Program Announcement

Department of Defense Congressionally Directed Medical Research Programs

Neurofibromatosis Research Program

Clinical Trial Award

Funding Opportunity Number: W81XWH-10-NFRP-CTA

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I. FUNDING OPPORTUNITY DESCRIPTION

A. Program Description

The Neurofibromatosis Research Program (NFRP) was established in 1996 to promote the understanding, diagnosis, and treatment of neurofibromatosis (NF). Appropriations for the NFRP from fiscal year 1996 (FY96) through FY09 totaled $200.3 million (M). The FY10 appropriation is $13.75M.

FY10 NFRP Vision: The vision of the FY10 NFRP is to find and fund the best research to eradicate the clinical impact of NF. Toward this goal, the NFRP seeks to:

- Support innovative, high-impact research that will foster new directions for and address neglected issues in NF research,
- Sponsor multidisciplinary and multi-institutional collaborations that will bring new perspectives to the field,
- Foster the next generation of NF investigators,
- Promote translational and clinical studies to move promising ideas from bench to bedside,
- Develop a balanced portfolio of meritorious research related to all aspects of NF1, NF2, and Schwannomatosis.

Areas of Encouragement: The FY10 NFRP encourages research proposals that specifically address the critical needs of the NF community in the following areas:

- Complications of NF with high mortality such as neoplasms and cerebrovascular abnormalities;
- Complications of NF with high morbidity such as skeletal maladies, learning deficits, hormone-associated effects, and pain;
- Refinement and standardization of imaging techniques, molecular and cellular markers, and quality of life metrics for use in future clinical trials; and
- Translational research such as the development or preclinical testing of therapeutic agents for the treatment of NF.

NFRP Research Resources Initiative: Resources developed through NFRP funding that are available to the scientific community can be found at http://cdmrp.army.mil/nfrp/nfrpresources Investigators are urged to leverage and contribute to these resources and include a sharing and distribution plan in the proposal. For more guidance on data sharing, refer to General Application Instructions, Appendix 4.

B. Award Description

The NFRP Clinical Trial Award (CTA) mechanism was first offered in FY99. Since then, 23 CTA applications have been received, and 6 have been recommended for funding.

The NFRP CTA supports research with the potential to have a major impact on the treatment or management of neurofibromatosis and/or Schwannomatosis. ***Funding from this award mechanism must support a clinical trial.*** In general, a clinical trial is defined as a prospective accrual of patients for a study where an intervention (e.g., device, drug, behavioral, surgical procedure, or other) is tested on human subjects for a measurable outcome. Refer to the General Application Instructions, Appendix 5, for additional information about studies involving human subjects. ***The proposed clinical trial is expected to begin no later than 12 months after the award date.***

Preliminary data, unpublished results from the laboratory of the Principal Investigator (PI) or collaborators named on this application, that is relevant to the proposed research project **is required**. Proposals should also be based on a sound scientific rationale that is established through logical reasoning and critical review and analysis of the literature.

Funding from this award mechanism cannot be used for preclinical research studies. PIs seeking funding for a preclinical research project should consider one of the other award mechanisms/funding opportunities being offered.

Each application should contain only one clinical trial with a distinct study design. Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications should be submitted or approved prior to application submission. If the study is in support of an application to the U.S. Food and Drug Administration (FDA), Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications should be submitted prior to the grant application submission. The Government reserves the right to withdraw funding if an active exemption from marketing approval for the IND or IDE has not been acquired within 6 months of the award date. If an IND or IDE is required to conduct the proposed research, but is not received within 6 months of the award date, the Government reserves the right to revoke funding. For descriptions of each type of clinical trial, please refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and http://www.clinicaltrials.gov. Refer to the General Application Instructions, Appendix 5, for helpful information about distinguishing clinical trials and research utilizing human anatomical substances. ***Again, the proposed clinical trial is expected to begin no later than 12 months after the award date.***

The following are important aspects of submission for the CTA:

- Include a prospective accrual of subjects for a study where an intervention (e.g., drug, device, behavioral, surgical procedure, or other) is tested on human subjects for a measurable outcome.
- Demonstrate availability of, and access to, a suitable volunteer population that will support a meaningful outcome for the study. Discuss how accrual goals will be achieved and how standards of care may impact the study population.
- Describe clearly defined and appropriate endpoints for the proposed clinical trial.
- Clearly articulate the statistical analysis plan. Include a power analysis reflecting sample size projections that will clearly answer the objectives of the study.
- Discuss the potential impact of the study results for patients with neurofibromatosis or Schwannomatosis.

- Include a study coordinator(s) who will guide the clinical protocol through Institutional Review Board (IRB), Human Subjects Research Review Board, and other regulatory approval processes, coordinate activities from all sites participating in the trial, and coordinate participant accrual.
- Demonstrate institutional support.

Use of Human Subjects and Human Biological Substances*:* All Department of Defense (DOD)-funded research involving human subjects and human biological substances must be reviewed and approved by the US Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO), in addition to local IRBs. ***NOTE: 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 conducted or supported by the DOD. These laws and directives are rigorous and detailed, and will require information in addition to that supplied to the local review board. ***Allow a minimum of 6 months for regulatory review and approval processes for studies involving human subjects***. Refer to the General Application Instructions, Appendix 5, for detailed information.

C. Eligibility

PIs must be independent investigators at any academic level (or equivalent). Refer to General Application Instructions, Appendix 1, for general eligibility information.

D. Funding

- The maximum period of performance is **4** years.
- The maximum allowable funding for the entire period of performance is **$900,000** in direct costs.
- The applicant may request the entire maximum direct cost amount for a project that may be less than the maximum 4-year period of performance.
- Regardless of the period of performance proposed, the applicant may not exceed the maximum direct cost. In addition to the direct costs, indirect costs may be proposed in accordance with the organization's negotiated rate agreement.

Within the guidelines provided in the General Application Instructions, funds can cover:

- Salary
- Research supplies
- Equipment
- Clinical costs
- Travel between collaborating institutions
- Travel costs of up to $1,800 per year to attend scientific/technical meetings
- Other direct costs as described in the General Application Instructions for the Detailed Budget and Justification

The Office of the Congressionally Directed Medical Research Programs (CDMRP) expects to allot approximately $2.7M of the $13.75M FY10 NFRP 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.

E. Award Administration

Quarterly technical progress reports will be required.

The transfer of an award to another institution is strongly discouraged. A transfer will not be allowed for any institution that includes a study site/clinical trial at its location. Approval of a transfer request from an institution that does not include a study site at its location will be at the discretion of the Grants Officer. Awards will be made approximately 4 to 6 months after receiving a funding notification letter, but no later than September 30, 2011. Refer to the General Application Instructions, Appendix 4, for general award administration information.

II. TIMELINE FOR SUBMISSION AND REVIEW

- **Pre-application Submission Deadline: 5:00 p.m. Eastern time (ET), April 29, 2010**
- **Application Submission Deadline: 11:59 p.m. ET, May 20, 2010**
- **Scientific Peer Review: July 2010**
- **Programmatic Review: August 2010**

Application submissions will not be accepted unless the pre-application process is completed by the pre-application deadline.

III. SUBMISSION PROCESS

Submission is a two-step process requiring both (1) pre-application submission through the CDMRP eReceipt system (https://cdmrp.org/) and (2) application submission through Grants.gov (http://www.grants.gov/).

Submission of the same research project to different funding opportunities within the same program and fiscal year is discouraged. The Government reserves the right to reject duplicative applications.

PIs and organizations identified in the application should be the same as those identified in the pre-application. If a change in PI or organization is necessary after submission of the pre-application, the PI must contact the eReceipt help desk at help@cdmrp.org or 301-682-5507.

A. Step 1 – Pre-Application Components

All pre-application components must be submitted through the CDMRP eReceipt system by ***5:00 p.m. ET on the deadline***.

The pre-application consists of the following components, which are organized in the CDMRP eReceipt system by separate tabs (Refer to the General Application Instructions for additional information on pre-application submission.):

- **Proposal Information – Tab 1**
- **Proposal Contacts – Tab 2**
- **Collaborators and Conflicts of Interest – Tab 3**
- **Required Files – Tab 4**

  Letter of Intent (LOI) Narrative (one-page limit): Provide a brief description of the research to be conducted. LOI Narratives are used for program planning purposes only (e.g., reviewer recruitment) and ***will not be reviewed*** during either the peer or programmatic review sessions.
- **Submit Pre-application – Tab 5**
- **Other Documents Tab**
  Not applicable.

B. Step 2 – Application Components

Applications are submitted by the Authorized Organizational Representative (AOR) through Grants.gov (http://www.grants.gov/). Applications must be submitted **by *11:59 p.m. ET on the deadline.***

Each application submission must include the completed application package of forms and attachments identified in Grants.gov for this Program Announcement/Funding Opportunity.

The Grants.gov application package consists of the following components (Refer to the General Application Instructions, Section II.B., for additional information on application submission.):

1. **SF 424 (R&R) Application for Federal Assistance Form:** Refer to the General Application Instructions, Section II.B., for detailed information.
2. **Attachments Form**
   - **Attachment 1: Project Narrative (no-page limit):** Upload as "ProjectNarrative.pdf."

     For the Clinical Trial Award application, the Project Narrative is the clinical protocol, which is the main body of the application. The clinical protocol must address the required components described in Section V, Clinical Protocol and Supporting Clinical Documentation.
   - **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. ***Each component has no page limit unless otherwise noted.***
     - References Cited: List all relevant references 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). The inclusion of Internet URLs to references is encouraged.

- List of Acronyms and Symbols: Provide a list of acronyms and symbols (e.g., PCR = polymerase chain reaction).
- 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 US Army Medical Research and Materiel Command (USAMRMC). Indicate if Government-owned facilities or equipment are proposed for use. Reference should be made to the original or present contract 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 they must be included. Extra items will not be reviewed.

  Letters of Organizational Support (two-page limit per letter): Provide a letter (or letters if applicable), signed by the Department Chair or appropriate organization official, reflecting the laboratory space, equipment, and other resources available for the project. If the PI is a practicing clinician, the institution must clearly demonstrate a commitment to the clinician's research.
- Letters of Collaboration (if applicable) (two-page limit per letter): Provide a signed letter from each collaborating individual or organization that will demonstrate that the PI has the resources necessary for the proposed work.
- Intellectual and Material Property Plan (if applicable): Provide a plan for resolving intellectual and material property issues among participating organizations.
- Include plans for sharing data and research resources.

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

  Technical abstracts should be written using the outline below.

  - Background: 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.
  - Clinical Impact: Briefly describe how the proposed project will have an impact on neurofibromatosis or Schwannomatosis research or patient care.
- **Attachment 4: Public Abstract (one-page limit):** Upload as "PublicAbs.pdf."

  Public abstracts should be written using the outline below.

- Clearly describe, in a manner readily understood by lay persons, the rationale and objective for the proposed work.
  - Do not duplicate the technical abstract.
- Describe the ultimate applicability 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 are the likely contributions of this study to advancing the field of research?

- **Attachment 5: Statement of Work (SOW) (three-page limit):** Upload as "SOW.pdf."

  Refer to the General Application Instructions, Section II.B., for detailed information.
- **Attachment 6: Detailed Budget and Justification (no page limit):** Upload as "Budget.pdf." Use the Detailed Budget and Justification form (available for download on the Full Announcement page in Grants.gov). Refer to the General Application Instructions, Section II.B., for detailed information.
- **Attachment 7: Subaward Detailed Budget and Justification (if applicable) (no page limit):** Use a separate Detailed Budget and Justification form for each subaward budget. Combine into a single file and upload as "SubBudgets.pdf." Refer to the General Application Instructions, Section II.B., for detailed information.
- **Attachment 8: Impact Statement (one-page limit).** Upload as "Impact.pdf."
  - Identify the volunteer population(s) that will participate in the proposed intervention, and describe the potential impact of the proposed clinical trial on the outcomes of individuals with NF.
  - Describe the short-term impact: Detail the anticipated outcomes that will be directly attributed to the results of the proposed clinical trial.
  - Describe the long-term impact: Explain the long-range vision for implementation of the intervention in the clinic or field, and describe the anticipated long-term benefits for the targeted population.
  - Compare the proposed intervention to pharmacologic agents, devices, and/or clinical guidance currently available, if applicable.

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

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

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

IV. INFORMATION FOR APPLICATION REVIEW

A. Application Review and Selection Overview

All applications are evaluated by scientists, clinicians, and consumer advocates using a two-tier review process. The first tier is a scientific peer review of applications against established criteria for determining scientific merit. The second tier is a programmatic review that compares applications to each other and makes recommendations for funding to the Commanding General, USAMRMC, based on scientific merit, the overall goals of the program, and 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 review process used by the CDMRP may be found at http://cdmrp.army.mil/fundingprocess

All CDMRP review processes are conducted confidentially to maintain the integrity of the merit-based selection process. Each level of review requires panelists to sign a nondisclosure statement attesting that application and evaluation information will not be disclosed outside the panel. Violations of the non-disclosure statement can result in the dissolving of a panel(s) and other corrective actions. Organizational personnel and PIs 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 panelists or PIs that compromise the confidentiality of the review process may also result in suspension or debarment of their employing organizations from Federal awards. Furthermore, it is a crime for Federal officials to disclose confidential information of one party to another third party (Title 18 United States Code 1905).

B. Review Criteria

1. Peer Review: All applications will be evaluated according to the following criteria, which are of equal importance:

- **Clinical Impact**
  - How the results of the proposed clinical trial will affect the magnitude and scope of potential clinical applications (e.g., detection, diagnosis, treatment, management, and/or quality of life).
  - How relevant the anticipated outcomes of the proposed clinical trial are to individuals with NF.
  - How the potential outcomes of the proposed clinical trial will improve outcomes for individuals with NF within the near-term future once the trial is completed.

- How well the anticipated long-term benefits for the targeted population are described.

- **Ethics**
  - How well the risks to subjects are minimized, and evidence of a monitoring plan which is appropriate with the level of risk.
  - How well the evidence that 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 the selection of subjects is equitable, informed consent is sought and appropriately documented, and appropriate safeguards are in place for vulnerable populations.
- **Intervention, Drug, or Device**
  - Whether the intervention, drug, or device to be tested is available and appropriate for the proposed clinical trial.
  - How the proposed intervention compares to pharmacologic agents, devices, and/or clinical guidance currently available, if applicable.
  - Whether the timeline proposed for IND/IDE application is appropriate (if applicable).
  - Whether measures are described to ensure the consistency of dosing of active ingredients for nutritional supplements (if applicable).
- **Volunteer Recruitment and Accrual**
  - How the recruitment, informed consent, screening, and retention processes for volunteers will be conducted to meet the needs of the proposed clinical trial.
  - Evidence of a contingency plan to resolve potential delays (e.g., slow accrual, patient dropout) in clinical trial completion.
  - How the protocol addresses the availability of volunteers for the clinical trial, the prospect of their participation, and the consideration of likelihood of volunteer attrition.
- **Personnel**
  - How the clinical study team's background and expertise are appropriate to accomplish the proposed work (i.e., statistical expertise, expertise in the disease, and clinical studies).
  - How the levels of effort of the clinical team are appropriate for successful conduct of the proposed trial.
  - Evidence that a study coordinator with appropriate expertise is or will be identified at an appropriate level of effort.
- **Statistical Plan (as appropriate to phase of study)**
  - How the statistical plan, including sample size projections and power analysis, is adequate for the study and all proposed correlative studies.

- **Study Design**
    - How well the scientific rationale and preliminary data, including critical review and analysis of the literature, and laboratory and preclinical evidence support the rationale for testing the intervention.
    - How well the study aims, hypotheses or objectives, experimental design, methods, data collection procedures, and analyses are designed to clearly answer an important clinical objective.
    - How well the logistical aspects of the proposed clinical trial (e.g., communication plan, data transfer and management, and standardization of procedures) meet the needs of the proposed clinical trial.
    - How well the inclusion, exclusion, and randomization criteria meet the needs of the proposed clinical trial.
    - To what extent the proposed clinical trial affects the daily lives of study participants (e.g., Will participants still be able to take their regular medications while participating in the clinical trial? Are participants required to stay overnight in a hospital?).

The following will not be individually scored, but may impact the overall evaluation of the application:

- **Environment**
    - How the evidence indicates an appropriate scientific environment, clinical setting, and the accessibility of institutional resources to support the clinical trial at each participating center or institution (including collaborative arrangements).
    - The evidence for appropriate institutional commitment from each participating institution.
    - If applicable, how the intellectual and material property plan that is agreed upon by each participating institution is appropriate for the proposed clinical trial.
- **Budget**
    - Whether the budget is appropriate for the proposed research and within the limitations of this Program Announcement/Funding Opportunity.
- **Application Presentation**
    - How the writing and components of the application influenced the review.

2. Programmatic Review: The following equally weighted criteria are used by programmatic reviewers to make funding recommendations.

- Ratings and evaluations of the peer reviewers
- Programmatic relevance
- Relative innovation and impact
- Program portfolio composition

- Adherence to the intent of the award mechanism

V. CLINICAL PROTOCOL AND SUPPORTING CLINICAL DOCUMENTATION

A. Required Elements of the Protocol: Upload as Attachment 1 "ProjectNarrative.pdf" on the Attachments Form in Grants.gov.

Please note that the protocol should address the following elements:

- Trial design.
- Intervention, drug, or device to be tested.
- Feasibility of the study.
- How the protocol addresses the availability of volunteers for the clinical trial, the prospect of their participation, and the consideration of likelihood of volunteer attrition.
- The statistical plan.
- The personnel involved in the study.
- Ethics and/or regulatory issues.

Protocol elements:

1. Protocol Title

2. Phase or Class: Designate the phase of the trial (i.e., Phase I, II, III, or a combination of phases), or class of device, if applicable. For descriptions of each type of clinical trial, please refer to http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and http://www.clinicaltrials.gov.

3. Principal Investigator/Study Staff: List the complete name, address, telephone and fax number, and email address of the PI. List the names of all key study personnel who will have significant involvement in the study; include their professional credentials (e.g., M.D. or R.N.), highest degree(s), job title, and employing institution.

4. Study Location(s): List all centers, clinics, or laboratories where the study is to be conducted. Provide the Federal-wide or DOD Assurance number for each institution engaged in study. Include the name, degree(s), title, employing institution, and complete address of the investigator(s) for each study site. **Multi-institutional Clinical Trials:** If the proposed clinical trial is multi-institutional, plans for communication and data transfer between the collaborating institutions, as well as how specimens and/or imaging products obtained during the study will be handled, should be included in the appropriate sections of the Clinical Protocol. In addition, a separate intellectual and material property plan agreed upon by all participating institutions should be provided for multi-institutional clinical trials.

5. Time Required to Complete the Study: State the month and year of the expected start and completion times.

6. Background (suggested limit: 10 pages): Include a literature review that describes in detail the rationale for conduct of the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. 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.

> ***Note: If the protocol was initiated using other funding prior to obtaining the DOD funding, explain the history and evolution of the protocol and declare the source of prior funding. Specifically identify the portions of the study that will be supported with DOD funds. For ongoing protocols, HRPO approval is required prior to initiation of any human subjects research activities supported by the USAMRMC.***

7. Objectives/Specific Aims/Study Questions: Provide a description of the purpose and objectives of the study with detailed specific aims and/or study questions/hypotheses.

8. Study Design: Describe the type of study to be performed (e.g., prospective, retrospective, randomized, controlled, etc.) and outline the proposed methodology in sufficient detail to show a clear course of action.

- Define the study variables and describe how they will be measured.
- Describe the methods that will be used to obtain a sample of volunteers from the accessible population (i.e., convenience, simple random, stratified random).
- If applicable, describe the subject-to-group assignment process (e.g., randomization, block randomization, stratified randomization, age-matched controls, alternating group, or other procedures).
- Explain the specific actions to accomplish the group assignment (e.g., computer assignment, use of table of random numbers).
- Describe the reliability and validity of psychometric measures, if applicable.

9. 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 which the sample will be recruited/drawn). Demonstrate that the research team has access to the proposed study population. Furthermore, discuss past efforts in recruiting volunteers from the target population for previous clinical trials (if applicable), any potential barriers to accrual, such as a change in the target population demographics, a change in medical practices, or competing clinical trials; and plans for addressing unanticipated delays (e.g., slow accrual). Volunteer selection should be equitable. The protocol should include justification of any age, race, ethnicity, or sex limitations provided.

10. Inclusion/Exclusion Criteria: List the inclusion and exclusion criteria in the protocol. 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. Ensure that exclusions are justified. Clearly state the exclusion criteria for volunteers with disease, taking medications, or from certain groups.

Inclusion of Women and Minorities in Study. Consistent with the Belmont Report and recent congressional legislation, special attention is given to inclusion of women and 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. If women and/or minorities will be excluded from the protocol, an appropriate justification must be included.

11. Description of the Recruitment Process: Explain methods for identification of potential volunteers (e.g., medical record review, obtaining sampling lists, health care provider identification, etc.).

- Describe the recruitment process ***in detail***. Address who will identify potential volunteers, who will recruit them, and what methods will be used to recruit them.

- If volunteers will be compensated for participation in the study, a detailed description of the compensation plan should be included in the protocol. Ensure that the compensation plan is fair and does not provide undue inducement. If the study requires multiple visits, a plan for pro-rating payments in the event of volunteer withdrawal should be considered.

- Describe the recruitment and advertisement materials. The recruitment materials should not be coercive or offer undue inducements, and should accurately reflect the study. An ombudsman should be considered for use with particularly vulnerable populations.

- Some important considerations for recruitment materials include***:***

    - Recruitment materials should not promise a cure or benefit beyond what is mentioned in the protocol or consent form.

    - If the volunteers will be paid, the amount of payment should not be presented in bold type, larger than other text, or otherwise overemphasized.

    - Recruitment materials should not promise “free medical treatment” when treatment is not the true intent of the study.

12. Sample Size Justification: A complete power analysis must be included in the protocol to ensure that the sample size is appropriate to meet the objectives of the study. The protocol should specify the approximate number of volunteers that will be enrolled. If the protocol involves multiple sites, the number enrolled at each site should be stated

13. Description of the Informed Consent Process: Specifically describe the plan for obtaining informed consent from volunteers. Provide the Informed Consent Form.

- Identify who is responsible for explaining the study, answering questions, and obtaining informed consent.
- Include information regarding the timing and location of the consent process.

- If applicable, address issues relevant to the mental capacity of the potential volunteer (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 volunteer age).
- Address how privacy and time for decision making will be provided, and whether or not the potential volunteer will be allowed to discuss the study with anyone before making a decision.
- As consent is an ongoing process, 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.
- If volunteers who cannot give their own consent to participate will be included in the study, there must be a plan for the consent of the individual's Legally Authorized Representative (LAR) to be obtained prior to the volunteer's participation in the study. State law defines who may act as the LAR. The IRB of record should be consulted for guidance regarding who can serve as LAR for research at the study site.
- If illiterate volunteers are anticipated, the consent process to be followed for illiterate volunteers should be outlined in the protocol. The consent form should be verbally read/explained to the volunteer in the presence of a witness. The volunteers must sign or make a mark (such as a thumbprint) to indicate agreement to participate, and the witness must sign to attest that the content of the written consent form was accurately conveyed to the volunteer.
- If it is anticipated that volunteers who do not speak the primary language of the host country will be enrolled in a trial, all documentation provided to volunteers (consent form, information sheets, etc.) should be translated with a copy provided to the HRPO for review at a later date. A plan for ensuring that volunteers' questions will be addressed during the consent process and throughout the trial should be included.

NOTE: When consent will be obtained in a language other than English, documentation that the foreign language version of the consent form is an accurate translation of the English version of the consent form must be provided to the HRPO at a later date. Documentation from a qualified translator certifying the translation must be provided along with the English and foreign language version of the consent forms. The documentation of translation should include the following statement: "I certify that this is an accurate and true translation." The signature, name, address, phone number, and, if available, fax number of the translator should also be included.

- If a waiver of all or parts of the consent process is being sought, or a waiver of documentation of consent is desired, include justification of why the waiver should be considered. This justification should include how the protocol meets the criteria set forth in 32 CFR 219 (Title 32 of the Code of Federal Register, Section 219). If consent to use existing samples or data in a future study was provided as part of another study protocol, this should be clearly explained. If the institution is a covered entity, justification for Health Insurance Portability and Accountability Act (HIPAA) waiver requests should also be provided.

Assent. When minors are included in a study, a plan to obtain assent (agreement) from those with capacity to provide it, or a justification for a waiver of assent should be provided. Age-appropriate assent forms should be developed for use with minors when assent is obtained. Capacity to provide assent should also be considered for other populations that cannot provide informed consent, and assent should be obtained whenever possible.

14. Volunteer 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.

15. Study Procedures/Study Interventions: Describe the study intervention or activity that the volunteer will experience. Provide sufficient detail in chronological order for a person uninvolved in the study to understand what the volunteer will experience and when it will occur. Provide a schedule of study evaluations and follow-up procedures. Provide all case report forms, data collection forms, questionnaires, rating scales, and interview guides, etc. that will be used in the study.

16. Description of Protocol Drugs or Devices: If the protocol uses a drug, biologic, device, or dietary supplement, provide the following information:

- For medical products regulated by the Food, Drug, and Cosmetic Act, designate the protocol as Phase II or III clinical trials research (or class of device, if applicable.)
- If the study is in support of an application to the FDA or other appropriate agency, provide the IND/IDE number and name of the sponsor.
- Provide complete names and composition of all medications, devices, or placebos.
- Identify the source of medications, devices, or placebos.
- Describe the location of storage for study medications.
- Describe the dose range, schedule, and administration route of test articles.
- Describe washout period, if used, in detail.
- Describe the duration of drug or device treatment.
- Declare concomitant medications allowed.
- Identify any antidotes and treatments available for potential side-effects.
- Describe the plan for disposition of unused drug.
- For FDA-regulated studies, describe the procedure by which the IND sponsor will monitor the protocol in accordance with Title 21 of the Code of Federal Register, Section 312 (21 CFR 312).

17. Laboratory Evaluations:

- **Specimens to be collected, schedule, and amount.** All specimens that will be collected for study purposes must be clearly stated in the protocol. The collection schedule and amount of material collected must also be clearly described. This may be represented using a table or schematic for more involved protocols.
- **Evaluations to be made.** All evaluations that will be made for study purposes should be stated in the protocol. Copies of all data collection forms must be provided. The protocol should explain how the results of laboratory evaluations will be used to meet the objectives of the study (or to monitor safety of volunteers).
- **Storage.** Specimen storage must be described in the protocol, to include where, how long, any special conditions required, labeling, and disposition. If there is a plan to store specimens for future use (either by the investigator or through an established repository), this should be outlined in the protocol. If samples will be collected for future use in other studies (and if this is not the sole purpose of the protocol), volunteers should be given the chance to opt out. Potential future uses of samples should be addressed to the degree possible. If volunteers are given a menu of options regarding sample donation for future research, procedures should be in place to ensure that volunteers' wishes for use of the samples are honored. Procedures for withdrawal of samples at the request of the volunteer should be described if samples will remain coded or identified.
- **Labs performing evaluations and special precautions.** The laboratory performing each evaluation should be clearly identified in the protocol, as well as any special precautions that should be taken in handling the samples. Special precautions that should be taken by the volunteer before, during, or after the laboratory procedure should be clearly defined. If transport of samples is required, provisions for ensuring proper storage during transport should be included in the protocol.

18. Data Analysis: Describe the data analysis plan. The data analysis plan should be consistent with the study objectives.

19. Data Management:

- **Methods used for data collection.** All methods used for data collection should be described in the protocol. Copies of data collection forms and any test instruments administered should be provided. Data collection forms should be adequate and accurate according to the data collection plan described in the protocol. Whenever possible, identifiers should be removed from data collection forms. Critical measurements used as endpoints should be identified.
- **Volunteer identifiers.** If unique identifiers or a specific code system will be used to identify volunteers, this process should be described in the protocol.
- **Confidentiality:**
    - The protocol should explain measures taken to protect the privacy of study volunteers and maintain confidentiality of study data. Strategies to protect the privacy and confidentiality of study records, particularly those containing

identifying information, should be addressed. Investigators collecting particularly sensitive information should consider obtaining a Certificate of Confidentiality.

- The protocol should address who will have access to study records, data, and specimens. The protocol should acknowledge that representatives of USAMRMC are eligible to review study records.
- Requirements for reporting sensitive information to state or local authorities should be addressed in the protocol. Examples of sensitive information that may require reporting include positive HIV (human immunodeficiency virus), hepatitis, or tuberculosis test results, illegal residency, child or spouse abuse, or participation in other illegal activities. These requirements will vary from state to state. Investigators should consult with his/her IRB for assistance with state requirements.

- **Disposition of data.** Describe where data (both electronic and hard copy) will be stored, who will keep the data, how the data will be stored, and the length of time data will be stored. Note that records of IND studies must be kept for 2 years after a New Drug Application is approved/issued, or for 2 years after the IND is withdrawn. Records required for IDE studies should be retained for 2 years following the date that the investigation is terminated or completed, or the date that the records are no longer required for support of the pre-market approval application, whichever is sooner.
- **Sharing study results.** In cases where the volunteer could possibly benefit medically or otherwise from the information, the protocol should explain whether or not the results of screening and/or study participation will be shared with volunteers or their primary care provider, to include results from any screening or diagnostic tests performed as part of the study. The potential benefits of providing volunteers with the information should be weighed against the potential risks. It is generally not advisable to use experimental assays or techniques to guide clinical care.

20. Risks/Benefits Assessment:

- **Foreseeable risks.** The protocol should clearly identify all study risks. Study risks include any risks that the volunteer is subjected to as a result of participation in the protocol. Consider psychological, legal, social, and economic risks as well as physical risks. If the risks are unknown, this should be stated in the protocol. If applicable, any potential risk to the study personnel should be identified.
- **Risk management and emergency response:**
  - The protocol should clearly list all measures to be taken to minimize and/or eliminate risks to volunteers and study personnel, or to manage unpreventable risks. All safety measures in place to mitigate risk (e.g., core temperature monitoring, electrocardiogram monitoring, observation periods, special procedures to avoid disclosure of potentially damaging information) should be described.
  - Planned responses such as dose reduction or stopping criteria based on toxicity grading scales or other predetermined alert values, and other safeguards should be detailed in the protocol.
  - If there is a chance a volunteer may require emergency care or treatment for an adverse event, the protocol should discuss the overall plan for provision of care for

study-related injuries, to include who will be responsible for the cost of such care. For example, if a study sponsor or institution has committed to providing care for study-related injury at no cost to volunteers, this provision should be explained in the protocol. The clinical site must have adequate personnel and equipment to respond to expected adverse events, and the nearest medical treatment facility should be identified in the emergency response plan.

- Any special precautions to be taken by the volunteers before, during, and after the study (e.g., medication washout periods, dietary restrictions, hydration, fasting, pregnancy prevention, etc.) must be addressed. If pregnant volunteers will be excluded from participation in the study, the method used to determine pregnancy status in women of childbearing potential must be specified. Also, the time that will elapse between the pregnancy test and exposure to study procedures or medical products must be stated, as well as how long the non-pregnant volunteer should use effective contraceptive practices after participating in the study. Please note that contraceptive practices may be necessary for male volunteers participating in certain types of studies. For IND studies, pregnancy testing is recommended within 48-72 hours before the start of the study. Consideration should be given to repeating testing prior to administration of test articles.
- 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 volunteers enrolled in the study must be described in the protocol.

- **Potential benefits.** Describe real and potential benefits of the study to the volunteer, a specific community, or society. Ensure that the benefits are not overstated. ***NOTE: Payment and/or other compensation for participation are not considered to be benefits and must be addressed in a separate section.***

- **Intent to benefit.** If volunteers cannot give their own consent to participate in an experimental study, and Title 10 United States Code Section 980 (10 USC 980) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=browse_usc&docid=Cite:+10USC980 applies, a clear intent to benefit each volunteer must be described in the protocol. Please refer to the General Application Instructions, Appendix 5, for more information.

21. Study Personnel:

- **Roles and responsibilities of key study personnel.** Briefly describe the duties of key study personnel. Describe their roles in the study effort. A study coordinator is required at an appropriate level of effort whose duties may include the following: Recruit and consent volunteers, maintain study records, administer study drug, take and record vital signs, and enter data into computer database. A key person must be identified who will be responsible for guiding the protocol through the IRB, HRPO, and other regulatory approval processes, coordinating activities from all sites participating in the trial, and coordinating participant accrual.

- **Conflicts of interest.** Investigators and key study staff must disclose any real or apparent conflicts of interest (financial or other). This information may be provided in the protocol or by submission of a conflict of interest declaration form. (Many institutions have a form for this purpose, as does the FDA. A Financial Disclosure Form for Investigators is also available on the HRPO website at https://mrmc-www.army.mil/rodorphrpo.asp that will meet this requirement.) Measures taken to mitigate the impact of conflicts of interest must be provided. Information regarding conflicts of interest should be disclosed to volunteers in the consent form. All protocols that support development of a drug, device, biologic, or other intellectual property require completion of a conflict of interest declaration by all investigators on the protocol. Other protocols may require conflict of interest statements on a case by case basis.

22. Roles and Responsibilities of Medical Monitor: The DOD requires that a medical monitor be assigned to greater-than-minimal-risk protocols. The specific roles fulfilled by the medical monitor should be outlined in the protocol.

NOTE: The HRPO requires that the medical monitor review all unanticipated problems involving risk to volunteers or others, serious adverse events, and all volunteer deaths associated with the protocol, and provide an unbiased written report of the event within 10 calendar days. At a minimum, the medical monitor should comment on the outcomes of the adverse event, and the relationship of the event to the protocol or test article. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the PI. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation, and reports of events resulting in death should be promptly forwarded to the HRPO.

23. Study Organization and Management Plan: Provide an organizational chart and a timetable for completion for the clinical trial and publication. Provide a plan for ensuring the standardization of procedures among staff and across sites (if applicable). Provide a plan for real-time communication among collaborating institutions (if applicable).

24. Withdrawal from the Protocol: Volunteers may discontinue participation in the study at any time without penalty or loss of benefits to which the volunteer is otherwise entitled. The protocol should describe the procedure in place to support an orderly end of the volunteer's participation (e.g., exit exam or follow-up safety visits outside of the context of the research study, information regarding prorated payment for partial participation, etc.) and the consequences of a volunteer's decision to withdraw from the study. The anticipated circumstances under which the volunteer's participation may be terminated by the investigator or others should also be addressed (e.g., noncompliance, safety issues, loss of funding, etc.).

25. Modifications to the Protocol: Describe the procedures to be followed if the protocol is to be modified, amended, or terminated before completion. Note that any modification to the protocol, consent form, and/or questionnaires, including a change to the PI, must be submitted to the local IRB for review and approval. Major modifications to the study protocol and any modifications that could increase risk to volunteers must be submitted to the HRPO for approval ***prior to implementation***. Some examples of major modifications include a change in PI,

addition of a study site, changes in study design, and addition or widening of a study population. All other amendments will be submitted with the continuing review report to the HRPO for acceptance. Address the procedure for submitting amendments even if modifications to the protocol are not anticipated.

- **Protocol Deviations.** Describe procedures and notifications to be made in the event of deviations from the approved protocol to include both the local IRB and the HRPO. ***NOTE: Any deviation to the protocol that may have an effect on the safety or rights of the volunteer, or the integrity of the study must be promptly reported to the HRPO.***

26. Reporting of Serious Adverse Events and Unanticipated Problems:

- Reporting procedures will differ from institution to institution, so it is important for investigators to identify the reporting requirements for all entities involved in review of the protocol, and to clearly define this procedure within the protocol.
- Serious adverse events and unanticipated problems can occur in any and all types of studies, not just experimental interventions or clinical trials.
- Include a definition of what constitutes an adverse event in the study. For IND or IDE studies, include definitions as described in 21 CFR 312.32 and the ICH (International Conference on Harmonization) E2A Guidelines (http://www.ich.org/cache/compo/475-272-1.html).
- Describe agencies or offices to be notified with point of contact information in the event of an unanticipated problem or serious adverse event.

All protocols should contain the following language regarding the HRPO reporting requirements for adverse events and unanticipated problems: "Unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study, and all volunteer deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the US Army Medical Research and Materiel Command's Office of Research Protections, Human Research Protections Office. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-ZB-P, 504 Scott Street, Fort Detrick, Maryland 21702-5012."

For protocols that have a medical monitor assigned, the following language should also be included:

"The medical monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events, and all volunteer deaths associated with the protocol, and provide an unbiased written report of the event to the USAMRMC ORP, HRPO. At a minimum, the medical monitor should comment on the outcomes of the event or problem, and in the case of a serious adverse event or death comment on the relationship to participation in the study. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related

to participation, and reports of events resulting in death should be promptly forwarded to the HRPO."

27. Continuing Review and Final Report: The protocol should acknowledge that a copy of the approved continuing review report and the local IRB approval notification will be submitted to the HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the HRPO as soon as these documents become available.

B. Surveys, Questionnaires, and Other Data Collection Instruments: If the study involves surveys, questionnaires, case report forms, data collection forms, rating scales, interview guides, or other instruments, include a copy of the most recent version of each of these documents with the protocol submission. For each instrument that is used, the following information at a minimum should be addressed.

- Information collected with study instrument must be related to the objectives of the study.
- Procedures for use of study instruments should be clear in the protocol. Study instruments should be coded to protect confidentiality whenever possible.
- For study instruments provided to and/or completed by volunteers, the study instrument should be legible and presented at a reading level appropriate to the population. Copies of instruments submitted for review must also be legible.

C. Additional Protocol Language Requirements

The following are reporting requirements and responsibilities of the PI to the USAMRMC ORP, HRPO, and should be reflected in the protocol:

- The protocol will be conducted in accordance with the protocol submitted to and approved by the USAMRMC ORP, HRPO, and will not be initiated until written notification of approval of the research project is issued by the USAMRMC ORP, HRPO.
- Accurate and complete study records will be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records will be stored in a confidential manner so as to protect the confidentiality of subject information.

The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning clinical investigation or research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any Regulatory Agencies, including legal or medical actions, and any instances of serious or continuing noncompliance with the regulations or requirements will be reported immediately to USAMRMC ORP, HRPO.

VI. ADMINISTRATIVE ACTIONS

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

A. Rejection

The following will result in administrative rejection of the application:

- Project Narrative exceeds page limit.
- Project Narrative is missing.
- Budget is missing.
- Page size is larger than 8.5 inches x 11.0 inches (approximately 21.59 cm x 27.94 cm).

B. Modifications

- Pages exceeding the specified limits will be removed prior to review for all documents other than the Project Narrative.
- Documents not requested will be removed.
- Following the application deadline, you may be contacted by CDMRP via email with a request to provide certain missing supporting documents (excluding those listed in Section V-A, Rejection). The missing documents must be provided by 5:00 p.m. ET on the second full business day following the date the email was sent. Otherwise, the application will be reviewed as submitted.

C. Withdrawal

The following may result in administrative withdrawal of the application:

- FY10 NFRP Integration Panel (IP) member(s) is found to be involved in the preapplication or application processes including, but not limited to, concept design, application development, budget preparation, and the development of any supporting document. A list of the FY10 NFRP IP members may be found at http://cdmrp.army.mil/nfrp/panel10
- Submission of the same research project to different funding opportunities within the same program and fiscal year.
- The application does not conform to this Program Announcement/Funding Opportunity description to an extent that precludes appropriate review.
- Direct costs as shown on the detailed budget form exceed maximum allowed by this Program Announcement/Funding Opportunity.
- Inclusion of URLs with the exception of links to published references.
- The proposed research is not a clinical trial.
- The PI does not meet the eligibility criteria as described in this Program Announcement/Funding Opportunity.

D. Withhold

Applications that appear to involve research misconduct will be administratively withheld from further consideration pending institutional investigation. The institution will be requested to provide the findings of the investigation to the US Army Medical Research Acquisition Activity (USAMRAA) Contracting/Grants Officer for a determination of the final disposition of the application.

VII. CONTACT INFORMATION

A. CDMRP Program Announcement Help Desk: Questions related to Program Announcement/Funding Opportunity content or submission requirements should be directed to the CDMRP Program Announcement help desk, which is available Monday through Friday from 7:30 a.m. to 4:00 p.m. ET. Submit questions as early as possible. Response times will vary depending upon the volume of inquiries. Every effort will be made to answer questions within 5 working days.

Phone: 301-619-7079
Email: cdmrp.pa@amedd.army.mil

B. CDMRP eReceipt System Help Desk: Questions related to the submission of the pre-application through the eReceipt system should be directed to the CDMRP eReceipt system help desk, which is available Monday through Friday from 8:00 a.m. to 5:00 p.m. ET.

Phone: 301-682-5507
Email: help@cdmrp.org

C. Grants.gov Contact Center: Questions related to application submission through the Grants.gov portal should be directed to Grants.gov help desk, which is available 24 hours a day, 7 days a week. Please note that the CDMRP Program Announcement and eReceipt system help desks are unable to provide technical assistance regarding Grants.gov submissions.

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. If the application package is updated or changed, the original version of the application package may not be accepted by Grants.gov.

VIII. APPLICATION SUBMISSION CHECKLIST

Grants.gov Application Components	Action	Completed
SF-424 (R&R) Application for Federal Assistance Form	Complete form as instructed	
Attachments Form	Upload Project Narrative (ProjectNarrative.pdf) as Attachment 1	
	Upload Supporting Documentation (Support.pdf) as Attachment 2	
	Upload Technical Abstract (TechAbs.pdf) as Attachment 3	
	Upload Public Abstract (PublicAbs.pdf) as Attachment 4	
	Upload Statement of Work (SOW.pdf) as Attachment 5	
	Upload Detailed Budget and Justification (Budget.pdf) as Attachment 6	
	Upload Subaward Detailed Budget and Justification (SubBudgets.pdf) as Attachment 7	
	Upload Impact statement (Impact.pdf) as Attachment 8	
Research & Related Senior/Key Person Profile (Expanded)	Attach PI Biographical Sketch (Biosketch_LastName.pdf) to the appropriate field	
	Attach PI 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 Current & Pending Support (Support_LastName.pdf) for each senior/key person to the appropriate field	
Project/Performance Site Location(s) Form	Complete form as instructed	