Program Announcement

Department of Defense Congressionally Directed Medical Research Programs

Neurofibromatosis Research Program

Clinical Consortium Award

Funding Opportunity Number: W81XWH-11-NFRP-CCA
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), June 22, 2011
- **Invitation to Submit an Application:** by July 13, 2011
- **Application Submission Deadline:** 11:59 p.m. ET, September 15, 2011
- **Scientific Peer Review:** October 2011
- **Programmatic Review:** December 2011

New for fiscal year 2011 (FY11): The Grants.gov Research & Related Budget form is a mandatory component of all Grants.gov application packages.

TABLE OF CONTENTS

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 FY96 through FY10 totaled $214.05 million (M). The FY11 appropriation is $16.0M.

FY11 NFRP Vision: The vision of the FY11 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 NF which includes NF1, NF2, and Schwannomatosis

Areas of Encouragement: The FY11 NFRP encourages research applications 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/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 award. For more guidance on data sharing, refer to the General Application Instructions, Appendix 4.

B. Award Information

The NF Clinical Consortium Award mechanism was first offered in FY06. Two applications were received and one was funded.

The FY11 NFRP Clinical Consortium Award is intended to support a major goal/product-driven Consortium of exceptional institutions and investigators that will accelerate the clinical translation of basic NF research and ultimately decrease the impact of the disease. The objectives of the Consortium shall be to conceive, design, develop, and conduct collaborative Phase I and II clinical evaluations of promising therapeutic agents for the management or treatment of NF1 and NF2.

General Information

The NF Clinical Consortium is to be a collaboration of multiple organizations and individuals for the purpose of rapidly executing clinical trials. The Consortium must consist of a single Operations Center and a minimum of five Clinical Trial Sites with a demonstrated history of collaborative research. The participants will be jointly responsible for prioritizing, proposing, conducting and analyzing Phase I and Phase II clinical trials focused on NF1 and NF2 therapeutic interventions.

The Operations Center and associated Clinical Trial Sites must apply to this announcement through a single application submitted by the Operations Center. The Operations Center may also serve as a trial site. A single award will be made to the Operations Center. Award funds will be used to support the Operations Center's efforts as well as Consortium-associated studies at each of the Clinical Trial Sites. The Operations Center will provide management and funding through the appropriate subcontract or other instruments for the Clinical Trial Sites.

Award selection will depend upon evaluation of the proposed plans for initial clinical trials to be implemented, available capabilities, organization of the Consortium, and feasibility of the collective group to accomplish the overall award objectives (see Section III.B). During the performance period of the award, the Operations Center and all Clinical Trial Sites will be responsible for working collaboratively to identify new clinical trials for implementation by the Consortium.

The NFRP is allocating a total of $9M in support of the Consortium. The Consortium will be funded initially for a total of $5M with allocations from the FY11 NFRP congressional appropriation. Two additional option periods, to be included in the application, will be funded for a total of $2M each, subject to receipt of future congressional appropriations. See Section I.D. for additional information. There also exists the possibility of expanding the Consortium, contingent on receipt of sufficient future congressional appropriations. Therefore, a supplemental research plan that is within the scope of work of the Consortium will be requested during the period of performance of the award to allow for expansion (i.e. additional clinical trials and/or more clinical sites) of the Consortium should additional funds be allocated by the NFRP. The NFRP concept for this NF Clinical Consortium is that, following the initial award period of 5 years, the Consortium will be an ongoing, self-sustaining entity.

1. Consortium Structure:

Operations Center

The Consortium shall consist of one central Operations Center that will be responsible for facilitating the rapid selection, design, execution and analysis of clinical trials within the Consortium, and will provide the administrative, protocol development and review, regulatory, statistical, resource, and data management/storage functions necessary to facilitate Consortium clinical trials in a timely manner. The Operations Center must contain multidisciplinary expertise and extensive experience in developing and conducting multi-institutional clinical trials of treatment approaches in support of NF research.

The Principal Investigator (PI) of the Consortium must be located at the Operations Center and must provide evidence of prior experience with the design and administration of multi-institutional clinical studies. The PI must also demonstrate a broad understanding of research, including knowledge of the current state of clinical studies and clinical priorities related to the NFRP Areas of Encouragement. It is expected that there be a succession plan provided to account for any unforeseen change in the Consortium PI.

The application should identify and describe core facilities (i.e. pathology, radiology, etc.) available at the Operations Center and at any member organizations that will serve as official Consortium research core facilities.

Clinical Trial Sites

The Consortium shall consist of a minimum number of five Clinical Trial Sites necessary to effectively participate in multiple trials. All sites must be identified and have clinical trials experience and multidisciplinary expertise in supporting NF1 and/or NF2 clinical research. The exact number of sites is to be proposed by the applicant and inclusion as a Clinical Trial Site must be based on factors including:

- Lead Site PIs' commitment to and experience in NF clinical research. It is expected that there be a succession plan provided to account for any unforeseen change in the Lead Site PI;
- Evidence of multidisciplinary clinical and/or laboratory expertise within the institution that could serve as the basis for the development of clinical protocols by the Consortium;
- Demonstration of adequate resources for coordinating with the Operations Center and other sites;
- Demonstration of adequate resources and expertise for data management, and maintenance of data security/confidentiality;
- Evidence of institutional commitment to using facilities and resources in the conduct of Consortium studies as required;
- Documentation of procedures to resolve intellectual and material property issues;

- Demonstration of adequate resources and expertise in NF patient recruitment and processing, including specimen collection;
- Ability to enroll at least 10-12 evaluable individuals with NF1 or NF2 per year into Consortium-sponsored studies per site

Additional competencies of proposed sites may be identified and justified as being essential to the success of the Consortium.

Steering Committee

Collectively, each Clinical Trial Site PI and Operations Center PI will constitute the Consortium Steering Committee, which will be responsible for proposing and conducting Phase I and II clinical evaluations of promising therapeutic agents for the management or treatment of NF, and for determining which Consortium Trial Sites will participate in each study. The Operations Center staff will be responsible for facilitating and coordinating this process.

External Advisory Board

The United States Army Medical Research and Materiel Command (USAMRMC) will appoint members to an External Advisory Board (EAB) that will be comprised of selected members of the NFRP Integration Panel (IP) and additional ad hoc representatives (as needed). The role of the EAB will be to advise the NFRP regarding Consortium progress and activities. The Consortium must present written and/or oral annual briefings to the EAB and USAMRMC staff at 1-day meetings, typically held in the Baltimore, MD/Washington, DC area.

2. Proposed Clinical Trials:

Applications must include letters of intent for conducting a **minimum of four clinical trials including at least one NF1- and one NF2-focused study** during the performance period of the award. Two of these studies must be initiated during the first year of the award. Proposed studies should include a range of scope, size, and type that is representative of the overall goals of the Consortium and needs of the NF community. **Clinical trials that include an adult patient population are encouraged.**

The Operations Center will be responsible for coordinating an external scientific peer review of all clinical trial protocols proposed for funding. The results of each review will be provided to the NFRP for final approval and release of funds to commence the clinical trial(s).

In addition to clinical trials proposed as part of the FY11 NFRP Clinical Consortium application submission, the Consortium is encouraged to submit additional applications to the NFRP when additional funding opportunities are announced. Funding from additional sources including industry, private sector, and other federal organizations is also encouraged.

3. Summary of Responsibilities:

Responsibilities of all Consortium Participants: Procedures for the Consortium, while proposed by the Operations Center staff, should be fully developed and agreed upon by all

participants working collaboratively. The process shall be codified in a Manual of Operations or Standard Operating Procedures document, which will be provided with the application.

Consortium Operations Center will:

- Provide the PI for the Consortium who will be the primary liaison with the Grants Officer Representative (GOR)/Science Officer (SO);
- Ensure that the Consortium adheres to the planned timeline and milestones for overall study execution;
- Manage the Consortium organizational structure;
- Manage Consortium-developed procedures for external scientific review, prioritization, and implementation of clinical studies proposed by or through Consortium members;
- Manage procedures to ensure that all sites maintain compliance with local Institutional Review Boards (IRBs) and the USAMRMC Human Research Protection Office (HRPO) for the proper conduct of clinical studies and the protection of human subjects;
- Provide a Consortium Clinical Research Manager who will oversee the efforts of the Research Coordinators at each of the Clinical Trial Sites. The Consortium Clinical Research Manager will be responsible for coordinating and facilitating clinical protocol approval, patient accrual, and study activities across all sites;
- Ensure that all investigators are U.S. Food and Drug Administration (FDA) registered to use Investigational New Drugs (INDs); and manage procedures for ensuring compliance with FDA requirements for investigational agents, devices, and procedures;
- Manage a communications plan and a real-time communications system between the Operations Center and Clinical Trial Sites;
- Manage standardization and, when appropriate, centralized review of imaging, histopathology, neuropsychological, and other data through committees and scientific core facilities;
- Manage Consortium-developed quality assurance and quality control mechanisms for study monitoring, including but not limited to:
    - On-site monitoring program (to include safety)
    - Management plan for the handling, distribution, and banking of specimens and imaging products generated from Consortium studies
    - Registration, tracking, and reporting of participant accrual
    - Timely medical review, rapid reporting and communication of adverse events as well as establishment of a safety committee to provide timely analysis of adverse events
    - Interim evaluation and consideration of measures of outcome
- Manage Consortium-developed comprehensive data collection and data management systems that address the needs of all Clinical Trial Sites in terms of access to data, data security, and data integrity measures;
- Implement statistical execution plans/support for all Consortium clinical studies;

- Manage costs to support the Clinical Trial Sites, including provision of personnel, equipment, and materials required to conduct approved clinical studies;
- Manage Consortium-developed intellectual and material property issues among organizations participating in the Consortium;
- Manage Consortium-developed procedures for the timely publication of major findings and other public dissemination of data;
- Coordinate the preparation of written and/or oral yearly briefings to the EAB and USAMRMC staff at 1-day meetings to be held in the Baltimore, MD/Washington DC area.
- Develop, organize, and submit quarterly written progress reports, annual reports, and a final written comprehensive report to the USAMRMC.

Clinical Trial Sites will:

- Designate a lead site PI, and develop a succession plan in case of departure of the site PI; the site PI must participate fully in the Consortium Steering Committee;
- Identify potential studies and develop proposals in accordance with the Consortium Standard Operating Procedure (SOP) for consideration for funding by the NFRP during the performance period of the award;
- Collaborate with other Consortium Clinical Trial Sites;
- In accordance with Consortium-developed guidelines, maintain a minimum combined accrual across all Consortium-associated studies, as well as a maximum contributed percentage for each individual study in accordance with Consortium-developed guidelines;
- Provide a Clinical Research Coordinator who will interact with the Clinical Research Coordinators of other Clinical Trial Sites and the Consortium Clinical Research Manager at the Operations Center to expedite and guide clinical protocols through regulatory approval processes, and to coordinate patient accrual and study activities across sites;
- Implement the Consortium's core data collection methodology and strategies;
- Comply with Consortium-developed quality assurance and quality control procedures, as appropriate, including:
    - Participation in an on-site monitoring program to be managed by the Operations Center
    - Implementation of the Consortium-developed management plan for acquisition and aggregation of protocol-specified specimens, biological fluids, and relevant clinical data to the appropriate laboratories for testing or storage necessary for the conduct and analyses.
    - Submission of appropriate data and materials to allow for verification and review of protocol-related procedures (e.g., pathology, imaging techniques, surgical methods, and therapeutic use)

- Implement procedures established by the Operations Center for ensuring compliance with FDA requirements for investigational agents, as appropriate;
- Implement procedures established by the Operations Center to meet local IRB and USAMRMC HRPO requirements for the conduct of clinical trials and the protection of human subjects;
- Serve as a resource or core for the conduct of protocol-specified laboratory projects (including correlative studies), as appropriate;
- Participate in Consortium-developed procedures for the timely publication of major findings;
- Participate in Consortium-developed procedures for resolving intellectual and material property issues among organizations participating in the Consortium;
- Participate in the preparation of written and oral yearly briefings to the EAB and USAMRMC staff at 1-day meetings to be held in the Baltimore, MD/Washington DC area.
- Assist with the preparation of quarterly written progress reports, annual reports, and a final comprehensive report;
- Prepare for a site visit audit, if requested by the NFRP.

4. Performance Metrics: Applicants must provide a plan for the number and types of clinical studies the Consortium expects to execute. As a preliminary guideline, the Consortium should be prepared to execute a minimum of 4 clinical trials during the performance period of the award, depending upon the size and complexity of each study. Within the first year of the performance period, at least one NF1- and one NF2-focused study must have been initiated. A timeline outlining the overall plan for study initiation, performance, and analyses shall be developed, with clear milestones to which the Consortium will be held accountable. The Consortium Steering Committee will determine appropriate overall minimum and maximum accrual metrics for the Clinical Trial Sites per trial as part of the Consortium SOP. It is anticipated that at a minimum, each Clinical Trial Site will have the ability to enroll at least 10-12 evaluable individuals with NF1 or NF2 per year into Consortium-sponsored studies. For individual clinical studies, the Operations Center should ensure the maintenance of overall patient accrual per year, appropriate for the target population. The Consortium SOP should also contain a plan to address underperforming sites, and a succession plan for any unforeseen change in the lead PI. The Operations Center will be required to submit quarterly and annual written reports that outline accrual and retention statistics, any problems with study execution, and actions to disseminate study results.

5. Oversight of the Consortium: An EAB comprised of government and non-government personnel will be appointed by the USAMRMC. The EAB will provide recommendations to the NFRP regarding progress and proposed Consortium studies prior to implementation, and it may recommend future studies to the Consortium. The Consortium must present written and oral briefings to the EAB and USAMRMC. Based on these reports and presentations, the EAB will advise the GOR. USAMRMC staff will evaluate progress, provide feedback, and invoke modifications as needed to facilitate the success of the Consortium. The Consortium Steering Committee, through the Operations Center PI, will be expected to maintain monthly or more

frequent contact with a government appointed GOR/SO. The US Army Medical Research Acquisition Activity (USAMRAA) Grants Officer will issue final approvals to release funds for initiation of any proposed clinical trial.

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 USAMRMC Office of Research Protections (ORP), 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 4 months for HRPO regulatory review and approval processes. Refer to the General Application Instructions, Appendix 5, for more information.

C. Eligibility Information

- The Operations Center PI must be an independent investigator at or above the level of Associate Professor (or equivalent) at an eligible organization.
- Cost sharing/matching is not an eligibility requirement.
- Refer to the General Application Instructions, Appendix 1, for general eligibility information.

D. Funding

A single award to the Operations Center applicant will be made to support the FY11 NFRP Clinical Consortium. The Operations Center will provide funding support for the selected Clinical Trial Sites as subawards or other appropriate contracting instrument.

All applicants are to propose a minimum of four clinical trials in letters of intent to address at least 1 NF1- and 1 NF2-focused trial that must be initiated in the first year of the award. Proposed studies should include a range of scope, size, and type that is representative of the overall goals of the Consortium. Budget out-years should be projected based on the proposed costs of the initial studies, with appropriate escalation factors included. Provide an estimated budget for each trial using the R&R Subaward Budget Attachment Form. Following award, a budget for each study will be negotiated individually once study selections are made.

- The maximum period of performance is **5** years.
- The maximum allowable total costs for the entire period of performance is **$9M**, of which only **$5M** is currently available.
- The applicant may request up to $5M in total costs for the full proposed period of performance (up to 5 years) to cover Operations Center costs, Consortium activities, and clinical trials. This will be funded using allocations from the FY11 NFRP congressional appropriation. A budget for the Operations Center should be submitted using the SF424 Research & Related Budget Form. Separate budgets for each clinical

trial should be submitted using R&R Subaward Budget Attachment Forms. The total for this segment must not exceed $5M in total costs.

- In addition, the applicant may request two option periods of up to $2M in total costs each, to fund additional clinical trials and associated Operations Center costs and Consortium activities. Funding for these option periods is contingent upon receipt of future congressional appropriations. A budget for the Operations Center and budgets for each clinical trial should be shown on separate R&R Subaward Budget Attachment Forms. The total for these two option periods must not exceed $4M in total costs. Also, these option periods, if funded, are to be conducted within the maximum period of performance (up to 5 years).
- Regardless of the period of performance proposed, the applicant may not exceed the maximum allowable total costs. Indirect costs shall be proposed in accordance with the organization's negotiated rate agreement.

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

May be requested for (not all-inclusive):

- Salary support;
- Implementation of Consortium-developed standardization plan, data management program, real-time communications system, and administration plans for the Consortium;
- Support of Consortium-related meetings, teleconferences, and travel among participating investigators;
- Costs associated with the external scientific peer review of clinical studies/research;
- Purchase of computers, specialized software, and specialized software licenses for Clinical Study Sites when required to fulfill Operations Center-specific tasks;
- Purchase of minor equipment necessary for specimen collection and data storage and transfer;
- Costs associated with using Consortium Core facilities;
- Costs associated with conducting the IRB review of the clinical protocols and informed consent/assent forms;
- Research-related subject costs;
- Clinical research costs;
- Costs associated with the supply or availability of intervention(s);
- Other costs directly associated with planning and developing the Consortium;
- Travel costs of up to $3,600 per year to attend scientific/technical meetings.

The PI must also include funds for travel to yearly 1-day briefings with the EAB and USAMRMC staff.

Direct transfer of funds to a government organization or agency is not allowed except under very limited circumstances and is subject to prior Grants Officer approval. **Funds provided through this award may not be used to support government salaries.** Details on exceptions to the prohibition of direct fund transfer to government entities can be found in Section II.C.4.K (Federal Agency Financial Plan) of the General Application Instructions.

The Office of the Congressionally Directed Medical Research Programs (CDMRP) expects to allot approximately $5M of the $16M FY11 NFRP appropriation to fund approximately 1 Clinical Consortium Award application, 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 discouraged. The Government reserves the right to 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-11-NFRP-CCA.

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/). Because the invitation to submit an application is based on the contents of the pre-application, investigators should not change the title or research objectives after the pre-application is submitted.

PIs and organizations identified in the 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 CDMRP Help Desk at help@cdmrp.org or 301-682-5507. Changes will only be allowed under extenuating circumstance.

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 (COI) – Tab 3**
- **Required Files – Tab 4**

  Preproposal Narrative (five-page limit): The Preproposal Narrative page limit applies to text and any figures, tables, graphs, photographs, diagrams, chemical structures, pictures, pictorials, and cartoons.

  The Preproposal Narrative should include the following:

  - **Overarching Goals:** Provide a brief description of the overall goals of the Consortium in the clinical evaluations of promising therapeutic agents for the management or treatment of NF1 and NF2.
  - **Consortium Structure:** Outline the organizations that will participate in the Consortium. Briefly discuss the qualifications of key personnel in the administration and conduct of multi-institutional clinical studies. Discuss potential core facilities, shared resources, and other elements of the Consortium that will promote synergy.
  - **Research Plan:** Provide a brief description of the initial clinical studies to be proposed. Identify the NFRP Clinical Consortium Award Area(s) of Encouragement relevant to each study. Describe the reasoning on which the studies are based, the target patient population(s), and the outcomes to be measured. Include a table and description of potential pharmaceuticals to be used in the proposed clinical trials which should include:
    - Stage of development, indication in NF1 and/or NF2, the sites involved in conducting the clinical trial, and the state of each intervention's IND status, if applicable.

  Pre-Application Supporting Documentation: The items to be included as supporting documentation for the pre-application are limited to:

  - References Cited: List 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.
  - Key Personnel Biographical Sketches (four-page limit per individual)

- **Submit Pre-application – Tab 5**
- **Other Documents Tab**

  No additional documents are required**.**

Pre-Application Screening

- **Pre-Application Screening Criteria**

  To determine the technical merits of the pre-application and the relevance to the mission of the DOD and CDMRP, pre-applications will be screened based on the following criteria:

  - **Overarching Goals:** How well the overarching goals of the Consortium will have an impact on the clinical evaluation of promising therapeutic agents for the management or treatment of NF1 and NF2.
  - **Consortium Structure:** How well the outlined Consortium structure will support timely and efficient multi-institutional clinical trials of varying scope and size. The appropriateness of the administrative and research teams' background and expertise with respect to clinical evaluations of promising therapeutic agents for the management or treatment of NF.
  - **Research Plan:** How well the proposed initial studies align with the NFRP Clinical Consortium Award's goals. The degree to which the proposed studies address important questions that will further the clinical approaches for the management or treatment of NF.

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

  Following the pre-application screening, PIs will be notified by e-mail of whether or not they are invited to submit an application; however, they will not receive feedback (e.g., a critique of strengths and weaknesses) on their pre-application.
  Pre-application notification dates are indicated on the title page of this Program Announcement/Funding Opportunity.

C. Application Submission Content and Form

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

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

Grants.gov application package components: For the NFRP Clinical Consortium 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**

   - **Attachment 1: Project Narrative (70-page limit):** Upload as "ProjectNarrative.pdf."

Describe the key features of the Consortium in detail using the outline below.

- **Overall Structure and Goals:** Identify the major gaps in the field that the Consortium seeks to address. Describe the broad research goals of the Consortium and how the Consortium structure is suited to meet its goals. Identify all proposed sites, ad hoc sites, and future potential sites. Include descriptions of any committees and/or working groups. Reference and include Consortium Standard Operating Procedures/Manual of Operations and By-laws in Attachment 8.
- **Operations Center Expertise and Resources**
  - Describe the previous experience of the Operations Center, the PI, and key personnel with the design, administration, and day-to-day management of multi-institutional clinical studies.
  - Describe a succession plan for the Operations Center PI and lead PIs for the Clinical Trial Sites.
  - Describe information technology infrastructure and resources necessary to coordinate and implement proposed trials, and a plan for making those resources available.
  - Describe key core facilities and resources available to support Consortium-initiated clinical trials.
  - Describe plans for addressing human subject protection requirements as described by HRPO, and coordinating IRB submissions and approvals at participating sites.
  - Describe plans for oversight and coordination of Clinical Trial Sites. Include relevant personnel and organizational experience with implementing multi-institutional real-time communications.
  - Describe Site Performance monitoring plans, including strategies to deal with sites with low performance and missed patient recruitment goals.
- **Clinical Trial Site(s) Expertise and Resources**
  - Identify current, ad hoc and potential future Clinical Trial Site(s) and describe previous experience of key personnel at each site with the development and conduct of clinical studies, specifically any multi-institutional clinical trials that demonstrate past experience and willingness to participate in the Consortium.
  - Describe any site-specific areas of clinical research interest or expertise, such as novel drugs, surgical interventions, and imaging techniques. Include a description of the multi-disciplinary capabilities of each site**.**
  - Describe the patient populations at each current and potential future Clinical Trial Site, and elaborate on the ability to enroll adequate patient numbers into Consortium-sponsored studies. Provide an estimate of case enrollment/patient load and the track record of research in this area for each Clinical Trial Site and each Site PI.

- Describe the resources and expertise available within each Clinical Trial Site for the care of NF1 and/or NF2 patients.
- Describe the resources and expertise of each participating Clinical Trial Site for data management and maintenance of data security/confidentiality.
- Describe the previous experience of conducting multi-institutional trials.

- **Clinical Trial Development and Implementation:** Include a projection of the types of clinical trials to be conducted by the Consortium over the entire award period. Outline a plan for the conceptualization, design, development, and prioritization of potential future Consortium trials for implementation. Include a mechanism for determining Clinical Trial Site participation. Describe plans for coordinating the submission, review, and implementation of clinical trials within the Consortium. Include plans for appropriate approvals/clearances from the FDA, when applicable.
- **Study Management and Monitoring:** Describe plans for real-time communication among all organizations participating in the Consortium (including the rapid dissemination of adverse events). Include a named Consortium Clinical Research Manager who will interact with other individual Clinical Trial Site research coordinators to guide clinical protocols through the regulatory approval processes, coordinate participant accrual, and coordinate study activities across sites. Outline procedures for quality assurance, quality control, safety, and study monitoring, including an independent safety oversight group to invoke stopping rules as necessary after defined adverse events.
- **Specimen Handling and Distribution:** Describe plans and methods for the handling, distribution, analysis, banking, and security of any specimens and/or imaging products generated from Consortium-sponsored studies.
- **Fiscal Administration:** Describe previous experience with the financial management of multi-institutional clinical research studies. Outline a strategy for achieving financial self-sufficiency of the Consortium after the end of the performance period for the Clinical Consortium Award. Describe any plans to leverage existing clinical or translational funding programs and infrastructure for the proposed Consortium.

- **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 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 at the Operations Center and each Clinical Trial Site for performance of the proposed project, and any additional facilities or equipment proposed for acquisition at no cost to the award. Indicate if Government-owned facilities or equipment are proposed for use. Reference should be made to the original or present contract/assistance agreement under which the facilities or equipment items are now accountable. There is no form for this information.
- Publications and/or Patent Abstracts: Include relevant publication URLs and/or patent abstracts. If publications are not publicly available, then they must be included.
- Letters of Organizational Support: Provide a letter from the Operations Center and each Clinical Trial Site signed by the Department Chair or appropriate organization official, reflecting the laboratory space, equipment, and other resources available for the project.
- Letters of Collaboration: Provide a signed letter from each Clinical Trial Site PI that will demonstrate that the proposed Consortium has the support or resources necessary for the proposed work.
- Intellectual and Material Property Plan: Provide a plan for resolving intellectual and material property issues among participating organizations.

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

  Technical abstracts should be written using the outline below.

  - Background: Describe the general management and organizational structure of the Consortium. Outline the management and clinical expertise of Consortium personnel at the Operations Center and Clinical Trial Sites.
  - Objectives: Describe the Consortium's overall clinical research goals and agenda.
  - Research Plan: Briefly describe the clinical studies the Consortium plans to pursue during the performance period. State how the proposed projects address the NFRP Clinical Consortium Award Areas of Encouragement.

- **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 clinical objectives and rationale for the application.
    - Do not duplicate the technical abstract.
  - Describe the ultimate applicability of the Consortium's clinical research.
    - What types of patients will it help, and how will it help them?
    - What are the potential clinical applications, benefits, and risks?
    - What is the projected time it may take to achieve a clinically relevant outcome?

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

- **Attachment 5: Statement of Work (SOW) (ten-page limit):** Upload as "SOW.pdf." Refer to the General Application Instructions, Section II.C., for detailed information.
- **Attachment 6: Clinical Trial Letters of Intent:** Upload as "Trials.pdf." Include Letters of Intent for a minimum of four clinical trials addressing at least one NF1- and one NF2-focused study for implementation by the Consortium within the first year of the performance period. Each trial plan must include the following:
  - **Research Idea:** For each proposed clinical trial, describe the ideas and reasoning on which it is based, and how the study addresses a central problem in NF1 or NF2.
  - **Research Strategy:** Concisely state each clinical trial's objectives and specific aims. Describe the patient populations and study sites that will be utilized for each study. Include recruitment goals and timelines for study implementation. Define study endpoints and outcomes, and the probability that each described trial will have sufficient power with the suggested patient accrual to answer the study questions within the defined time period of trial execution.
  - **Clinical Impact:** Briefly describe how the proposed clinical trial will have an impact on NF patient treatment, quality of life, or patient care.
- **Attachment 7: Data Management Plan:** Upload as "DataPlan.pdf." Provide a data management plan that includes: (1) Descriptions of the overall approach to data collection and management, (2) a statistical plan that includes methods to monitor quality and consistency of data collection, and methods to measure outcomes, (3) a plan for real-time data transfer, and (4) data security measures.
- **Attachment 8: Manual of Operations and By-Laws:** Upload as "Manual.pdf." Provide a copy of a Manual of Operations or SOPs by which the Consortium will operate. Also include documents that describe governance and guidelines by which the Consortium membership operates.
- **Attachment 9: Data and Research Resources Sharing Plan:** Upload as "DataSharing.pdf." Describe how data and resources generated during the performance period of the project will be shared with the research community. Refer to the General Application Instructions, Appendix 4, for more information about the CDMRP's expectations for making data and research resources publically available.

3. **Research & Related Senior/Key Person Profile (Expanded) Form:** 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. Use this form to provide individual clinical trial budgets and option year budgets.

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 shall 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 Number 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 CDMRP, 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, 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. 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:

   - **Consortium Structure and Goals**
     - How well the overarching goals of the Consortium will have an impact on the clinical evaluation of promising therapeutic agents for the management or treatment of NF1 and NF2.
     - To what extent the proposed overall organizational structure of the Consortium is appropriate to rapidly develop and implement clinical trials for NF1 and NF2.
     - How well the Operations Center addresses a plan to oversee and coordinate all Consortium Clinical Trial Sites.
     - How well the Operations Center and each Clinical Trial Site will function as an integrated unit.
     - To what degree the appropriate resources are provided for full participation at each Consortium Site.
   - **Operations Center Expertise and Resources**
     - To what extent the Operations Center's experience, track record, and expertise are appropriate with respect to the ability to manage and oversee multi-institutional NF clinical studies.
     - How well the plan for the establishment and maintenance of core facilities and other resources will effectively support Consortium activities.
     - The degree to which the information technology and real-time communications capabilities are appropriate.
     - To what extent the plans for addressing human subject protection requirements as described by HRPO and coordinating IRB submissions and approvals at participating sites are appropriate.
     - The degree to which the ability and experience of the organization with the financial management of multi-institutional research studies is appropriate.

- **Clinical Trial Site(s) Expertise and Resources**
    - To what extent the research teams' background, track record, and expertise at each Clinical Trial Site are appropriate with respect to the successful conduct of NF studies and participation in multi-center clinical studies.
    - Whether the organizations have demonstrated access to appropriate patient populations for conduct of Consortium clinical studies.
    - How the facilities and resources within each Clinical Trial Site are appropriate for NF patients.
    - How the resources and expertise at each organization are appropriate for data management and coordination of specimen collection and processing.
- **Clinical Trial Development and Implementation**
    - The degree to which plans for conceptualization, design, development, and prioritization of clinical trials within the performance period are appropriate.
    - How well appropriate plans for developing procedures to ensure compliance with FDA regulations for investigational agents are considered.
    - How well the planned trials address the NFRPs Areas of Encouragement.
- **Study Management and Monitoring**
    - How the plans for real-time communication among all organizations participating in the Consortium, including complete and timely reporting, review, and appropriate responses to adverse events (including suspension of a trial, modification of a trial protocol, or cessation of a trial) are appropriate to facilitate Consortium activities.
    - The extent of the named Consortium Clinical Research Manager's experience with guiding clinical protocols through the regulatory approval processes, coordinating participant accrual, and coordinating study activities across sites.
    - How the outlined procedures for quality assurance, quality control, safety, and study monitoring are adequate for conducting multi-institutional clinical studies.
    - How the plans for specimen handling, distribution, analysis, banking, and security are appropriate to facilitate Consortium activities.
- **Data Management**
    - The degree to which the overall approach to data collection, management, analysis, and security measures is appropriate.
    - How clearly the effective application of methods to monitor quality and consistency of data collection, and methods to measure outcomes in previously conducted clinical trials have been demonstrated by the PI and key personnel.
    - How the plan for real-time data transfer is adequate for supporting the Consortium-associated activities.

- **Clinical Trials**
    - The extent to which the plans for the estimated number and types of studies to be conducted during the duration of this award is appropriate and feasible.
    - How well the scientific rationale and preliminary data support each of the proposed initial study's design and objectives.
    - The degree to which the patient populations and sample size are appropriate for each proposed initial study.
    - The degree to which proposed methods and outcome measures are appropriate for the purposes of each proposed initial study.
    - The degree to which each proposed initial study makes an impact on the treatment of NF or on the quality of life of patients.

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

- **Personnel**
    - The extent to which the PI and other key personnel at the Operations Center have expertise in the design, administration, and financial management of multi-institutional NF clinical studies, including the distribution and management of funds.
    - To what extent the levels of effort are appropriate for successful conduct of the proposed work.
    - Whether Consortium personnel at the participating Clinical Trial Sites have appropriate training, experience, and expertise in NF1 clinical research/trials, particularly Phase I and II clinical trials and multi-institutional studies.
    - The qualifications of the Consortium Clinical Research Manager who will interact with all Clinical Trial Site Research Coordinators to coordinate regulatory approvals and Consortium activities.
    - The extent to which all participating personnel are willing to commit adequate time, resources, and human subjects to the Consortium.
    - The extent to which members have collaborated previously in the conduct of multi-institutional clinical trials.
- **Budget**
    - Whether the budget is appropriate for the proposed research and within the limitations of this Program Announcement/Funding Opportunity.
- **Application Presentation**
    - To what extent the writing, clarity, and presentation of the application components influenced the review.

2. **Programmatic Review:** To determine the application's relevance to the mission of the DOD and CDMRP, 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
    - 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. PIs will receive a scientific peer review summary statement on the strengths and weaknesses of the application.

IV. ADMINISTRATIVE ACTIONS

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

A. Rejection

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

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

The following will result in administrative rejection of the application:

- Project Narrative exceeds page limit.
- Project Narrative is missing.
- Budget is missing.
- Clinical Trial Letters of Intent are missing.
- Submission of an application for which a letter of invitation was not received.
- Pre-application was not submitted.

B. Modification

- Pages exceeding the specified limits will be removed prior to review for all documents other than the Project Narrative and Preproposal 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 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 pre-application or application:

- FY11 NFRP Integration Panel (IP) member 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 FY11 NFRP IP members may be found at http://cdmrp.army.mil/nfrp/panels/panels11.
- 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.
- Total costs as shown on the Research and Related Budget form exceed the maximum allowed by this Program Announcement/Funding Opportunity.
- Inclusion of URLs with the exception of links to published references.
- Page size is larger than 8.5 inches x 11.0 inches (approximately 21.59 cm x 27.94 cm).

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 US 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, 2012. 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 C, for general information regarding administrative and national policy requirements.

C. Reporting

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

Quarterly technical progress reports will be required in addition to annual and final reports. Reports must be in the form of a single comprehensive report encompassing activities at the Operations Center and all Clinical Trial Sites.

In addition to written progress reports, awardees may expect requests for formal progress presentations in clinical symposia to accelerate transition into clinical practice.

D. Award Transfers

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

The Operations Center of the NFRP Clinical Consortium Award cannot be transferred to another organization. Clinical Trial Sites cannot be transferred to another organization.

E. Pre-Award Meeting

At the Government's discretion, the Consortium PI, Clinical Trial Site lead PIs, and Clinical Research Manager may be requested to participate in a pre-award meeting.

VI. AGENCY CONTACTS

A. CDMRP Help Desk

Questions related to Program Announcement/Funding Opportunity content or submission requirements and 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 Public Abstract (PublicAbs.pdf) as Attachment 4.	
	Upload Statement of Work (SOW.pdf) as Attachment 5.	
	Upload Clinical Trial Letters of Intent (Trials.pdf) as Attachment 6.	
	Upload Data Management Plan (DataPlan.pdf) as Attachment 7.	
	Upload Manual of Operations and By-Laws (Manual.pdf) as Attachment 8.	
	Upload Data and Research Resources Sharing Plan (DataSharing.pdf) as Attachment 9.	
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 form 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.	