Program Announcement

Department of Defense

Congressionally Directed Medical Research Programs

Neurofibromatosis Research Program

Clinical Trial Award

Funding Opportunity Number: W81XWH-12-NFRP-CTA

Catalog of Federal Domestic Assistance Number: 12.420

SUBMISSION AND REVIEW DATES AND TIMES

- **Pre-Application Submission Deadline:** 5:00 p.m. Eastern time (ET), May 10, 2012
- **Application Submission Deadline:** 11:59 p.m. ET, May 31, 2012
- **Peer Review:** July 2012
- **Programmatic Review:** September 2012

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I. FUNDING OPPORTUNITY DESCRIPTION

A. Program Description

The Neurofibromatosis Research Program (NFRP) was established in 1996 to provide support for research of exceptional scientific merit that promotes the understanding, diagnosis, and treatment of neurofibromatosis (NF) including neurofibromatosis type 1 and type 2 and Schwannomatosis. Appropriations for the NFRP from FY96 through FY11 totaled $230.1 million (M). The FY12 appropriation is $12.8 M**.**

FY12 NFRP Vision: The vision and goals of the FY12 NFRP are to decrease the clinical impact of NF. Toward this end, 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 Emphasis: The FY12 NFRP strongly encourages research applications that specifically address the critical needs of the NF community in the following areas of emphasis:

- Cognitive and social dysfunction in the setting of NF
- Drug discovery for the treatment of NF
- Effects of aging, including hormonal changes and cardiovascular disease in the setting of NF
- Epigenetics, including non-coding RNAs, such as microRNAs, in causation or progression of abnormalities from NF
- Novel disease markers, such as imaging and proteomics, of NF
- Pain in the setting of NF
- Plexiform and dermal neurofibromas
- Tumor heterogeneity in NF-associated neoplasia

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/resources/nfrpresources. Investigators are urged to leverage and contribute to these resources and include a sharing and distribution plan in the application for data and resources generated during the performance of the project. For more guidance on data sharing, refer to the General Application Instructions, Appendix 4.

B. Award Information

The NFRP Clinical Trial Award mechanism was first offered in FY99. Since then, 33 Clinical Trial Award applications have been received, and 9 have been recommended for funding.

The NFRP Clinical Trial Award supports pilot and Phase 0, I, or II clinical trials with the potential to have a major impact on the treatment or management of NF. ***Funding from this award mechanism must support a 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. Principal Investigators (PIs) seeking funding for a preclinical research project should consider one of the other funding opportunities being offered. The term "human subjects" is used in this Funding Opportunity to refer to individuals who will be recruited for or who will participate in the proposed clinical trial. For more information on clinical trials, a Human Subject Resource Document is provided at https://cdmrp.org/Program_Announcements_and_Forms/.

If the study proposed involves the use of a drug that has not been approved by the Food and Drug Administration (FDA) for its investigational use, evidence that an Investigational New Drug (IND) exemption application has been submitted or will be submitted **within 60 days of award** is required. If the investigational product is a device, evidence that an Investigational Device Exemption (IDE) has been submitted or will be submitted **within 60 days of award**, or that the device is exempt from an IDE, is required.

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

- The proposed intervention to be tested should offer significant potential impact for individuals affected by NF.
- 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.
- Inclusion of preliminary data relevant to the proposed research project is required.
- The application should include a clearly articulated statistical analysis plan, appropriate statistical expertise, and a power analysis reflecting sample size projections that will clearly answer the objectives of the study.
- The application must demonstrate documented availability of, and access to, the drug/ compound, device, and/or other materials needed, as appropriate.
- The application must demonstrate availability of, and access to, a suitable patient population that will support a meaningful outcome for the study. The PI should discuss how accrual goals will be achieved and how standards of care may impact the study population.
- The application should, as appropriate, include a study coordinator(s) who will guide the clinical protocol through the local Institutional Review Board (IRB) of record and other regulatory approval processes, coordinate activities from all sites participating in the trial, and coordinate participant accrual.

- The application must include a Transition Plan (including potential funding and resources) showing how the product will progress to the next clinical trial phase and/or delivery to the market after the successful completion of the NFRP Clinical Trial Award.
- The application must demonstrate evidence of institutional support and commitment.
- The proposed clinical trial is expected to begin no later than 12 months after the award date.
- The proposed clinical trial must include clearly defined and appropriate endpoints.

Use of Human Subjects and Human Anatomical Substances: All Department of Defense (DoD)-funded research involving new and ongoing research with human subjects and human anatomical substances must be reviewed and approved by the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of Research Protections (ORP), Human Research Protection Office (HRPO), in addition to the local IRB of record. Local IRB approval at the time of submission is NOT required. The HRPO is mandated to comply with specific laws and directives governing all research involving human subjects that is supported by the DoD. These laws and directives are rigorous and detailed and will require information in addition to that supplied to the local IRB. Allow a minimum of 2 to 3 months for regulatory review and approval processes. Refer to the General Application Instructions, Appendix 5, for more information.

The Congressionally Directed Medical Research Programs (CDMRP) intends that data and research resources generated by CDMRP-funded research activities be made available to the research community (which includes both scientific and consumer advocacy communities) and to the public at large. For additional guidance, refer to the General Application Instructions, Appendix 4, Section K.

C. Eligibility Information

- PIs ***at or above*** the level of Assistant Professor (or equivalent) are eligible to submit applications.
- Cost sharing/matching is not an eligibility requirement.
- Refer to the General Application Instructions, Appendix 1, for general eligibility information.

D. Funding

- The maximum period of performance is **4** years.
- The maximum allowable direct costs for the entire period of performance are **$900,000** plus indirect costs.
- 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 **4** years.
- Regardless of the period of performance proposed, the applicant may not exceed the maximum allowable direct costs. Indirect costs shall be proposed in accordance with the organization's negotiated rate agreement.

Refer to the General Application Instructions, Section II.C., for budget regulations and instructions for the Research & Related Budget. In addition, for this award mechanism, direct costs:

May be requested for (not all-inclusive):

- Salary
- Research-related subject costs
- Clinical research costs
- Research supplies
- Equipment
- Travel between collaborating organizations
- Travel costs of up to $1,800 per year to attend scientific/technical meetings

Shall not be requested for:

- Preclinical research studies

The CDMRP expects to allot approximately $2.88M of the $12.8M FY12 NFRP appropriation to fund approximately 2 Clinical Trial Award applications, depending on the quality and number of applications received. Funding of applications received in response to this Program Announcement/Funding Opportunity is contingent upon the availability of Federal funds for this program.

II. SUBMISSION INFORMATION

Submission is a multi-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 prohibited. The Government will reject duplicative applications.

A. Where to Obtain the Application Package

To obtain the complete application package, including all required forms, perform a Grants.gov (http://www.grants.gov/) basic search using the Funding Opportunity Number: W81XWH-12-NFRP-CTA.

B. Pre-Application Submission Content and Form

All pre-application components must be submitted by the PI through the CDMRP eReceipt System (https://cdmrp.org/).

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

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, Section II.B., for additional information on pre-application submission):

- **Application Information – Tab 1**
- **Application Contacts – Tab 2**
- **Collaborators and Conflicts of Interest – Tab 3**

  FY12 NFRP 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@cdmrp.org or 1-301-682-5507.
- **Required Files – Tab 4**

  Letter of Intent (LOI) (one-page limit): Provide a brief description of the research to be conducted. Include the NFRP Area(s) of Emphasis under which the application will be submitted. LOIs 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**

  This tab must be completed for the pre-application to be accepted and processed by CDMRP.
- **Other Documents Tab**

  No additional documents are required**.**

C. Application Submission Content and Form

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

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

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

2. Attachments Form

The Project Narrative is NOT the formal clinical trial protocol (in contrast with previous years). 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, 7, and 8, described below. Failure to submit these attachments as part of the application package will result in rejection of the entire application.

- **Attachment 1: Project Narrative 20-page limit):** Upload as "ProjectNarrative.pdf."

  Describe the proposed project in detail using the outline below.

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

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

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

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

    - Identify the intervention to be tested and describe the projected outcomes.
    - Define the study variables and describe how they will be measured. Include a description of appropriate controls and the endpoints to be tested.
    - Describe the methods that will be used to recruit a sample of human subjects from the accessible population (e.g., convenience, simple random, stratified random).
    - Clearly describe the tissue or tumor type to be studied, where applicable (e.g., encapsulated versus diffuse plexiform neurofibroma).

- 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).
- Describe the reliability and validity of psychometric measures, if applicable.

  - **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 that will 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.

- **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 component unless otherwise noted. Include only those components described below; inclusion of items not requested may result in administrative rejection 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-owned facilities or equipment are proposed for use. Reference should be made to the original or present award under which the facilities or equipment items are now accountable. There is no form for this information.
  - Publications and/or Patent Abstracts (five-document limit): Include relevant publication URLs and/or patent abstracts. If publications are not publicly available, then a copy/copies of the published manuscript(s) must be included in Attachment 2. Extra items will not be reviewed.
  - Letters of Organizational Support: Provide a letter (or letters, if applicable), signed by the Department Chair(s) or appropriate organization official(s), reflecting the institution's commitment to the completion of the trial, including laboratory space, equipment, and other resources available for the project.
  - Letters of Collaboration (if applicable): Provide a signed letter from each collaborating individual or organization that will demonstrate that the PI has the support or resources necessary for the proposed work.

- Letter of Commitment (if applicable): If the study uses a proprietary intervention, such as a drug or device, then include a signed letter from the source documenting a commitment to provide the intervention under investigation for the duration of the study.
- Intellectual and Material Property Plan (if applicable): Provide a plan for resolving intellectual and material property issues among participating organizations.
- Data and Research Resources Sharing Plan (if applicable): Describe how data and resources generated during the performance of the project will be shared with the research community. Refer to the General Application Instructions, Appendix 4, 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."

  Technical abstracts should be written using the outline below. The technical abstract is used by all reviewers; however, programmatic reviewers do not typically have access to the full application and rely on the technical abstract for appropriate description of the project's key aspects.

  - 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 and endpoints.
  - Clinical Impact: Briefly describe how the proposed project will have an impact on NF research or patient care.

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

  Lay abstracts should be written using the outline below. Do not duplicate the technical abstract. The lay abstract is used by consumer peer reviewers along with other components of the application package.

  - 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 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 are the likely contributions of this study to advancing the field of NF research or patient care?

- **Attachment 5: Statement of Work (SOW) (three-page limit):** Upload as "SOW.pdf." Refer to the General Application Instructions, Section II.C., for detailed information.
- **Attachment 6: Human Subject Recruitment and Safety Procedures (no page limit):** Upload as "HumSubProc.pdf." The Human Subject Recruitment and Safety Procedures attachment should include the components listed below.

  a. Study Population: Describe the target population (to whom the study findings will be generalized) and the nature, approximate number, and pertinent demographic characteristics of the accessible population at the study site (population from which the sample will be recruited/drawn). Demonstrate that the research team has access to the proposed study population, including historical details of the number of eligible patients per month at each study site. 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.

  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.
  - Describe the recruitment and advertisement materials. The recruitment materials should not be coercive or offer undue inducements and should accurately reflect the study.

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

- ***For the proposed study, provide a draft, in English, of the Informed Consent Form.***
- Identify who is responsible for explaining the study, answering questions, and obtaining informed consent. Include a plan for ensuring that human subjects' questions will be addressed during the consent process and throughout the trial.
- Include information regarding the timing and location of the consent process.
- Address issues relevant to the mental capacity of the potential human subject (e.g., altered capacity due to administration of any mind-altering substances such as tranquilizers, conscious sedation or anesthesia, brain injury, stress/life situations, or human subject age), if applicable.
- Address how privacy and time for decision making will be provided and whether or not the potential human subject will be allowed to discuss the study with anyone before making a decision.
- Consider the need for obtaining ongoing consent or for re-assessing capacity over the course of a long-term study and describe any relevant procedures to assure continued consent.
- Describe the plan for the consent of the individual's Legally Authorized Representative (LAR) to be obtained prior to the human subject's participation in the study. State law defines who may act as the LAR. The local IRB of record should be consulted for guidance regarding who can serve as LAR for research at the study site. Note: The PI must describe a clear intent to benefit for human subjects who cannot give their own consent to participate in the proposed clinical trial to be in compliance with Title 10 United States Code Section 980 (10 USC 980). 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. 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 all safety measures to minimize and/or eliminate risks to human subjects and study personnel or to manage unpreventable risks. Include safeguards and planned responses such as dose reduction or stopping criteria based on toxicity grading scales or other predetermined alert values.
  - Discuss the overall plan for provision of emergency care or treatment for an adverse event for study-related injuries, to include who will be responsible for the cost of such care.
  - Address any special precautions to be taken by the human subjects before, during, and after the study (e.g., medication washout periods, dietary restrictions, hydration, fasting, pregnancy prevention).
  - Describe any special care (e.g., wound dressing assistance, transportation due to side effects of study intervention impairing ability to drive) or equipment (e.g., thermometers, telemedicine equipment) needed for human subjects enrolled in the study.
- **Potential benefits:** Describe known and potential benefits of the study to the human subject, a specific community, or society.

- **Attachment 7: Intervention (no page limit):** Upload as "Intervention.pdf." The Intervention attachment should include the components listed below.

a. Description of the Intervention: As applicable, the description of the intervention should include the following components: complete name and composition, storage and handling information, source, dose, schedule, administration route, washout period, duration of the intervention, and concomitant medications allowed.

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 Clinical Practices, Good Manufacturing Practices, and other regulatory considerations will be established, monitored, and maintained, as applicable.

- **Attachment 8: Data Management (no page limit):** Upload as "Data_Manage.pdf." The Data Management attachment should include the components listed below.

  a. Data Management: Describe all methods used for data collection to include the following:

  - **Identifiers:** Describe the unique identifiers or specific code system to be used to identify human subjects, if applicable.
  - **Confidentiality:**
    - Explain measures taken to protect the privacy of study human subjects and maintain confidentiality of study data. Strategies to protect the privacy and confidentiality of study records, particularly those containing identifying information, should be addressed.
    - Address who will have access to study records, data, and specimens, including an acknowledgment that representatives of USAMRMC are eligible to review study records.
    - Address requirements for reporting sensitive information to state or local authorities.
  - **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.
  - **Sharing study results:** In cases where the human subject could possibly benefit medically or otherwise from the information, explain whether or not the results of screening and/or study participation will be shared with human subjects or their primary care provider, to include results from any screening or diagnostic tests performed as part of the study.

  b. Laboratory Evaluations:

  - **Specimens to be collected, schedule, and amount.** All specimens that will be collected for study purposes must be clearly stated. The collection schedule and amount of material collected must also be clearly described.
  - **Evaluations to be made.** Describe all evaluations that will be made for study purposes. Explain how the results of laboratory evaluations will be used to meet the objectives of the study (or to monitor safety of human subjects).
  - **Storage.** Describe specimen storage, to include location of storage, how long specimens will be stored, any special conditions required, labeling, and disposition. Outline the plan to store specimens for future use to include considerations for informed consent and providing human subjects with an opportunity to decline participation in the study.
  - **Labs performing evaluations and special precautions.** Identify the laboratory performing each evaluation, as well as any special precautions that should be taken in handling the samples. Special precautions that

should be taken by the human subject before, during, or after the laboratory procedure should be clearly defined. If transport of samples is required, describe provisions for ensuring proper storage during transport.

- **Attachment 9: Study Personnel and Organization (no page limit):** Upload as "Personnel.pdf." The Study Personnel and Organization attachment should include the components listed below.

  a. Principal Investigator/Study Staff: Provide an organizational chart identifying key members of the study team including institution/center/ department. Briefly describe their roles on the project. A medical monitor (external to the study and not reimbursed by the study) and study coordinator(s) should be included.

  b. Study Management Plan: Provide a plan for ensuring the standardization of procedures among staff and across sites (if applicable). If the proposed clinical trial is multi-institutional, plans for communication and data transfer between the collaborating institutions, as well as how data, specimens, and/or imaging products obtained during the study will be handled, should be included. Provide a plan for real-time communication among collaborating institutions (if applicable).

- **Attachment 10: Surveys, Questionnaires, and Other Data Collection Instruments, if applicable (no page limit):** Upload as "Surveys.pdf." The Surveys, Questionnaires, and Other Data Collection Instruments attachment should include a copy of the most recent version of surveys, questionnaires, data collection forms, rating scales, interview guides, or other instruments. For each instrument, describe how the information collected is related to the objectives of the study.

- **Attachment 11: 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.
  - Describe any relevant controversies or treatment issues that will be addressed by the proposed clinical trial.
  - Describe any potential issues that might limit the impact of the proposed clinical trial.
  - Compare the proposed intervention to pharmacologic agents, devices, and/or clinical guidance currently available, if applicable.

- **Attachment 12: Transition Plan (one-page limit).** Upload as "Transition.pdf." Provide information on the methods and strategies proposed to move the product to the next phase of clinical trials and/or delivery to the commercial market after successful completion of the award. The transition plan should include the components listed below.
    - Details of the funding strategy that will be used to bring the outcomes to the next level of clinical trials and/or delivery to the commercial market (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 of the intervention.
    - A brief schedule and milestones for bringing the outcome(s) to the next phase of clinical trials and/or delivery to the commercial market.
    - 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 has been submitted, an explanation of the status of the IND or IDE must be provided (e.g., past the critical 30-day period, pending response to questions raised by the Agency, on clinical hold). Inclusion of a copy of the Agency meeting minutes is encouraged but not required. 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 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.

3. **Research & Related Senior/Key Person Profile (Expanded):** Refer to the General Application Instructions, Section II.C., 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. **Research & Related Budget:** Refer to the General Application Instructions, Section II.C., for detailed information.
    - Budget Justification (no page limit): Upload as "BudgetJustification.pdf."

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

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

D. 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 any one of the deadlines will result in application rejection.

E. Other Submission Requirements

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

All applications must be submitted through Grants.gov. Organizations are required to provide a Data Universal Numbering System (DUNS) number and register with the Central Contractor Registry (CCR) to submit applications through the Grants.gov portal. Refer to the General Application Instructions, Appendix 3, for information on Grants.gov requirements.

III. APPLICATION REVIEW INFORMATION

A. Application Review and Selection Process

All applications are evaluated by scientists, clinicians, and consumer advocates using a two-tier review process. The first tier is a peer review of applications against established criteria for determining technical 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 technical merit, the relevance to the mission of the DoD and NFRP and 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 review 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. Each level of review requires panelists to sign a non-disclosure 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, 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 Criteria

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**
     - How relevant the anticipated outcomes of the proposed clinical trial are to individuals with NF.
     - How well the sample population represents the targeted patient population that might benefit from the proposed intervention.
     - How the potential outcomes of the proposed clinical trial will provide/improve the short-term benefits for individuals with NF.
     - How significantly the long-term benefits for implementation of the intervention may impact patient care and/or quality of life.
   - **Intervention**
     - Whether there is evidence of support, indicating availability of the intervention from its source, for the duration of the proposed clinical trial (if applicable).
     - To what degree the intervention addresses the clinical need(s) described.
     - To what degree the PI has provided preclinical and/or clinical evidence to support the safety of the intervention.
     - How the intervention compares with currently available interventions and/or standards of care.
     - Whether a member of the study team holds the IND/IDE and whether the timeline proposed for IND/IDE application is appropriate (if applicable).
     - For investigator-sponsored INDs, whether there is institutional support to serve as a sponsor and whether they are equipped to assume the monitoring required by the FDA.
   - **Research Strategy**
     - How well the scientific rationale for testing the intervention is supported by the preliminary data, critical review and analysis of the literature, and/or laboratory/ preclinical evidence.
     - How well the study aims, hypotheses or objectives, experimental design, methods, data collection procedures, and analyses are designed to clearly answer the clinical objective.

- How well the inclusion and randomization criteria meet the needs of the proposed clinical trial.
- How well the exclusion criteria are justified.

- **Recruitment, Accrual, and Feasibility**
  - How well the PI addresses the availability of human subjects for the clinical trial and the probability of their participation.
  - Whether the PI has demonstrated access to the proposed human subjects population.
  - The degree to which the recruitment, informed consent, screening, and retention processes for human subjects will meet the needs of the proposed clinical trial.
  - How well the application identifies possible delays (e.g., slow accrual, attrition) and presents adequate contingency plans to resolve them.
  - To what extent the proposed clinical trial might affect the daily lives of the individual human subjects participating in the study (e.g., Will human subjects still be able to take their regular medications while participating in the clinical trial? Are human subjects required to stay overnight in a hospital?).
- **Ethical Considerations**
  - How the level of risk to human subjects is minimized and whether there is sufficient evidence of a monitoring plan that is appropriate for the level of risk.
  - How well the evidence shows that the procedures are consistent with sound research design and, when appropriate, that these procedures are already in use for diagnostic or treatment purposes.
  - To what degree privacy issues are appropriately considered.
  - To what degree the process for seeking informed consent is appropriate and whether safeguards are in place for vulnerable populations.
- **Statistical Plan and Data Analysis**
  - How the statistical plan, including sample size projections and power analysis, is adequate for the study and all proposed correlative studies.
- **Transition Plan**
  - Whether the funding strategy described to bring the outcome(s) to the next level of clinical trials and/or delivery to the commercial market is appropriate.
  - Whether appropriate collaborations and other resources for providing continuity of development are established and/or well described.
  - How the schedule and milestones for bringing the outcome(s) to clinical trial and/or delivery to the commercial market is appropriate.

- How well the potential risk analysis for cost, schedule, manufacturability, and sustainability is developed.
- How well the application identifies intellectual property ownership, describes any appropriate intellectual and material property plan among participating organizations (if applicable), and addresses any impact of intellectual property issues on product development and subsequent Government access to products supported by this Program Announcement/Funding Opportunity.

- **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.

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

2. **Programmatic Review:** To determine the application's relevance to the mission of the DoD and NFRP, as well as to make funding recommendations, the following equally considered criteria are used by programmatic reviewers:
    - Adherence to the intent of the award mechanism
    - Program portfolio composition, with consideration of the FY12 Areas of Emphasis
    - Programmatic relevance
    - Ratings and evaluations of the peer reviewers
    - Relative impact

C. Recipient Qualification

Refer to the General Application Instructions, Appendix 1, for additional information on organization and Government agency requirements.

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 notification of the funding recommendation. Each PI will receive a scientific peer review summary statement on the strengths and weaknesses of the application.

IV. 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:

- Pre-application is not submitted.
- 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 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, the PI may be contacted by CDMRP via email with a request to provide certain missing supporting documents (excluding those listed in Section IV.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:

- A FY12 NFRP 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 document. A list of the FY12 NFRP IP members can be found at http://cdmrp.army.mil/nfrp/panels/panels12.
- 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 Research & Related Budget exceed the maximum allowed by this Program Announcement/Funding Opportunity.
- Inclusion of URLs, with the exception of links in References Cited and Publication and/or Patent Abstract sections.
- Page size is larger than 8.5 inches x 11.0 inches (approximately 21.59 cm x 27.94 cm).
- Inclusion of any employee of CDMRP review contractors in applications for funding without adequate plans to mitigate conflicts of interest. Refer to the General Application Instructions, Section II.B., for detailed information.
- The proposed research is not a clinical trial.
- The PI does not meet the eligibility criteria.

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 U.S. Army Medical Research Acquisition Activity (USAMRAA) Contracting/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, 2013. Refer to the General Application Instructions, Appendix 4, for additional award administration information.

B. Administrative and National Policy Requirements

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

C. Reporting

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

Quarterly technical progress reports will be required.

D. Award Transfers

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.

Refer to the General Application Instructions, Appendix 4, Section F, 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 the CDMRP eReceipt System 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: 1-301-682-5507

Email: help@cdmrp.org

B. Grants.gov Contact Center

Questions related to application submission through the 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: 1-800-518-4726

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.

VII. 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 Lay Abstract (LayAbs.pdf) as Attachment 4.	
	Upload Statement of Work (SOW.pdf) as Attachment 5.	
	Upload Human Subject Recruitment and Safety Procedures (HumSubProc.pdf) as Attachment 6.	
	Upload Intervention (Intervention.pdf) as Attachment 7.	
	Upload Data Management (Data_Manage.pdf) as Attachment 8.	
	Upload Study Personnel and Organization (Personnel.pdf) as Attachment 9.	
	Upload Surveys, Questionnaires, and Other Data Collection Instruments, if applicable Upload (Surveys.pdf) as Attachment 10.	
	Upload Impact Statement (Impact.pdf) as Attachment 11.	
	Upload Transition Plan (Transition.pdf) as Attachment 12.	
	Upload IND/IDE Documentation (IND-IDE.pdf) as Attachment 13.	
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.	
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.	