	1	Project Narrative: Upload as Attachment 1 with file name "ProjectNarrative.pdf."	
	2	Supporting Documentation: Upload as Attachment 2 with file name "Support.pdf."	
	3	Technical Abstract: Upload as Attachment 3 with file name "TechAbs.pdf."	
	4	Lay Abstract: Upload as Attachment 4 with file name "LayAbs.pdf."	
	5	Statement of Work: Upload as Attachment 5 with file name "SOW.pdf."	
	6	Human Subject Recruitment and Safety Procedures: Upload as Attachment 6 with file name "HumSubProc.pdf."	
	7	Intervention: Upload as Attachment 7 with file name "Intervention.pdf."	
	8	Data Management: Upload as Attachment 8 with file name "Data_Manage.pdf."	
	9	Study Personnel and Organization: Upload as Attachment 9 with file name "Personnel.pdf."	
	10	Surveys, Questionnaires, and Other Data Collection Instructions: Upload as Attachment 10 with file name "Surveys.pdf," if applicable.	
	11	Impact and Innovation Statement: Upload as Attachment 11 with file name "ImpAndInn.pdf."	
	12	Transition Plan: Upload as Attachment 12 with file name "Transition.pdf."	
	13	IND/IDE Documentation: Upload as Attachment 13 with file name "IND-IDE.pdf."	
	14	Outcomes Statement: Upload as Attachment 14 with file name "Outcomes.pdf," if applicable.	
	15	Collaborating DoD Military Facility Budget Form(s): Upload Attachment 15 with file name "MFBudget.pdf," if applicable.	

Grants.gov Application Components	Upload Order	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		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.	