Announcement of Federal Funding Opportunity

Summary

I. GENERAL INFORMATION

The Fiscal Year 2005 (FY05) Appropriation Bill was signed by President Bush on August 5, 2004. This program announcement is being released prior to the receipt of funds appropriated in the bill for this research program; funding of proposals received in response to this program announcement is contingent on the receipt of funds at the United States Army Medical Research and Materiel Command (USAMRMC).

A. Title of Award: Clinical Trial Award (CTA).

B. Program Name: Department of Defense (DOD) FY05 Neurofibromatosis Research Program (NFRP).

C. Funding Opportunity Number: NF05-CTA.

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, proposal format, or required documentation may be addressed to the CDMRP at:

Phone:	301-619-7079
Fax:	301-619-7792
E-mail:	cdmrp.pa@det.amedd.army.mil
Mail:	Commander US Army Medical Research and Materiel Command ATTN: MCMR-ZB-C (NF05-CTA) 1077 Patchel Street (Building 1077) Fort Detrick, MD 21702-5024

2. Questions related to electronic submission: The help line phone number(s) is 301-682-5507 and is also provided on the Web. Other help desk contact information is:

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

F. Anticipated Instrument Type(s): Grants/Cooperative Agreements.

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

H. Website Address to Access Application Package: Proposals must be submitted electronically at https://cdmrp.org. The website contains all the information, forms, documents, and links needed to apply.

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

Applicants who are approved for funding for the award mechanism under this announcement may be required to attend a pre-award meeting and protocol workshop at Fort Detrick, Maryland.

II. FUNDING OPPORTUNITY DESCRIPTION

The goal of the Clinical Trial Award mechanism is to sponsor novel clinical research, specifically a Phase I or Phase II clinical trial that has the potential to substantially improve today's approach to the treatment and/or management of neurofibromatosis 1 (NF1), NF2, and/or Schwannomatosis.

III. AWARD INFORMATION

- Type of award: grant/cooperative agreement.
- Approximately $2.8 million (M) is available to fund the FY05 NFRP Clinical Trial Awards.
- Depending on the number and quality of the applications, it is anticipated that one to two proposals will be funded.
- Although there are no total dollar amount restrictions to these awards, programmatic priority will be given to smaller-scale, cost-efficient clinical trials. Funding for Phase I clinical trials can be requested for up to 3 years, whereas funding for Phase II clinical trials can be requested for up to 4 years.

IV. ELIGIBILITY INFORMATION

A. Applicants: 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 below.

B. Institutions: Eligible institutions include for-profit, nonprofit, public, and private organizations.

C. Cost Sharing: It is expected that institutions will cost share. Please see "Major Equipment" located in Subsection V.H.2.c of the Full Text of Program Announcement for details.

D. Other Eligibility Criteria: Please see the Full Text of Program Announcement description for details regarding duplicate submissions, applications from Historically Black Colleges and Universities/Minority Institutions (HBCU/MI), and administrative compliance issues.

V. PROPOSAL PREPARATION AND SUBMISSION INFORMATION

A. Proposal Information: Applicants are required to submit the Proposal Information prior to upload of the proposal. Complete the Proposal Information as described at https://cdmrp.org.

B. Proposal Preparation: All proposals must be converted into an electronic PDF (Portable Document Format) file for electronic proposal submission. Please see the Full Text of Program Announcement for details.

C. Submission Date and Time: Deadline: February 22, 2005. Proposals must be approved on the CDMRP eReceipt system by the Contract Representative at the applicant's institution's Sponsored Programs Office (or equivalent) by 5:00 p.m. Eastern time.

D. Electronic Submission Requirements: Electronic submission is required. No paper copy submissions will be accepted. Proposals must be submitted electronically at https://cdmrp.org. Please see the Full Text of Program Announcement for details.

VI. PROPOSAL REVIEW INFORMATION

The CDMRP uses a two-tier review process for proposals: scientific peer review, followed by programmatic review. Details of both tiers of review can be found in the Full Text of Program Announcement.

VII. AWARD ADMINISTRATION INFORMATION

A. Award Notices and Administrative Requirements: Details of award notification procedures and administrative requirements including regulatory documents (Certificate of Environmental Compliance, Research Involving Human Subjects and/or Anatomical Substances, Research Involving Animals, and Safety Program Plan) can be found in the Full Text of Program Announcement.

B. Reporting Requirements: Annual reporting requirements apply.

C. Reverse Site Visit: One reverse site visit per award is anticipated in the Baltimore-Washington, DC area during the period of performance.

Full Text of Program Announcement

I. GENERAL INFORMATION

The Fiscal Year 2005 (FY05) Appropriation Bill was signed by President Bush on August 5, 2004. This program announcement is being released prior to the receipt of funds appropriated in the bill for this research program; funding of proposals received in response to this program announcement is contingent on the receipt of funds at the United States Army Medical Research and Materiel Command (USAMRMC).

A. Title of Award: Clinical Trial Award (CTA).

B. Program Name: Department of Defense (DOD) FY05 Neurofibromatosis Research Program (NFRP).

C. Funding Opportunity Number: NF05-CTA.

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, 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@det.amedd.army.mil
Mail:	Commander US Army Medical Research and Materiel Command ATTN: MCMR-ZB-C (NF05-CTA) 1077 Patchel Street (Building 1077) Fort Detrick, MD 21702-5024

2. Questions related to electronic submission: Help lines will be available to answer specific questions regarding the preparation of proposals for electronic submission or the process of electronic submission. The help line phone number is 301-682-5507 and is also provided on the Web. Other help desk contact information is:

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

F. Anticipated Instrument Type(s): The USAMRMC implements 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@det.amedd.army.mil
Mail:	Director US Army Medical Research Acquisition Activity ATTN: MCMR-ZB-A 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 electronically at https://cdmrp.org. This website will contain all the information, forms, documents, and links needed to apply. If you experience difficulties in downloading documents, contact the CDMRP as indicated in Subsection E.2 above.

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

Applicants who are approved for funding for the award mechanism under this announcement may be required to attend a pre-award meeting and protocol workshop at Fort Detrick, Maryland.

II. FUNDING OPPORTUNITY DESCRIPTION

A. Program History: The Clinical Trial Award is part of the DOD NFRP, which was established in FY96 to promote research directed toward decreasing the impact of neurofibromatosis (NF). Appropriations for the NFRP since FY96 total $155.3 million (M). The program history of the FY96-04 NFRP is shown in Table 1. The FY05 appropriation is $25M.

Table 1: History of the DOD's Peer Reviewed NFRP

Program History	FY96-03	FY04
Congressional Appropriations for NFRP	$110.3M	$20M
Total Proposals Received	361	95
Total Proposals Funded	117	~21[1]
Clinical Trial Award Proposals Received	11	3
Clinical Trial Award Proposals Funded	2	0

[1]Includes two FY03 proposals funded with FY04 appropriations. Award negotiations will be finalized by September 2005.

B. Program Objectives: The overall goal of the FY05 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. Additionally, proposals that address the needs of minority, low-income, rural, and other underrepresented and/or medically underserved populations may be submitted from any eligible institutional source. Proposals are encouraged from investigators working at Historically Black Colleges and Universities/Minority Institutions (HBCU/MI).

C. Award Mechanism Description: The intent of Clinical Trial Awards is to sponsor clinical research with the potential to have a major impact on the treatment and/or management of NF1, NF2, and/or Schwannomatosis. Clinical Trial Awards will support Phase I and Phase II clinical trials; separate discussions are provided below for each type of clinical trial. Applicants should clearly specify in their proposals which type of Clinical Trial Award is being requested (i.e., Phase I or Phase II).

Phase I Clinical Trials

These trials should focus on determining the safety, toxicity, tolerability, and pharmacokinetics/pharmacodynamics of new interventions or devices, or treatment schedules in humans. It is expected that this award will allow the recipient the opportunity to obtain the data and experience necessary to conduct a Phase II clinical trial, if appropriate. Applicants for Phase I trials must include a clear scientific rationale for the trial as well as adequate preclinical supplemental data to support the feasibility of their hypotheses and approaches. Applicants must include a detailed plan for completing the Phase I trial during the award and a clear experimental and appropriately powered statistical plan to perform the clinical trial. Phase I applicants are encouraged to pursue correlative studies.

Phase II Clinical Trials

These trials should focus on defining the efficacy of new interventions or devices. Applicants for Phase II clinical trials must include Phase I or pilot clinical trial data, adequate preclinical supplemental data to support the feasibility of their hypotheses and approaches, and a detailed

plan for completion of the Phase II clinical trial during the award. **Applicants also must include a clear experimental and appropriately powered statistical plan to perform the Phase II clinical trial.** Applicants are encouraged to submit studies that further test the safety of a novel combination of agents before it is used on a larger number of participants in a Phase III clinical trial. Applicants also are encouraged to pursue correlative studies.

If the trial is multi-institutional, applicants should include plans for communication and real-time data transfer between the collaborating institutions as well as how specimens and/or imaging products obtained during the study will be handled in the appropriate sections of the main body of the proposal (see Subsection V.F.6.e). An intellectual and material property plan agreed upon by all participating institutions is also required for multi-institutional clinical trials as part of the administrative documentation of this proposal (see Subsection V.F.6.f).

Please note that all DOD-funded research involving human subjects, human anatomical substances, cadavers, and/or laboratory animals must be reviewed and approved by the USAMRMC Human Subjects Research Review Board (HSRRB) in addition to local Institutional Review Boards (IRBs). It is recommended that all protocols be prepared according to the guidelines provided in the document titled "Research Involving Human Subjects and/or Anatomical Substances," which can be found at https://cdmrp.org/Program_Announcements_and_Forms under "Regulatory Document Forms." An HSRRB-approved template for clinical protocols also can be found at this site.

All proposals for the Clinical Trial Award should include:

- The objective(s) and rationale of the proposed clinical trial, including any preclinical science and preliminary clinical research relevant to the trial to include data supporting the feasibility of the hypothesis and approaches;
- The relevance of the proposed clinical trial to NF1, NF2, or Schwannomatosis;
- A clear description of the particular target, pathway, molecule, or device that is the focus of the clinical trial;
- The proposed intervention(s) to be tested in the clinical trial and a brief description, as appropriate, of its:
    - Source,
    - Investigational New Drug (IND) status,
    - Evidence of the availability of the substance in sufficient quantity under current Good Manufacturing Practice (cGMP) production. If the substance is to be provided from industrial sources, evidence of a cost-sharing plan also must be provided,
    - Dosing and toxicity,
    - Mechanisms of action, and
    - Preclinical/clinical evidence of efficacy.

- A named study coordinator who will guide the clinical protocol through the IRB, HSRRB, and other regulatory approval processes, coordinate activities from all sites participating in the trial, and coordinate participant accrual;
- The sample size for the clinical trial with appropriate statistical analyses presented to verify power for the sample size; a participant accrual/recruitment schedule including inclusion and exclusion criteria; and evidence of access to appropriate participant population(s) that support rapid execution of the Clinical Trial Award following receipt of funds;
- A clinical protocol, a Manual of Operations and Procedures (if available), and informed consent/assent form(s) that include HSRRB-prescribed content and address human subjects protection requirements as outlined by the HSRRB at https://cdmrp.org/Program_Announcements_and_Forms under "Regulatory Document Forms";
- Internal scientific and local IRB review documents for the clinical protocol and informed consent forms that indicate the level of IRB review achieved prior to submission to the Clinical Trial Award. Indicate the highest possible level of IRB review within the participating institutions prior to submission of a proposal;
- A clinical trial management plan, including a plan for ensuring the standardization of procedures across sites and among staff;
- Evidence of institutional commitment(s) for the proposed clinical trial; and
- A description of the clinical trial team to include names, background, qualifications, time commitments, and contributions made to the trial.

The Clinical Trial Award is not limited to therapeutic studies. Applicants also are encouraged to submit proposals focusing on the development of endpoints and tools for measuring outcomes. However, as noted above, a clinical trial must be conducted as part of the study.

III. AWARD INFORMATION

Although there are no total dollar amount restrictions to these awards, programmatic priority will be given to smaller-scale, cost-efficient clinical trials. Approximately $2.8M is available for this award mechanism. Depending on the number and quality of the applications, it is anticipated that approximately one to two proposals will be funded.

Funding for Phase I clinical trials can be requested for up to 3 years, whereas funding for Phase II clinical trials can be requested for up to 4 years. Direct costs can cover salary, expenses including research supplies, and travel to scientific meetings. The amount for this travel may not exceed $1,800 per year per investigator. Applicants also should budget for travel to a pre-award meeting and protocol workshop at Fort Detrick, Maryland, and a reverse site visit in the Baltimore-Washington, DC area during the period of performance.

Applicants must provide evidence of sufficient institutional support and commitment for the proposed studies, such as the provision of access to adequate laboratory facilities and equipment.

Consideration of cost sharing with other funding sources and multi-institutional/multidisciplinary research collaborations are encouraged. Applicants are encouraged to use the existing infrastructures of the NFRP-funded NF1 and NF2 natural history studies as infrastructures for their proposed clinical trials. The nature of this Program does not allow for renewal of grants or supplementation of existing grants with DOD funds.

IV. ELIGIBILITY INFORMATION

A. Applicants: 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 below.

B. Institutions: Eligible institutions include for-profit, nonprofit, public, and private organizations. Examples include universities, colleges, hospitals, laboratories, companies, and agencies of local, state, and federal governments. The USAMRMC is especially interested in receiving applications from HBCU/MI.

C. Cost Sharing: It is expected that institutions will cost share. Please see full details under "Major Equipment" in Subsection V.H.2.c.

D. Other Eligibility Criteria

1. Duplicate Submissions: Submission of the same research project to the FY05 NFRP under different award mechanisms or to other CDMRP programs is discouraged. The Government reserves the right to reject duplicative proposals.

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

3. 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. Nonadherence 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 or a lower global priority score.

The following will result in administrative rejection of the entire proposal prior to peer review:

- Font size is less than 12 point.

[1] Executive Orders 12876, 12900, and 13021

- Font type is not Times New Roman.
- Line spacing is greater than six lines per vertical inch.
- Margins are less than 0.5 inch on any side.
- Proposal body exceeds page limit.
- Proposal body is missing.
- Clinical protocol is missing.
- Detailed cost estimate is missing.
- Proposal is incomplete after the deadline.

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

Unless specifically requested by the Government, any material submitted after the submission deadline will not be forwarded for peer review.

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.

The Principal Investigator (PI) is responsible for uploading the following information:

- **Proposal Information:** The Proposal Information consists of two parts, both of which are entered as data fields. A Letter of Intent is generated when Part 1 of the Proposal Information is saved.
- **Proposal Contacts:** Contact information for both the PI and the Contract Representative is required to complete the proposal submission process.
- **Statement of Work (SOW) and Proposal Abstracts:** The SOW, Technical Abstract, and Public Abstract are each entered as a separate data field.
- **Proposal:** The proposal is uploaded as a PDF (Portable Document Format) file under the "Required Files" tab.
- **Clinical Protocol and Supporting Clinical Documents:** The clinical protocol and supporting clinical documents are uploaded as a PDF file under the "Required Files" tab.
- **Budget Information:** The budget information is uploaded as a PDF file under the "Required Files" tab.
- **Regulatory Documents:** The Certificate of Environmental Compliance and the Principal Investigator Safety Program Assurance form are each uploaded as separate PDF files under the "Required Files" tab.

The Contract Representative or institutional official responsible for sponsored program administration (or equivalent) from the applicant's institution is responsible for the following:

- **The Contract Representative's contact information profile must be completed prior to electronic approval of all proposal components.**
- **USAMRAA Required Documents:** The institution's currently negotiated "Rate Agreement," "Certifications and Assurances for Assistance Agreements," and the "Representations for Assistance Agreements" are to be uploaded as separate PDF files under the Contract Representative's "My Profile" tab.
- **Approval:** The Contract Representative or institutional official responsible for sponsored program administration (or equivalent) must provide approval of all proposal components (Proposal Information, Proposal Contacts, SOW, Abstracts, Proposal, Clinical Protocol and Supporting Clinical Documents, Budget Information, and regulatory documents). Contract Representative approval must occur prior to the submission deadline of 5:00 p.m. Eastern time February 22, 2005. The eReceipt system will **not** accept data entry, file uploads, or approvals submitted after the 5:00 p.m. Eastern time deadline.

B. Proposal Information: Applicants are required to submit the Proposal Information, Parts 1 and 2, prior to upload of the proposal and the budget information. Complete the Proposal Information as described in https://cdmrp.org. The Proposal Information **must** include the e-mail address of a representative from the Sponsored Programs Office (or equivalent) who is authorized to negotiate on behalf of the institution. The Proposal Information may be "Verified & Saved" for editing purposes until "Submit Final" for approval by their Sponsored Programs Office's (or equivalent's) representative.

- **Letter of Intent:** An electronic Letter of Intent should be submitted by January 25, 2005. To accomplish this, the applicant should complete Part 1 of the Proposal Information section at https://cdmrp.org, then save the information by clicking on the "Save and Forward Letter of Intent" button. This information may be changed at any time until the applicant submits the final Proposal Information by clicking on the "Submit Final" button.

C. Proposal Contacts: The Proposal Contacts **must** include the e-mail address of a representative from the Sponsored Programs Office (or equivalent) who is authorized to negotiate on behalf of the institution. The Proposal Contacts must be "Finalized" for approval by the applicant's Sponsored Programs Office's (or equivalent) representative.

D. SOW – 11,400-character limit, including spaces (approximately two pages): The SOW is captured as a data field under the "SOW/Abstract" tab in the CDMRP eReceipt system. To submit the SOW, the applicant may either type in the SOW or "cut and paste" it from a word processing application into the data field. Sample SOWs can be found at https://cdmrp.org/samples.cfm.

The SOW is a concise restatement of the research proposal that outlines, step by step, how each of the major goals or objectives of the proposed research/services 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 (animal or human) projected or required for each task;
- Identify methods; and
- Identify outcomes, products, and deliverables for each phase of the project.

E. Proposal Abstracts – 5,700-character limit, including spaces (approximately one page), for each abstract: Both a structured technical abstract and a public (nontechnical) abstract are required. These abstracts are vitally important to both the peer and programmatic review process.

Programmatic review is based on the Integration Panel's (IP's) review of these two abstracts as part of the peer review summary statements; therefore, it is paramount that the PI submit abstracts that fully describe the proposed work.

Each abstract must contain the title of the proposal and the name of the PI. Each abstract must be submitted as a data field under the "SOW/Abstracts" tab of the CDMRP eReceipt system. Applicants can either type in their abstracts or "cut and paste" them from a word processing application into the respective data fields. Do not include figures or tables in either abstract. Spell out all Greek or other non-English letters.

Abstracts of all funded proposals will be posted on the CDMRP website at https://cdmrp.army.mil. Thus, proprietary or confidential information should not be included in the abstract.

1. Technical Abstract: Sample technical abstracts can be found at https://cdmrp.org/samples.cfm. The structured technical abstract should provide a clear and concise overview of the proposed work, including the background, objective, or hypothesis and its supporting rationale, specific aims of the study, study design, and significance of the proposed work to the Program's goals.

Use the outline below for preparing the structured technical abstract.

- Background: Provide a brief statement of the ideas and reasoning behind the proposed clinical trial. Briefly describe the studies that led to the proposed clinical trial.
- Intervention: State the intervention or device to be tested. Provide evidence or rationale that supports the intervention or device.

- Trial Design: Briefly describe the proposed clinical trial, including proposed participant sample size, accrual, and outcome measures. Indicate the phase (I or II) of the clinical trial.
- Relevance: Provide a brief statement explaining the relevance of the proposed clinical trial to the treatment and/or management of NF1, NF2, and/or Schwannomatosis.

2. Public Abstract: Sample public abstracts can be found at https://cdmrp.org/samples.cfm. The public abstract is intended to communicate the purpose of, and rationale for, the study to non-scientific audiences. 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. It must be composed in a way to make the scientific objectives and rationale for the proposal understandable to non-scientifically trained readers. **The public abstract should not be a duplicate of the technical abstract**, but should describe the goals and objectives of the research project and its relevance to the Program.

In addition to describing the project, the public abstract must answer the following questions:

(1) What are the ideas and reasoning behind the proposed clinical trial?

(2) What will be the ultimate applicability of the clinical trial to NF1, NF2, and/or Schwannomatosis?

- What types of affected individuals will it help and how?
- What are the potential clinical applications, benefits, and risks?
- What is the projected time it may take to achieve a consumer-related outcome?

F. Proposal

1. Format: All proposal components (proposal body, biographical sketches, publications, letters of support, etc.) must be converted into a single PDF file for electronic submission. Proposals must be uploaded under the "Required Files" tab of the CDMRP eReceipt system. Applicants unfamiliar with the preparation of PDF files are encouraged to acquire appropriate software and learn the process before the submission deadline. To prepare proposals for PDF submission, the instructions in this subsection must be followed carefully.

Please Note New Format Requirements

The proposal must be clear and legible and conform to the following guidelines:

- **Font size: 12 point or larger.**
- **Font type: Times New Roman.**
- **Spacing: Single-spaced between lines of text, no more than six lines of type within a vertical inch.**

- **Margins: Minimum of 0.5 inch in all directions.**
- **Print area: 7.5 inches x 10.0 inches (approximately 19 cm x 25.5 cm).**

Failure to adhere to the requirements for font size, font type, spacing, margins, and print area will result in administrative rejection of the entire proposal prior to peer review.

- Color, 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, but applicants should keep in mind that 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.
- Language: English.

2. Title/Referral Page: No page limit. Complete the Title/Referral Page. Please note that all forms are available on the "Summary Tab" of eReceipt. Complete each section as described:

a. Proposal title (up to 160 characters).

b. Proposal log number (this will be automatically provided when the Proposal Information is completed and saved).

c. PI's full name (first, middle initial, last).

d. Submitting institution.

e. Award mechanism: Type in "Clinical Trial Award." Indicate the clinical trial phase (Phase I or II).

f. Indicate if this is a NEW proposal or a RESUBMITTED proposal to this program.

g. Keyword descriptive technical terms: To assist the staff in assigning proposals to the appropriate scientific peer review panel, please specify the subject area of the proposal. Also, list specific keywords and descriptive technical terms that would best describe the technical aspects of the project.

h. Conflicts of interest: To avoid real and apparent conflicts of interest during the review process, list the names of all scientific participants in the proposal including consultants, collaborators, and subawardees. In addition, list the names of other individuals outside the scope of this proposal that may have a conflict of interest in the review of this proposal. Provide the following information for each participant: name, institutional affiliation(s), and, if applicable, his or her role(s) on the proposed project.

3. Table of Contents/Checklist: Start section on a new page; two-page limit. Prepare a Table of Contents/Checklist, with page numbers. Number all pages consecutively at the bottom center, beginning with the Title/Referral Page. 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.

4. Proposal Relevance Statement: Start section on a new page; one-page limit. Applicants should state explicitly how the proposed clinical trial will have a major impact on the treatment and/or management of NF1, NF2, or Schwannomatosis.

5. Proposal Resubmission Statement (suggested for resubmissions): Start section on a new page; two-page limit. Proposals that have been declined for funding in a previous year may be resubmitted to the FY05 NFRP. Resubmitted/revised proposals must meet all requirements for the Clinical Trial Award mechanism described in this program announcement. If an applicant designates the proposal as a resubmission, the resubmission box on the Title/Referral page must be marked, and a two-page Proposal Resubmission Statement and the previous year's peer review summary statement must be included with the proposal. This two-page Proposal Resubmission Statement must address the issues identified in the peer review summary statement of the previously unfunded submission. In addition, this section must address all aspects of the critique from the previous peer and programmatic reviews, and it should reference any new preliminary data. A copy of the summary statement from the unfunded submission also must be included and placed immediately after the two-page Resubmission Statement.

Applicants should be aware that the year-to-year status of funding for the NFRP does not permit establishment of standing panels for scientific peer review. Therefore, the submission of a revised proposal does not guarantee funding or an improved global priority score.

6. Main Body: Start section on a new page; 25-page limit inclusive of any figures, tables, graphs, photographs, diagrams, chemical structures, pictures, pictorials, cartoons, and other relevant information needed to judge the proposal. All Clinical Trial Award applicants must submit promising and well-founded preliminary data relevant to NF and/or Schwannomatosis and the proposed project. In addition, the inclusion of Phase I or pilot clinical trial data is required for Phase II clinical trial applicants.

Describe the proposed project using the following general outline. The main body of the proposal will be reviewed as a stand-alone document. Therefore, include the appropriate information from the clinical protocol to discuss the topics listed below. Do not reference the clinical protocol.

a. Background: Describe the ideas and reasoning behind the proposed work and previous experience most pertinent to the proposal. Cite relevant literature references.

b. Rationale: State the purpose of the study and the expected results.

c. Objectives: State the specific aims of the study.

d. Preliminary Studies: Present the studies that led to the proposed clinical trial. In addition, Phase II clinical trial applicants must provide Phase I or pilot clinical trial data.

State the relevance of the proposed clinical trial to the treatment and/or management of NF1, NF2, and/or Schwannomatosis.

e. Methods and Data Analyses: Provide a brief discussion of the topics listed below.

- Include a named study coordinator who will be charged with guiding the protocol through the IRB, HSRRB, and other regulatory approval processes, coordinating activities from all sites participating in the trial, and coordinating participant accrual.
- Description of the intervention or device to be tested. Provide evidence that a sufficient quantity of the substance is available and is produced under cGMP conditions. Include a cost-sharing plan if the substance or device is to be provided from industrial sources.
- Study design for the intervention(s) to be used.
- Potential biases in the protocol and how they will be addressed.
- Clinical, behavioral, laboratory, and physiological tests and protocols.
- Participant recruitment, including (1) participant availability; (2) inclusion and exclusion criteria; (3) methods for recruiting, retention, and follow-up; (4) data to support recruitment/retention estimates; (5) participant assignment to experimental groups and methods of randomization (if any); and (6) study endpoints.
- Data management, including the (1) overall approach to data management; (2) a plan for real-time data transfer; (3) a statistical plan that includes sample size calculations and methods to monitor quality and consistency of the intervention(s) and data collection; and (4) data security measures. For multi-institutional trials, include plans for communication and real-time data transfer between the collaborating institutions.
- Methods for the handling, distribution, analysis, and security of specimens and/or imaging products (primary and secondary endpoints should be clearly defined and related to the power calculation). For multi-institutional trials, include a specimen handling and distribution plan agreed upon by all collaborating institutions.
- Any issues that may lead to concern for the welfare of human subjects and confidentiality, including a plan for addressing human subjects protection requirements as outlined by the HSRRB at https://cdmrp.org/Program_Announcements_and_Forms under "Regulatory Document Forms."
- Internal scientific and local IRB reviews for the clinical protocol and informed consent/assent form(s) at the highest possible level within the participating institutions, up to and including preliminary IRB approval if available at the institution(s).
- A study organization and management plan, including a plan for real-time communication among collaborating institutions, if appropriate; a plan for ensuring the standardization of procedures across sites and among staff; and an

organizational chart and a timetable for completion of the clinical trial and publication.

f. Intellectual and Material Property: Provide a brief description of an intellectual and material property plan agreed upon by all institutions involved in the clinical trial detailing how all involved are willing to resolve intellectual and material property issues.

Please note that the clinical protocol, Manual of Operations and Procedures (if available), informed consent forms, and other supporting clinical documents must be submitted in the appropriate section of the proposal (see Subsections V.G.1 and V.G.2). Ensure that the information describing the clinical protocol in the main body matches that in Subsections V.G.1 and V.G.2. In addition, any available IRB approvals for this work must be submitted as supporting clinical documents (see Subsection V.G.2).

7. Abbreviations: Start section on a new page; one-page limit. Provide a list of all acronyms, abbreviations, and symbols used.

8. 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).

9. Biographical Sketches: Four-page limit per individual. Biographical sketches should be included for each of the key personnel listed on the budget page, 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 global priority 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.

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

11. Facilities/Equipment Description: No page limit. Describe the facilities available for performance of 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 if government-owned facilities or equipment are proposed for use.

12. Administrative Documentation: No page limit. Submit only material specifically requested or required in this program announcement. **This section is not for additional figures, tables, graphs, photographs, diagrams, chemical structures, pictures, pictorials,**

cartoons, or other relevant information needed to judge the proposal. Unrequested material that is submitted may be construed as an attempt to gain a competitive advantage and will be removed; it may be grounds for administrative rejection of the proposal.

The first item in this section must be a list of all the items included in the Administrative Documentation section.

- Provide letters of support from any collaborating individuals or institutions in this section of the proposal.
- Provide letters of commitment from senior leaders at the institutions participating in the clinical trial.
- Provide documentation that the participating institutions have an intellectual and material property plan and are willing to resolve intellectual and material property issues.
- Provide documentation of the availability of the substance or device to be used in the clinical trial. If the substance or device is to be provided from industrial sources, provide documentation of a cost-sharing plan.

All administrative documentation must be incorporated into the electronic PDF version of your proposal. Support documentation will not be accepted separately from the electronic proposal submission. All documents or letters requiring signatures must be signed and then incorporated into the submitted proposal.

13. 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 such items are included in the submission, the extra items will not be peer reviewed.

G. Clinical Protocol and Supporting Clinical Documents

1. Clinical Protocol: No page limit. The clinical protocol is a required element for the Clinical Trial Award. The protocol must be prepared according to the HSRRB-approved template for clinical protocols, which is adapted below from 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.

It is critical that the information entered in the main body of the proposal matches the information contained within the clinical protocol.

Required elements for submission of a **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.

c. PI: 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 part p of this section for details on the Medical Monitor requirement.)

NOTE: 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 (Subsection V.G.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.

d. 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.

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

f. Background: Include a background section that describes the rationale for conducting the study as well as the study's relevance and applicability of findings. 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.

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

h. 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).

i. Protocol Design: Describe the type of study to be performed (prospective, retrospective, 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 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.

j. 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.

k. 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 study.

(1) For IND or Investigational Device Exemption (IDE) research, include definitions as described in 21 CFR 312.32.[2]

(2) All IND protocols must address the following requirements.

"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 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."

[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.

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 Army Surgeon General's Human Subjects Research Review Board. A complete written report should follow the initial telephone call. 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 (ORP's) website at https://mrmc.detrick.army.mil/index.asp?EntryURL=/crprcq.asp.

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

l. 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 Food and Drug Administration (FDA).

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

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]

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]

m. 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.

[3]Investigational New Drug Application procedures and requirements; additional information can be found at http://www.fda.gov/cber/ind/21cfr312.pdf.

[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.

n. 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 to the PI, must be submitted to the local IRB for review and approval and then the HSRRB for second level review and approval. Address this procedure even if you do not anticipate making any modifications.

o. 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.

p. 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 of all documents included in this section. Provide the following in this section of the proposal:

- Manual of Operations and Procedures (if available)
- Informed consent/assent forms
- IRB approvals (if any)
- Questionnaires
- Survey instruments
- Participant recruitment brochures
- Case report forms
- Investigator's Brochure for proposals with INDs
- Documentation that an IND application has been submitted to the FDA. It is required that all IND approvals will be obtained prior to January 31, 2006. Please note that no award will be made until IND approval is obtained. If IND approval is not received by January 31, 2006, the Government reserves the right to not fund the award.
- 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.

H. Budget Information: Budget Information includes the Detailed Cost Estimate form and Budget Justification form . Budget Information is uploaded under the "Required Files" tab of the CDMRP eReceipt system.

1. Funding Restrictions: There are no total dollar amount restrictions to these awards. Funding for Phase I clinical trials can be requested for up to 3 years, whereas funding for Phase II clinical trials can be requested for up to 4 years. Direct costs can cover salary, expenses including research supplies, costs for research-related injury medical costs (if applicable), and travel to scientific meetings. The amount for this travel may not exceed $1,800 per year per investigator. Travel costs also should be included for a pre-award meeting and protocol workshop at Fort Detrick, Maryland, and a reverse site visit in the Baltimore-Washington, DC area during the period of performance.

2. Detailed Cost Estimate Form and Budget Justification Instructions: Budget is an important consideration in both peer 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.** The Detailed Cost Estimate form and Budget Justification for your proposal must be uploaded as a PDF file, separate from the proposal.

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).

The following section provides instructions for preparing the Detailed Cost Estimate form. All amounts entered should be in U.S. dollars.

a. Personnel

i. Name: Starting with the PI, list the names of all participants who will be involved in the project during the initial budget period, regardless of whether salaries are requested. Include all collaborating investigators, research associates, individuals in training, and support staff. Only **ONE** person may be identified as the PI of the proposal.

ii. Role on Project: Identify the role of each individual listed on the project. 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 DOD staff 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 project.

v. Percentage of Effort on Project: The qualifications of the PI and the amount of time that he or she and other professional personnel will devote to the research are important factors in selecting research proposals for funding. For each key staff

member identified on the budget form, list the percentage of each appointment to be spent on this project.

vi. Salaries Requested: Enter the salaries in whole dollar figures for each position for which funds are requested. The salary requested is calculated by multiplying an individual's institutional base salary by the percentage of effort on the project.

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

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

b. Consultant Costs: Regardless of whether funds are requested, provide the names and organizational affiliations of all consultants.

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 in which specific additional equipment is approved for commercial and nonprofit organizations, such approved cost elements shall be separately negotiated. Moreover, it is expected that institutions will share 50% of the cost of equipment purchased for this research proposal when individual equipment costs are equal to or exceed $5,000.

d. Materials, Supplies, and Consumables: A general description and total estimated 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 are to be purchased, state the species, strain (if applicable), and the number 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 trial. However, if costs are incurred, state the source of the intervention and provide a cost-sharing plan.

e. Travel Costs: Travel costs for 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 at Fort Detrick, Maryland, and a reverse site visit in the Baltimore-Washington, DC area during the period of performance.

f. Research-Related Subject Costs: Itemize costs of subject participation in the research study. These costs are strictly limited to expenses specifically associated with the proposed study. The USAMRMC will not provide funds for ongoing medical care costs that are 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 that are to be awarded by subcontract or subgrant is required. For awards totaling $10,000 or more, provide the following specific information:

- Identification of the type of award to be used (e.g., cost reimbursement, fixed price);
- Identification of the proposed subcontractor or subgrantee, if known, and an explanation of why and how the subcontractor or subgrantee was selected or will be selected;
- Whether the award will be competitive and, if noncompetitive, rationale to justify the absence of competition; and
- 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 under 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. Total costs for the entire proposed period of support should equal the amount previously entered online in the Proposal Information https://cdmrp.org.

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

I. 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 Subsections V.G.1 and V.G.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.

J. USAMRAA Required Documents: The most current version of the institution's negotiated "Rate Agreement," the "Certifications and Assurances for Assistance Agreements", and the "Representations for Assistance Agreements" must be uploaded by the Contract Representative from the Sponsored Programs Office (or equivalent). These documents must be uploaded as separate PDF files under the Contract Representative's "My Profile" tab of the CDMRP eReceipt system prior to negotiations.

K. Submission Date and Time: Proposals must be approved on the CDMRP eReceipt system by the Contract Representative at the applicant's institution's Sponsored Programs Office (or equivalent) by the deadline. If your proposal is either incomplete or not approved electronically before the deadline, it 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 February 22, 2005 deadline.

The timeline for the Clinical Trial Award is:

Online Letter of Intent:	Expected by **January 25, 2005**
Online Proposal Information:	Prior to proposal submission
Proposal Submission/Approval Deadline:	**5:00 p.m. Eastern time February 22, 2005**
Peer Review:	April 2005
Programmatic Review:	July 2005
Request for Additional Documents:	As early as 2 weeks after the completion of programmatic review
Notification Letter:	Approximately 4 weeks after programmatic review
IND Approval	Required before award start, but no later than January 31, 2006
Award Start Date:	Anticipated between September 2005 and August 2006

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

Several steps are critical to successful proposal submission:

- The Proposal Information must be submitted prior to submission of the proposal. Applicants are encouraged to begin this part of the submission process early.
- Proposal Contacts must be submitted prior to submission of the proposal. The e-mail address of a Contract Representative from the Sponsored Programs Office (or equivalent) must be included in the Proposal Contacts. Applicants are encouraged to begin this part of the submission process early.
- Applicants are encouraged to coordinate early with their Sponsored Programs Office (or equivalent).

- The Contract Representative from the Sponsored Programs Office (or equivalent) who is authorized to negotiate on behalf of the 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 February 22, 2005 deadline.
- Any supporting documentation that the applicant includes with the proposal must be incorporated into the PDF file prior to upload.
- Some items to be included in the proposal will need to be scanned. These items might include figures, tables, letters, or publications. All scanned documents, including figures, tables, and graphs, should be scanned at a resolution of 300-400 dpi or less.
- Budget Information includes the Detailed Cost Estimate form and the Budget Justification form. Budget Information must be uploaded under the "Required Files" tab of the CDMRP eReceipt system.
- The regulatory documents required at submission include a completed, signed Certificate of Environmental Compliance and a completed, signed Principal Investigator Safety Program Assurance form. These must be uploaded under the "Required Files" tab of the CDMRP eReceipt system. Please refer to Subsection VII.D for information regarding the submission of other regulatory documents required for this award.

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 are fundamentally different. The first tier is a scientific peer review of proposals and clinical protocols against established criteria for determination of 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 as well as overall program goals.

2. Peer Review: Peer review is conducted by panels organized according to scientific discipline or specialty area. The primary responsibility of the peer review panels is to provide unbiased, expert advice on the scientific/technical merit and relevance of proposals and clinical protocols, based on the review criteria published for each award mechanism.

Peer review panels are composed of a chair, scientific reviewers, consumer reviewers, and a nonvoting scientific review administrator. Scientific reviewers are selected based on their expertise and their 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 by bringing the patient perspective to the assessment of science and to the relevance of 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 and clinical protocols as assessed by the peer reviewers according to the evaluation criteria published in this program announcement.

3. Programmatic Review: The second tier is programmatic review. Programmatic review is accomplished by the IP, which is composed of scientists, clinicians, and consumer advocates. The scientific members of the IP represent diverse disciplines and specialty areas, and the consumer members represent national advocacy constituencies. One of the functions of programmatic review is to maintain 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. IP members primarily use the peer review summary statements and the proposal abstracts. SOWs may also be reviewed. Full proposals are not forwarded to programmatic review.

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

B. Review Criteria

1. Peer Review

a. Proposal: Clinical Trial Award proposals will be evaluated according to the following criteria:

- **Trial Design:** Are the conceptual framework, design, methods, and analyses adequately developed and well integrated? Is there adequate laboratory and other preclinical evidence to support the clinical feasibility and promise of the approach? Does the applicant provide the background and a clear scientific rationale for the trial? Have the logistical aspects of the proposed clinical trial been appropriately addressed (e.g., plans for communication, real-time data transfer, and standardization of procedures among collaborating institutions, as appropriate)? Is there sufficient availability of subjects for the clinical trial, and are the prospect of their participation and the likelihood of subject attrition addressed? Is the recruitment schedule reasonable?
- **Clinical Relevance:** Does the study address an important problem(s) related to the treatment or management of NF or Schwannomatosis? If the aims of the proposal are achieved, are they likely to have a substantial clinical impact?
- **Intervention or Device:** Is the proposed intervention or device to be tested in the clinical trial adequately described and available? Is the intervention or device novel? Has the applicant provided evidence of the availability and purity of the substance to be used in the clinical trial? Are there assurances that interventions to be used are available? If a drug, biologic, or device has been budgeted, is there a cost-sharing plan?

- **Statistical Plan:** Is a clear statistical plan, including sample size projections and power analysis, outlined in the proposal? Is the appropriate statistical expertise represented on the research team?
- **PI and Personnel:** Does the PI have expertise in NF/Schwannomatosis and experience in clinical trials? Is the PI appropriately trained to carry out this work? Are the other scientific personnel well qualified to participate in the project and do they complement the experience of the PI? Is there representation from all the areas of expertise needed to conduct the clinical trial successfully?
- **Environment:** Is there evidence for an appropriate clinical setting and the availability of institutional resources to support the study at each participating center? Are letters of institutional commitment included from each participating institution? Is there an intellectual and material property plan that is agreed upon by all participating centers?
- **Budget:** Is the budget appropriate for the research proposed? Is there evidence of adequate funding from this funding agency and other funding agencies, as appropriate, to support completion of this clinical trial?

b. Protocols: Clinical Trial Award protocols will be evaluated according to the following criteria:

- **Protocol Preparation:** Are the key elements of the clinical protocol (specific aims, methods, analyses, sample size, etc.) consistent with the information provided in the main body of the proposal?
- **Research Question:** Is the literature review thorough and up-to-date? Are the aims of the study clear and concise? Is the conceptual framework of the project adequately developed and well integrated with the project's design, methods, and analyses?
- **Protocol Design:** Is the proposed methodology described in sufficient detail? Are the recruitment, informed consent, subject screening, and subject randomization processes appropriate and adequately described? Is the research, the research intervention, or activity that the participant will experience fully described? If the proposal uses an IND or IDE, is it fully described?
- **Feasibility:** Is there adequate evidence to support the clinical feasibility and promise of the approach? Have the availability of subjects for the clinical trial, the prospect of their participation, and the likelihood of subject attrition been addressed? Is the recruitment schedule reasonable? Has the applicant provided evidence of the availability and quality of the substance to be used in the clinical trial? Have preliminary institutional IRB approval(s) for the clinical protocol and informed consent form been obtained at the highest level possible? If applicable, has an IND been submitted for the intervention? Have the FDA regulatory components of an IND trial been adequately addressed?
- **Personnel and Environment:** Do the personnel described as having significant involvement in the research study match those listed in the proposal? Are the roles and responsibilities of all study personnel clearly described? Are the clinical

team, laboratories, and setting appropriate and adequate to support the trial?

- **Statistical Plan:** Is a clear statistical plan, including sample size projections and power analysis, provided? Are all data collection procedures to be used in conducting the study adequately described and appropriate? Is the data analysis plan consistent with the study objectives?
- **Ethics and/or Regulatory Issues:** Are ethical considerations and information privacy appropriately addressed? Is there an adequate assessment of the risks and benefits of participation in the clinical trial? Is there a 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? Have potential adverse events been defined for the intervention, and are there named agencies or offices to be notified in this event? Is there a plan for data disposition during and after the clinical trial? Are procedures in place for protocol modifications during the course of the study? If a Medical Monitor is required, is he or she appropriately qualified?

2. Programmatic Review: The ratings and evaluations of scientific peer review panels are primary factors in programmatic review. The IP also considers other criteria to maintain the NFRP's broad portfolio. The criteria the IP uses to make funding recommendations are:

- Ratings and evaluations of the scientific peer review panels;
- Programmatic relevance;
- Relative innovation; and
- Program portfolio balance.

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 IP and recommended to the Commanding General, USAMRMC, for funding.

VII. AWARD ADMINISTRATION INFORMATION

A. Award Notices: After the two-tier evaluation process is completed, every applicant will receive notification of the award status of his or her proposal and a copy of the peer review summary statement. Applicants can expect to be notified of the agency's decision in August 2005.

B. Administrative Requirements: All awards are made to organizations, not individuals. A PI should 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. To be eligible for an award, a prospective recipient should meet certain minimum standards pertaining to institutional support, financial resources, prior 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). *Any organization requesting receipt of an award from*

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/

Transferring the grant from the original institution will not be permitted for the Clinical Trial Award. PI relocations may be permitted under certain conditions; the PI must inform the USAMRAA of the pending relocation to discuss available options.

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 from the Sponsored Programs Office (or equivalent) who is authorized to negotiate contracts and grants at the applicant's institution. As part of the negotiation process, additional documentation and justifications related to the proposed SOW and associated budgets may be required.

Note that the award start date will be determined during the negotiation process.

For Clinical Trial Award recipients, IND approval must be received before an award can be made. If IND approval is not received by January 31, 2006, the Government reserves the right to not fund the award.

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 Army regulations are met. Applicants who are approved for funding may be required to attend a pre-award meeting and protocol workshop at Fort Detrick, Maryland.

2. Certificate of Environmental Compliance: The Certificate of Environmental Compliance must be submitted with the proposal. If multiple research sites/institutions are funded in your 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 also required and will be requested at a later date. However, your institution may already have an approved Facility Safety Plan. To determine the status of approval, check the USAMRMC website at https://mrmc.detrick.army.mil/crprcqsohdfsplan.asp. If your institution is not listed on the aforementioned website, contact your Facility Safety Director/Manager to initiate completion of the institution-based Facility Safety Plan. Specific requirements for the Safety Program Plan can be found at https://mrmc.detrick.army.mil/docs/rcq/FY02FSPAppendix.doc.

If multiple research sites/institutions are funded in your proposal, then 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: Animal use documents should not be submitted with the proposal and will be requested at a later date. Specific requirements for research involving animals can be found at https://mrmc.detrick.army.mil/docs/rcq/FY05AnimalAppendix.doc.

5. Research Involving Human Subjects/Anatomical Substances/Cadavers: (See Subsections V.I and V.J for information pertaining to the submission of human subjects and/or human anatomical substances documents or cadavers.) In addition to local IRB approval to conduct research involving human subjects and/or anatomical substances or cadavers, a second tier of IRB review and approval is also required by the DOD. This second review is conducted by the HSRRB, which is administered by the USAMRMC ORP. 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. For example:

- Intent to Benefit. In the development of a research protocol for submission to the DOD, the applicant must specifically address, if applicable, the Intent to Benefit. An individual not legally competent to consent (e.g., minors) may not be enrolled in DOD-sponsored research unless the research is intended to benefit each and every subject enrolled in the study. Applicants 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.
- The DOD considers cell lines of human origin to be human anatomical substances/cadavers. Use of these cell lines is subject to HSRRB review and approval.

Specific requirements for research involving human subjects, human anatomical substances, and/or cadavers can be found at https://mrmc.detrick.army.mil/docs/rcq/HumanSubjectsAppendix(13May04).doc.
An informed consent form template can be located at https://mrmc.detrick.army.mil/docs/rcq/Proconsent/ConsentFormGuidelines.doc.

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

E. Reporting: All research awards will require the timely delivery of several reports during the research effort.

- **Research Progress Report Requirements:** 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.
- **Fiscal Report Requirements:** 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.

VIII. OTHER INFORMATION

A. Disclosure of Proprietary Information outside the Government: By submission of 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 will not be 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. To the extent practical, all other sources should also be consulted for the same purpose.

D. Inquiry Review Panel: Applicants can 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. [5]), title to inventions and patents resulting from such federally funded research may be held by the grantee or its collaborator, but the U.S. Government shall, at a minimum, retain nonexclusive rights for the use of such inventions. An investigator must follow

[5]Title 35, United States Code, Section 200 et seq.

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 Video Interleave
CCR	Central Contractor Registration
CDMRP	Congressionally Directed Medical Research Programs
CFDA	Catalog of Federal Domestic Assistance
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CTA	Clinical Trial Award
DOD	Department of Defense
FAR	Federal Acquisition Regulations
FDA	Food and Drug Administration
FY	Fiscal Year
GCP	Good Clinical Practices
HBCU/MI	Historically Black Colleges and Universities/Minority Institutions
HSRRB	Human Subjects Research Review Board
IDE	Investigational Device Exemption
IND	Investigational New Drug
IP	Integration Panel
IRB	Institutional Review Board
M	Million
MPEG	Moving Picture Experts Group
MTF	Medical Treatment Facility
NFRP	Neurofibromatosis Research Program
OMB	Office of Management and Budget
ORP	Office of Research Protections (formerly Regulatory Compliance and Quality)
PDF	Portable Document Format
PI	Principal Investigator
SOW	Statement of Work
USAMRAA	US Army Medical Research Acquisition Activity
USAMRMC	US Army Medical Research and Materiel Command
USC	United States Code
WAV	Wave