Program Announcement

I. GENERAL INFORMATION

This program announcement is being released before the receipt of Federal funds appropriated in a bill for this program; funding of proposals received in response to this program announcement is contingent on the receipt of these funds at the United States Army Medical Research and Materiel Command (USAMRMC).

A. Title of Award: ***Neurofibromatosis Research Program (NFRP) NF Consortium Award.***

B. Program Name: Department of Defense (DOD) Fiscal Year 2006 (FY06) NFRP.

C. Funding Opportunity Number: W81XWH-06-NFRP-NFCA.

D. Agency Name: USAMRMC, Office of the Congressionally Directed Medical Research Programs (CDMRP), 1077 Patchel Street, Fort Detrick, Maryland 21702-5024.

E. Agency Contact(s)

1. Questions related to the program announcement, proposal format, or required documentation: Applicants should submit questions as early as possible. Every effort will be made to answer questions within 5 working days.

Phone:	301-619-7079
Fax:	301-619-7792
E-mail:	cdmrp.pa@amedd.army.mil
Mail:	Commander US Army Medical Research and Materiel Command ATTN: MCMR-ZB-C (NF06-NFCA) 1077 Patchel Street (Building 1077) Fort Detrick, MD 21702-5024

2. Questions related to electronic submission: A help line for questions relating to proposal submission and the CDMRP eReceipt Online Proposal Submission System is available Monday through Friday from 8:00 a.m. to 5:00 p.m. Eastern time at 301-682-5507. Help also is available on the CDMRP website or by e-mail as follows:

Website:	https://cdmrp.org (User's Guide located in upper right corner of the proposal submission website)
E-mail:	help@cdmrp.org

F. Anticipated Instrument Type(s): The USAMRMC executes its extramural research program predominantly through the award of grants and cooperative agreements. More information on these funding instruments may be obtained by request from:

Fax:	301-619-2937
E-mail:	qa.baa@amedd.army.mil
Mail:	Director US Army Medical Research Acquisition Activity ATTN: MCMR-AAA-R 820 Chandler Street Fort Detrick, MD 21702-5014

G. Catalog of Federal Domestic Assistance (CFDA) Number 12.420: Military Medical Research and Development.

H. Website to Access Application Package: Proposals must be submitted at https://cdmrp.org. This website contains all the information, forms, documents, and links needed to apply. Applicants experiencing difficulty in downloading documents should contact the CDMRP as indicated in Subsection I.E.2.

I. Award/Regulatory Approval: The applicant may not use, employ, or subcontract for the use of any human subjects, human biological substances, cadavers, or laboratory animals until applicable regulatory documents are requested, reviewed, and approved by the USAMRMC.

Applicants who are approved for funding for the FY06 NF Consortium Award may be required to attend a pre-award meeting and protocol workshop in the Baltimore, MD–Washington, DC area after notification of award status and before disbursement of funds. FY06 NF Consortium Award recipients also will be required to prepare oral and written briefings for presentation at semi-annual 1-day meetings with an External Advisory Board (EAB) and USAMRMC staff in the Baltimore, MD–Washington, DC area.

II. FUNDING OPPORTUNITY DESCRIPTION

A. Program History: The NF Consortium Award is one of the mechanisms of the Neurofibromatosis Research Program (NFRP), which was established in FY96 to promote research directed toward decreasing the impact of NF. Appropriations for the NFRP from FY96 through FY05 totaled $155.3 million (M). The FY06 appropriation is $17M. The NF Consortium Award is a new award mechanism for FY06.

B. Program Objectives: The overall goal of the FY06 NFRP is to develop effective therapies for NF1, NF2, and Schwannomatosis. Within this context, support for the training of NF researchers, the encouragement of established scientists in the field, and the attraction of new scientific expertise from other fields are essential to the NF community. Proposals to the NFRP are sought across all areas of laboratory, clinical, behavioral, and epidemiological research including all disciplines within the basic, clinical, psychosocial, behavioral, sociocultural, and environmental sciences, nursing, occupational health, alternative therapies, public health and policy, and economics. Proposals that address the needs of minority, low-income, rural, and other underrepresented and/or medically underserved populations are encouraged and may be submitted from any eligible institutional source.

C. Award Mechanism Description

1. General Information: The FY06 NFRP NF Consortium Award will support a major goal/product-driven consortium of exceptional investigators to accelerate the clinical translation of basic NF1 research and ultimately decrease the overall impact of the disease. The consortium shall conceive, develop, and conduct collaborative pilot and Phase I and II clinical evaluations of promising therapeutic agents or approaches for the management or treatment of NF1. The consortium shall include 5 to 10 participant clinical research sites with clinical trials experience and multidisciplinary expertise in supporting NF1 clinical research. The consortium also shall have a single Operations Center responsible for providing operational and data management/analysis support to implement consortium protocols in a timely manner.

Although there is also a critical need for better treatments for NF2 and Schwannomatosis, the FY06 NF Consortium Award is intended to fund an NF1 consortium. However, the funded consortium may expand to encompass NF2- and Schwannomatosis-directed studies at the discretion of its Governing Body and the USAMRMC.

As stated in the FY05 NFRP NF Consortium Development Operations Center Award and FY05 NFRP NF Consortium Development Site Award program announcements, recipients of those awards must jointly compete for the FY06 NF Consortium Award. This mechanism is also open to any group of institutions that wishes to form an NF1 clinical consortium. A ***Letter of Intent (LOI) is required*** and must be submitted by ***March 7, 2006***. All proposals must include at least one protocol for an NF1 ***therapeutic*** clinical trial (i.e., not a natural history study protocol) and associated clinical documents. Investigational New Drug (IND) and/or Institutional Review Board (IRB) approvals should be in process or completed before submission of the proposal to the NF Consortium Award mechanism. Clinical trials must begin within 6 months of the award date. If an IND or Investigational Device Exemption (IDE) is required, additional time may be granted. However, preference will be given to protocols that have US Food and Drug Administration (FDA) approval at the time the award is made. Please note that all DOD-funded research involving human subjects, human anatomical substances, and/or cadavers must be reviewed and approved by the USAMRMC Human Subjects Research Review Board (HSRRB) in addition to local IRBs.

The HSRRB has different requirements than the local IRBs. The average time to obtain HSRRB approval is approximately 6 months. Therefore, it is strongly suggested that the applicant plan the budget and timeline accordingly.

In addition to trials proposed as part of the FY06 NF Consortium Award submission, the consortium will be permitted at any time during the performance period of this award to submit additional clinical protocols for review and funding through the NFRP Clinical Trial Award mechanism and/or award mechanisms offered through other funding agencies. The NFRP Clinical Trial Award is expected to be openly competed each fiscal year pending receipt of appropriations by the NFRP. Please note that all clinical protocols funded through the NFRP Clinical Trial Award mechanism must receive local IRB and HSRRB approval before implementation by the consortium.

The NFRP anticipates that the development, submission, review, and implementation of new clinical protocols by the consortium will be carried out as follows:

- The Governing Body, which includes Principal Investigators (PIs) from each participating site, Operations Center representatives, and consumer advocates, will develop recommendations for new clinical trials based on proposals from participating sites and/or external institutions. Collaboration with institutions outside the consortium to develop and implement clinical trials is encouraged.
- The Operations Center will coordinate and oversee the development of protocols and associated clinical documents for each proposed clinical trial. All protocols and associated documents will be presented to the Governing Body for internal review and approval before submission to the NFRP and/or other funding agency. The Operations Center also will coordinate the submission of protocols and related documents for IRB approval at participating institutions.
- The Operations Center will prepare submissions to the NFRP Clinical Trial Award mechanism (pending the receipt of appropriations by the NFRP) and/or award mechanisms offered by other funding agencies.
- The Governing Body will prioritize the proposals/protocols that were recommended for funding by the NFRP Integration Panel and/or other funding agency and prepare for their implementation as funding becomes available.

After the initial 6 months of the performance period of the award, the consortium is expected to have two or more clinical trials open at any given time. In addition, the consortium is expected to present one or more clinical trials each year for consideration. Furthermore, each site should maintain accrual of 10 to 12 evaluable individuals with NF1 per year.

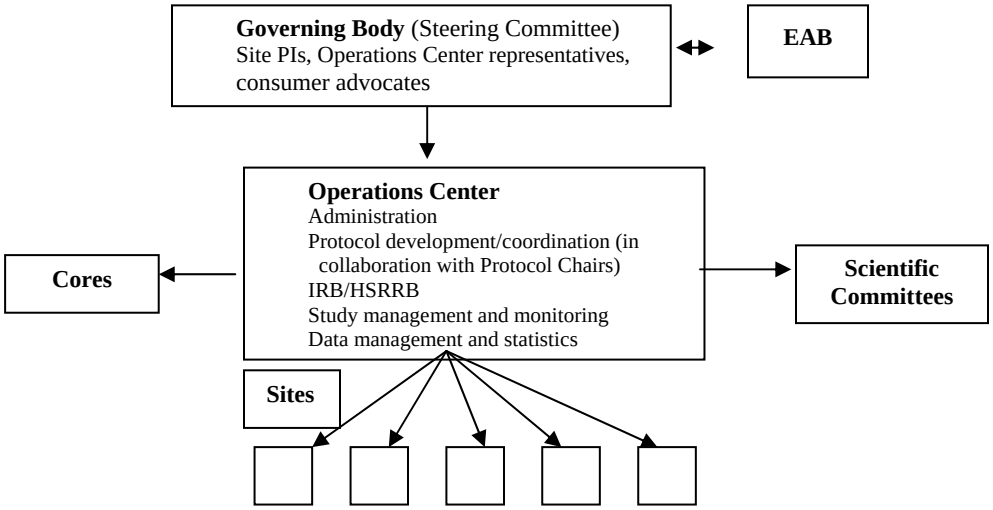
2. Oversight of the Consortium: An External Advisory Board (EAB) composed of experts in NF clinical research, neuro-oncology, and/or other relevant areas who are not involved with the consortium will provide scientific guidance and oversight. Program staff from the NFRP will appoint individuals to the EAB. The EAB may include members of the NFRP Integration Panel. The EAB Chair and a representative from USAMRMC must be invited to all meetings of the Governing Body and must be provided agendas and minutes for these meetings. PIs must present written and oral briefings to the EAB and USAMRMC staff at semi-annual 1-day meetings in the Baltimore, MD–Washington, DC area. Based on these reports and presentations, the EAB and USAMRMC staff will evaluate progress, provide feedback, and invoke modifications and terminations as needed to facilitate the success of the consortium. PIs also will be required to submit annual written progress reports and a final written comprehensive report.

To assess data collection and accuracy, each participant institution, at the discretion of the Government, may be expected to participate in an on-site audit by the Government or its designee.

Failure to achieve the minimum requirements for the consortium described in this program announcement may result in termination of this award.

3. Summary of Proposal Requirements: (See Subsection V.K for complete details.)
All FY06 NF Consortium Award proposals must include:

- Descriptions of the consortium organizational structure, including any core facilities and/or scientific committees, as depicted in the diagram below:



- A draft charter and by-laws for the consortium, which shall be maintained by the Operations Center;
- Evidence of institutional commitment(s) to the consortium;
- A comprehensive consortium management plan;
- Names, backgrounds, training, qualifications, and time availability of each participating investigator and collaborator;
- Descriptions of previous experience with multi-institutional NF1 clinical studies, particularly Phase I clinical trials;
- Demonstration of multidisciplinary clinical and/or laboratory expertise within the participating clinical research sites;
- Descriptions of resources and expertise available within each participating clinical research site for specimen collection and processing, data management, and maintenance of data security/confidentiality;
- Description(s) of the NF1 population(s) and documentation of ability to enroll sufficient evaluable participants in consortium-sponsored studies;
    - A clinical protocol and associated clinical documents that include HSRRB-prescribed content for an NF1 ***therapeutic*** clinical trial to be conducted during the award period. Applicants are encouraged to propose more than one clinical trial or study for implementation during the award period but must (1) include clinical protocols and associated documents for ***each*** trial/study and (2) rank the trials/studies in order of priority. Separate, freestanding protocols should be generated for each site and/or task for all research that involves (a) multiple sites;

(b) multiple tasks requiring different study designs, samples, sampling procedures, or methods; and (c) inter-institutional cooperative or collaborative agreements. Please note that each project of a multi-project application will be individually evaluated for compliance with applicable regulatory requirements. Documentation of local IRB review and approval of each protocol will be required at the time of the HSRRB regulatory review for all funded proposals.

- Plans for the development and submission of additional clinical protocols and related documents to the NFRP Clinical Trial Award mechanism and/or award mechanisms offered by other funding agencies during the award period (as appropriate);
- Plans for the timely submission of consortium protocols for IRB and HSRRB review and approval;
- Descriptions of procedures for ensuring compliance with institutional IRB and HSRRB requirements for the conduct of clinical studies and the protection of human subjects;
- Descriptions of procedures for ensuring compliance with FDA requirements for investigational agents, as appropriate;
- A named Supervising Clinical Coordinator at the Operations Center;
- Named Clinical Coordinators at each participating site who will interact with the Supervising Clinical Coordinator and the Clinical Coordinators at other sites;
- A comprehensive, coordinated data management plan;
- Descriptions of quality control, quality assurance, and study monitoring procedures;
- Descriptions of methods for the handling, distribution, analysis, banking, and security of specimens and/or imaging products generated from consortium-sponsored studies;
- A plan for the timely publication of major findings and other public dissemination of data generated by consortium-sponsored studies that addresses all relevant privacy issues; and
- An intellectual and material property plan agreed upon by all participating institutions. An Intellectual/Material Property Coordinator at the Operations Center responsible for managing and resolving intellectual and material property issues among consortium institutions must be named in the proposal.

III. AWARD INFORMATION

The NFRP plans to provide $6M in direct costs to fund the NF Consortium Award, plus indirect costs as appropriate. A total of $2M in direct costs (plus appropriate indirect costs) will be allocated from the FY06 budget with $2M in direct costs (plus appropriate indirect costs) expected from each of the FY07 and FY08 budgets. ***Funding beyond FY06 is contingent on receipt of sufficient congressional appropriations to the NFRP.*** Funding for the Operations Center can be requested for a maximum of $2M for direct costs over a 3-year performance period, plus indirect costs as appropriate. Funding for clinical studies can be requested for a

maximum of $4M for direct costs over a 3-year performance period, plus indirect costs as appropriate.

Clinical trials must begin within 6 months of the award date. If an IND or IDE is required, additional time may be granted. However, preference will be given to protocols that have FDA approval at the time the award is made. Local IRB approvals should be in process or completed before submission of the proposal to the NF Consortium Award mechanism.

Funds for the Operations Center can cover administrative support including salary, consortium-related meetings and travel among participating investigators, database generation and software development, purchase of computers, design of websites, teleconferences, coordination of IRB reviews, and other costs directly associated with maintaining/managing the consortium and developing clinical protocols. Funds for clinical studies can cover salary, expenses including research supplies, equipment, and travel to scientific meetings. Based on programmatic requirements, funding amounts may be tailored to produce the most efficient, cost-effective consortium possible; the NFRP Integration Panel reserves the right to recommend modifications to budgets to meet the needs of the consortium.

Applicants must budget for travel to a pre-award meeting and protocol workshop in the Baltimore, MD–Washington, DC area after notification of award status and before disbursement of funds. Applicants must also budget for semi-annual 1-day meetings with EAB and USAMRMC staff in the Baltimore, MD–Washington, DC area.

Consideration of cost-sharing with other funding sources is encouraged. The nature of this award mechanism does not allow for renewal of awards or supplementation of existing awards with DOD funds. ***It is fully expected that the consortium will have secured funds from other agencies to continue their operations and clinical research/trial activities by the end of the performance period of this award.***

The CDMRP expects to allot approximately $3M of the $17M FY06 NFRP appropriation to fund one NF Consortium Award.

IV. ELIGIBILITY INFORMATION

A. Applicants: Applicants must be independent investigators at the Assistant Professor level (or equivalent) or higher to be eligible to submit proposals.

All individuals, regardless of ethnicity, nationality, or citizenship status, may apply as long as they are employed by, or affiliated with, an eligible institution as defined in Subsection IV.B, "Institutions" below.

To protect the public interest, the Federal Government ensures the integrity of Federal programs by only conducting business with responsible recipients. The USAMRMC uses the Excluded Parties List System (EPLS) to exclude recipients ineligible to receive Federal awards. The EPLS

is online at http://epls.arnet.gov. (Reference Department of Defense Grant and Agreement Regulations (DODGAR) 25.110.)

B. Institutions: Eligible institutions include for-profit, nonprofit, public, and private organizations, such as universities, colleges, hospitals, laboratories, and companies. The USAMRMC is especially interested in receiving applications from Historically Black Colleges and Universities/Minority Institutions (HBCU/MI).

A DOD goal is to allocate funds for the CDMRP peer-reviewed research to fund proposals from HBCU/MI. This provision is based on guidance from Executive Orders.[1] Proposals are assigned HBCU/MI status when the submitting institution is so designated by the Department of Education on the date the program announcement is released. The most current Department of Education list is posted on the CDMRP website at http://cdmrp.army.mil/spp under "Minority Institutions."

Local, state, and Federal government agencies are eligible to the extent that proposals do not overlap with their fully funded intramural programs. Federal agencies are expected to explain how their proposals do not overlap with their intramural programs.

Proposals from Federal agencies ***must*** provide a plan delineating how all funds will be obligated by September 30, 2007, and how funds will be available to cover research costs over the entire award period. The plan must include the funding mechanism(s) that will be used to carry over funds between fiscal years, such as administrative agreements with foundations, non-Federal institutions, and universities.

C. Duplicate Submissions: Submission of the same research project to different FY06 NFRP award mechanisms or to other CDMRP programs is discouraged. The Government reserves the right to reject duplicative proposals. However, the same clinical protocol may be submitted to both the FY06 NFRP NF Consortium Award and the FY06 NFRP Clinical Trial Award.

V. PROPOSAL PREPARATION AND SUBMISSION INFORMATION

A. Proposal Components Summary: This subsection is a summary of submission requirements. Details, URLs, and other links are provided in the appropriate subsections of this program announcement. Proposals will be evaluated according to peer and programmatic review criteria in Section VI.

[1]Executive Orders 12876, 12900, and 13021

1. Applicant Responsibility: The applicant is responsible for entering and/or uploading the following information into the CDMRP eReceipt Online Proposal Submission System at https://cdmrp.org:

Item	Tab	Format	Action
Letter of Intent (LOI)	Proposal Information	Typed	Copy the LOI into the data field. Click the "Save and Forward Letter of Intent" button to automatically create the LOI ***before*** the submission deadline of 5:00 p.m. Eastern time, ***March 7, 2006.***
Proposal Information	Proposal Information	Typed	Enter the appropriate information in data fields.
Proposal Contacts	Proposal Contacts	Typed	Enter contact information for the applicant and the Contract Representative at the applicant's institution.
Collaborators and Conflicts of Interest (COI)	Collaborator/COI	Typed	Enter information about collaborators and others outside the scope of the proposal who may have a COI in the review of this proposal.
Proposal Abstracts, Impact Statement, and Statement of Work (SOW)	Abstract/Impact/ SOW	Typed or Cut and Paste	Enter the Technical Abstract, Public Abstract, and SOW in separate data fields. An Impact Statement is not required; type N/A into the data field.
Proposal Main Body	Required Files	PDF	Upload as a PDF file.
Supporting Documentation	Required Files	PDF	Upload as a PDF file.
Clinical Protocol	Required Files	PDF	Upload as a PDF file.
Budget Information	Required Files	PDF	Upload as a PDF file.
Regulatory Documents	Required Files	PDF	Upload the Certificate of Environmental Compliance and the Principal Investigator Safety Program Assurance forms.

2. Contract Representative Responsibility: The Contract Representative (CR) or institutional official responsible for sponsored program administration (or equivalent) at the applicant's institution is responsible for the following:

Item	Tab	Format	Action
Contract Representative's Contact Information Profile	My Profile for the CR	Typed	Complete before electronic approval of all submission components.
USAMRAA[a]-Required Documents	My Profile for the CR	PDF	Upload the Rate Agreement, Certifications and Assurances for Assistance Agreements, and Representations for Assistance Agreements.
Approval	CR Approval	Click Approval Button	Click the button to approve the Proposal Information, Proposal Contacts, Collaborators and COI, Abstracts/SOW, and Required Files ***before*** the submission deadline of 5:00 p.m. Eastern time, ***August 8, 2006.***

[a]US Army Medical Research Acquisition Activity

B. Proposal Format: Proposals must be uploaded under the "Required Files" tab of the CDMRP eReceipt Online Proposal Submission system at https://cdmrp.org. Applicants unfamiliar with the preparation of PDF files are encouraged to acquire and learn to use the appropriate software well in advance of the submission deadline. The instructions in this subsection must be followed carefully to prepare proposals for PDF submission.

The main body of the proposal must be clear and legible and conform to the formatting guidelines described below. The font size, spacing, page size, and margins may differ between the word processing, PDF, and printed versions. These guidelines apply to the document properties of the electronic version of the PDF file(s) as viewed on the computer screen and submitted via the CDMRP eReceipt Online Proposal Submission System.

- **Font Size:** 12 point or larger.
- **Font Type:** Times New Roman is strongly recommended.
- **Spacing:** No more than six lines of type within a vertical inch (2.54 cm).
- **Page Size:** No larger than 8.5 inches x 11.0 inches (approximately 21.59 cm x 27.94 cm).
- **Margins:** Must be at least 0.5 inch (1.27 cm) in all directions.
- **Print Area:** 7.5 inches x 10.0 inches (approximately 19.05 cm x 25.40 cm).

- **Color, High-Resolution, and Multimedia Objects:** Proposals may include color, high-resolution, or multimedia objects (e.g., MPEG, WAV, or AVI files) embedded in the PDF files; however, these objects must not exceed 15 seconds in length and a size of 10 MB. Since some reviewers work from black and white printed copies, applicants may wish to include text in the proposal directing the reviewer to the electronic file for parts of the proposal that may be difficult to interpret when printed in black and white. Photographs and illustrations must be submitted in JPEG format; bit map or TIFF formats are not allowed.
- **Internet URLs:** URLs directing reviewers to websites containing significant additional information about the proposed research are not allowed in the proposal or its components. Inclusion of such URLs may be perceived as an attempt to gain an unfair competitive advantage. Links to publications referenced in the proposal are allowed.
- **Language:** English.

Please note that headers should not be included, as the proposal log number will be electronically captured on each page of the proposal after receipt.

C. Administrative Compliance Issues: Compliance guidelines have been designed to ensure the presentation of all proposals in an organized and easy-to-follow manner. Peer reviewers expect to see a consistent, prescribed format for each proposal. ***Failure to adhere to format requirements makes proposals difficult to read, may be perceived as an attempt to gain an unfair competitive advantage, and may result in proposal rejection.***

The following will result in administrative rejection of the entire proposal before it reaches peer review:

- Proposal body exceeds page limit.
- Proposal body is missing.
- Detailed cost estimate is missing.
- Proposal is incomplete after the deadline.

For any sections of a proposal with a defined page limit, pages exceeding the specified limit will be removed from the proposal and not forwarded for peer review.

Material submitted after the submission deadline, unless specifically requested by the Government, will not be forwarded for peer review.

The electronic PDF file uploaded in the CDMRP eReceipt Online Proposal Submission System is the official proposal submission file. After conversion of word processing documents to PDF files and before electronic submission, applicants should review their files to ensure that the proposal complies with the preparation guidelines outlined in this program announcement.

D. Letter of Intent (LOI): ***An LOI is required and must be submitted by March 7, 2006*** at https://cdmrp.org. The LOI (a brief description of the proposal) is entered in a data field under

"My Proposals: Create New Proposal." The LOI is saved when the "Save and Forward Letter of Intent" button is selected. The LOI may be modified under "Proposal Information" at any time before the applicant submits this information by clicking "Finalize for CR Approval."

E. Proposal Information: Applicants are required to submit the Proposal Information as described in https://cdmrp.org before uploading the proposal, supporting documentation, and budget information.

- A ***Title/Referral Page*** for the proposal will be generated from the information uploaded in eReceipt and appended to the proposal electronically by the CDMRP eReceipt system.

F. Proposal Contacts: The Proposal Contacts ***must*** include the e-mail address of a Contract Representative authorized to negotiate on behalf of the applicant's institution. The Proposal Contacts must be approved by the Contract Representative at the applicant's institution.

G. Collaborators and Conflicts of Interest (COI): To avoid COI during the review process, list the names of all scientific participants in the proposal including collaborators, consultants, and subawardees. In addition, list the names of individuals outside the scope of this proposal who may have a COI in reviewing this proposal.

H. Proposal Abstracts – 5,700-character limit including spaces (approximately one page), for each abstract: Each abstract must include the applicant's name and the title of the proposal. A structured technical abstract and a public (nontechnical) abstract are required. These abstracts are vitally important in both the peer review and programmatic review processes. Programmatic review is based on the Integration Panel's review of these two abstracts as part of the peer review summary statements; therefore, it is of paramount importance that the applicant submit abstracts that describe the proposed work fully. Each abstract must be entered into the appropriate data field under the "Abstract/Impact/SOW" tab of the CDMRP eReceipt system.

Applicants can type abstracts or "cut and paste" them from a word processing application into the respective data fields. ***Spell out all Greek letters, other non-English letters, and symbols.***

Abstracts of all funded proposals will be posted on the CDMRP website at http://cdmrp.army.mil. Proprietary or confidential information should ***not*** be included in either the technical or the public abstract.

1. Technical Abstract: Sample technical abstracts can be found at https://cdmrp.org/samples.cfm. The structured technical abstract must provide a clear and concise overview of the proposed work. Use the outline below when preparing the structured technical abstract.

- 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 the participating clinical research sites.

- Objective/Hypothesis: Describe the consortium's overall clinical research agenda. Outline the clinical studies that the consortium plans to pursue during the performance period.
- Specific Aims: State concisely the specific aims of the clinical protocol(s) included with the proposal.
- Study Design: Briefly describe the experimental plan or methodologies behind the research of the consortium.
- Goals and End Products: Clearly define measurable outcomes, research milestones, and end products and their applications for the consortium.
- Impact: Provide a brief statement explaining how the proposed consortium will have an impact on the treatment and/or management of NF1.

2. Public Abstract: Sample public abstracts can be found at https://cdmrp.org/samples.cfm. The public abstract is intended to communicate the purpose and rationale of the study to a non-scientifically trained audience. The public abstract is an important component of the proposal review process because consumer advocates, who are part of the review and funding decision process, use this abstract as a part of their review.

- Describe the clinical objective and rationale for the proposal in a manner readily understood by non-scientists.
  - 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 consumer-related outcome?

I. Impact Statement: Not required for this award mechanism.

J. Statement of Work – 11,400-character limit including spaces (approximately two pages): The SOW is captured as a data field under the "Abstract/Impact/SOW" tab in the CDMRP eReceipt system. Applicants can type in the SOW into the data field or "cut and paste" it from a word processing application.

The SOW is a concise restatement of the research proposal that outlines, step by step, how each major goal or objective of the proposed research/services will be accomplished during the period for which the USAMRMC will provide financial support. When a proposal requesting funding as part of a larger study is submitted, the proposal's SOW must include DOD-funded tasks only. Sample SOWs can be found at https://cdmrp.org/samples.cfm.

The SOW should:

- Describe the work to be accomplished as tasks (tasks may relate to specific aims);

- Identify the timeline and milestones for the work over the performance period for the proposed effort;
    - Allow 4 to 6 months for regulatory review and approval processes for human use studies;
- If applicable, indicate the sample size (including tissue, anatomical, or biological substances) projected or required for each task;
- Identify methods; and
- Identify outcomes, products, and deliverables for each stage of the project.

K. Proposal Main Body: Start section on a new page; 45-page limit inclusive of any figures, tables, graphs, photographs, diagrams, chemical structures, pictures, pictorials, cartoons, and other information needed to judge the proposal.

The proposal main body is uploaded as a PDF file under the "Required Files" tab of the CDMRP eReceipt system.

It is the responsibility of the applicant to clearly articulate the ability of his or her group to serve as an NF1 consortium and to support the design, development, and conduct of collaborative clinical evaluations of promising new NF1 therapeutic agents or treatment approaches.

Describe the qualifications of the group and the key features of the consortium using the following general outline:

- **Consortium and Institutional Expertise and Resources**
    - Describe previous experience and accomplishments of the Operations Center related to the design, administration, and fiscal management of multi-institutional NF1 clinical studies, particularly Phase I clinical trials. Describe previous experience establishing communications systems and data management resources for multi-institutional projects. Reference relevant publications and submit reprints with the proposal (see Subsection V.L).
    - Describe previous experience of consortium personnel at each clinical research site with the development and conduct of NF1-relevant clinical studies, particularly Phase I clinical trials and multi-institutional studies. Reference relevant publications and submit reprints with the proposal (see Subsection V.L).
    - Describe the NF1 population(s) at each participating clinical research site (including size, age range, and clinical manifestations) and provide evidence of ability to enroll at least 10 to 12 evaluable individuals with NF1 per site per year into consortium-sponsored studies. Provide evidence of commitment to addressing quality of life issues for all participants enrolled in consortium studies.
    - Provide evidence of expertise in the following disciplines ***within each participating clinical research site:***
        - Basic Research Science,

- Dermatology,
- Genetics,
- Neurology,
- Neuropsychology,
- Neurosurgery,
- Oncology,
- Ophthalmology,
- Orthopedics,
- Pain Management,
- Pathology,
- Pediatrics,
- Plastic Surgery, and
- Radiology.

As appropriate, describe any additional clinical and/or laboratory expertise that could serve as the basis for the development of clinical protocols by the consortium.

- Describe the resources and expertise available within each participating clinical research site for the collection and processing of specimens from consortium-sponsored studies.
- Describe the resources and expertise in each participating clinical research site for data management and maintenance of data security/confidentiality.
- Provide evidence of institutional commitment for the Operations Center and each participating clinical research site for the use of facilities and resources in the conduct of consortium operations.

- **Overall Consortium Organization and Management**
  - Provide a charter and by-laws for the consortium.
  - Provide a detailed description of the overall consortium organizational structure, which should include the following key features (see also the figure in Subsection II.C.3):
    - An Operations Center for administration and day-to-day management of consortium operations, developing the clinical trial selection process, protocol coordination, regulatory coordination, study management and monitoring, data collection, management and statistics, and intellectual/material property coordination.
    - Clinical research sites for conceiving, developing, and conducting NF1-relevant clinical trials.
    - A Governing Body for the continuous development and operation of the Consortium. The Governing Body shall be composed of PIs from each

participating clinical research site, Operations Center representatives, and consumer advocates.

- Pro bono scientific committees, composed of investigators from participating clinical research sites, that provide input on study feasibility and design.
- Core facilities that provide scientific support (e.g., biology, pathology, radiology) (as necessary).
- Protocol Chairs, who are responsible for the development, coordination, and monitoring of specific clinical protocols in accordance with consortium policies and procedures. The Governing Body will designate a single investigator from a participating clinical research site as Protocol Chair for each protocol.

- Describe plans for real-time communication between the Operations Center and all participating clinical research sites.
- Describe plans for ensuring standardization of procedures across institutions and among staff.
- Outline procedures for evaluating the performance of participating institutions.
- Describe plans for the financial administration of the consortium.
- Describe plans for recruiting additional clinical research sites as full member institutions and/or as affiliates who contribute to and participate in consortium studies on an ad hoc basis. Please note that new full member institutions must meet the criteria stated in the FY05 NFRP NF Consortium Development Site Award program announcement.

- **Clinical Protocol Development, Clinical Trial Implementation, and Human Subjects Protection**
  - Describe at least one NF1 ***therapeutic*** clinical trial that the consortium plans to implement using funds from this award, as well as any other clinical trials or studies proposed for the award period. Describe any other trials or studies that the consortium intends to implement. If more than one trial/study is proposed, rank them in order of priority. Clinical protocols, informed consent forms, and other supporting clinical documents must be submitted for ***each*** proposed trial or study (see Subsections V.M.1 and V.M.2). In addition, any available IRB approvals must be submitted as supporting clinical documents (see Subsection V.M.2).

    If any of the proposed trials/studies are part of a larger study, the aims and research strategy should be presented for DOD-funded tasks only. The applicant must address how the research plan will be affected if all large study components do not receive funding (e.g., Can the DOD-funded research be completed as proposed if funding is not received for all components? What adjustments would be needed in the study design to meet such a contingency?).
  - Outline plans for coordinating IRB and HSRRB submissions and approvals.
  - Describe procedures for ensuring compliance with institutional IRB and HSRRB requirements for the conduct of clinical studies and the protection of human subjects.

- Include a ***named*** Supervising Clinical Coordinator at the Operations Center and ***named*** Clinical Coordinators at each participating clinical research site who will work collaboratively to guide clinical protocols through the regulatory approval processes, coordinate participant accrual, and coordinate study activities across sites.
- Describe procedures for ensuring compliance with FDA requirements for investigational agents, as appropriate.
- As appropriate, outline plans for the development and submission of new clinical protocols and associated clinical documents to the NFRP Clinical Trial Award mechanism and/or other funding agencies during the award period.

- **Study Management and Monitoring**
  - Describe procedures for quality assurance, quality control, and study monitoring, to include:
    - Registration, tracking, and reporting of participant accrual,
    - Timely medical review and assessment of participant data,
    - Evaluation of pathological, therapeutic, neurosurgical, and imaging data and materials submitted to the Operations Center by participating sites, as appropriate, for central review, verification, and determination of protocol compliance,
    - An on-site monitoring program established and managed by the Operations Center,
    - Rapid reporting and communication of adverse events, and
    - Interim evaluation and consideration of measures of outcome.
  - Describe methods for the handling, distribution, analysis, banking, and security of specimens and/or imaging products generated from consortium-sponsored studies. A specimen handling and distribution plan agreed upon by all institutions in the consortium must be submitted with the proposal (see Subsection V.L).
  - Include a ***named*** coordinator at the Operations Center responsible for managing and resolving material and intellectual property issues among consortium institutions. An intellectual and material property plan agreed upon by all institutions in the consortium must be submitted with the proposal (see Subsection V.L).
- **Data Management:** Provide a comprehensive data management plan that includes:
  - Descriptions of the overall approach to data collection and management,
  - A statistical plan that includes sample size calculations, methods to monitor quality and consistency of data collection, and methods to measure outcomes,
  - A plan for real-time data transfer,
  - Data security measures, and
  - Plans for ensuring rapid publication and other public dissemination of data while maintaining participant privacy.

L. Supporting Documentation: Submit only material specifically requested in this program announcement. ***This section is not intended for additional figures, tables, graphs, photographs, diagrams, chemical structures, pictures, pictorials, cartoons, or other information needed to judge the proposal.*** Submitting material that was not requested may be construed as an attempt to gain a competitive advantage and such material will be removed; submitting such material may be grounds for administrative rejection of the proposal.

Supporting Documentation must be uploaded as a single PDF file under the "Required Files" tab of the CDMRP eReceipt system. All documents or letters that require signatures must be signed and incorporated into the Supporting Documentation file before it is submitted.

The first item in the Supporting Documentation file is the Checklist/Table of Contents page . The requested, allowable items in this section must be listed in the Checklist/Table of Contents; these include:

1. Abbreviations: Start section on a new page; one-page limit. Provide a list of all acronyms, abbreviations, and symbols used in the main body of the proposal.

2. References: Start section on a new page; no page limit. List all relevant references using a standard reference format that includes the full citation (i.e., author(s), year published, title of reference, source of reference, volume, chapter, page numbers, and publisher, as appropriate).

3. Biographical Sketches: Four-page limit per individual. Include biographical sketches for all key personnel including collaborating investigators and support staff. These documents are a critical component of the review process. Incomplete or missing biographical sketches may result in lower proposal scores. The Biographical Sketch form may be used. Use of this form is not mandatory, but the information requested shall be presented in a similar format.

4. Existing/Pending Support: Start section on a new page; no page limit. List the titles, time commitments, supporting agencies, durations, and levels of funding for all existing and pending research projects involving the applicant and key personnel on a separate page. If no support exists, enter "None." Proposals submitted under this program announcement should not duplicate other funded research projects.

5. Facilities/Equipment Description: No page limit. Describe the facilities available for performing the proposed research/services. Describe the institutional commitment, including any additional facilities or equipment proposed for purchase or available for use at no cost to the USAMRMC. Indicate whether Government-owned facilities or equipment are proposed for use.

6. Letters of Support: Provide letters of support from any collaborating individuals or institutions.

7. Letters of Commitment: Provide letters of commitment from senior administrators at each institution participating in the consortium. Letters should detail the willingness of each institution to provide the necessary facilities and resources for the consortium's administrative and clinical activities (as appropriate).

8. Publications and/or Patent Abstracts: Five-document limit. Include up to five relevant publication reprints and/or patent abstracts. A patent abstract should provide a non-proprietary description of the patent application. If more than five publications are included in the submission, the extra items will not be peer reviewed.

9. Intellectual and Material Property Plan: Provide an intellectual and material property plan agreed upon by all institutions participating in the consortium.

10. Specimen Handling and Distribution Plan: Provide a specimen handling and distribution plan agreed upon by all institutions in the consortium.

11. Evidence of Substance/Device Availability: Provide evidence that a sufficient quantity of the substance(s) to be used for the proposed clinical trials is/are available and produced under Good Manufacturing Practice conditions. Include a cost-sharing plan if the substance or device is to be provided from industrial sources.

M. Clinical Protocol and Supporting Clinical Documents

The clinical protocol and supporting clinical documents are uploaded as a single PDF file under the "Required Files" tab of the CDMRP eReceipt system.

1. Clinical Protocol: No page limit. At least one ***NF1 therapeutic*** clinical protocol must be submitted with the FY06 NFRP NF Consortium Award proposal. There is no limit to the number of additional clinical protocols that may be submitted with the proposal. ***In order to facilitate the initiation of work on funded projects, the clinical protocol should be a standalone document that can be submitted to the HSRRB for review.***

Separate, freestanding protocols should be generated for each site and/or task for all research that involves (a) multiple sites; (b) multiple tasks requiring different study designs, samples, sampling procedures, or methods; and (c) inter-institutional cooperative or collaborative agreements. Please note that each project of a multi-project application will be individually evaluated for compliance with applicable regulatory requirements. Documentation of local IRB review and approval of each protocol will be required at the time of the HSRRB regulatory review for all funded proposals.

It is critical that the information entered in the main body of the proposal matches the information contained within each clinical protocol. When a proposal is submitted requesting funding for part of a larger study, the clinical protocol must include DOD-funded tasks only.

Required elements for submission of each ***clinical protocol*** are:

a. Protocol Title: The protocol title must be the same as the proposal title unless multiple protocols are being submitted within one proposal. In a proposal with multiple protocols, the proposal title must be referenced consistently across all protocols.

b. Phase: Designate the protocol as Phase I or II (as appropriate).

c. Principal Investigator: List the complete name, address, telephone and fax number, and e-mail address of the PI. List the names of all personnel who will have significant involvement in the research study; include their practice license (e.g., MD or RN), highest degree(s), job title, and employing institution. In addition, include the name of the Medical Monitor with his or her current curriculum vitae for Greater Than Minimal Risk Studies. (See Subsection V.M.1.r for details on the Medical Monitor requirement.)

d. Documentation of Required Training: Research investigators must complete appropriate institutional training before conducting human subjects research. Documentation of the most recent ethics training must be submitted for investigators of all protocols in the Supporting Clinical Documents section of the proposal (see Subsection V.M.2). In addition, for all investigational drug and device protocols, documentation of successful completion of a course in the conduct of clinical research in accordance with Good Clinical Practices (GCP) must be submitted for all investigators. The most recent ethics training and GCP course must be successfully completed within 1 year of the planned initiation of the protocol.

e. Location of Study: List all centers, clinics, or laboratories where the study is to be conducted. Include the name, degree(s), title, employing institution, and complete address of the investigator(s) for each site.

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

g. Background: Include a background section that describes the rationale for conducting the study as well as the study's impact on NF1 and applicability of findings. Describe the particular target, pathway, molecule, or device that is the focus of the clinical trial. Include descriptions of any preliminary studies and findings that led up to the development of the protocol. If the protocol was initiated using other findings prior to obtaining funding managed by the USAMRMC, explain the history and evolution of the protocol and declare the source of prior funding. HSRRB approval is required prior to continuing enrollment using USAMRMC-managed funds.

h. Objectives: Provide a detailed description of the purpose and objectives of the study.

i. Statement of Work: The SOW is a concise restatement of the clinical protocol that outlines, step by step, how each of the major goals or objectives of the clinical trial/study will be accomplished during the timeline for which the USAMRMC will provide financial support.

As appropriate, the SOW should:

- Describe the work to be accomplished as tasks (tasks may relate to specific aims);
- Identify the timeline and milestones for the work over the period of the proposed effort;
- Indicate the number of research subjects projected or required for each task;
- Identify methods; and
- Identify outcomes, products, and deliverables for each phase of the trial/study.

j. Study Population

i. 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).

ii. Describe the methods that will be used to obtain a sample of subjects from the accessible population (e.g., convenience, simple random, stratified random) together with the inclusion and exclusion criteria (include age, gender, and ethnicity). Present appropriate statistical analyses to verify power for the sample size.

k. Protocol Design: Describe the type of study to be performed (prospective, randomized, controlled, etc.). Outline the proposed methodology in sufficient detail to show a clear course of action. Technological reliability and validity of procedures should be indicated. Minimum guidance for the plan should include:

i. Subject Identification: Describe the code system to be used to maintain the confidentiality of subjects.

ii. Description of the Recruitment Process: Describe who will identify potential subjects, who will recruit them, and how they will be recruited. Provide copies of all recruitment and advertisement materials for review.

iii. Description of the Informed Consent Process: Specifically describe the plan for the informed consent process by stating who will perform the informed consent interview and when the interview will take place relative to the subject beginning study participation and in relation to any stressful situation (e.g., being informed he or she has a malignant tumor) or in relation to the administration of any mind-altering substances such as tranquilizers, conscious sedation, or anesthesia. Address how privacy and time for decision making will be provided and whether the potential subject will be allowed to discuss the study with anyone before making a decision. Two copies of the Informed Consent form should be completed so that the subject can get an original copy and a copy can be kept for the PI's study records. A third copy may be needed for the participant's medical record; check with the participating site for specific study site requirements.

iv. Subject Assignment: Describe the randomization process or other procedures used for subject group assignments.

v. Subject Screening Procedures: List and describe any evaluations (e.g., laboratory procedures, history, and/or physical examination) that are required to determine eligibility/suitability for study participation. Please note that some screening procedures may need a separate consent or a two-stage consent process.

vi. Data Collection Procedures: Describe all data collection procedures to be used in conducting the study (e.g., laboratory evaluations, specimens to be collected, schedule and amounts, storage to include where and whether special conditions are required, labeling, and disposition). For studies using multiple measures or tests over time, it is helpful to display the data collection schedule in a spreadsheet or tabular format.

vii. Clinical Assessments: Provide a schedule of clinical evaluations and follow-up procedures. Provide any case report forms, data collection forms, questionnaires, rating scales, and/or interview guides that will be used in the study.

viii. Research Interventions: Describe the research intervention or activity that the subject will experience. Provide sufficient detail in chronological order for a person uninvolved in the research to understand what the subject will experience.

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

l. Risks/Benefits Assessment

i. Describe risks (physical [including pain and discomfort, disfigurement, infection, injury, death], psychological, social, economic, legal, and privacy/confidentiality risks) associated with the research, measures to be taken to minimize and/or eliminate risks or to manage unpreventable risks, and special medical or nursing care that will be needed prior to, during, or following participation.

ii. Describe benefits of the research to the subject. If there will be no benefits to the subjects (other than knowing he or she has contributed to science), state this in the protocol and Informed Consent form.

iii. Payment or compensation for participation is not considered to be a benefit and must be addressed in a separate section.

m. Reporting of Serious or Unexpected Adverse Events

i. Serious or unexpected adverse events can occur in any and all types of studies, not just experimental interventions or clinical trials.

ii. Include a definition of what constitutes an adverse event in the proposed study.

(1) For IND or IDE research, refer to definitions as listed in 21 CFR 312.32.[2] for assistance.

(2) All IND protocols must describe how the following requirements will be addressed.

> "An adverse event temporally related to participation in the study should be documented whether or not considered to be related to the test article. This definition includes intercurrent illnesses and injuries and exacerbations of preexisting conditions. Include the following in all IND safety reports: Subject identification number and initials; associate investigator's name and name of medical treatment facility (MTF); subject's date of birth, gender, and race/ethnicity; test article and dates of administration; signs/symptoms and severity; date of onset; date of resolution or death; relationship to the study drug; action taken; concomitant medication(s) including dose, route, and duration of treatment, and date of last dose."

iii. Describe agencies or offices to be notified with point of contact information in the event of a serious and unexpected adverse event.

All protocols should contain the following language regarding the HSRRB reporting requirements for adverse events and unanticipated problems. (Note that unanticipated problems can occur in a study that does not require a research/clinical intervention.)

> "Unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study and all volunteer deaths should be promptly reported by phone (301-619-2165), by e-mail (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the U.S. Army Medical Research and Materiel Command's Human Subjects Research Review Board. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-P, 504 Scott Street, Fort Detrick, Maryland 21702-5012."

Refer to the "HSRRB Information Sheet for Investigators: Unanticipated Problems" for examples of unanticipated problems located on the Office of Research Protections's website at https://mrmc.detrick.army.mil/rodorphrpo.asp.

For protocols that have a Medical Monitor assigned (see part r in this section), the

[2]Title 21, Code of Federal Regulations, Part 312.32; for more information, go to http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=312.32.

following language also should be included.

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

n. Description of Protocol Drugs or Devices: If the protocol uses an investigational drug or device, provide the following information:

i. IND/IDE number and name of sponsor, if the study is in support of an application to the FDA.

ii. Complete names and composition of all medication(s), device(s), or placebo(s), and, as appropriate, mechanisms of action.

iii. Source of medications, devices, or placebos.

iv. Location of storage for study medications.

v. Dose range, schedule, and administration of test articles.

vi. Washout period, if used, should be described in detail.

vii. Duration of drug or device treatment.

viii. Concomitant medications allowed.

ix. Antidotes and treatments available.

x. Disposition of unused drug.

xi. The procedure by which the IND sponsor will monitor the protocol in accordance with 21 CFR 312.[3]

[3]Investigational New Drug Application procedures and requirements; additional information can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312

xii. In addition to the above list of requirements to be included in the protocol, the following additional items need to be submitted:

(1) A copy of the Investigator's Brochure and/or device manual and associated case report/data collection forms. If the study involved the testing of an approved drug for a new indication, provide a copy of the package insert.
(2) A signed Form FDA 1572 for IND Applications filed with the FDA, including the following information. Also, for non-FDA new drug protocols, the following information should be included in the protocol:

(a) Name, address, and a statement of the qualifications for each investigator and the name of each sub-investigator working under the PI.

(b) Names and addresses of facilities to be used.

(c) Name and address of each IRB reviewing the protocol.

(3) For investigational devices, include your local IRB's assessment of the risk (nonsignificant or significant) of the investigational device you plan to use in your study. If the device poses significant risk to research subjects, specify the IDE number obtained from the FDA, the name of the sponsor, and the procedure by which the sponsor will monitor the protocol in accordance with 21 CFR 812.[4]

o. Disposition of Data: Describe where data will be stored, who will keep the data, how the data will be stored, and the length of time the data will be stored. Note that records of IND studies must be kept until 2 years after a New Drug Application is approved/issued or for 2 years after the IND is withdrawn. Records required for IDE studies should be retained for 2 years following the date that the investigation is terminated or completed or the date that the records are no longer required for support of the pre-market approval application, whichever is sooner.

p. Modification of the Protocol: Describe the procedures to be followed if the protocol is to be modified, amended, or terminated before completion. Note that any modification to the protocol, Informed Consent form, and/or questionnaires, including a change of PI, must be submitted to the local IRB for review and approval and the HSRRB for second-level review and approval. Address this procedure even if you do not anticipate making any modifications.

q. Departure from the Protocol: Describe procedures and notifications to be made in the event of deviations from the approved protocol to include both the local IRB and the HSRRB.

[4]Investigational Device Exemptions; additional information can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1.

r. Roles and Responsibilities of Study Personnel: Briefly describe the duties of all study personnel to include each of the persons listed as investigators, research staff, consultants, and the Medical Monitor. Describe their roles in the research effort (e.g., Research Coordinator, 80%, recruit and consent subjects, maintain study records, administer study drug, take and record vital signs, enter data into computer database). Duties of the Medical Monitor, as defined in HSRRB Clause 8.02, are as follows:

> "A Medical Monitor must be assigned to Greater Than Minimal Risk protocols. The name and curriculum vitae of the Medical Monitor, who is someone other than the PI, must be provided. This individual should be a qualified physician who is not associated with the protocol, able to provide medical care to research subjects for conditions that may arise during the conduct of the study, and able to monitor subjects during the conduct of the study. In some studies it may be acceptable to have a qualified health care provider other than a physician serve as Medical Monitor, depending upon the type of risk that might occur in the study (e.g., a clinical psychologist). The Medical Monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events, and all volunteer deaths associated with the protocol and to provide an unbiased written report of the event. At a minimum the Medical Monitor should comment on the outcomes of the adverse event and relationship of the event to the protocol or test article. The Medical Monitor should also indicate whether he or she concurs with the details of the report provided by the PI. Reports for events determined by either the investigator or Medical Monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to the HSRRB."

The Medical Monitor will forward reports to the US Army Medical Research and Materiel Command, ATTN: MCMR-ZB-P, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

2. Supporting Clinical Documents: No page limit. Information on requirements for the following supporting clinical documents can be found in the document titled "Research Involving Human Subjects and/or Anatomical Substances," which can be found under "Regulatory Document Forms" at https://cdmrp.org/Program_Announcements_and_Forms.

The first item in this section must be a table of contents listing all documents included in this section. Provide the following in this section of the proposal:

- Informed Consent/Assent forms,
- IRB approvals (if any),
- Questionnaires,
- Survey instruments,
- Participant recruitment brochures,
- Case report forms,
- Investigator's brochure for proposals with IND/IDEs,

- Documentation that an IND/IDE has been submitted or a plan for submission of IND/IDE application to the FDA for therapeutic clinical trial protocols, and
- A plan for the study investigators to successfully complete institutional ethics training and a course in the conduct of clinical research in accordance with GCP within 1 year of initiation of the protocol.

N. Budget Information: Applicants must complete the Detailed Cost Estimate form and the Budget Justification form for the Operations Center and ***each*** clinical trial/study, and upload them as a single PDF file under the "Required Files" tab of the CDMRP eReceipt system. When a proposal requesting funding as part of a larger study is submitted, the proposal's budget justification should include only DOD-funded tasks.

1. Funding Restrictions: The NFRP plans to provide a total of $6M in direct costs to fund the NF Consortium Award (plus indirect costs as appropriate), only a portion of which will be allocated from the FY06 NFRP budget. A total of $2M in direct costs (plus appropriate indirect costs) will be allocated from the FY06 budget with $2M in direct costs (plus appropriate indirect costs) expected from each of the FY07 and FY08 budgets. ***Funding beyond FY06 is contingent on receipt of sufficient congressional appropriations to the NFRP.*** Funding for the Operations Center and administrative costs can be requested for a maximum of $2M for direct costs over a 3-year performance period, plus indirect costs as appropriate. Funds for the Operations Center can cover administrative support including salary, consortium-related meetings and travel among participating investigators, database generation and software development, purchase of computers, design of websites, teleconferences, coordination of IRB reviews, and other costs directly associated with maintaining/managing the consortium and developing clinical protocols.

Funding for clinical studies can be requested for a maximum of $4M for direct costs over a 3-year performance period, plus indirect costs as appropriate. Funds for clinical studies can cover salary, expenses including research supplies, equipment, and travel to scientific/technical meetings. The amount for this travel may not exceed $1,800 per year per investigator. Based on programmatic requirements, funding amounts may be tailored to produce the most efficient, cost-effective consortium possible; the NFRP Integration Panel reserves the right to recommend modifications to budgets to meet the needs of the consortium.

Applicants must budget for travel to a pre-award meeting and protocol workshop in the Baltimore, MD–Washington, DC area after notification of award status and before disbursement of funds. Applicants also must budget for semi-annual 1-day meetings with EAB and USAMRMC staff in the Baltimore, MD–Washington, DC area. It is anticipated that two to five participants from each consortium site will attend each meeting. Justification must be provided if additional personnel are included in the travel budget.

There is no guarantee that funds will be available for the NF Consortium Award in FY07 or FY08.

2. Detailed Cost Estimate Form and the Budget Justification Instructions: Budget is an important consideration in both peer review and programmatic review, and applicants are cautioned to use discretion in budget requests. Budgets also will be reviewed during award negotiations. ***Organizations must provide sufficient detail and budget justification so that the Government can determine the proposed costs to be allocable and reasonable for the proposed research.*** All costs must be entered in U.S. dollars.

The USAMRMC encourages in-kind contributions and cost-sharing for CDMRP-supported research. In-kind contributions may include support of services (e.g., laboratory services and salaries of personnel), real property and equipment, and/or supplies (e.g., drugs, devices, reagents) directly benefiting and specifically identifiable to the research project. ***It is expected that institutions will share the cost of equipment purchased for this research proposal. Please see full details under "Major Equipment" in Subsection V.M.2.c.***

Costs proposed must conform to the following regulations and principles:

- **Commercial Firms:** Federal Acquisition Regulations (FAR) Part 31 and Defense FAR Supplement Part 31 (http://farsite.hill.af.mil), Contract Cost Principles and Procedures.
- **Educational Institutions:** Office of Management and Budget (OMB) Circular A-21, Cost Principles for Educational Institutions (http://www.whitehouse.gov/omb/grants/grants_circulars.html).
- **Nonprofit Organizations:** OMB Circular A-122, Cost Principles for Nonprofit Organizations. OMB Circular A-133, Audits of Institutions of Higher Education and Other Nonprofit Organizations (http://www.whitehouse.gov/omb/grants/grants_circulars.html).
- **State, Local, and Tribal Governments:** OMB Circular A-87, Cost Principles for State, Local, and Indian Tribal Governments (http://www.whitehouse.gov/omb/grants/grants_circulars.html).

Follow the instructions below when providing the information requested in each Detailed Cost Estimate form.

a. Personnel

i. Name: Beginning with the applicant from the Operations Center or the clinical trial/study investigator, list all participants who will be involved in the Operations Center or the clinical trial/study during the initial budget period, whether or not salaries are requested. Include all collaborating investigators, research associates, individuals in training, Clinical Coordinators, Intellectual/Material Property Coordinators, and support staff. ***The applicant must be identified as the Principal Investigator of the proposal.***

ii. Role on Project: Identify the role of each participant listed in the Operations Center or the clinical trial/study. Describe his or her specific functions in the Budget Justification section of the Detailed Cost Estimate form.

iii. Type of Appointment (Months): List the number of months per year reflected in an individual's contractual appointment with the applicant organization. The Government assumes that appointments at the applicant organization are full time for each individual. If an appointment is less than full time, e.g., 50%, note this with an asterisk (*) and provide a full explanation in the Budget Justification section of the Detailed Cost Estimate form. Individuals may have split appointments (e.g., for an academic period and a summer period). For each type of appointment, identify and enter the number of months on separate lines.

iv. Annual Base Salary: Enter the annual institutional base salary for each individual listed for the Operations Center or the clinical trial/study.

v. Percentage of Effort on Project: The qualifications of the Operations Center applicant or the clinical trial/study investigators and the amount of time that he or she and other professional personnel will devote to the consortium are important factors in selecting research proposals for funding. List the percentage of each appointment to be spent on the Operations Center or the clinical trial/study for each key staff member. Include the percent effort of all unpaid collaborators and consultants. The consortium must have a Supervising Clinical Coordinator at the Operations Center and Clinical Coordinators at each participating site who have sufficient time dedicated to the consortium to carry out the record keeping, coordination, and/or other administrative duties the project entails.

vi. Salaries Requested: Enter the salaries in whole U.S. dollars for each position for which funds are requested. Calculate the salary request by multiplying an individual's institutional base salary by the percentage of effort on the Operations Center or the clinical trial/study.

vii. Fringe Benefits: Fringe benefits for each position may be requested in accordance with institutional guidelines, provided the costs for all sponsors are treated consistently by the applicant's organization. Provide documentation to support the fringe benefits.

viii. Totals: Calculate the totals for each position and enter these as subtotals in the columns indicated.

b. Consultant Costs: Provide the names and organizational affiliations of all consultants whether or not funds are requested.

c. Major Equipment: It is the policy of the DOD that all commercial and nonprofit recipients provide the equipment needed to support proposed research. In those rare

cases where specific additional equipment is approved for commercial and nonprofit organizations, such approved cost elements shall be negotiated separately.

i. If the purchase of equipment for this research project is requested, it is expected that the applicant's institution will share 50% of the cost.

ii. Permanent equipment is any article of nonexpendable tangible property having a useful life of 2 years or longer and an acquisition cost of $5,000 or more per unit.

iii. The basis for the cost of each item of permanent equipment included in the budget must be disclosed.

iv. Title of equipment or other tangible property purchased with Government funds may be vested in institutions of higher education or with nonprofit organizations whose primary purpose is the conduct of scientific research. Normally, the title will vest in the recipient if vesting will facilitate scientific research performed by the institution or organization for the Government.

d. Materials, Supplies, and Consumables: A general description and estimated total cost of expendable equipment and supplies are required. Itemize supplies in separate categories (e.g., glassware, chemicals, radioisotopes). Categories in amounts less than $1,000 do not need to be itemized. If animals will be purchased, state the species, strain (if applicable), and the number of animals to be used. If human cell lines are to be purchased, state the source and the description. It is anticipated that the drug, device, or other therapeutic agent will be provided at no cost to the clinical trials submitted with this proposal. However, if costs are incurred, state the source of the intervention(s) and provide a cost-sharing plan.

e. Travel Costs: Costs for travel to scientific/technical meetings may not exceed $1,800 per year per investigator. Applicants also should budget for travel to a pre-award meeting and protocol workshop and semi-annual 1-day meetings with EAB and USAMRMC staff in the Baltimore, MD–Washington, DC area. It is anticipated that two to five participants from each consortium site will attend each meeting. Justification must be provided if additional personnel are included in the travel budget.

Travel costs associated with the execution of the proposed work should be entered in this section. If applicable, reasonable costs for travel between collaborating institutions should be included and are not subject to the yearly $1,800 limitation on travel to meetings. Justification for these travel costs should be provided. Travel outside the U.S. requires prior approval from the US Army Medical Research Acquisition Activity (USAMRAA).

f. Research-Related Subject Costs: Itemize costs of subject participation in the research study. These costs are strictly limited to expenses associated specifically with the proposed study. The USAMRMC will not provide funds for ongoing medical care costs not related to a subject's participation in the research study.

g. Other Direct Costs: Itemize other anticipated direct costs such as publication and report costs, rental for computers and other equipment (provide hours and rates), and communication costs. Unusual or expensive items should be fully explained and justified. Estimate the costs of publishing and reporting research results, including direct charges for clerical preparation, illustrations, reprints, and distribution.

h. Subaward Costs: A description of services or materials to be awarded by subcontract or subgrant is required. For awards totaling $10,000 or more:

- Identify the type of award to be used (e.g., cost reimbursement, fixed price);
- Identify the proposed subcontractor or subgrantee, if known, and provide an explanation of why and how the subcontractor or subgrantee was selected or will be selected;
- Specify whether the award will be competitive and, if noncompetitive, provide a rationale to justify the absence of competition; and
- Provide the proposed acquisition price.

i. Indirect Costs (overhead, general and administrative, and other): The most recent rates, dates of negotiation, base(s), and periods to which the rates apply should be disclosed with a statement identifying whether the proposed rates are provisional or fixed.

j. Total Costs for the Entire Proposed Period of Support (second page of the Detailed Cost Estimate form): Enter the totals in each budget category for all additional years of support requested and itemize these totals in the Budget Justification section of the Detailed Cost Estimate form. Note with an asterisk (*) and explain any significant increases or decreases from the initial year budget. All amounts should be in U.S. dollars. Directs costs, indirect costs, and the total cost for the Operations Center and each proposed clinical study/trial combined for the entire proposed period of support should equal the amount entered in the "Required Files" tab at https://cdmrp.org.

3. Budget Justification (third page of the Detailed Cost Estimate form): Each item in the budget must be clearly justified in the Budget Justification section of the Detailed Cost Estimate form.

4. Federal Agency Financial Requirement: Proposals from Federal agencies ***must*** provide a plan delineating how all funds will be obligated by September 30, 2007, and how funds will be available to cover research costs over the entire award period. The plan must include the funding mechanism(s) that will be used to carry over funds between fiscal years, such as administrative agreements with foundations, non-Federal institutions, and universities.

Start the plan on a new page at the end of the Budget Information section. The Federal Agency Financial Plan must be uploaded as part of the budget information before the submission deadline of ***5:00 p.m. August 8, 2006***.

O. Regulatory Requirements: Completed and signed copies of the Certificate of Environmental Compliance and Principal Investigator Safety Program Assurance form must be uploaded under the "Required Files" tab of the CDMRP eReceipt system as separate PDF files.

In addition, regulatory documents pertaining to research involving human subjects and/or human anatomical substances or cadavers must be submitted within the Clinical Protocol and Supporting Clinical Documents section of the proposal (see Subsection V.M.1 and Subsection V.M.2) as a required file. Any other regulatory documents should not be submitted with the proposal. Instead, the applicant should provide these documents to the USAMRMC only upon request

P. USAMRAA-Required Documents: The Contract Representative at the applicant's institution must upload the current version of the institution's negotiated Rate Agreement, the Certifications and Assurances for Assistance Agreements, and the Representations for Assistance Agreements. These documents must be uploaded as separate PDF files under the Contract Representative's "My Profile" tab of the CDMRP eReceipt system by the proposal submission deadline.

Q. Submission Date and Time: Proposals must be approved on the CDMRP eReceipt system by the Contract Representative at the applicant's institution by the deadline. Proposals that are incomplete or not approved electronically before the deadline will not be considered for review. The eReceipt system will ***not*** accept data entry, file uploads, or approvals submitted after the 5:00 p.m. Eastern time, August 8, 2006 deadline.

The timeline for the NF Consortium Award is:

Online Letter of Intent:	***Required by March 7, 2006***
Online Proposal Information:	Required prior to proposal submission
Proposal Submission/Approval Deadline:	***5:00 p.m. Eastern time, August 8, 2006***
Peer Review (First Tier):	September 2006
Programmatic Review (Second Tier):	October 2006
Request for Additional Documents:	As early as 2 weeks after the completion of programmatic review
Notification Letter:	Approximately 4 weeks after the completion of programmatic review
Award Start Date:	Anticipated between December 2006 and April 2007

R. Electronic Submission Requirements: Electronic submission is required. Only proposals submitted as PDF files through the CDMRP eReceipt system at https://cdmrp.org will be accepted.

Several steps are critical to successful proposal submission:

- The Proposal Information must be "Finalized for CR Approval" before the proposal is submitted. Applicants are encouraged to begin this part of the submission process early.
- Proposal Contacts must be "Finalized for CR Approval" before the proposal is submitted. The e-mail address of a Contract Representative at the applicant's institution must be included in the Proposal Contacts. Applicants are encouraged to begin this part of the submission process early.
- Applicants are encouraged to coordinate with their Contract Representative early in the application process.
- The Contract Representative authorized to negotiate on behalf of the applicant's institution is required to provide final approval before the proposal is accepted.
- The eReceipt system will ***not*** accept data entry, file uploads, or approvals submitted after the 5:00 p.m. Eastern time, August 8, 2006 deadline.
- Some items in the proposal including figures, tables, graphs, letters, or publications will need to be scanned electronically. These documents should be scanned at a resolution of 300 dpi or less.
- Applicants are encouraged to retain a date and time-stamped copy of the proposal component files as prepared by word processing software (e.g., Microsoft Word, WordPerfect) as well as the original PDF conversion file.
- The Detailed Cost Estimate form and the Budget Justification form must be uploaded under the "Required Files" tab of the CDMRP eReceipt system.
- The regulatory documents required at submission include a completed and signed Certificate of Environmental Compliance and a completed and signed Principal Investigator Safety Program Assurance form. These forms must be uploaded under the "Required Files" tab of the CDMRP eReceipt system.

VI. PROPOSAL REVIEW INFORMATION

A. Proposal Review and Selection Overview

1. Process: The CDMRP uses a two-tier review process for proposal evaluation. The two tiers differ fundamentally. The first tier is a scientific peer review of proposals against established criteria for determining scientific merit. The second tier is a programmatic review of proposals that compares submissions to each other and recommends proposals for funding based on scientific merit and overall goals of the program.

2. Peer Review: Peer review is conducted by scientific and consumer reviewers. The primary responsibility of the peer reviewers is to provide unbiased, expert advice on the scientific/technical merit and relevance of proposals based on the review criteria published for each award mechanism.

Scientific reviewers are selected for their subject matter expertise and experience with scientific peer review. Consumer reviewers are nominated by an advocacy or support

organization and are selected on the basis of their leadership skills, commitment to advocacy, and interest in science. Consumers augment the peer review process by bringing the patient perspective to the assessment of science and the relevance of the research.

The peer review summary statement is a product of scientific peer review. Each summary statement includes the peer review scores and an evaluation of the project as assessed by the peer reviewers according to the evaluation criteria published in this program announcement.

3. Programmatic Review: Programmatic review is conducted by the Integration Panel, which is composed of scientists, clinicians, and consumer advocates. The scientific members of the Integration Panel represent diverse disciplines and specialty areas, and the consumer members represent national advocacy constituencies. A function of programmatic review is to structure a broad portfolio of grants across all disciplines. Programmatic review is a comparison-based process in which proposals from multiple research areas compete in a common pool. Integration Panel members base programmatic review primarily on the peer review summary statements and the proposal abstracts. The Integration Panel also may review SOWs. Full proposals are not forwarded to programmatic review.

HBCU/MI proposals are reviewed concurrently with others in the same research area during scientific peer review. However, they may be evaluated separately during programmatic review. Consistent with the CDMRP's goal, recommendations for funding HBCU/MI proposals are based on scientific excellence and program relevance.

B. Review Criteria

1. Peer Review

a. Proposal: NF Consortium Award proposals will be evaluated with emphasis on the ***infrastructure, architecture, and governance*** of the consortium. Specifically, the reviewers will evaluate:

- **Personnel**
  - The extent to which the applicant and other key personnel at the Operations Center have expertise in the design, administration, and financial management of multi-institutional NF1 clinical studies, including the distribution and management of funds.
  - Whether consortium personnel at the participating clinical sites have appropriate training, experience, and expertise in NF1 clinical research/trials, particularly Phase I clinical trials and multi-institutional studies.
  - The capability of the institutional Clinical Coordinators to guide clinical protocols through the regulatory approval processes and interact with other consortium Clinical Coordinators.
  - The qualifications of the Supervising Clinical Coordinator who will interact with all Clinical Coordinators to coordinate regulatory approvals and consortium activities.

- Whether a coordinator responsible for managing and resolving intellectual and material property issues among consortium institutions is named.
- The extent to which all participating personnel are willing to commit adequate time, resources, and human subjects to the consortium.

- **Institutional Resources and Commitment**
  - The evidence for institutional commitment from each participating institution, and for the availability of sufficient resources to support the consortium at each participating institution.
  - Evidence that each participating clinical research site possesses sufficient expertise in the following disciplines within each participating clinical research site: oncology, dermatology, basic research science, neurology, genetics, radiology, pathology, neurosurgery, plastic surgery, orthopedics, neuropsychology, ophthalmology, pediatrics, and pain management.
  - The adequacy of resources and expertise for specimen collection and processing at each participating clinical research site.
  - Adequacy of resources and expertise for data management and maintenance of security/confidentiality at each participating clinical research site.
  - Intellectual and material property plan that is agreed upon by all participating institutions.
- **Consortium Structure and Governance**
  - The suitability and thoroughness of the charter and by-laws included in the proposal.
  - Whether the proposal includes all required consortium components (e.g., Governing Body, Operations Center, and clinical research sites).
  - The extent to which the various components of the consortium will function as an integrated unit.
  - The plans for real-time communication between the Operations Center and all participating clinical research sites.
  - The plans for the financial management of the consortium.
  - The plans for recruiting additional clinical research sites to join the consortium as full members and/or to participate in consortium studies on an ad hoc basis.
- **Clinical Protocol Development and Human Subjects Protection**
  - Evidence of access to an appropriate and sufficiently large NF1 population.
  - Inclusion of a protocol and supporting clinical documents for at least one NF1 ***therapeutic*** clinical trial (i.e., not a natural history study).
  - Inclusion of protocols and supporting documents for each trial/study ranked in order of priority if more than one clinical trial/study is proposed for implementation during the award period.

- The plans for coordinating and addressing institutional IRB and HSRRB submissions and approvals for all consortium protocols.
- The plan for ensuring compliance with FDA regulations for investigational agents.
- How well quality of life issues for all participants involved in consortium studies were addressed.
- The plans for the development, submission, review, and implementation of new clinical trials (as appropriate).

- **Study and Data Management**
  - Whether coordinated and comprehensive plans for data collection, data management, and statistical analysis are presented in the proposal.
  - Whether these plans provide real-time access to data, data security, and data integrity.
  - The plans for ensuring standardization of study procedures across sites and among staff.
  - Appropriateness of study management plan, including plans for quality control, quality assurance, and study monitoring.
  - The quality and completeness of the plans for specimen handling, distribution, analysis, and banking agreed upon by all consortium institutions.
  - The plans for rapid publication and other public dissemination of data generated by the consortium, and evidence that all relevant privacy issues have been addressed.
- **Budget**
  - Whether the budget is appropriate for the proposed research, and adequate to support the consortium's administrative and clinical activities during the award period.

b. Protocols: Each submitted NF Consortium Award clinical trial protocol will be evaluated with emphasis on ***scientific rationale and study design, clinical impact, ethical issues, and compliance with applicable regulatory requirements.*** Specifically, the reviewers will evaluate:

- **Study Design**
  - Whether the trial is focused on a therapeutic intervention for NF1. If more than one protocol is submitted, whether at least one of the trials is focused on an NF1 therapeutic intervention.
  - How the scientific rationale supports the proposed trial and its feasibility as demonstrated by a critical review and analysis of the literature, preliminary data, and logical reasoning.
  - How well the aims, hypothesis or objectives, experimental design, methods,

and analyses are developed.

- Appropriateness of the recruitment, informed consent, and screening processes.
- Adequacy of the description of the research, research intervention, or activity that the participant will experience.
- Adequate description of an IND or IDE (if applicable).

- **Feasibility**
  - Clinical feasibility and promise of the proposed study.
  - Availability of subjects for the clinical trial, the prospect of their participation, and the likelihood of subject attrition.
  - Reasonable and realistic recruitment schedule.
  - Evidence of the availability and quality of the substance to be used in the clinical trial.
  - If a drug, biologic, or device has been budgeted, evidence of a cost-sharing plan.
- **Clinical Impact**
  - How the study makes an original and important contribution to the goal of advancing research on the treatment and/or management of NF1.
  - The difference this proposal will make, if successful, on NF1 research or patient care.
  - The magnitude and scope of the project's potential clinical applications, benefits, and risks.
- **Personnel and Environment**
  - Whether the applicant meets the eligibility requirements.
  - The extent to which the applicant and research team possess the background, experience, and expertise to accomplish the proposed work (i.e., statistical expertise, expertise in NF1, and clinical trials).
  - Whether or not the levels of effort are consistent with the successful conduct of the proposed work.
  - How well the roles and responsibilities of all study personnel are described.
  - Evidence for an appropriate clinical setting and the availability of institutional resources to support the study at each participating center.
  - The qualifications of Medical Monitor (if applicable).
- **Statistical Plan**
  - How well a clear statistical plan, including sample size projections and power analysis, are outlined in the proposal.

- The adequacy of described data collection procedures to be used in conducting the study.
- Consistency of data analysis plan with the study objectives.

- **Ethics and/or Regulatory Issues**
  - How well ethical considerations such as informed consent, information privacy, and the assessment of risks and benefits for participants have been addressed.
  - The plan for the study investigators to complete an ethics training program and a course in the conduct of clinical research in accordance with GCP within 1 year of protocol initiation.
  - The plan for dealing with adverse events, which should include named agencies or offices to be notified in this event.
  - The plan for data disposition during and after the clinical trial.
  - The proposed procedures for protocol modifications during the course of the study.
  - The plans for data and safety monitoring.
  - Progress toward obtaining local IRB approval of the clinical protocol and Informed Consent form.
  - Documentation that an IND/IDE has been submitted (if applicable).
  - The FDA regulatory components of IND/IDE trials (if applicable).

2. Programmatic Review: Criteria used by the Integration Panel to make funding recommendations that maintain the NFRP's broad portfolio include:

- Ratings and evaluations of the peer reviewers (scientific and consumer),
- Programmatic relevance,
- Relative innovation and impact,
- Program portfolio balance,
- Unique consortium or institutional resources and/or expertise that could serve as the basis for the development of clinical protocols that are of programmatic interest, and
- Adherence to the intent of the award mechanism.

Scientifically sound proposals that best fulfill the above criteria and most effectively address the unique focus and goals of the program are selected by the Integration Panel and recommended for funding to the Commanding General, USAMRMC.

VII. AWARD ADMINISTRATION INFORMATION

A. Award Notices: Each applicant will receive notification of the award status of his or her proposal. A copy of the peer review summary statement will be posted to the CDMRP eReceipt system. Applicants can expect to receive notification approximately four weeks after programmatic review.

B. Administrative Requirements: Awards are made to organizations, not individuals. An applicant must submit a proposal through, and be employed by or affiliated with, a university, college, nonprofit research institution, commercial firm, or Government agency (including military laboratories) to receive support. A prospective recipient must meet certain minimum standards pertaining to institutional support, financial resources, record of performance, integrity, organization, experience, operational controls, facilities, and conformance with safety and environmental statutes and regulations (OMB Circular A-110 and DOD Grant and Agreement Regulations) to be eligible for an award. ***Any organization requesting receipt of an award through this announcement must be registered in the Central Contractor Registration (CCR) database. Access to the CCR online registration is through the CCR homepage at http://www.ccr.gov.***

Proposals from Federal agencies ***must*** provide a plan delineating how all funds will be obligated by September 30, 2007, and how funds will be available to cover research costs over the entire award period. The plan must include the funding mechanism(s) that will be used to carry over funds between fiscal years, such as administrative agreements with foundations, non-Federal institutions, and universities.

Transferring the award from the original institution will not be permitted for the NF Consortium Award.

C. Award Negotiation: Award negotiation consists of discussions, reviews, and justifications of critical issues involving the USAMRAA. A Contract Specialist and/or representative from the USAMRAA will contact the Contract Representative authorized to negotiate contracts and grants at the applicant's institution. Additional documentation and justifications related to the budget may be required as part of the negotiation process.

For multi-institutional studies, collaborating institutions must be willing to resolve potential intellectual and material property issues and remove institutional barriers to achieving high levels of cooperation to ensure the successful establishment and maintenance of the research project. An intellectual and material property plan agreed to by all participating institutions may be required during award negotiations.

The award start date will be determined during the negotiation process.

Clinical trials must begin within 6 months of the award date. If an IND or IDE is required, additional time may be granted. However, preference will be given to protocols that have FDA approval at the time the award is made. Local IRB approvals should be in process or completed before submission of the proposal to the NF Consortium Award mechanism.

D. Regulatory Review

1. Overview: Concurrent with the USAMRAA negotiation, the Office of Surety, Safety and Environment will review the Certificate of Environmental Compliance and the Principal Investigator Safety Program Assurance form submitted with the proposal. The applicable USAMRMC regulatory office will review documents related to research involving animal use, human subjects/anatomical substance use, and cadaver use submitted upon request to ensure that DOD regulations are met. Applicants who are approved for funding may be required to attend a pre-award meeting and protocol workshop in the Baltimore, MD–Washington, DC area after notification of award status and before disbursement of funds. FY06 NFRP NF Consortium Award recipients also must prepare oral and written briefings for presentation to the EAB and USAMRMC at semi-annual 1-day meetings in the Baltimore, MD–Washington, DC area.

2. Certificate of Environmental Compliance: The Certificate of Environmental Compliance must be submitted with the proposal. If multiple research sites/institutions are funded in the proposal, then a Certificate of Environmental Compliance for each site will be requested at a later date.

3. Safety Program Documents: The Principal Investigator Safety Program Assurance form must be submitted with the proposal.

A Facility Safety Plan is required; it will be requested at a later date. A Facility Safety Plan from the applicant's institution may have been received previously and approved by the USAMRMC. A list of institutions that have approved Facility Safety Plans can be found on the USAMRMC website at https://mrmc.detrick.army.mil/crprcqsohdfsplan.asp. If the applicant's institution is not listed on the website, contact the institution's Facility Safety Director/Manager to initiate completion of the institution-based Facility Safety Plan. Specific requirements for the Facility Safety Plan can be found at https://mrmc.detrick.army.mil/docs/rcq/FY02FSPAppendix.doc.

If multiple research sites/institutions are funded in the proposal, a Facility Safety Plan for each site/institution not listed in the aforementioned website will be requested at a later date.

4. Research Involving Animal Use: Not applicable for this award mechanism.

5. Research Involving Human Subjects/Biological Substances/Cadavers: In addition to local IRB approval to conduct research involving human subjects and/or human biological substances or cadavers, a second tier of IRB review and approval also is required by the DOD. This second review is conducted by the HSRRB, which is administered by the USAMRMC Office of Research Protections. The HSRRB is mandated to comply with specific laws and directives governing all research involving human subjects that is conducted or supported by the DOD. These laws and directives are rigorous and detailed and will require information in addition to that supplied to the local review board.

a. Requirements: Specific requirements for research involving human subjects, human biological substances, and/or cadavers can be found at https://mrmc.detrick.army.mil/docs/rcq/HumanSubjectsAppendix.pdf.

Personnel involved in human subjects research must have appropriate instruction in the protection of human subjects. Documentation confirming that this instruction has been completed will be required during the regulatory review process.
It is expected that there will be timely resolutions of human subjects protocols submitted to the investigator's local IRB.

Additional information pertaining to the human subjects regulatory review process, guidelines for developing protocols, and suggested language for specific issues can be found at: https://mrmc.detrick.army.mil/rodorphrpo.asp.

b. Informed Consent Form: An Informed Consent form template is located at https://mrmc.detrick.army.mil/docs/rcq/Proconsent/ConsentFormGuidelines.doc.

c. Intent to Benefit: Investigators must consider the requirements of Title 10 United States Code Section 980 (10 USC 980) applicable to DOD-sponsored research before writing a research protocol. Title 10 United States Code Section 980 requires that "Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject."

Furthermore and consistent with the Common Federal Policy for the Protection of Human Subjects, if an individual cannot give his or her own consent to participate in a research study, consent of the individual's legally authorized representative must be obtained before the individual's participation in the research. Moreover, an individual not legally competent to consent (e.g., incapacitated individuals, incompetents, minors) may not be enrolled in DOD-sponsored research unless the research is intended to benefit each subject enrolled in the study. For example, a subject may benefit directly from medical treatment or surveillance beyond the standard of care. Investigators should be aware that this law makes placebo-controlled clinical trials problematic because of the "intent to benefit" requirement whenever participation is sought of subjects from whom consent must be obtained by the legally authorized representative.

d. Conditions Regarding DOD Funding of Research on Human Embryonic Stem Cells: Research involving the derivation and use of human embryonic germ cells from fetal tissue may be conducted with DOD support ***only*** when the research is in compliance with 45 CFR 46, Subpart B (Title 45 of the Code of Federal Regulations, Section 46, Subpart B); 42 USC 289g through 289g-2; US Food and Drug Administration regulations; and any other applicable Federal, state, and local laws and regulations.

Research on existing human embryonic stem (hES) cell lines may be conducted with Federal support through the DOD ***only*** if the cell lines meet the current US Federal

criteria as listed on the following National Institutes of Health (NIH) website (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html). A list of the currently approved cell lines can be obtained from the NIH Human Embryonic Stem Cell Registry (http://stemcells.nih.gov/research/registry). The NIH code should be used to identify the cell lines in the proposal.

Research involving the derivation of new stem cells from human embryos or the use of hES cells not listed on the NIH Human Embryonic Stem Cell Registry may not be conducted with Federal support through the DOD.

This restriction applies to hES cells derived from blastocysts remaining after infertility treatments and donated for research, blastocysts produced from donated gametes (oocytes and sperm) for research purposes, and the products of nuclear transfer. The research is subject to all applicable local, state, and Federal regulatory requirements.

e. Clinical Trial Registry: All applicants are required to register clinical trials individually on http://www.clinicaltrials.gov/ using the Secondary Protocol ID number designation of: CDMRP-CDMRP Log Number. If several protocols exist under the same proposal, the Secondary Protocol ID number must be: CDMRP-CDMRP Log Number-A, B, C, etc. ***Clinical trials must be registered prior to enrollment of the first patient.*** All trials that meet the definition on the NIH database (see http://prsinfo.clinicaltrials.gov/, click on "Data Element Definitions," see section 6, "Study Phase" and "Study Type"), including all Phase I-IV clinical trials and trials that do not fit into one or more phases, but that are clearly interventional or observational (e.g., some epidemiological or behavioral studies) are required to register. Address questions on registration to the www.clinicaltrials.gov administrator.

6. Award/Regulatory Approval: The applicant may not use, employ, or subcontract for the use of any human subjects, human anatomical substances/cadavers, or laboratory animals without written approval from the applicable USAMRMC regulatory office once an award is made. The applicable USAMRMC regulatory office will forward written approvals directly to the applicant.

E. Reporting Requirements: The Government requires reports to be submitted for continuation of the research and funding. The specific reports due to the Government will be described in each award instrument. (Full USAMRMC reporting requirements can be found at https://mrmc-www.army.mil, under "Links and Resources.") ***Failure to submit required reports by the required date may result in a delay in or termination of award funding.***

Reporting requirements include the following:

1. Research Progress Reports: Reporting requirements consist of an annual report (for each year of research except the final year) that presents a detailed summary of scientific issues and accomplishments and a final report (submitted in the last year of the award period) that details the findings and issues for the entire project. Copies of all scientific publications and patent applications resulting from CDMRP funding should be included in the progress

reports. PIs also must prepare written and oral briefings to the EAB and USAMRMC staff at semi-annual meetings in the Baltimore, MD–Washington, DC area.

2. Fiscal Reports: Quarterly fiscal report requirements may include the Standard Form Report, SF 272, Federal Cash Transaction, used for grants and cooperative agreements to track the expenditure of funds on the research project.

3. Non-Exempt Human Studies Reports: For non-exempt human subjects research, documentation of local IRB continuing review (in the intervals specified by the local IRB but at least annually) and approval for continuation must be submitted directly to the Office of Research Protections – Human Research Protection Office.

4. Animal Use Reports: Not applicable for this award mechanism.

VIII. OTHER INFORMATION

A. Disclosure of Proprietary Information outside the Government: By submitting a proposal, the applicant understands that proprietary information may be disclosed outside the Government for the sole purpose of technical evaluation. The USAMRMC will obtain a written agreement from the evaluator that proprietary information in the proposal will only be used for evaluation purposes and will not be further disclosed or used. Funded proposals may be subject to public release under the Freedom of Information Act; proposals that are not selected for funding are not subject to public release.

B. Government Obligation: Applicants are cautioned that only an appointed Contracting/Grants Officer may obligate the Government to the expenditure of funds. No commitment on the part of the Government to fund preparation of a proposal or to support research should be inferred from discussions with a technical project officer. Applicants who, or organizations that, make financial or other commitments for a research effort in the absence of an actual legal obligation signed by the USAMRAA Contracting/Grants Officer do so at their own risk.

C. Information Service: Offerors may use the technical reference facilities of the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161, for the purpose of surveying existing knowledge and avoiding needless duplication of scientific and engineering effort and the expenditure thereby represented. All other sources also should be consulted to the extent practical for the same purpose.

D. Inquiry Review Panel: Applicants may submit a letter of inquiry to the USAMRMC in response to funding decisions made for a given proposal. Members of the CDMRP staff, the USAMRMC Judge Advocate General staff, and USAMRAA Grants Officers constitute an Inquiry Review Panel and review each inquiry to determine whether factual or procedural errors in either peer or programmatic review have occurred, and if so, what action should be taken.

E. Title to Inventions and Patents: In accordance with the Bayh-Dole Act (35 USC 200 et seq.), title to inventions and patents resulting from such Federally funded research may be held by the grantee or its collaborator, but the US Government shall, at a minimum, retain nonexclusive rights for the use of such inventions. An investigator must follow the instructions in the assistance agreement concerning license agreements and patents.

F. J-1 Visa Waiver: It is the responsibility of the awardee to ensure that the research staff is able to complete the work without intercession by the DOD for a J-1 Visa Waiver on behalf of a foreign national in the United States under a J-1 Visa.

IX. ACRONYM LIST

AVI	Audio Visual Interleave
CCR	Central Contractor Registration
CDMRP	Congressionally Directed Medical Research Programs
CFDA	Catalog of Federal Domestic Assistance
COI	Conflict of Interest
CR	Contract Representative
DOD	Department of Defense
EAB	External Advisory Board
EPLS	Excluded Parties List System
FAR	Federal Acquisition Regulations
FDA	US Food and Drug Administration
FY	Fiscal Year
GCP	Good Clinical Practice
HBCU/MI	Historically Black Colleges and Universities/Minority Institutions
hES	Human Embryonic Stem Cells
HSRRB	Human Subjects Research Review Board
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
JPEG	Joint Photographic Experts Group
LOI	Letter of Intent
M	Million
MB	Megabyte
MPEG	Moving Picture Experts Group
NFRP	Neurofibromatosis Research Program
NIH	National Institutes of Health
OMB	Office of Management and Budget
PDF	Portable Document Format
SOW	Statement of Work
TIFF	Tagged Image File Format
USAMRAA	US Army Medical Research Acquisition Activity
USAMRMC	US Army Medical Research and Materiel Command
USC	United States Code
WAV	Waveform