

# Announcement of Federal Funding Opportunity

## Summary

### I. GENERAL INFORMATION

The Fiscal Year 2005 (FY05) Natural History Study Award is open to all eligible applicants with natural history studies relevant to the tuberous sclerosis complex (TSC). In addition, as stated in the FY04 Natural History Development Award Program Announcement, recipients of the FY04 Natural History Development Award are required to compete for the FY05 Natural History Study Award. All applicants must submit proposals, clinical protocols, and other supporting clinical documents.

**A. Title of Award:** Natural History Study Award (NHSA).

**B. Program Name:** Department of Defense (DOD) FY05 Tuberous Sclerosis Complex Research Program (TSCR).

**C. Funding Opportunity Number:** TS05-NHSA.

**D. Agency Name:** United States Army Medical Research and Materiel Command (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](mailto:cdmrp.pa@det.amedd.army.mil)  
Mail: Commander  
US Army Medical Research and Materiel Command  
ATTN: MCMR-ZB-C (TS05-NHSA)  
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](mailto: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 intent of the Natural History Study Award is to sponsor **focused, hypothesis-driven** natural history studies that will enhance the current knowledge of TSC manifestations and improve clinical management of the disorder and/or the design, implementation, and interpretation of clinical trials. This mechanism is **not** intended to support descriptive, broad-based studies that are limited to collecting information (clinical, pathological, radiographical, or other) with no accompanying analysis or hypothesis testing. Instead, the TSCRCP is soliciting proposals for studies that will test a specific hypothesis or answer a clearly defined question regarding the natural history of TSC.

**Proposals must include a clinical protocol and informed consent/assent forms, as well as detailed and comprehensive plans for participant recruitment, data management, study management, and specimen handling and distribution. Thus, the TSCRCP highly encourages investigators to consider applying for the [FY05 Natural History Development Award](#) to properly develop the appropriate resources for subsequent submission of a Natural History Study Award proposal (for example, in FY06, pending availability of funds). However, FY05 Natural History Study Award proposals may be submitted without prior submission to or receipt of an FY04 Natural History Development Award.**

## **III. AWARD INFORMATION**

- Type of award: grant/cooperative agreement.
- Approximately \$1 million (M) is available to fund the FY05 TSCRCP Natural History Study Awards.

- Depending on the number and quality of the applications, it is anticipated that one to two proposals will be funded.
- Funding for FY05 Natural History Study Awards can be requested for a maximum of \$1M over a 3-year performance period, inclusive of both direct and indirect costs.

#### **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 (in addition to the pre-award meeting and protocol workshop that also may be required).

# Full Text of Program Announcement

## I. GENERAL INFORMATION

The Fiscal Year 2005 (FY05) Natural History Study Award is open to all eligible applicants with natural history studies relevant to the tuberous sclerosis complex (TSC). In addition, as stated in the FY04 Natural History Development Award Program Announcement, recipients of the FY04 Natural History Development Award are required to compete for the FY05 Natural History Study Award. All applicants must submit proposals, clinical protocols, and other supporting clinical documents.

**A. Title of Award:** Natural History Study Award (NHSA).

**B. Program Name:** Department of Defense (DOD) FY05 Tuberous Sclerosis Complex Research Program (TSCRCP).

**C. Funding Opportunity Number:** TS05-NHSA.

**D. Agency Name:** United States Army Medical Research and Materiel Command (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](mailto:cdmrp.pa@det.amedd.army.mil)  
Mail: Commander  
US Army Medical Research and Materiel Command  
ATTN: MCMR-ZB-C (TS05-NHSA)  
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](mailto: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](mailto: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 Natural History Study Award is part of the DOD TSCRCP, which was established in FY02 to promote innovative research directed toward improved prevention, diagnosis, and/or treatment of TSC. Appropriations for the TSCRCP since FY02 total \$9.2 million (M). The program history of the TSCRCP is shown in Table 1. The FY05 appropriation is \$3.2M.

**Table 1: History of the DOD’s Peer Reviewed TSCR**

<b>Program History</b>	<b>FY02</b>	<b>FY03</b>	<b>FY04</b>
Congressional Appropriations for TSCR	\$1M	\$2M	\$3M
Total Proposals Received	13	13	40
Total Proposals Funded	3 <sup>1</sup>	4	~12 <sup>2</sup>
Natural History Study Award Proposals Received	N/A	N/A	N/A
Natural History Study Award Proposals Funded	N/A	N/A	N/A

<sup>1</sup>One FY02 proposal was partially funded with FY03 funds.

<sup>2</sup>Award negotiations will be finalized by September 2005.

**B. Program Objectives:** The overall goal of the FY05 TSCR is to decrease the impact of TSC. Within this context, the encouragement of established scientists in the field and the attraction of new scientific expertise from other fields are essential to the TSC community. 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 the Natural History Study Award is to sponsor focused, hypothesis-driven natural history studies that will enhance the current knowledge of TSC manifestations and improve clinical management of the disorder and/or the design, implementation, and interpretation of clinical trials. This mechanism is **not** intended to support descriptive, broad-based studies that are limited to collecting information (clinical, pathological, radiographical, or other) with no accompanying analysis or hypothesis testing. Instead, the TSCR is soliciting proposals for studies that will test a specific hypothesis or answer a clearly defined question regarding the natural history of TSC.

**Proposals must include a clinical protocol and informed consent/assent forms, as well as detailed and comprehensive plans for participant recruitment, data management, study management, and specimen handling and distribution. Thus, the TSCR highly encourages investigators to consider applying for the [FY05 Natural History Development Award](#) to properly develop the appropriate resources for subsequent submission of a Natural History Study Award proposal (for example, in FY06, pending availability of funds). However, FY05 Natural History Study Award proposals may be submitted without prior submission to or receipt of an FY04 Natural History Development Award proposal.**

If the study is multi-institutional, applicants should include in the main body of the proposal (see Subsection V.F.5) plans for communication and real-time data transfer between the collaborating institutions, as well as details of how specimens and/or imaging products obtained during the study will be handled. An intellectual and material property plan agreed upon by all participating institutions is required as part of the administrative documentation of this proposal (see Subsection V.F.11).

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](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 Natural History Study Award must include:

- A statement of the hypothesis or the hypothesis-driven question that is the focus of the proposed natural history study. Applicants must articulate how the study will test the hypothesis or answer the question and describe any relevant preclinical science and preliminary clinical research that support the feasibility of the hypothesis and approaches. **Proposals must include a clearly stated hypothesis or hypothesis-driven question to be considered for funding. Proposals lacking a hypothesis or hypothesis-driven question may be administratively withdrawn;**
- The specific expected outcomes of the study as they relate to the hypothesis or question, the statistical methods that will be used to measure outcomes, and the timeframe in which the outcomes are expected to be met;
- The relevance of the proposed natural history study to TSC, including a discussion of how the results of the study may improve clinical management of the disorder and/or the design, implementation, and interpretation of clinical trials;
- The sample size for the natural history study with appropriate statistical analyses to verify power for the anticipated effect size and pre-determined level of significance; 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 Natural History Study 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 all HSRRB human subjects protection requirements (outlined at [https://cdmrp.org/Program\\_Announcements\\_and\\_Forms](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/assent form(s) that indicate the status of IRB review achieved prior to submission of the Natural History Study Award. Indicate the highest possible level of IRB review within the participating institutions before submission of a proposal;
  - For multi-institutional studies, as appropriate, include a plan for the coordination of IRB submissions;
- A description of the natural history study team, to include names, background, qualifications, time commitments, and contributions of each team member. The study team must include:

- A named study coordinator who will guide the clinical protocol through the IRB, HSRRB, and other regulatory approval processes; coordinate activities at all participating sites; and coordinate participant accrual, and
- A named biostatistician;
- A comprehensive data management plan, including:
  - Appropriate data collection forms,
  - A statistical plan that includes sample size calculations, methods to monitor quality and consistency of data collection, and methods to measure outcomes,
  - A plan for real-time data transfer, and
  - Data security measures;
- A comprehensive study management plan, including:
  - A plan for real-time communication among collaborating institutions, if appropriate,
  - A plan for ensuring standardization of procedures across sites and among staff, and
  - An organizational chart that includes a steering committee and an advisory panel consisting of scientists and consumers;
- Descriptions of methods for the handling, distribution, analysis, banking, and security of specimens and/or imaging products. For multi-institutional studies, include a specimen handling and distribution plan agreed on by all collaborating institutions;
- A plan for public dissemination of data generated by the study that addresses all relevant privacy issues; and
- Evidence of institutional commitment(s) to the proposed natural history study, including descriptions of institutional resources to be committed to the study.

### III. AWARD INFORMATION

Funding for the FY05 Natural History Study Award can be requested for a maximum of \$1M over a 3-year performance period, inclusive of both direct and indirect costs. Direct costs can cover salary, expenses including research supplies, and travel to scientific/technical 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. Approximately \$1M is available for this award mechanism. Depending on the number and quality of the applications, it is anticipated that one to two proposals will be funded.

**The FY05 Natural History Study Award is open to all eligible applicants with natural history studies relevant to TSC. In addition, as stated in the FY04 Natural History Development Award Program Announcement, recipients of the FY04 Natural History Development Award are required to compete for the FY05 Natural History Study Award. All applicants must submit proposals, clinical protocols, and other supporting clinical documents.**

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 is encouraged. 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 TSCR P 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.<sup>1</sup> 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.
- Font type is not Times New Roman.

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<sup>1</sup>Executive Orders 12876, 12900, and 13021

- 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.
- Proposal does not include a hypothesis or hypothesis-driven question.

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.**
- **US Army Medical Research Acquisition Activity (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) 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 hypothesis or the hypothesis-driven question that is the focus of the proposed natural history study. Briefly describe the preliminary studies that led to the proposed project.

- Study Design: Briefly describe the proposed natural history study, including proposed participant sample size, accrual, and outcome measures.
- Relevance: Provide a brief statement explaining the relevance of the proposed natural history study to the clinical management of TSC and/or the design, implementation, and interpretation of clinical trials.

**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 natural history study?
- (2) What will be the ultimate applicability of the natural history study to the clinical management of TSC and/or the development and clinical testing of new treatments for the disorder?
  - 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:

- Proposal title (up to 160 characters).
- Proposal log number (this will be automatically provided when the Proposal Information is completed and saved).
- PI’s full name (first, middle initial, last).
- Submitting institution.
- Award mechanism: Type in “Natural History Study Award.”
- 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.
- 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 natural history study will have a significant impact on the clinical management of TSC and/or the development and clinical testing of new treatments for the disorder.

**5. Main Body: Start section on a new page; 40-page limit inclusive of any figures, tables, graphs, photographs, diagrams, chemical structures, pictures, pictorials, cartoons, and other relevant information needed to judge the proposal.** It is the responsibility of the investigator to clearly articulate how the proposed plan for a natural history study meets the intent of the mechanism. The proposal body should address the review criteria as outlined in Subsection VI.B of this program announcement.

Describe the proposed natural history study 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 study and previous experience most pertinent to the proposal. Cite relevant literature references.
- b. **Hypothesis:** State the **hypothesis** or the **hypothesis-driven question** that is the focus of the proposed natural history study. Describe how the study will test the hypothesis or answer the question. State the specific expected outcomes as they relate to the hypothesis or question and the timeframe in which the outcomes are expected to be met. **Proposals must include a clearly stated hypothesis or hypothesis-driven question to be considered for funding. Proposals lacking a hypothesis or hypothesis-driven question may be administratively withdrawn;**
- c. **Objectives:** State the specific aims of the study.
- d. **Preliminary Studies:** Present the preclinical and preliminary clinical studies that led to the proposed natural history study and support the feasibility of the hypothesis and approaches. State the relevance of the proposed study to the clinical management of the disorder and/or the design, implementation, and interpretation of clinical trials.
- e. **Methods and Data Analyses:** Provide a brief discussion of the topics listed below.
  - Study design, including clinical, behavioral, laboratory, and physiological tests and protocols;
  - Potential biases in the protocol and how they will be addressed;
  - Include a named study coordinator who will guide the clinical protocol through the IRB, HSRRB, and other regulatory approval processes; coordinate activities at all participating sites; and coordinate participant accrual;
  - Participant recruitment, including (1) a description of the participant population; (2) sample size; (3) inclusion and exclusion criteria; (4) methods and schedules for recruiting, retention, and follow-up; (5) data to support recruitment/retention estimates; and (6) study endpoints;

- Data management, including:
  - The overall approach to data management,
  - A plan for real-time data transfer,
  - A statistical plan that includes sample size calculations, methods to monitor quality and consistency of data collection, and methods to measure outcomes,
  - Data security measures, and
  - For multi-institutional studies, plans for communication and real-time data transfer between the collaborating institutions;
- A study organization and management plan, including:
  - A plan for real-time communication among collaborating institutions, if appropriate,
  - A plan for ensuring standardization of procedures across sites and among staff,
  - An organizational chart that includes a steering committee and an advisory panel consisting of scientists and consumers, and
  - A timetable for completion of the natural history study and publication;
- Methods for the handling, distribution, banking, analysis, and security of specimens and/or imaging products. For multi-institutional studies, include a specimen handling and distribution plan agreed upon by all collaborating institutions;
- A plan for public dissemination of data generated by the study that addresses all relevant privacy issues;
- 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](https://cdmrp.org/Program%20Announcements%20and%20Forms) 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);
  - For multi-institutional studies, as appropriate, include a plan for the coordination of IRB submissions; and
- Evidence of institutional commitment to the proposed natural history study, including descriptions of institutional resources to be committed to the study.

**f. Intellectual and Material Property:** Provide a brief description of an intellectual and material property plan agreed upon by all institutions involved in the natural history study 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).

- 6. Abbreviations: Start section on a new page; one-page limit.** Provide a list of all acronyms, abbreviations, and symbols used.
- 7. 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).
- 8. 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.
- 9. 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.
- 10. 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.
- 11. 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 natural history study.
- Provide documentation that the participating institutions have an intellectual and material property plan and are willing to resolve intellectual and material property issues.

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.

**12. 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 Natural History Study 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](https://cdmrp.org/Program%20Announcements%20and%20Forms).

**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. 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 n 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, 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.

**c. 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.

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

**e. 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.

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

**g. 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).

**h. 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, when the interview will take place relative to the participant beginning study participation and in relation to any stressful situation (e.g., being informed he or she has a malignant tumor) or in relation to the administration of any mind-altering substances such as tranquilizers, conscious sedation, or anesthesia. Address how privacy and time for decision-making will be provided and whether or not 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 Group 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.
- i. **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 before, during, or after 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.

**j. 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.
- 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’ (ORP’s) (formerly Regulatory Compliance and Quality) website at <https://mrmc.detrack.army.mil/index.asp?EntryURL=/crprcq.asp>.

For protocols that have a Medical Monitor assigned (see part n below), the following language should also be included.

“The Medical Monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events and all volunteer deaths associated with the protocol and provide an unbiased written report of the event. 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.”

**k. 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 data will be stored.

**l. 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.

**m. 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.

**n. 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, 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](https://cdmrp.org/Program_Announcements_and_Forms).

The first item in this section must be a table of contents listing all of the 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.
- 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:** Funding for the FY05 Natural History Study Award can be requested for a maximum of \$1M over a 3-year performance period, inclusive of both direct and indirect costs. Direct costs can cover salary, expenses including research supplies, and travel to scientific/technical meetings. The amount for this travel may not exceed \$1,800 per year per investigator. Applicants should also 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.

**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](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](http://www.whitehouse.gov/omb/grants/grants_circulars.html)).
- **State, Local, and Indian Tribal Governments:** OMB Circular A-87, Cost Principles for State, Local, and Indian Tribal Governments ([http://www.whitehouse.gov/omb/grants/grants\\_circulars.html](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.
- e. Travel Costs:** Travel costs for scientific/technical meetings may not exceed \$1,800 per year per investigator. The applicant should budget for additional travel costs 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.
- 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 Natural History Study Award is:**

Online Letter of Intent:	Expected by <b>January 25, 2005</b>
Online Proposal Information:	Prior to proposal submission
<b>Proposal Submission/Approval Deadline:</b>	<b>5:00 p.m. Eastern time February 22, 2005</b>
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
Award Start Date:	Anticipated between September 2005 and January 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:** Natural History Study Award proposals will be evaluated according to the following criteria:

- **Hypothesis:** Does the applicant provide a clear and focused hypothesis or hypothesis-driven question that will drive the proposed natural history study? Does the applicant convincingly demonstrate that the proposed study will test the hypothesis or answer the question?
- **Study Design:** Are the conceptual framework, design, methods, and analyses adequately developed and well integrated? Is the rationale for the choice of a retrospective or prospective study design provided? Are methods/means for accounting for intervening variables, e.g., medically prescribed therapies and/or alternative therapies initiated by the volunteer, included? Is there adequate evidence to support the clinical feasibility and promise of the approach? Does the applicant provide the background and a clear scientific rationale for the study? Have the logistical aspects of the proposed natural history study 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 natural history study, and are the prospect of their participation and the likelihood of subject attrition addressed? Is the recruitment schedule reasonable? Does the applicant describe the specific expected outcomes of the study as they relate to the hypothesis or question, the statistical methods that will be used to measure outcomes, and the timeframe in which the outcomes are expected to be met?
- **Clinical Relevance:** Do existing preclinical science and/or preliminary clinical research support the relevance of the natural history study to TSC? Does the proposed study address an important clinical and/or diagnostic problem related to TSC, and is it likely to have a substantial impact on the clinical management of

TSC and/or the design, implementation, and interpretation of clinical trials?

- **Statistical Plan:** Does the applicant provide a clear statistical plan, including sample size projections, power analysis, and methods for measuring outcomes? Is the appropriate statistical expertise represented on the research team? Does the data analysis plan address how the investigators will analyze data sets to account for the effect of intervening variables on the progression of the natural history of the disease?
- **PI and Personnel:** Does the PI have expertise in TSC? Are the PI and other key personnel appropriately trained and well suited to carry out this work? Is there representation from all the areas of expertise needed to conduct the natural history study 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 natural history study?

**b. Protocols:** Natural History Study 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, and subject screening processes appropriate and adequately described? Is the research or activity that the participant will experience fully described?
- **Feasibility:** Is there adequate evidence to support the clinical feasibility and promise of the approach? Have the availability of subjects for the natural history study, the prospect of their participation, and the likelihood of subject attrition been addressed? Is the recruitment schedule reasonable? Have preliminary institutional IRB approval(s) for the clinical protocol and informed consent form been obtained at the highest level possible? For multi-institutional studies, as appropriate, is there a plan for the coordination of IRB submissions?
- **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 study?

- **Statistical Plan:** Does the applicant provide a clear statistical plan, including sample size projections, power analysis, and methods for measuring outcomes? 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? Does the data analysis plan address how the investigators will analyze data sets to account for the effect of intervening variables on the progression of the natural history of the disease?
- **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 natural history study? 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, and are there named agencies or offices to be notified in this event? Is there a plan for data disposition during and after the natural history study? 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 TSCRP'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 Natural History Study 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.

#### **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/crpreqsohdfsplan.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](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 the 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.<sup>2</sup>), 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

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<sup>2</sup>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
DOD	Department of Defense
FAR	Federal Acquisition Regulations
FY	Fiscal Year
GCP	Good Clinical Practices
HBCU/MI	Historically Black Colleges and Universities/Minority Institutions
HSRRB	Human Subjects Research Review Board
IP	Integration Panel
IRB	Institutional Review Board
M	Million
MPEG	Moving Picture Experts Group
NHSA	Natural History Study Award
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
TSCRCP	Tuberous Sclerosis Complex Research Program
USAMRAA	US Army Medical Research Acquisition Activity
USAMRMC	US Army Medical Research and Materiel Command
USC	United States Code
WAV	Wave