Appendix A
FY01 NFRP Program Announcement
Letter of Intent

Please fill out one form for each proposal you intend to submit in response to the Department of Defense Neurofibromatosis Research Program Fiscal Year 2001 Program Announcement. Please fax, e-mail, or mail the Letter of Intent form to:

Fax: **301-682-5521**
E-mail: **cdmrp.pa@det.amedd.army.mil**
Mail: **Commander, U.S. Army Medical Research and Materiel Command**
ATTN: MCMR-PLF (NFRP01)
1077 Patchel Street (Building 1077)
Fort Detrick, MD 21702-5024

You may complete and submit this form via the Congressionally Directed Medical Research Programs web site at http://cdmrp.army.mil/funding/default

Principal Investigator's Name: _____
Principal Investigator's Address: _____
_____
Phone Number:_____ **Fax Number:**_____
E-mail:_____

Intended award mechanism to which the proposal will be submitted (please check ONLY one):

- ☐ New Investigator Award
- ☐ Idea Award
- ☐ Investigator-Initiated Research Award
- ☐ Investigator-Initiated Research Award with Nested Postdoctoral Traineeship(s)
- ☐ Therapeutic Development Award
- ☐ Clinical Trial Award

Content area that will be addressed in the proposal (check no more than five):

- ☐ Alternative Medicine
- ☐ Behavioral/Social Sciences
- ☐ Biological Response Modifiers
- ☐ Cell Biology
- ☐ Clinical/Experimental Therapeutic
- ☐ Clinical Genetics
- ☐ Endocrinology
- ☐ Epidemiology/Biostatistics
- ☐ Gene Expression
- ☐ Gene Sequencing/Gene Mapping
- ☐ Health Care Delivery
- ☐ Immunologic Sciences
- ☐ Molecular Genetics
- ☐ Neuroscience
- ☐ Nutrition
- ☐ Pathobiology
- ☐ Pharmacology/Toxicology
- ☐ Physiology
- ☐ Prevention
- ☐ Protein-Nucleic Acid Interactions
- ☐ Radiologic Sciences
- ☐ Surgery
- ☐ Technology Development
- ☐ Tumor Biology/Progression
- ☐ Virology
- ☐ Other, please specify _____

Proposal title and brief description:

_____
_____
_____

Use an additional page if needed. Please include the name of the principal investigator and applicant institution on each page.

Appendix B

Proposal Preparation

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Proposal Preparation

1. Who May Apply

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. All individuals, regardless of ethnicity, nationality, or citizenship status, may apply as long as they are employed by or affiliated with an eligible institution. The U.S. Army Medical Research and Materiel Command (USAMRMC) is especially interested in receiving applications from Historically Black Colleges and Universities and Minority Institutions (HBCU/MI).

Please refer to sections on specific award mechanisms for additional eligibility criteria.

Investigators are cautioned that awards are made to institutions. Should the Principal Investigator (PI) of a funded project leave the recipient institution, both the PI and an official of the recipient institution should contact the U.S. Army Medical Research Acquisition Activity (USAMRAA) awarding office prior to the PI leaving the recipient institution to discuss options available for continued support of the research project.

Historically Black Colleges and Universities and Minority Institutions

A goal of the Department of Defense (DOD) is to allocate funds for the Congressionally Directed Medical Research Programs' (CDMRP's) peer reviewed research to fund proposals from HBCU/MI. This provision is based upon guidance from Executive Orders[1] and is intended to "advance the development of human potential, provide quality education, increase opportunities to participate in and benefit from Federal Programs and strengthen the capacity of targeted institutions." An institution's minority status is established by the Department of Education (DOEd). Proposals submitted to the DOD are assigned HBCU/MI status if they are so designated by the DOEd on the date that the program announcement is released. The DOEd list is posted on the CDMRP web site at http://cdmrp.army.mil/funding/minority Any individual, regardless of ethnicity, nationality, or citizenship status, may apply for funding as long as they are employed by or affiliated with an eligible institution.

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 when award recommendations are determined. Consistent with the CDMRP's goal, recommendations for funding HBCU/MI submissions will be based upon scientific excellence and program relevance.

[1] Executive Orders 12876, 12900, and 13021

2. Proposal Acceptance Criteria

Please follow the compliance guidelines listed below when preparing your proposal. **Note that all proposals must be converted into an electronic PDF (Portable Document Format) file for electronic submission.** Compliance guidelines have been designed to ensure the presentation of all proposals in an organized and easy-to-follow manner to scientific reviewers responsible for reviewing their merit. Scientific peer reviewers will expect to see a consistent, prescribed format for each proposal. Nonadherence to format requirements (such as font size, margins, line spacing, proposal components out of order) 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 poorer global priority score in scientific peer review. **Excess pages may result in administrative rejection prior to scientific peer review.**

It is required that the instructions in this section be followed carefully. The proposal must be clear and legible and conform to the following format, spacing, font size, margin, and printing guidelines:

- Type Font: 12 point, 10 pitch.
- Type Density: No more than 15 characters per inch. (For proportional spacing, the average for any representative section of text should not exceed either 15 characters per inch or 114 characters per line.)
- Spacing: Single-spaced between lines of text, no more than five lines of type within a vertical inch.
- Margins: Minimum of 0.5-inch top, bottom, right, and left.
- Type Color: Black ink including all graphs, diagrams, tables, and charts. The proposal should contain only material that can be photocopied. Investigators are cautioned that color graphs or photographs may not reproduce in subsequent photocopies. Therefore, submission of color figures, tables, graphs, or photographs is not recommended.
- Printing: The original proposal must be single-sided.
- Spell out all acronyms the first time they are used. One page following the proposal body is allocated to spell out acronyms, abbreviations, and symbols.
- Language: English.
- Print Area: 7.5 x 10.0 inches. (Note to international applicants: A4 paper will be accepted if the text of the proposal does not exceed 7.5 x 10.0 inches [approximately 19 cm x 25.5 cm].)

To assist applicants, the following example is included.

This illustrates the minimum font size and margins and the required line spacing. This illustrates the minimum font size and margins and the required line spacing. This illustrates the minimum font size and margins and the required line spacing. This illustrates the minimum font size and margins and the required line spacing. This illustrates the minimum font size and margins and the required line spacing.

3. Resubmissions and Duplicate Submissions

Resubmission of a proposal reviewed in a previous fiscal year is acceptable. However, the applicant should be cautioned that the year-to-year status of funding for the Neurofibromatosis Research Program (NFRP) does not permit the establishment of standing panels for scientific peer review. Therefore, the submission of a revised proposal does not guarantee any funding advantage or an improved global priority score. Resubmitted/amended proposals should meet the requirements for the appropriate award category in this program announcement and adhere to this year's format guidelines. If applicants wish to include exactly what changes were made in response to the prior review, this information must be provided within the prescribed proposal page limits. Do not include summary statements of previously reviewed proposals.

Submission of the same research project to the FY01 NFRP under different award mechanisms in response to this program announcement will not be allowed. This includes submissions under different award mechanisms from different PIs. All such duplicate submissions may be administratively withdrawn. The Government reserves the right to reject any proposal.

4. Electronic Proposal Cover Booklet

Please complete the Electronic Proposal Cover Booklet as described on the CDMRP web site (http://cdmrp.army.mil). Instructions will be available through the web site no earlier than May 15, 2001 and no later than June 13, 2001. The Electronic Proposal Cover Booklet must accompany the electronic PDF version of your proposal. In addition, a printed version of the Electronic Proposal Cover Booklet must accompany your paper submission.

5. Title/Referral Page – No page limit

Please complete the Title/Referral Page, which can be found on page B-6 or downloaded from the CDMRP web site at http://cdmrp.army.mil/funding/default. Complete each section as described below.

a. Proposal title (up to 160 characters).

b. Proposal log number (this will be automatically provided when a draft of the Electronic Proposal Cover Booklet is completed and saved).

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

d. Award mechanism.

e. PI's phone number, fax number, and e-mail address.

f. Organization name and location (including city, state, zip or postal code, and country).

g. Name of administrative representative authorized to conduct negotiations.

h. Phone number, fax number, and e-mail address of administrative representative authorized to conduct negotiations.

i. 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 (e.g., cell signaling, apoptosis, angiogenesis, drug delivery systems, gene therapy, x-ray crystallography, genetic counseling, quality of life, nuclear medicine, immunology, clinical oncology, nutrition).

j. Conflicts of interest: Every effort is made to avoid real and apparent conflicts of interest during the peer review process. To assist the staff in this regard, list the names of all scientific participants in the proposal including the PI, co-investigators, research associates, research assistants, consultants, collaborators, and subcontractors. Provide the following information for each participant: name, degree(s), scientific discipline or medical specialty (e.g., radiology, immunology, clinical oncology, nutrition, pathology, cell biology, endocrinology), institutional affiliation(s), title(s), and role(s) on the proposed project.

Title/Referral Page
No Page Limit

Proposal title (up to 160 characters)

Proposal log number

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

Award mechanism

PI's phone number, fax number, and e-mail address

Organization name and location (including city, state, zip or postal code, and country)

Name of administrative representative authorized to conduct negotiations

Phone number, fax number, and e-mail address of administrative representative authorized to conduct negotiations

Keyword descriptive technical terms

Conflicts of interest: Include the following information (no page limit)

Name	Degree(s)	Scientific Discipline	Institutional Affiliation(s)	Title(s)	Role(s) on Proposed Project

6. Table of Contents – Start section on a new page – 1-page limit

Prepare a Table of Contents, with page numbers, using the outline provided in the Proposal Preparation section under each award mechanism. Number all pages consecutively at the bottom center, beginning with the Title/Referral Page. Provide a header on every page of the proposal that includes PI name (last name, first name, middle initial) and proposal log number (this will be automatically provided when a draft of the Electronic Proposal Cover Booklet is saved).

7. Checklist for Proposal Submission (Instructions)

The Checklist for FY01 NFRP Proposal Submission found on page B-9 must be completed and submitted with the electronic and printed versions of your proposal. Place it immediately after the Table of Contents.

Complete and place this form immediately after the Table of Contents to confirm that all components are included in your application.

Checklist for FY01 NFRP Proposal Submission

Yes	No	
☐	☐	Electronic Proposal Cover Booklet
☐	☐	Title/Referral Page
☐	☐	Table of Contents
☐	☐	Checklist for FY01 NFRP Proposal Submission
☐	☐	Structured Technical Abstract (1-page limit)
☐	☐	Lay Abstract (1-page limit)
☐	☐	Statement of Work (2-page limit)
☐	☐	Proposal Relevance Statement (1-page limit)
☐	☐	Proposal Body **(adhere to page limits for the individual mechanism)**
☐	☐	Abbreviations (1-page limit)
☐	☐	References (no page limit)
☐	☐	Biographical Sketches (3-page limit per individual)
☐	☐	Principal Investigator
☐	☐	Collaborating investigators and other key personnel
☐	☐	Existing/Pending Support (no page limit)
☐	☐	Facilities/Equipment Description (no page limit)
		Administrative Documentation:
☐	☐	List of items included in this section
☐	☐	Statement of Eligibility form (New Investigator Awards)
☐	☐	Letters of support from collaborating individuals and/or institutions (all awards)
☐	☐	Detailed Cost Estimate (no page limit)
☐	☐	Total cost estimate matches Proposal Cover Booklet, item 4
☐	☐	Instruments (no page limit)
☐	☐	List of documents included in Instruments Section (all awards)
☐	☐	Publications and Patent Abstracts (5-document limit)

By signing below (in the printed version of the electronic PDF file), you confirm that your proposal contains the information requested above.

_____ _____

Signature of Applicant Date

NOTE: Exceeding page limits may result in proposal rejection prior to peer review. Submit only materials specifically requested or required in this program announcement. Submission of additional materials may be construed as an attempt to gain an unfair advantage.

8. Proposal Abstracts – Start each abstract on a new page – 1 page each

Both a 1-page structured technical abstract and a 1-page lay (nontechnical) abstract are required. Each proposal abstract page should contain the title of the proposal and the name of the PI. Abstracts must be submitted as part of the proposal. **Do not include figures or tables in either abstract.**

These abstracts are vitally important to the review of the proposal. **Programmatic review is based upon the Integration Panel's review of these two abstracts as part of the peer review summary statements; therefore, it is paramount that the investigator submit abstracts that fully describe the proposed work.** Sample abstracts are included in Appendix D of this program announcement.

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, significance of the proposed work to the program's goals, specific aims of the study, and study design.

Please use the outline below for preparing the structured technical abstract.

a. Background: Provide a brief statement of the ideas and reasoning behind the proposed work.

b. Objective/Hypothesis: State the objective/hypothesis to be tested. Provide evidence or rationale that supports the objective/hypothesis.

c. Specific Aims: State concisely the specific aims of the study.

d. Study Design: Briefly describe the study design.

e. Relevance: Provide a brief statement explaining the potential relevance of the proposed work to the program's goals. For example, how the study will prevent or improve the detection or treatment of the disease.

The lay abstract is intended to communicate the purpose of and rationale for the study to the nonscientific community. It should be composed in a way to make the scientific objectives of and rationale for the proposal understandable to nonscientifically trained readers. The lay abstract should not duplicate the technical abstract.

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

9. Statement of Work (SOW) – Start section on a new page – 2-page limit

The SOW is a concise restatement of the research proposal that outlines and establishes the PI performance expectations and timeline for which the USAMRMC will provide financial support. Although some allowance is made for problems encountered and uncertainties that are part of research, the PI is expected to meet the provisions and milestones in the SOW.

The SOW should be a series of relatively short statements that outline, step-by-step, how each of the major goals or objectives of the proposed research/services will be accomplished. As appropriate, the SOW should:

a. Describe the work to be accomplished as tasks (tasks may relate to specific aims),

b. Identify the timeline and milestones for the work over the period of the proposed effort,

c. Indicate the numbers of research subjects (animal or human) for each task,

d. Identify methods, and

e. Identify products/deliverables for each phase of the project.

The SOW must not exceed two pages of single-spaced typing. Several sample SOWs are included in Appendix D of this program announcement.

10. Proposal Relevance Statement – Start section on a new page – 1-page limit

In the Proposal Relevance Statement, the investigator should describe how the proposed research/services are pertinent to one or more critical issues of the disease.

11. Proposal Body – Start section on a new page

Each award mechanism has specific instructions for the description of the project and page limits. Investigators should refer to the specific evaluation criteria listed under the award mechanism to which they are applying to ensure that the necessary information is included.

12. Abbreviations – Start section on a new page – 1-page limit

Provide a glossary of all acronyms, abbreviations, and symbols used.

13. 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).

14. Biographical Sketches – 3-page limit per investigator

Biographical sketches should be included for each of the key personnel listed on the budget page, including collaborating investigators and support staff. Each biographical sketch must not exceed three pages. The Biographical Sketch form can be found in Appendix E or downloaded from the CDMRP web site at http://cdmrp.army.mil/funding/default

15. Existing/Pending Support – 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. Proposals submitted under this program announcement should not duplicate other funded research projects. If no support exists, state "none."

16. 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 acquisition or available for use at no cost to the USAMRMC. Indicate if Government-owned facilities or equipment are proposed for use.

17. Administrative Documentation – No page limit

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

Provide letter(s) from proposed collaborating individuals or institutions confirming collaborative efforts that are necessary for the project's success. Other support documentation also may be required within specific award categories. Please follow specific instructions in each award mechanism. These letters **must be incorporated into the electronic PDF version of your proposal. Note: This section is not for additional data, figures, or other similar information.** Support documentation **will not** be accepted separately from the proposal submission.

18. Detailed Cost Estimate – No page limit

Budget is a key consideration in both scientific peer and programmatic review; applicants are cautioned to use discretion in budget requests. Use the Detailed Cost Estimate form to prepare a detailed cost estimate of the proposed research/services. This form can be found in Appendix F or downloaded from the CDMRP web site at http://cdmrp.army.mil/funding/default. The cost of preparing proposals in response to this program announcement is not considered an allowable direct charge to any resultant award.

19. Instruments – No page limit

Include an appropriately titled page listing the documents you have in this section. Questionnaires, survey instruments, or clinical protocols that apply to the proposal should be included in this section.

20. Publications and Patent Abstracts – 5-document limit

Include up to five relevant publication reprints and patent abstracts. A patent abstract should provide a nonproprietary description of the patent application. These documents **must be incorporated into the electronic PDF version of your proposal.** A help line will be available no earlier than May 15, 2001 and no later than June 13, 2001 to answer specific questions. If more than five such items are included in the submission, **the extra items will not be peer reviewed. Submit only material specifically requested or required in this program announcement. Submission of unrequested material may be construed as an attempt to gain a competitive advantage and will be removed.**

21. Proposal Submission

Both electronic and paper submissions are required.

a. Electronic Submission: One electronic PDF version of your proposal is required and will count as the official proposal submission. The electronic PDF version must be submitted through the Internet by the sponsored programs office (or equivalent) of your organization no later than **4:00 p.m. (your local time) on July 25, 2001** and must be accompanied by the Electronic Proposal Cover Booklet. Instructions for electronic submissions will be available on the CDMRP web site (http://cdmrp.army.mil) no earlier than May 15, 2001 and no later than June 13, 2001.

b. Paper Submission: One printed version of the electronic PDF file is to be received by **July 31, 2001** at the address listed below. The paper submission will be used to confirm that the electronic PDF version of your proposal has been successfully transmitted. The paper submission must be accompanied by a printed version of the Electronic Proposal Cover Booklet. Please submit the required documents in one package to:

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-PLF (NFRP01)
1076 Patchel Street (Building 1076)
Fort Detrick, MD 21702-5024

If acknowledgment of proposal receipt is desired, enclose a self-addressed, stamped postcard with the printed version of the electronic PDF file. This postcard should state the proposal title, proposal log number, and the PI's name.

22. Receipt Deadlines

The transmission deadline for all proposals requested in this program announcement is 4:00 p.m. (your local time) on July 25, 2001. The electronic PDF version of your proposal, which will serve as the official proposal submission, must be sent through the Internet by the sponsored programs office (or equivalent) of your organization by that time. In addition, one printed version of the electronic PDF file is to be received by July 31, 2001 and must be accompanied by one printed version of the Electronic Proposal Cover Booklet.

If your proposal is sent electronically after 4:00 p.m. (your local time) on July 25, 2001, it may not be considered for review.

23. Regulatory Compliance and Quality Requirements – To be submitted at a later date

Documentation related to Regulatory Compliance and Quality issues (Certificate of Environmental Compliance, Research Involving Human Subjects and/or Anatomical Substances, Research Involving Animals, and Safety Program Plan) should be provided by the PI to the USAMRMC immediately upon request but should not be submitted with the original proposal. Institutional Review Board (IRB) documentation should be submitted and pending approval from the local IRB before the programmatic review of proposals is conducted.

Appendix C

Electronic Proposal Cover Booklet Instructions

The Electronic Proposal Cover Booklet and instructions for completing it will be available at the Congressionally Directed Medical Research Programs web site (http://cdmrp.army.mil) no earlier than May 15, 2001 and no later than June 13, 2001. The Electronic Proposal Cover Booklet must accompany the electronic PDF (Portable Document Format) submission of your proposal. In addition, a printed version of the Electronic Proposal Cover Booklet must accompany the printed version of the electronic PDF file of your proposal. For questions concerning the Electronic Proposal Cover Booklet, a help line will be available no earlier than May 15, 2001 and no later than June 13, 2001.

Appendix D

Sample Abstracts and Statements of Work

Page
Sample Abstracts (Technical and Lay)..... D-2
Sample Statements of Work..... D-6

TECHNICAL ABSTRACT

Steroid Hormones in NF1 Tumorigenesis
Margaret R. Wallace, Ph.D., Investigator-Initiated Research Award Recipient

Background: Clinical literature suggests that steroid hormones may play a role in NF1 since neurofibroma growth shows some parallels with hormonal changes. For example, many patients develop neurofibromas at puberty, pregnancy often increases tumor size/number, women with NF1 may have a higher risk of malignancy and a higher neurofibroma burden, and neurofibroma development often slows in older adults. The steroid hormone field is being intensely researched in many types of cancer, but virtually nothing is known about these pathways in normal or NF1-tumor derived Schwann cells. Schwann cells comprise the bulk of these tumors, in which they are somatically mutated.

Objective/Hypothesis: The growth responses of normal and NF1 tumor Schwann cells to steroid hormones will be characterized, focusing on estrogen and progesterone. The hypothesis is that human neurofibroma (and malignant peripheral nerve sheath tumor [MPNST]) Schwann cells have increased hormone responsiveness compared to normal Schwann cells, leading to tumor growth.

Specific Aims: (1) To determine steroid hormone receptor expression in human normal, NF1 neurofibroma, and NF1 MPNST Schwann cells pre- and post-hormone treatment, (2) to test in vitro responses (proliferation and cell survival) of cultured human Schwann cells from normal nerve, NF1 neurofibromas and NF1 MPNSTs to estrogen and progesterone and their antagonists, and (3) to test in vivo responses of NF1-derived tumor Schwann cell lines to estrogen and progesterone, through a xenoplant model in *Nf1*/*scid* mice.

Study Design: We have developed a set of neurofibromin-negative Schwann cell cultures from NF1 patient tumors. The steroid receptor profile of normal and tumor-derived Schwann cells will be characterized before and after steroid treatment to establish a basis for the mechanism of action of these hormones. The cells will be tested for increased proliferation and survival rates in response to these hormones in vitro. These cells will also be analyzed in vivo by reconstitution of tumors through sciatic nerve injection of these cells into *Nf1* heterozygous mutant mice that are also immunodeficient (carry the *scid* genotype). This mouse line is being established in our group. The mice carrying xenoplants will be treated with estrogen and progesterone to determine if there are any hormone-regulated proliferative or survival effects in the in vivo situation.

Relevance: There is a crucial need for information about how NF1 tumors respond to steroid hormones, especially for patients who are candidates for hormone therapies for various reasons. Understanding steroid hormone signaling in tumor cells will help predict responses to such therapies in order to establish guidelines. Also, differences in neurofibroma/MPNST receptor profiles or responses compared to normal ones could be a target for antitumor therapies. The in vivo work will produce an animal model for testing such therapies. Many selective estrogen receptor modulators are being developed for this purpose in other tumor types that could be useful in NF1 if there is a research-based rationale supporting clinical trials. Our work will address this need.

LAY ABSTRACT

Steroid Hormones in NF1 Tumorigenesis
Margaret R. Wallace, Ph.D., Investigator-Initiated Research Award Recipient

Neurofibromatosis type 1 (NF1) is a common genetic disease with a wide variety of features primarily involving the nervous system and related tissues. NF1 is characterized by abnormal cell growth, the most common form being the neurofibroma, a generally slow-growing benign nerve tumor composed mostly of Schwann cells. Dermal neurofibromas can cause disfigurement and affect function, depending on location and size. Plexiform neurofibromas can grow very large and may be disabling or fatal. There are clinical reports suggesting that neurofibromas may be initiated or aggravated in growth at times of hormonal fluctuations, particularly when steroid sex hormones increase (infancy, puberty, pregnancy). This is an area of great interest in research of cancer. However there has been virtually no research in this field in NF1 or Schwann cells. This project will determine scientifically whether the hormones estrogen or progesterone have a growth-promoting effect in neurofibromas. The results of these studies will have relevance for doctors prescribing hormone therapies (for reasons such as birth control, menopause, and breast cancer, for example), and for therapy development aimed specifically at stopping or preventing neurofibroma growth. We will also study the malignancy (malignant peripheral nerve sheath tumor [MPNST]) that can develop in plexiform tumors.

Since there is no established neurofibroma animal model to test hormone effects, we will use Schwann cell cultures we obtained from NF1 neurofibromas and MPNSTs. These cultures can grow after transplantation into the mouse nerve, developing a small version of the original human tumor. The goal of this project is to use this unique set of cultures to test the tumor growth-promoting effects of steroid hormones in tissue culture and in the animals carrying the engrafted tumors. Furthermore, we will use a new line of immunodeficient mice that we are developing that carry an *NF1* gene mutation to better replicate the human situation and provide a future model to test new therapies.

The first specific aim will examine the genes responsible for transmitting the hormone signals (steroid receptors) and other genes that are turned on or off by hormones. Thus, we can examine which genes are affected by hormone treatments and relate that to cell growth. The second aim is to test whether these tumor cells show increased growth or cell survival in tissue culture in response to estrogen or progesterone and to see if these effects can be reversed with hormone antagonists such as tamoxifen. The third aim will then test for this growth-promoting property in tumors grown in mice. This project takes an innovative approach to studying steroid hormone effects in NF1 tumorigenesis by using human neurofibroma or MPNST cells and using a unique mouse transplant model. The combination of tissue culture and animal work using human tumor cells (from both sexes) should provide data most closely translatable to the patient situation. The results of these experiments will be the basis for future patient clinical trials. It is possible that the results will be mixed, suggesting that these effects may vary between individuals or tumors. But this, too, would be an important observation to help physicians choose therapies best suited to individual patients or tumors (perhaps through use of screening tests based on our work).

TECHNICAL ABSTRACT

Structure-Function Relationships in Merlin, the Product of the NF2 Causal Gene
Zygmunt S. Derewenda, Ph.D., Investigator-Initiated Research Award Recipient

Background: The NF2 causal gene encodes a protein known as merlin (or schwannonin). This protein is a member of the ERM (ezrin, radixin, moesin) family of regulatory molecules, which play a role in the control of cytoskeletal functions mediated by the small cytosolic GTPases from the Rho family. These proteins contain two interacting domains, connected via a helical linker, which bind other components of signaling pathways, linking surface receptors to cytoskeleton. One of the presumed functions of ERM proteins is transient interaction with RhoGDI (Rho guanine nucleotide exchange inhibitor). This process may lead to the activation of nucleotide exchange factors and promote cell growth, transformation, etc. Malfunction of this pathway due to mutations in the NF2 gene is the likely cause of tumors in neurofibromatosis.

Objective: The objective of this project is to obtain direct information regarding the atomic structure of merlin, its internal dimerization, and of the way in which its N-terminal domain interacts with RhoGDI. An additional objective is to map the functional domains on RhoGDI and merlin and to analyze the contributions of the individual amino acids through systematic site-directed mutagenesis and microcalorimetry.

Specific Aims: The project will result in the crystallization and crystal structure determination of the N-terminal fragment of merlin, its complex with the C-terminal lobe, and the complex of the N-domain with the smallest fragment of RhoGDI, which would show the wild-type affinity. Structure solution and refinement will be conducted at the highest possible resolution, hopefully better than 2Å.

Study Design: Individual proteins will be overexpressed in *Escherichia coli* in fusion with affinity tags, typically GST (glutathione S transferase), and purified by a combination of affinity and gel filtration, and/or ion exchange chromatography. The complexes will be typically isolated by size exclusion chromatography. Crystallization will be carried out by hanging and sitting drop methods following established protocols. The 'minimum entropy' method recently developed in the Principal Investigator's laboratory will be used to increase the efficiency of the crystallization process. Diffraction data will be collected using synchrotron radiation to achieve the highest possible resolution and precision. The structures will be solved by a combination of molecular replacement and MAD (multiwavelength anomalous dispersion methods) and refined by standard methods using software packages CNS, CCP4, and SHELX, depending on the resolution of the data. Thermodynamics of the merlin-RhoGDI interactions will be assessed by isothermal titration calorimetry and analyzed using ORIGIN software.

Relevance: The proposal is directly related to the main objectives of the neurofibromatosis research program. It addresses the very nature of the type II disease, its molecular causes and mechanisms involved in the onset. It also relates directly to key problems of cell regulation and cell transformation in general.

LAY ABSTRACT

Structure-Function Relationships in Merlin, the Product of the NF2 Causal Gene
Zygmunt S. Derewenda, Ph.D., Investigator-Initiated Research Award Recipient

Neurofibromatosis type II is a fairly common syndrome that leads to multiple tumors on nerves and other lesions of the brain and spinal chord, often affecting hearing nerves. It is distinct from neurofibromatosis type I in its symptoms and roots. The disease is known to be caused by mutations, i.e., changes in the DNA sequence, in the gene known as the NF2 causal gene. The NF2 gene contains genetic code that leads, in living cells, to the synthesis of a specific protein molecule—merlin—also called schwannonin. The mutations in the gene, which occur in afflicted individuals, result in the changes in the chemistry of the protein, so that 'incorrect' amino acids are incorporated in place of normal ones. Merlin is a fairly large protein made up of nearly 500 amino acids and folded into a structure that is not fully understood. What is known is that this molecule contains three distinct lobes, two of which—located at either end—are involved in interactions with other protein molecules that in turn regulate many of the functions in a normal cell. It has been shown that inert merlin folds onto itself, with the two terminal lobes (or domains) interacting with each other. The biologically active molecule is open, with each lobe involved in contacts with its partners from the signaling cascade. One of such partner molecules for merlin is known as GDI, a protein involved in the activation of many cells leading to transformation and tumor growth. We propose in our application to study the atomic structure of merlin both in its inactive form and when one of its domains is bound to GDI. This will lead to a better understanding of the mechanisms, the malfunction of which appears to be associated with the onset of NF2.

We propose to accomplish our goal by first producing samples of both terminal lobes of merlin and of GDI in the bacterium *Escherichia coli* using recombinant DNA methods and by crystallizing these protein alone and in complexes. Once single crystals become available, we will use the technique of x-ray crystallography to obtain accurate three-dimensional models of the atomic structure of the protein molecules. The technique of x-ray crystallography is uniquely suited to probe the issues of structure and function in biomolecules and the structural models generated by this approach are very reliable. Using the model structures, we will identify the surfaces in the proteins that are involved in signaling, and we will probe the specific function of each amino acid involved in those surfaces (or epitopes) using site directed mutagenesis and another experimental technique known as microcalorimetry.

The results generated by our research are likely to dissect the functionality of merlin and to explain, at least in part, the impact that NF2-causing mutations have on merlin. This improved understanding in the causes of the disease may then be used by those who are involved in the design of novel therapeutic approaches.

JONES, REBECCA E.

Statement of Work

Development of Peptide Inhibitors of the "Cancer" Receptor (CR)

Task 1. To identify the minimal region of the CR polypeptide able to inhibit intact CR when co-expressed in cultured cells (Months 1-18):

a. Develop a series of plasmids for expressing the CR open reading frame (Months 1-7).
b. Perform assays to ascertain which fragments of CR block DNA-binding (Months 7-18).
c. Confirm that fragments of the CR open reading frame that block DNA-binding activity also inhibit CR function *in vivo* (Months 18-24).

Task 2. To identify short peptides modeled after the receptor that act as inhibitors of DNA binding and subunit association (Months 18-36):

a. Obtain synthetic CR peptides (Months 18-21).
b. Test the effect of synthetic peptides on the DNA-binding activity of CR (Months 20-24).
c. Characterize the inhibitory potency of active peptides and attempt to optimize the effect by testing additional overlapping peptides (Months 21-36).
d. Perform feasibility experiments to assess the ability of selected peptides to inhibit CR function in cultured cells (Months 20-36).

WILSON, JOHN R.

Statement of Work

Ultrasound Imaging

Task 1. Modification of ultrasound imaging gantry, Months 1-12:

a. Modify imaging gantry to permit measurements of the optics.
b. Perform measurements using a multi-modal scanning configuration.
c. Design of final optics.

Task 2. Extensive evaluation of ultrasound imaging gantry with the final optics, Months 13-36:

a. Repeat measurements using the final optics.
b. Measure the contrast improvement provided by the new detector configuration relative to conventional detector configuration.
c. Conduct specimen experiments to evaluate the increase in resolution provided by the magnification.
d. Investigate the extent of artifacts in fixed and scanning modes.
e. Participate in design of a clinical evaluation study comparing modified ultrasound mammography with conventional mammography.

YOUNG, SUSAN D.

Statement of Work

Follow-up Care for Men and Women with Cancer

Task 1. Develop Plan for Follow-up Patient Interviews, Months 1-3:

a. The tracking system shell from the previous cancer project will be modified to track patient recruitment and contact process.
b. The follow-up patient interview will be pre-screened with cancer patients from our hospital who are not enrolled in our study and modifications will be incorporated.
c. The environmental process interview (EPI) used for the baseline interview will be adapted for the follow-up interview.
d. Institutional Review Board approval will be obtained from all hospital sites.
e. The patient interviewer will be trained in medical terminology, measures of the interview, and use of the modified EPI system.

Task 2. Preparation for Medical Record Abstractions, Months 3-9:

a. The Medical Record Abstract form will be finalized and the investigator trained to perform patient data reviews using the instrument.
b. The Medical Record Abstract form will be revised for direct computer data entry.

Task 3. Subject Recruitment and Data Collection, Months 9-20:

a. Patients enrolled in our previous study will be recruited for the proposed follow-up study.
b. Interviews subsequent to the first follow-up will be modified as necessary to reflect issues relevant to patients beyond the period of adjuvant therapy.
c. Surveys will be sent to and data collected from enrolled patients every 6 months.

Task 4. Abstraction of Medical Records, Months 12-24:

a. Medical record abstractions will be performed for surviving enrolled patients annually.
b. Data entry and quality control measures will be ongoing.
c. Follow-up interviews will be conducted once annually with surviving enrolled patients over the 4-year study period.

Task 5. Interim Analyses, Months 24-44:

a. Interim statistical analyses of data obtained from interviews and medical record abstractions will be performed periodically.
b. Annual reports will be written.

Task 6. Final Analyses and Report Writing, Months 44-48:

a. Final analyses of data from interviews and medical record abstractions will be performed.
b. A final report and initial manuscripts will be prepared.

Appendix E

Biographical Sketches

Provide the following information for the key personnel listed on page 1 of the Detailed Cost Estimate form (see Appendix F) for the initial budget period.

NAME	POSITION TITLE

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE (IF APPLICABLE)	YEAR(S)	FIELD OF STUDY

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past 3 years and representative earlier publications pertinent to this application. PAGE LIMITATIONS APPLY. DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

RESEARCH AND PROFESSIONAL EXPERIENCE (CONTINUED). PAGE LIMITATIONS APPLY. DO NOT EXCEED THREE PAGES FOR THE ENTIRE BIOGRAPHICAL SKETCH PER INVESTIGATOR.

Appendix F

Detailed Cost Estimate Form Instructions

The following sections describe the categories of costs that should be recorded on the Detailed Cost Estimate form. All amounts entered should be in U.S. dollars.

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	Detailed Cost Estimate Form	F-5

1. Personnel

- **Name:** Starting with the Principal Investigator (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.

- **Role on Project:** Identify the role of each individual listed on the project. Describe his/her specific functions in the "Justification" section (page 3 of the Detailed Cost Estimate form).

- **Type of Appointment (Months):** List the number of months per year reflected in an individual's contractual appointment with the offering organization. The Department of Defense (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 percent, note this with an asterisk (*) and provide a full explanation in the "Justification" section (page 3 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.

- **Annual Base Salary:** Enter the annual institutional base salary for each individual listed for the project.

- **Percentage of Effort on Project:** The qualifications of the PI and the amount of time that he/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.

- **Salary 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.

- **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 as a direct cost to all sponsors. A copy of the rate agreement or other documentation to support the fringe benefits should be provided.

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

2. Consultant Costs

Regardless of whether funds are requested, provide the names and organizational affiliations of all consultants, other than those involved in consortium arrangements.

3. Major Equipment

It is the policy of the DOD that all commercial and nonprofit recipients provide the equipment needed to support proposed research. In those rare cases where specific additional equipment is approved for commercial and nonprofit organizations, such approved cost elements shall be separately negotiated.

4. 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, and 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.

5. Travel Costs

Travel costs are allotted as a flat rate that varies depending on award mechanism. Please consult the appropriate award mechanism section of this program announcement and enter the amount specified for travel in the Detailed Cost Estimate form.

6. Research-Related Patient Costs

Itemize costs of patient participation in the research study. These costs are strictly limited to expenses specifically associated with the proposed study. The U.S. Army Medical Research and Materiel Command will not provide funds for ongoing medical care costs that are not related to a subject's participation in the research study.

7. Other Expenses

Itemize other anticipated direct costs such as publication and report costs, rental for computers and other equipment (giving 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.

8. Consortium 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:

a. the identification of the type of award to be used (e.g., cost reimbursement, fixed price);

b. the 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;

c. whether the award will be competitive and, if noncompetitive, rationale to justify the absence of competition; and

d. the proposed acquisition price.

9. 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 along with a statement identifying whether the proposed rates are provisional or fixed. A copy of the negotiation memorandum should be provided.

Training awards frequently have a different institutional overhead charge. All training investigators are encouraged to check with their institution concerning overhead costs.

10. 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 "Justification" section (page 3 of the Detailed Cost Estimate form). **Note with an asterisk (*) and explain any significant increases or decreases from the initial year budget. Also, explain any escalations of the budget from the initial to the future year(s) of support.** All amounts should be in U.S. dollars. Total costs for the entire proposed period of support on the last line of page 2 should agree with the amount entered in item 4 of the Proposal Cover Booklet (Bubble Sheet) (see Appendix C).

11. Justification (third page of the Detailed Cost Estimate form)

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

12. Relocation of Principal Investigator

Awards are made to institutions. If the PI leaves the recipient institution, both the PI and an official of the recipient institution should notify the U.S. Army Medical Research Acquisition

Activity before the PI leaves to discuss options for continued support of the research project.

Detailed Cost Estimate Form

Name of Principal Investigator ***(last, first, middle)***

DETAILED BUDGET						**FROM**	**THROUGH**
PERSONNEL		**TYPE APPT. (MONTHS)**	**ANNUAL BASE SALARY**	**% EFFORT ON PROJECT**	**DOLLAR AMOUNT REQUESTED (OMIT CENTS)**		
NAME	**ROLE ON PROJECT**				**SALARY REQUESTED**	**FRINGE BENEFITS**	**TOTALS**
	Principal Investigator						
SUBTOTALS →→→→→							**$**
CONSULTANT COSTS							
MAJOR EQUIPMENT (ITEMIZE)							
MATERIALS, SUPPLIES, AND CONSUMABLES (ITEMIZE BY CATEGORY)							
TRAVEL COSTS							
RESEARCH-RELATED PATIENT COSTS							
OTHER EXPENSES (ITEMIZE BY CATEGORY)							
SUBTOTAL OTHER DIRECT COSTS FOR INITIAL BUDGET PERIOD →→→→→							$
CONSORTIUM COSTS	**DIRECT COST**						
	INDIRECT COST						
TOTAL PERSONNEL AND OTHER DIRECT COSTS FOR INITIAL BUDGET PERIOD							$
TOTAL INDIRECT COSTS FOR INITIAL BUDGET PERIOD							$
TOTAL COSTS FOR INITIAL BUDGET PERIOD							$

Name of Principal Investigator ***(last, first, middle)***

BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT							
BUDGET CATEGORY TOTALS*		**INITIAL BUDGET PERIOD** (FROM FORM PAGE 1)	**ADDITIONAL YEARS OF SUPPORT REQUESTED**				**TOTAL**
			2nd	**3rd**	**4th**	**5th**	
PERSONNEL							
FRINGE BENEFITS							
CONSULTANT COSTS							
MAJOR EQUIPMENT							
MATERIALS, SUPPLIES, AND CONSUMABLES							
TRAVEL COSTS							
RESEARCH-RELATED PATIENT COSTS							
OTHER EXPENSES							
SUBTOTAL DIRECT COSTS							
CONSORTIUM COSTS	**DIRECT**						
	INDIRECT						
TOTAL DIRECT COSTS							
TOTAL INDIRECT COSTS							
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT					**$**		
TOTAL INDIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT					**$**		
TOTAL COSTS FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT **THIS AMOUNT SHOULD AGREE WITH THAT ENTERED ON THE PROPOSAL COVER BOOKLET, ITEM 4**					**$**		

* **Itemize all budget categories for additional years on the Justification page that follows.**

JUSTIFICATION: FOLLOW THE BUDGET JUSTIFICATION INSTRUCTIONS EXACTLY. USE CONTINUATION PAGES AS NEEDED.

Appendix G

General Information

Appendix G of this program announcement contains general information relating to U.S. Army Medical Research and Materiel Command (USAMRMC) policies and procedures.

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General Information

1. U.S. Army Medical Research and Materiel Command Award

The USAMRMC implements its extramural research program predominantly through the award of grants and cooperative agreements. Proposals selected for funding are processed by the U.S. Army Medical Research Acquisition Activity (USAMRAA).

All awards are made to organizations, not individuals. A Principal Investigator (PI) should submit a proposal through, and be employed by or affiliated with, a university, college, nonprofit research institute, commercial firm, or Government agency (including military laboratories) in order to receive support.

2. Procurement Integrity, Conflicts of Interest, and Other Improper Business Activities

The Procurement Integrity Act, Title 41 U.S. Code 423, et seq., contains prohibitions against certain activities between Offerors and Government officials. Any questions regarding these prohibitions should be directed to the USAMRMC legal staff at 301-619-2221. Proposed military/civilian collaborations should pay special attention to the Procurement Integrity Act.

3. Disclosure of Information outside the Government

By submission of an application, the applicant understands that disclosure of information outside the Government shall be for the sole purpose of technical evaluation. The USAMRMC will obtain a written agreement from the evaluator that information in the proposal will only be used for evaluation purposes and will not be further disclosed or utilized. Funded projects 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.

4. Award Eligibility

To be eligible for 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 (Office of Management and Budget Circular A-110).

5. Government Obligation

PIs 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. PIs 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.

6. 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.

7. Funding Instrument

All awards under this program announcement are anticipated to be grants or cooperative agreements.

More information on these funding instruments may be obtained by request from:

Fax: 301-619-2937
E-mail: q&a.baa@det.amedd.army.mil
Mail: Director
U.S. Army Medical Research Acquisition Activity
ATTN: MCMR-AAA
820 Chandler Street
Fort Detrick, MD 21702-5014

8. 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 Congressionally Directed Medical Research Programs staff, USAMRMC Judge Advocate General staff, and USAMRAA Grants Officers constitute an Inquiry Review Panel and review each inquiry to determine whether factual or procedural errors in either peer or programmatic review have occurred, and if so, what action should be taken.

9. Equipment/Property

It is the policy of the Department of Defense that all commercial and nonprofit recipients possess the equipment and facilities needed to support proposed research. In those rare cases when additional specific equipment is approved for commercial and nonprofit organizations, such approved cost elements shall be separately negotiated.

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

Appendix H

Acronym List

AR	Army Regulation
CDMRP	Congressionally Directed Medical Research Programs
CEQ	Council on Environmental Quality
CFR	Code of Federal Regulations
CPA	Cooperative Projects Assurance
CR	Cancer Receptor
CV	Curriculum Vitae
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
DOD	Department of Defense
DOEd	Department of Education
EPI	Environmental Process Interview
ERM	Erzin, Radixin, Moesin
FDA	Food and Drug Administration
FY	Fiscal Year
GAP	GTPase-Activating Protein
GCP	Good Clinical Practices
GST	Glutathione S Transferase
GTMR	Greater Than Minimal Risk
HAZCOM	Hazard Communication
HBCU/MI	Historically Black Colleges and Universities/Minority Institutions
HSRRB	Human Subjects Research Review Board
IACUC	Institutional Animal Care and Use Committee(s)
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IIRA	Investigator-Initiated Research Award
IND	Investigational New Drug
IP	Integration Panel
IRB	Institutional Review Board
MAD	Multiwavelength Anomalous Dispersion Methods
MPA	Multiple Project Assurance
MPNST	Malignant Peripheral Nerve Sheath Tumor
N/A	Not Applicable
NFRP	Neurofibromatosis Research Program
NGTMR	No Greater Than Minimal Risk
NIH	National Institutes of Health
OTSG	Office of The Surgeon General
PDF	Portable Document Format
PI	Principal Investigator
RCQ	Regulatory Compliance and Quality

RhoGDI	Rho Guanine Nucleotide Exchange Inhibitor
SPA	Single Project Assurance
TSG	The Surgeon General
USAMRAA	U.S. Army Medical Research Acquisition Activity
USAMRMC	U.S. Army Medical Research and Materiel Command
USC	United States Code
USDA	U.S. Department of Agriculture

Appendix I

Certificate of Environmental Compliance

The Certificate of Environmental Compliance should be executed by the institution's official responsible for environmental compliance.

The Council on Environmental Quality (CEQ) regulations (40 CFR 1500-1508) that implement the National Environmental Policy Act (PL 91-190, as amended) require all federal agencies to examine possible environmental consequences of their proposed and ongoing actions.

The U.S. Army Medical Research and Materiel Command (USAMRMC) examines all medical research and development projects, whether inside or outside the United States, for their potential environmental impacts. In most cases, awardees conducting research in established laboratories that are in compliance with environmental laws and regulations, or are already covered by existing environmental documentation, will not be required to provide additional information about the environmental impact of their proposed research. Such projects will receive a "categorical exclusion" according to the Army regulations that implement the CEQ regulations (AR 200-2). After a proposal has been selected for award, the USAMRMC will determine if a categorical exclusion is warranted. If there are any extraordinary circumstances surrounding the research (e.g., research that involves the transfer of recombinant DNA molecules into the genome of one or more human subjects, requires Biosafety Levels 3 and 4, or uses animals captured from the wild), further information may be requested from the investigator to determine the environmental impact of the proposed research. This information should be submitted in a timely manner in order to receive an award.

Certificate of Environmental Compliance

The offeror currently ☐ IS ☐ IS NOT (check appropriate category) in compliance with applicable national, state, and local environmental laws and regulations. (If not in compliance, attach details and evidence of approved mitigation measures.)

The offeror has examined the activities encompassed within the proposed action entitled

"_____

_____"

(enter title and Principal Investigator's name), for compliance with environmental laws and regulations. The offeror states that the conduct of the proposed action:

1. WILL NOT violate any applicable national, state, or local environmental law or regulation, and

2. WILL NOT have a significant impact on the environment.

The offeror agrees that if the work required under the proposed action at any time results in a significant impact on the environment or a violation of any applicable environmental law or regulation, the offeror will immediately take appropriate action, to include notifying and/or coordinating with the appropriate regulatory agencies as required by law and notifying the Grants Officer.

_____	_____
Name of Official Responsible for Environmental Compliance	Signature
_____	_____
Title	Date
_____	
Name of Organization	

Appendix J

Research Involving Human Subjects and/or Anatomical Substances

This appendix contains the required approvals, forms, and descriptions for research involving human subjects and/or human anatomical substances (including human organs, tissues, cells, body fluids from human subjects as well as graphic, written, or recorded information derived from human subjects). Specific guidelines are subject to change as governing regulations, policies, and procedures are updated. Consult "Guidelines for Research Involving Human Subjects and/or Anatomical Substances" at http://mrmc-www.army.mil/rcq/hspd.htm for additional information and updates.

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Research Involving Human Subjects and/or Anatomical Substances

1. Introduction

In 1991, the Department of Defense (DOD), together with 15 other federal agencies, adopted regulations that are known collectively as the Common Federal Rule. These regulations embody the ethical principles of the Belmont Report. Title 32 Code of Federal Regulations Part 219 (32 CFR 219), "Protection of Human Subjects" applies to all research involving human subjects conducted or supported by the DOD. The Department of Health and Human Services (DHHS) National Institutes of Health (NIH) corollary is 45 CFR 46. Research conducted or funded by the U.S. Army Medical Research and Materiel Command (USAMRMC) is also governed by Army Regulation (AR) 70-25, January 1990 and Office of The Surgeon General (OTSG) Regulation 15-2, January 1989. The USAMRMC also adheres to the Food and Drug Administration (FDA) regulation, Title 21 Code of Federal Regulations for research involving investigational drugs or devices. The OTSG maintains the overall responsibility for protecting human research subjects for the Department of the Army.

2. Definitions

2-a. Research

In the Common Federal Rule, research is defined as " . . . a systematic investigation, including research development, testing and evaluation designed to develop or contribute to generalizable knowledge" (32 CFR 219.102). Activities that meet this definition constitute research for purposes of this policy, whether they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

The FDA defines clinical investigation as " . . . any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects" (21 CFR 312.3). This definition applies to research involving the use of FDA-regulated products.

2-b. Human Subjects

In the Common Federal Rule, a human subject is defined as "a living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information" (32 CFR 219.102).

The FDA defines a human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient" (21 CFR 312.3).

2-c. Human Anatomical Substances (and Privileged or Protected Health Information)

The Common Federal Rule applies to the use of human organs, tissues, cells, or body fluids from individually identifiable human subjects and graphic, written, or recorded information derived from individually identifiable human subjects.

3. Human Subjects Research Review Board

3-a. Review Levels for DOD-Sponsored Research

In addition to first level of review and approval by the local Institutional Review Board (IRB), a second level of review and approval is required for DOD-sponsored research. If a research proposal is recommended for funding and the research involves human subjects, human anatomical substances, or privileged or protected health information, a research protocol must be submitted to the Human Subjects Research Review Board (HSRRB) for review and approval. HSRRB approval must be obtained prior to initiation of the research protocol. The HSRRB is functionally similar to a civilian IRB. The HSRRB is supported administratively by the Office of Regulatory Compliance and Quality, USAMRMC.

If a claim of exemption is submitted, the Acting Chair of the HSRRB will review the protocol and make a determination of exempt status.

If the local IRB has made an assessment that the proposed research is no greater than minimal risk (NGTMR) and the research is eligible for expedited review, the Acting Chair of the HSRRB will review the protocol. If the protocol is not eligible for expedited review, it will receive a full HSRRB review at a convened Board meeting.

If the local IRB has made an assessment that the proposed research is greater than minimal risk (GTMR), the protocol will receive a full HSRRB review. The protocol must be submitted through the Office of Regulatory Compliance and Quality to the HSRRB for full review and approval prior to initiation of the research.

3-b. Timelines and Outcomes

Initial feedback from the HSRRB is given to the Principal Investigator (PI) within 1 month after submission of a complete protocol packet. After the protocol is approved, any revisions to the protocol, consent form, advertisements, questionnaires, or other related study documentation must be submitted through the local IRB to the HSRRB for approval prior to implementation. The Surgeon General (TSG) of the U.S. Army must approve the recommendations of the HSRRB. The HSRRB will make one of the following recommendations to TSG:

Approval. The protocol should be approved without further revisions.

Conditional Approval. Approval of the protocol is contingent upon revisions being made and/or additional information being provided. The PI should address the Board's recommendations and submit a revised protocol and related documents to the Acting Chair, who can approve the revised protocol when all of the Board's recommended revisions and requests for additional information have been adequately addressed.

Disapproval. A protocol is not approved when there are substantive concerns about the conduct of the protocol and/or safety of the subjects. The PI should address the Board's recommended revisions and requests for additional information and submit a revised protocol and related documents to the Acting Chair for review at another convened meeting of the HSRRB.

Deferral. A protocol may be deferred or tabled for action at another meeting when there is a lack of sufficient information to make a more definitive recommendation.

3-c. Multi-site Protocol Review

For multi-site protocols involving the use of human subjects, the protocol and consent form for the primary site are first reviewed and approved by expedited or full Board review as appropriate. If the same protocol used by the primary site will be used at each of the other sites, each site-specific consent form can receive expedited review after review and approval of the protocol and consent form for the primary site. In addition, all domestic and foreign sites are required to assure compliance with the federal policy for the protection of human subjects. If an awardee institution or any of the collaborating sites does not have an assurance number, such as a Multiple Project Assurance (MPA) with the DHHS Office for Human Research Protections, then an application for a DOD single project assurance (SPA) must be completed by each site that does not have an assurance and the application must be submitted to the Human Subjects Protection Branch of the USAMRMC. Refer to part 12, "Assurances" in this appendix for further details regarding submission of an SPA application.

4. Claim of Exemption

4-a. Approval of Exempt Status for Research Involving Human Subjects or Anatomical Substances

Certain categories of research are exempt from review by the HSRRB in accordance with federal guidelines. If your research fits in one or more of these categories, you may request exempt status for your protocol. Your protocol and Claim of Exemption form will be reviewed to evaluate your claim of exemption.

4-b. Exempt Categories

The following list taken from 32 CFR 219.101 details the exemption categories.

1. Research conducted in established or commonly accepted educational settings involving normal educational practices, such as:

a. research on regular and special education instructional strategies, or

b. research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless:

   a. information obtained is recorded in such a manner that human subjects can be identified directly or through identifiers linked to the subjects; and

   b. any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph 2 of this section, if:

   a. the human subjects are elected or appointed public officials or candidates for public office, or

   b. federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are publicly available of if the information is recorded by the investigator in such a manner that subjects cannot be identified directly or through identifiers linked to the subjects.

5. Research and demonstration projects that are conducted by or subject to the approval of Department or Agency heads, and that are designed to study, evaluate, or otherwise examine:

   a. public benefit or service programs,

   b. procedures for obtaining benefits or services under those programs,

   c. possible changes in or alternatives to those programs or procedures, or

   d. possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies,

   a. if wholesome foods without additives are consumed, or

b. if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

4-c. Claiming Exemption

Investigators who believe that their protocol is exempt from review should submit (1) a completed Claim of Exemption Form and (2) documentation from the local IRB stating that the protocol has been determined to be exempt.

5. Minimal Risk Research

5-a. Approval of NGTMR Research Involving Human Subjects or Human Anatomical Substances

Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests" in 32 CFR 219.102(i). If the research protocol is assessed as minimal risk in accordance with this definition and regulation, it can be approved by expedited review if the study involves one of the research categories that qualifies for expedited review, as listed in the Federal Register, Notices, Vol. 63, No. 216, dated November 9, 1998. For example, the following is a brief synopsis of these categories:

1. Clinical studies of drugs for which an Investigational New Drug (IND) application is not required or of medical devices for which an Investigational Device Exemption (IDE) application is not required or the medical device has been cleared/approved for marketing and the device is being used for its cleared/approved labeling.

2. Collection of blood samples by finger, heel or ear stick, or by venipuncture, where the amount of blood drawn does not exceed 550 mL in an 8-week period and collection does not occur more frequently than two times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means, such as hair and nail clippings, teeth extracted as routine patient care, excreta and external secretions, saliva, placenta removed at delivery, amniotic fluid obtained at the time of membrane rupture or during labor, dental plaque and calculus that is not more invasive than routine care, mucosal and skin cells collected by buccal scraping, mouthwashings or swab, and sputum.

4. Collection of data through noninvasive procedures not involving general anesthesia or sedation.

5. Research involving materials, such as data, documents, records or specimens, that have been collected or will be collected solely for nonresearch purposes (e.g. medical treatment or diagnosis).

6. Collection of data from voice, video, digital or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior, or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation or quality assurance methodologies.

8. Continuing review of previously approved research.

5-b. Approval of a NGTMR Research Study with a Waiver of Informed Consent

A minimal risk protocol approved by expedited review can have the requirement for a written informed consent document waived if it meets the following four criteria, as outlined in 32 CFR 219.116(d):

1. The research involves no more than minimal risk to the subjects.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.

3. The research could not practicably be carried out without the waiver or alteration.

4. Whenever appropriate, the subjects will be provided with additional information after participation.

If the local IRB has approved a protocol with waiver of informed consent and the study includes use of human anatomical substances, submit a copy of the consent form used to document individuals' consent to use their tissue, blood, or other medical information or records for research purposes.

6. Training for Research Investigators

Research investigators must complete appropriate institutional training before conducting human subjects research. Documentation of the most recent ethics training must be submitted for all investigators and other research staff for all protocols. In addition, for all investigational drug and device protocols, documentation of successful completion of a course in the conduct of clinical research in accordance with Good Clinical Practices (GCP) must be submitted for all investigators and other research staff. The most recent ethics training and GCP course must be successfully completed within one year of the planned initiation of the protocol.

7. Guidelines for Writing Research Protocols Involving Human Subjects

7-a. Title 10 United States Code 980 (10 USC 980)

Before writing the research protocol, investigators must consider the requirements of 10 USC 980, which are applicable to DOD-sponsored research. 10 USC 980 requires that "Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless (1) the informed consent of the subject is obtained in advance, or (2) in the case of research intended to be beneficial to the subject, the informed

consent may be obtained from a legal representative of the subject." **Furthermore and consistent with the Common Federal Policy for the Protection of Human Subjects, if an individual cannot give his/her own consent to participate in a research study, consent of the individual's legally authorized representative must be obtained prior to the individual's participation in the research. Moreover, an individual not legally competent to consent (e.g., incapacitated individuals, incompetents, minors) may not be enrolled in DOD-sponsored research unless the research is intended to benefit each subject enrolled in the study. For example, a subject may benefit directly from medical treatment or surveillance beyond the standard of care. Proposers 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.**

7-b. Protocol Format

A detailed research protocol must be submitted for all protocols, including IND or IDE protocols, for human subjects protection review. In addition, the protocol must be reviewed and approved by the local IRB of Record before it can be reviewed by the HSRRB, and the approval letter from the local IRB must be submitted with the protocol for initial HSRRB review.

IND or IDE protocols will follow the format described in the International Conference on Harmonisation (ICH), Consolidated Guideline E6 (http://www.ifpma.org/pdfifpma/e6.pdf). Other protocols may follow the ICH Guideline and include applicable paragraphs.

7-c. Required Elements of the Protocol

1. Protocol Title. The protocol title must be the same as the project/proposal title unless multiple protocols are being submitted within one proposal.

2. Phase. For medical products regulated by the Food, Drug, and Cosmetic Act, designate the protocol as Phase I, II, III, or IV research.

3. Principal Investigator. List the complete name, address, phone number, and email address of the PI. Include a copy of the PI's curriculum vitae (CV) with the protocol. List the names of all personnel who will have significant involvement in the research study; include their practice license (i.e., MD or RN), highest degree(s), job title, and employing institution. In addition, if a Medical Monitor has been assigned to the study, which is required only for greater than minimal risk studies, include his/her name and provide a copy of the current CV.

4. 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.

5. Time Required to Complete. State the month and year of expected start and completion times.

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

7. Study Population.

   a. 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).

   b. Describe the methods that will be used to obtain a sample of subjects from the accessible population (i.e., convenience, simple random, stratified random) together with the inclusion and exclusion criteria (include age, gender, ethnicity).

   c. If pregnant subjects will be excluded from participation in the study, the method used to determine pregnancy status in women of childbearing potential must be specified. Also, state the time that will elapse between the pregnancy test and exposure to research procedures or medical products and how long the non-pregnant subject should use effective contraceptive practices after participating in the study. Please note that contraceptive practices may be necessary for male subjects participating in certain types of studies. For IND studies, pregnancy testing is required within 48 hours before the start of the study.

8. Protocol Design. 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:

   a. Subject identification. Describe the code system to be used.

   b. 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.

   c. 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 like being informed he/she has cancer, 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. Indicate who will serve as the witness to the informed consent interview. Please note that a witness is required to be present during the informed consent interview. Two copies of the 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 patient's medical record; check with the participating site for specific study-site requirements.

   d. Subject assignment (randomization).

e. Evaluations prior to entry. List and describe any evaluations (e.g., laboratory procedures, history, 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.

f. Evaluations to be made during the conduct of 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.

g. Clinical assessments (e.g., schedule of clinical evaluations and follow-up procedures). Provide a copy of all case report forms, data collection forms, questionnaires, rating scales, and/or interview guides that will be used in the study.

h. 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.

9. Risks/Benefits Assessment.

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

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

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

10. Reporting of serious or unexpected adverse events.

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

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

(1) For IND or IDE research, include definitions as described in 21 CFR 312.32.

(2) All research protocols must address the following requirements, which is language from HSRRB Clause 7.01:

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

c. Describe agencies or offices to be notified with point of contact information in the event of a serious and unexpected adverse event. For all protocols involving human subjects, including investigational new drug or device studies, the following information about reporting serious and unexpected adverse events, which is language from HSRRB Clause 1.02, must be included in the protocol:

"Adverse experiences that are both serious and unexpected will be immediately reported by telephone to the USAMRMC, Deputy for Regulatory Compliance and Quality (301-619-2165) and send information by facsimile to 301-619-7803). A written report will follow the initial telephone call within 3 working days. Address the written report to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012."

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

a. IND/IDE number and name of sponsor.

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

c. Source of medications, devices, or placebos.

d. Location of storage for study medications.

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

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

g. Duration of drug or device treatment.

h. Concomitant medications allowed.

i. Antidotes and treatments available.

j. Disposition of unused drug.

k. The procedure by which the IND sponsor will monitor the protocol in accordance with 21 CFR 312.

(1) In addition to the above list of requirements to address in the protocol, include the following with the protocol submission:

(a) A copy of the Investigator's Brochure and/or device manual and associated case report/data collection forms.

(2) A signed Form FDA 1572 for IND Applications that have been approved by the FDA, including the following information (for non-FDA new drug protocols, the following information should be included in the protocol):

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

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

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

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

12. 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. Note that records of IND studies must be kept until 2 years after a New Drug Application is approved/issued, or for 2 years after the IND is withdrawn. Records required for IDE studies should be retained for 2 years after the latter of the following dates: the date that the investigation is terminated or completed and the date that the records are no longer required for support of the pre-market approval application. For studies with minors, most states require keeping records for up to 7 years (dependent on state's statute of limitations) past the subject's age of majority.

13. 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, consent form and/or questionnaires must be submitted to both the local IRB and the HSRRB for review and approval. Address this procedure even if you do not anticipate making any modifications.

14. Departure from the Protocol. Describe procedures and notifications to be made in the event of deviations from the approved protocol requirements.

15. Roles and Responsibilities of Study Personnel. Briefly describe the duties of all study personnel, which should include each of the persons listed as investigators, research staff, consultants, and the medical monitor. Describe their roles in the research effort (e.g.,

Research Coordinator, 80%, recruit and consent subjects, maintain study records, administer study drug, take and record vital signs, enter data into computer data base). 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. The medical monitor is required to review all serious and unexpected adverse events associated with the protocol and provide an unbiased written report of the event within 10 calendar days of the initial report. At a minimum, the medical monitor should comment on the outcomes of the adverse event and relationship of the event to the test article. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the PI.

The medical monitor will forward reports to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

16. Investigators conducting greater than minimal risk research must include the following description of requirements of the Volunteer Registry Database (HSRRB Clause 2.01) in the protocol and consent form:

> "It is the policy of USAMRMC that data sheets are to be completed on all volunteers participating in research for entry into the U.S. Army Medical Research and Materiel Command Volunteer Registry Database. The information to be entered into this confidential database includes name, address, social security number, study name, and dates. The intent of the database is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by the USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at the USAMRMC for a minimum of 75 years."

Include in the protocol language to indicate that the Volunteer Registry Data Sheet must be completed. (See Parts 8 and 17 of this appendix.) In addition, include the completion of the data sheets in the study procedure timelines. Once completed, the data sheets must be sent to the following address:

> Commanding General, U.S. Army Medical Research and Materiel Command
> ATTN: MCMR-RCQ-HR
> 504 Scott Street
> Fort Detrick, Maryland 21702-5012

These data sheets may be submitted annually and upon completion of the study. In addition, some facilities have the capability to enter the information directly and may continue to do so. Use of the Volunteer Registry Data Sheets is not required for exempt or no greater than minimal risk studies, unless otherwise indicated.

7-d. Advertisements, Posters, and Press Releases to Recruit Subjects

If subjects will be recruited through an advertisement, newspaper article, or similar process, a copy of the local IRB-approved advertisement must be provided.

For studies involving investigational drugs or devices, local IRB review of advertisements is necessary to ensure that the information is not misleading to the subjects participating in IND studies. The FDA has established guidelines on advertisements for subjects. General guidance includes name and address of PI, summary of research purpose, brief eligibility criteria, truthful list of benefits, and the person to contact for further information.

7-e. Surveys, Questionnaires, and Other Data Collection Instruments

If the research involves surveys, questionnaires, or other instruments, include a copy of the most recent IRB-approved version of each of these documents with the protocol submission. For either of these instruments that is used, the following information at a minimum should be addressed:

The instrument should be labeled with the complete title of the study and instructions for completing and returning the instrument. The instructions should state that the subject can refuse to answer specific items without repercussions. The instrument should be related to the objectives of the study.

Address whether the instrument has been validated.

The instructions and item order should be comprehensible and unambiguous.

Describe the procedure for confidentiality of hardcopy data or electronic data in the protocol and consent form.

8. Informed Consent Document Requirements

8-a. Required Elements of the Informed Consent Document

The format of the informed consent document may vary in accordance with the requirements of the local IRB. However, the informed consent document title must be the same as the protocol title. The following information is required for informed consent documents (32 CFR 219.116 and AR 70-25):

A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental.

A description of any reasonably foreseeable risks or discomforts to the subject.

A description of any benefits to the subject or to others, which may reasonably be expected from the research.

A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. For example, describe procedures that will be followed to maintain the subject's privacy and confidentiality, how the identifying information or specimens will be stored and for how long. Also describe who will have access to the identifying data.

For research involving greater than minimal risk, include the following explanation of medical care available for research-related injury:

"Should you be injured as a direct result of participating in this research project, you will be provided medical care, at no cost to you, for that injury. You will not receive any injury compensation, only medical care. You should also understand that this is not a waiver or release of your legal rights. You should discuss this issue thoroughly with the Principal Investigator before you enroll in this study."

An alternative clause for medical care in the event of a research-related injury can be incorporated into the consent form and is as follows:

"This study is being funded by the Department of Defense and conducted by the United States Army. Army regulations provide that, as a volunteer in a study conducted by the United States Army, you are authorized all necessary medical care for any injury or disease that is a direct result of your participation in the research. The PI or his/her designee will assist you in obtaining appropriate medical treatment under this provision if it is required. If you have any questions concerning your eligibility for Army funded medical treatment, you should discuss this issue thoroughly with the PI or his/her designee before you enroll in this study. This is not a waiver or release of your legal rights."

Three possible mechanisms are available to offset the costs of this requirement:

a. The proposed recipient may absorb such costs into the institution's operating budget.

b. The proposed recipient's liability insurance, if available, may be sufficient to cover any medical care costs. The proposed recipient's business office and/or legal advisor must ensure that there is adequate coverage under this liability insurance.

c. The proposed recipient could negotiate an additional amount of funds, if available, into the award that will cover such medical care cost (such as liability insurance).

If private citizens are enrolled, the following statement should be added to the consent form with the medical care clause:

> "Other than medical care that may be provided and any other payment specifically stated in the consent form, there is no other compensation available for your participation in this research."

The name and contact information for someone to contact (a) about the research, (b) about research subjects' rights, and (c) about a possible research-related injury.

A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

8-b. Additional Elements of the Informed Consent Document

When appropriate, one or more of the following elements of information shall also be provided to each subject (32 CFR 219.116 and applicable state/local laws):

> A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable.
>
> Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
>
> Any additional costs to the subject that may result from participation in the research.
>
> The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
>
> A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
> The approximate number of subjects involved in the study.
>
> Documentation of consent for human immunodeficiency virus (HIV) antibody testing, if scheduled, may be addressed in the body of the consent form or as separate HIV test consent form. Documentation should address any notifications required by state or local laws as well as any specific issues regarding confidentiality of positive test results.

The signature block of the consent form should include a signature line for the subject or legally authorized representative, lines for the permanent address of the subject, and separate lines for the printed name and signature of the witness. On every page of the consent form, except the signature page, include lines for the initials of the subject and the witness.

8-c. Requirements Unique to DOD-Sponsored Research

Certification of Translation

Provide documentation that the foreign language version of the consent form is an accurate translation. Documentation of translation must be provided along with the English and foreign language version of the consent forms. The documentation of translation should include the following statement, "I certify that this is an accurate and true translation" as well as the signature, name, address, phone number and, if available, fax number of the translator.

Sample Donation

If the samples donated in this study will be used in other studies, the following statement should be included in the consent form:

> "During this study, you will be asked to provide _____ (clearly specify the type of samples to be provided). These samples will be used for _____ (enter all known and anticipated uses) and may also be used for purposes that are currently unknown. There is a chance that the samples that you are donating under this study may be used in other research studies and may have some commercial value. (If a commercial value is anticipated, that value should be clearly described at this point.) Should your donated sample(s) lead to the development of a commercial product, _____ will own it and may take action to patent and license the product. _____ does not intend to provide you with any compensation for your participation in this study nor for any future value that the sample you have given may be found to have. You will not receive any notice of future uses of your sample(s). (When the study involves treatment as well as research, the following language should be added: You may agree to participate in the research protocol, but refuse to provide the additional samples discussed above.)."

In addition, a donation form may be prepared for signature by the volunteer and a witness that states:

> "As a participant in _____ (insert the title of the study), I voluntarily donate any and all _____ (clearly specify the type of sample(s) to be provided) to _____. These samples will be used for (enter all known and anticipated uses) and may also be used by _____ for uses not currently known to me. There is a possibility that the samples that I am donating under this study may be used in other research studies and may have some commercial value. (If a commercial value is anticipated, that value should be clearly described at this point). Should my donated sample(s) lead to the development of a commercial product, _____ will own it and it is possible that it will be patented and licensed by _____. _____ does not intend to provide me any compensation for this and will not give me any notice of future uses of my sample(s)."

Please note that a separate sample donation form is not required. If you choose not to draft a separate sample donation form, the language from the first paragraph of this clause must be included in the informed consent document.

Payment for Study Participation: Active Duty Military Personnel

Under 24 USC 30, payment to Active Duty military personnel for participation in research is limited to blood donation and may not exceed $50 per blood draw. Active duty research subjects may not receive any other payment for participation in a research study.

Confidentiality

The following statement must be included in the consent form for all protocols that enroll military personnel:

> "All data and medical information obtained about you, as an individual, will be considered privileged and held in confidence; you will not be identified in any presentation of the results. Complete confidentiality cannot be promised to subjects, particularly to subjects who are military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities."

For studies involving civilian subjects and their donated samples, include language describing how the subject's confidentiality will be maintained, how long the samples will be retained, and who will have access to the samples. In addition, include language from HSRRB Clause 11.01-Review of Research Records, which states:

> "It should be noted that representatives of the U.S. Army Medical Research and Materiel Command are eligible to review research records as a part of their responsibility to protect human subjects in research."

Pregnant Women

If pregnant women will be excluded, the following statement must be included if pregnancy during or after the study constitutes a risk to the participant or fetus:

> "I should avoid becoming pregnant for at least (time period in days, weeks, or months) after participation in the study. To avoid becoming pregnant, I should either abstain from sexual relations or practice a method of birth control. Except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm-killing products are not totally effective in preventing pregnancy."

Volunteer Registry Database

For all studies involving greater than minimal risk, notification regarding the requirements of the Volunteer Registry Database, must be included in the consent form. The Volunteer Registry Database contains items of personal information, such as names, addresses, social security number, and the name of the respective study. Information in the database will only be disclosed in accordance with Army Regulation 340-21 (the Army Privacy Program) and the Privacy Act of 1974. This means that only a person for whom data is collected, or his/her designated agent or

legal guardian may request information from the database. Only authorized staff of the Office of Regulatory Compliance and Quality have access to information stored in the database.

The USAMRDC Form 60-R must be completed for each volunteer. Send all completed forms to the Human Subjects Protection Branch annually and at the completion of the study. An example of the form is located in part 17 of this appendix. The following statement is normally included in the "Confidentiality" section of the consent form:

> "It is the policy of USAMRMC that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Database. The information to be entered into this confidential database includes name, address, social security number, study name, and dates. The intent of the data base is twofold: first, to readily answer questions concerning an individual's participation in research sponsored by USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at USAMRMC for a minimum of 75 years."

9. Protocol Modifications and Amendments

As a second level review Board, the HSRRB continues to monitor protocols after the initial approval notification. All modifications to the protocol, consent form and/or questionnaires must be submitted to the HSRRB for review and approval prior to implementation. A list of proposed modifications or amendments to the protocol and an explanation of the need for these modifications should be submitted. The level of review required for approval depends on the nature of the modifications.

10. Continuing Review and Final Reports

All continuing review reports and the final report approved by the local IRB must be submitted to the HSRRB. A continuing review of the protocol must be completed by the local IRB at least once each year for the duration of the study.

11. Serious or Unexpected Adverse Event Reports

Include in the initial adverse event reports the name of the person submitting the report, if different from the PI, name of the study, the HSRRB log number (A-xxxx) assigned to the study, the number of subjects enrolled to date, and the number and type of serious and unexpected adverse events previously reported in the study.

If the adverse event occurs in an IND study, the initial report must be identified as the "Initial Report for Subject (# or initials) enrolled in the clinical study Title and Log No. A-XXXX under IND #."

The following information must be provided:

(1) Description of Study. Double or single blind. If the study is being conducted in phases, indicate what phase of the study the subject is participating in.

(2) Number of subjects enrolled. Total enrollment at the time of the adverse event.

(3) Synopsis of event. Provide a complete narrative of the event.

(4) Subject status. Did the subject recover? What was the patient status at the time of the report?

(5) Other serious and unexpected adverse events from this study. Please provide any information pertaining to other adverse events that may have occurred during the conduct of this study.

(6) Most frequently expected adverse events based on the nature of the product. What adverse events would you expect to see based on the nature of the product or based on information contained in the most current version of the Investigator's Brochure.

(7) Actions taken in response to the adverse event. Is the subject still enrolled in the study or have they been dropped? Were any modifications or changes made to the protocol in response to the event? Provide an assessment of the relationship of the adverse event to the subject's participation in the study.

(8) Identification of the individual who completed the report. Include the signature, printed name and identity (investigator, study physician, etc.) of the individual who is providing the information.

In addition to the initial report of the adverse event, the report of the medical monitor must include his/her evaluation of the relationship of the adverse event to the subject's participation in the study and a follow-up report describing the resolution of the adverse event.

12. Assurances

If an institution has a current MPA or Cooperative Projects Assurance (CPA) with the DHHS Office for Human Research Protections, submit a letter with the following protocol information: (a) MPA number, (b) risk level that the IRB classified the protocol (no greater than minimal risk or greater than minimal risk), (c) date of IRB approval, and (d) next continuing review date. This letter must be on official, institutional letterhead stationary and signed by the chairperson of the IRB that approved the protocol.

If the institution does not have a current MPA or CPA with the Office for Human Research Protections, a written Assurance of Compliance must be filed with the Human Subjects Protection Branch of the Office of the Deputy Chief of Staff for Regulatory Compliance and Quality. The obligation to obtain an assurance can be found in 32 CFR 219.103.

There are four requirements for a DOD SPA that must be submitted to the Human Subjects

Protection Branch. The first is to complete a DOD SPA application. This application can be found at http://mrmc-www.army.mil/rcq/hspd

The second requirement is to provide a table of the IRB membership with the credentials (e.g. M.D., Ph.D., etc.) of each member with his/her affiliation with the institute and the role fulfilled on the IRB (e.g. chairperson, alternate, scientist, etc.). An example of this table is provided in the SPA application.

The third requirement is to provide short CVs or biographical sketches of all of the IRB members. These CVs are used to verify qualifications of the IRB members. The last requirement is to provide the written policies and procedures for conducting its initial and continuing review of research that are used by the IRB as outlined in 32 CFR 219.103. The SPA number will be issued after the protocol is approved by the HSRRB.

A letter from the Chairperson of the IRB that approved the protocol must accompany the SPA application on official, institutional letterhead stationary. The risk level assigned to the protocol by the IRB must be included along with the date of approval by the IRB and the next continuing review date.

13. Inclusion of Women and Minorities in Research

Consistent with the Belmont Report and recent congressional legislation, special attention is given to inclusion of women and minorities in research funded or managed by the USAMRMC. This policy is intended to promote equity both in assuming the burdens and in receiving the benefits of human subjects research. If women and/or minorities will be excluded from the protocol, a justification must be included.

14. Where to Go for Help and Information

If your research involves human subjects, you should first contact your local IRB for institutional requirements. If you have questions regarding the HSRRB protocol and consent form requirements or the review and approval process, contact the Office of Regulatory Compliance and Quality at the address or phone number listed below.

Phone: 301-619-2165/2166
Mail: Commanding General, U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-HR
504 Scott Street
Fort Detrick MD 21702-5012

References:

- Title 32 Code of Federal Regulation, Part 219, Protection of Human Subjects
- Title 21 Code of Federal Regulation, Part 50, Protection of Human Subjects
- Title 21 Code of Federal Regulation, Part 56, Institutional Review Boards
- Title 21 Code of Federal Regulation, Part 312, Investigational New Drug Application
- Title 21 Code of Federal Regulation, Part 812, Investigational Devices

- Title 45 Code of Federal Regulation, Part 46, Subparts B, C, and D, Protection of Human Subjects
- Code of Federal Regulations is located at http://www.access.gpo.gov/nara/cfr/index.html
- Army Regulation 70-25, Use of Volunteers as Research Subjects
- Army Regulation 40-7, Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances
- Army Regulations can be located at http://www.usapa.army.mil
- Office of The Surgeon General Regulation 15-2, Human Subjects Research Review Board
- Title 10 United States Code, Section 980
- Department of Defense Directive 3216.2
- International Conference on Harmonisation, Good Clinical Practice, Consolidated Guideline is located at http://www.ifpma.org/pdfifpma/e6.pdf; all other ICH guidelines can be found in the ICH home page located at http://www.ifpma.org/ich1.html

Copies of the preceding references can be obtained from either the U.S. Government Printing Office or the National Technical Information Service at:

Phone: 202-512-1800
Web Site: http://www.access.gpo.gov/su_docs
Mail: Superintendent of Documents
P.O. Box 371954
Pittsburgh, PA 15250-7954

Phone: 703-605-6000; 800-553-NTIS
E-mail: orders@ntis.fedworld.gov
Mail: National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

15. Claim of Exemption Form

PROTOCOL TITLE:	
PRINCIPAL INVESTIGATOR'S NAME:	PROPOSAL NO:
INSTITUTION:	

1. Will existing or archived data, documents, medical records, or database records be used? Yes No

2. Will biological specimens (e.g., cells, tissues, blood) be used? Yes No

3. Indicate below the sources of existing or archived data or biological specimens or cell lines (e.g., cell lines purchased from ATCC).

_____

_____

4. Will the donors of the original biological specimens be able to be identified, directly or indirectly, through identifiers linked to the donor? Yes No

5. Will data be recorded in writing? Yes No

6. Will data be recorded by audiotape? Yes No

7. Will data be recorded by videotape? Yes No

8. If survey instruments are used, will sensitive or private topics be explored? Yes No

9. Will subjects be identifiable either by name or through demographic data? Yes No

If the answer to any question 4-9 is yes, describe on a separate sheet of paper how the confidentiality of a subject's identity will be maintained. Also describe plans for maintaining or destroying identifying links to subjects after the protocol has been completed.

_____

Principal Investigator's Signature Date

16. Protocol Submission Checklist

PROTOCOL TITLE:	
PRINCIPAL INVESTIGATOR'S NAME:	PROPOSAL NO:
INSTITUTION:	

Requirement for All Protocols as Appropriate:

___ Research Protocol

___ Consent Form(s)

___ Curriculum Vitae or Biosketch for Principal Investigator and Medical Monitor

___ Documentation of the most current ethics training for all research staff

___ Scientific Review/Peer Review Approval(s)

___ Letter from the IRB Chairperson with the following protocol information: (a) MPA number, (b) risk level that the IRB classified the protocol (exempt, NGTMR, GTMR), (c) date of IRB approval, (d) next continuing review date, and (e) risk for medical devices (nonsignificant risk or significant risk).

___ Recruitment advertisements, posters, and announcements

___ Case report form(s), data collection/recording form(s), questionnaires, interview guides, etc.

___ Radiation Control Committee/Biosafety Review Report

___ Data Collection Forms and Case Report Forms

____ If potential commercial use of sample(s) or future use of sample(s) in other studies, a Sample Donation is required to be in the consent form.

___ With HIV Testing, documentation of consent for HIV antibody testing, if scheduled, may be addressed in the body of the consent form or as separate HIV test consent form.

Additional Requirements for IND Protocols:

___ Documentation of the Investigator's most recent GCP training

___ Document specifying IND Number

___ Investigator's Brochure

___ Copy of Case Report Forms (blank)

Protocol Submission Checklist (cont.)

Additional Requirements for Medical Device Protocols:

___ Documentation of the Investigator's most recent GCP training

___ Document from manufacturer declaring level of risk for device (non-significant risk or significant risk) and IDE form

___ Document specifying IDE Number

___ Manufacturer's device manual/ device information

What type of study is proposed?

___	Phase I Clinical Trial	___	Survey/Medical Record Review	___	Community Intervention
___	Phase II Clinical Trial	___	Cohort (longitudinal study)	___	Laboratory Experiment
___	Phase III Clinical Trial	___	Retrospective (case-control)	___	Tissue Only
___	Multicenter Trial	___	Program/Policy Study	___	Qualitative Study
___	Pilot Study	___	Cross-Sectional (prevalence)	___	Other: _____

Check all procedures applicable to this protocol:

___	Experimental Drug/Medications IND#_____	___	Prosthetic Orthopedic Devices
___	Marketed Agent, but Unapproved Use IND# _____	___	Nutrition/Metabolism Study
___	Experimental Device, IDE# _____	___	Tissue/Organ Transplant
___	Immunological Study	___	Radiation or Radioactive Material
___	Artificial Organ Study	___	Human Embryos
___	Experimental Treatments	___	Diagnostic Procedures
___	Experimental Surgery	___	Anatomical Substances Biological Specimens

Other: _____

Drug (s) to be used: _____ Drug Type* _____
_____ _____
_____ _____

*Drug Type may be chosen from the following list or other type may be stated as appropriate:

Analgesics	Anti-cancer drugs	Cardiac drugs	Hematologic agents
Anesthetics	Anti-convulsants	Diuretics	Hormones
Anti-allergy drugs	Anti-hypertensive drugs	Drugs affecting respiration	Tranquilizers/psychotopic drugs
Anti-arrhythmic drugs	Anti-Parkinson agents	Eye/Optical drugs	Vitamins/Minerals
Antibiotics/anti-infective agent	Autonomic drugs	Gastrointestinal drugs	

Protocol Submission Checklist (cont.)

Human Subject Information:

Age range of subjects: _____

Total number of subjects expected to be enrolled: _____

Total number of subjects at each collaborating site:_____

Check all that apply:

Subject Gender:
___Male
___Female

Are subjects able to provide their own consent?
___Yes
___No

Vulnerable Subject Class:
___Prisoners
___Minorities
___HIV positive
___Psychologically impaired
___Impaired decision-making
___Psychiatric patient
___Military
___Employee/Student
___Trauma

Subject Recruitment:
___In-patients
___Out-patients
___Students/employees
___Paid volunteers

Other:

_____

Principal Investigator's Signature

17. USAMRDC Form 60-R

VOLUNTEER REGISTRY DATA SHEET (USAMRDC 60-R)

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

1. **AUTHORITY: 5 USC 301; 10 USC 1071-1090; 44 USC 3101; EO 9397**

2. **Principal and Routine Purposes: To document participation in research conducted or sponsored by the U.S. Army Medical Research and Materiel Command. Personal information will be used for identification and location of participants.**

3. **Mandatory or Voluntary Disclosure: The furnishing of the SSN is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide information may preclude your participation in the research study.**

PART A - INVESTIGATOR INFORMATION
(To Be Completed By Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

1. Study Number:_____ **2. Protocol Title:**

3. Contractor (Laboratory / Institute Conducting Study):

4. Study Period: From: _____/_____/_____ To: _____/_____/_____
DD MM YY DD MM YY

5. Principal / Other Investigator(s) Names(s): **6. Location / Laboratory**

1. _____ _____/_____
2. _____ _____/_____
3. _____ _____/_____

PART B - VOLUNTEER INFORMATION
(To Be Completed by Volunteer)

PLEASE PRINT, USING INK OR BALLPOINT PEN

7. SSN: _____/_____/_____ **8. Name: _____**

9. Sex: M____F____ **10. Date of Birth: _____/_____/_____** **11: *MOS/Job Series_____** **12: Rank/Grade _____**

13. Permanent Home Address (Home of Record) or Study Location:

_____ _____
(Street) **(P.O. Box / Apartment Number)**

_____ _____ _____
(City) **(Country)** **(State)** **(Zip Code)**

Permanent Home Phone Number: _____

14. * Local Address (If Different From Permanent Address):

_____ _____
(Street) **(P.O. Box / Apartment Number)**

_____ _____ _____
(City) **(Country)** **(State)** **(Zip Code)**

Local Phone Number: _____

15. * Military Unit: _____ Zip Code: _____

Organization: _____ Post: _____ Duty Phone Number: _____

VOLUNTEER REGISTRY DATA SHEET (USAMRDC 60-R) (continued)

PART C - ADDITIONAL INFORMATION
(To Be Completed by Investigator)

PLEASE PRINT, USING INK OR BALLPOINT PEN

16. Location of Study: _____

17. Is Study Completed: Y: _____ N: _____

Did volunteer finish participation: Y: _____ N: ____ If YES, date finished _____/_____/_____
DD MM YY

If NO, date withdrawn: _____/_____/_____ Reason Withdrawn:
DD MM YY

18. Did any Serious or Unexpected Adverse Incident or Reaction Occur: Y: _____ N: _____ If YES, Explain:

19. * Volunteer Follow-up: _____

Purpose: _____

Date: _____/_____/_____ Was contact made: Y: _____ N: _____ If no action taken, explain:

20. * Hard Copy Records Retired: Place: _____ File NR: _____

21. * Product Information:

Product: _____

Manufacturer: _____

Lot #: _____ Expiration Date: _____

NDA #: _____ IND/IDE #: _____

***Indicates that item may be left blank if information is unavailable or does not apply. Entries must be made for all other items.**

When completed, a copy of this form should be sent to the address below:

Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RCQ-HR
Fort Detrick, MD 21702-5012

Appendix K

Research Involving Animals

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Research Involving Animals

1. Introduction

If using animals, provide all information required by this appendix. Any and all subcontractors using animals must also provide the information required by this appendix.

Department of Defense (DOD) definition of **animal: Any live nonhuman vertebrate.**

The DOD Directive 3216.1, dated April 17, 1995, provides policy and requirements for the use of animals in DOD-funded research. **These requirements may differ from those of other funding agencies.** Each of the following items **must** be addressed in a proposal appendix entitled "Research Involving Animals." Questions concerning animal use should be directed to Ms. Joyce O'Brien:

Phone:	301-619-2144
Fax:	301-619-4165
Email:	joyce.o'brien@det.amedd.army.mil
Mail:	U.S. Army Medical Research and Materiel Command ATTN: MCMR-RCQ-AR 504 Scott Street Fort Detrick, MD 21702-5012

2. Alternatives to Painful Procedures

A painful procedure is defined as any procedure that would reasonably be expected to cause more than slight or momentary pain and/or distress in a human being to which that procedure is applied. The Animal Welfare Act specifically states that the Principal Investigator (PI) must provide a narrative description of the methods and sources (e.g., the Altweb [Johns Hopkins Center for Alternatives to Animal Testing], MEDLINE, Life Sciences Abstracts, AGRICOLA, and BIOSIS) that he/she used to determine that alternatives to the painful/distressful procedure, including those procedures in which pain/distress is alleviated, were not available. The minimal written narrative must include databases searched or other sources consulted, date of the search and the years covered by the search, key words and/or search strategy used, and a discussion of what alternatives were considered but not used. Where federal law requires specific testing procedures, state the appropriate Code of Federal Regulations (CFR) or legal guidance that requires this testing. (The U.S. Army Medical Research and Materiel Command [USAMRMC] reserves the right to request evidence that a literature search for alternatives to painful procedures was performed.)

3. Literature Search for Unnecessary Duplication

This search must be performed to prevent unnecessary duplication of previous experiments. A search of the Biomedical Research Database at http://www.scitechweb.com/acau/brd and the Computer Retrieval of Information of Scientific Projects Database https://www-commons.cit.nih.gov/crisp is required. Additional searches in databases specific to the area of research performed in your proposal are highly recommended. Information on your

search for duplication should include databases searched, keywords or search strategy used, period of search, and date search was performed.

4. Rationale for Using Animals

Provide a scientific justification for using animals in the proposed research. State which alternatives to animal use were considered, such as computer modeling or cell cultures, and explain why these alternatives cannot be used to obtain the research objectives. **It is USAMRMC policy that alternatives to the use of animals be thoroughly investigated prior to submission of any proposal involving animals.**

5. Species Identification and Rationale

Identify the species of animals used. If using mice, rats, or guinea pigs, state the strain. If using dogs, cats, or rabbits, state the breed. Provide a scientific justification for their use. Explain why this particular animal model was chosen over others. What unique morphological and physiological characteristics does this animal model possess that make it the best choice?

6. Number of Animals Used

State the total number of animals used by species. Additionally, provide the following information:

a. State the common names and number of animals used in research involving no pain, distress or use of pain-relieving drugs.

b. State the common names and numbers of animals used in research involving pain or distress that is relieved with anesthetics and/or analgesics.

c. State the common names and numbers of animals used in research involving pain or distress that is NOT relieved with anesthetics and/or analgesics.

7. Rationale for the Number of Animals Required

Describe the statistical methodology used to determine group size and total number of animals used. Include animals necessary for controls, technique development, expected losses, etc. Explain how **these numbers were statistically determined to be the minimum** required to obtain valid scientific results. State the statistical test(s) planned or describe the strategy intended to evaluate the data. Where federal law or regulations require specific group sizes, state the appropriate CFR or reference.

8. Experimental Design

Provide a complete description of experimental design to include a summary table of experimental groups and a flowchart indicating sequence of experimental events. Succinctly outline the formal scientific plan and direction of experimentation. If several experiments or sequential studies are included in the protocol, describe the experimental design of each separately. The number of animals listed in this section must correspond to the total number of animals requested in paragraph 6.

9. Technical Methods (Animal Procedures)

Provide a complete description of all procedures the animals will experience. Include surgical procedures, biosamples (i.e., frequency, volume, harvest site, and collection method), adjuvants, tissue sampling for DNA analysis (i.e., age of sampling, amount of tissue taken, anesthetic use), and injections (i.e., agent, dosage, route, and anatomical site of administration). State frequency of animal observation once experimental procedures start and describe health status determination criteria used. When using Complete Freund's Adjuvant and/or in vivo production of monoclonal antibodies, provide a scientific justification and state what alternatives were considered and why they were not used. If prolonged restraint, food or water restriction, or multiple major survival surgeries are performed during the protocol, provide a scientific justification.

10. Anesthesia/Analgesia/Tranquilization

Describe the methods or strategies planned to effectively relieve pain and distress. If analgesics are used for pain/distress relief, provide the time schedule for administration and the observation criteria utilized to determine if the animals are experiencing pain and/or distress. State the drug's name, dosage, frequency, route, and anatomical site of administration. Additional scientific justification is required if the following agents are used: neonatal hypothermia, chloral hydrate, alpha-chloralose, Avertin®, ether or urethane. If anesthetic/analgesic agents are not used, provide an explanation.

11. Study Endpoint

State the projected study endpoint for the animals (e.g., recovery, euthanasia, use in another protocol, etc.). Define specific criteria used to determine early study endpoints (e.g., percentage of weight loss, tumor size, number of abdominal taps, abdominal distention, anorexia, decreased activity, ruffled fur) when animals become distressed or ill as a result of the experimental procedure(s).

12. Euthanasia or Final Disposition

Describe the method of euthanasia by agent, dosage, route, and anatomical site of administration. If animals are not euthanized, state final disposition of the animals.

13. Institutional Animal Care and Use Committee(s) (IACUC) Approval(s)

Provide written documentation of protocol approval in the form of a letter on institutional stationery signed by the IACUC chair or the IACUC administrator. An IACUC approval letter is required from the facility where the animal research will be performed, including any subcontracted facilities. If IACUC approval is pending, provide a statement to this effect. Evidence of IACUC review and approval may follow proposal submission, but must be provided prior to start of animal experimentation.

14. U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service Animal Care Inspection Report

Include a copy of the most recent annual USDA Inspection Report for any and all facilities where animal research will be performed, including any subcontracted facility.

15. Qualifications

List all personnel working with animals under this protocol and all procedures (e.g., surgery, euthanasia, pre- and post-operative care), manipulations (e.g., injections, phlebotomy, restraint), and observations each individual will perform. Provide each individual's training, experience, and qualifications to perform these duties. Training should include institutional courses on species-specific care and handling. Qualifications should include educational degrees.

16. Accreditation

One of the following must be provided for each facility where the animal research will be conducted:

1. Evidence that the facility is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

2. A copy of the Institutional Letter of Assurance of Compliance with the "Public Health Service Policy on Humane Care and Use of Laboratory Animals," revised September 1986.

3. A statement signed by the Institutional Official that the care and use of animals will be performed according to the National Research Council 1996 "Guide for the Care and Use of Laboratory Animals" and applicable federal regulations.

17. Principal Investigator Assurances

The law specifically requires several written assurances from the PI. Please read and sign the assurances as indicated (this page may be photocopied and signed).

As the PI on this protocol, I acknowledge my responsibilities and provide assurances for the following:

A. Painful Procedures: I assure that discomfort and injury to animals will be limited to that which is unavoidable in the conduct of scientifically valuable research and that analgesic, anesthetic, and/or tranquilizing drugs will be used where indicated and appropriate to minimize pain and/or distress to animals.

B. Animal Use: The animals authorized for use in this protocol will be used only in the activities and in the manner described herein, unless a modification is specifically approved by the IACUC and the U.S. Army Medical Research and Materiel Command prior to its implementation.

C. Duplication of Effort: I have made a reasonable, good faith effort to ensure that this protocol is not an unnecessary duplication of previous experiments.

D. Statistical Assurance: I assure that I have consulted with a qualified individual who evaluated the experimental design with respect to the statistical analysis, and that the minimum number of animals needed for scientific validity will be used.

E. Training: I verify that the personnel performing the animal procedures/manipulations/ observations described in this protocol are technically competent and have been properly trained to ensure that no unnecessary pain or distress will be caused to the animals as a result of the procedures/manipulations.

F. Responsibility: I acknowledge the inherent moral, ethical and administrative obligations associated with the performance of this animal use protocol, and I assure that all individuals associated with this project will demonstrate a concern for the health, comfort, welfare, and well-being of the research animals. Additionally, I pledge to conduct this study in the spirit of the fourth "R", which the DOD has embraced, namely, "Responsibility" for implementing animal use alternatives where feasible, and conducting humane and lawful research.

G. Scientific Review: This proposed animal use protocol has received appropriate peer scientific review and is consistent with good scientific research practice.

_____	_____
(Principal Investigator Printed Name)	(Principal Investigator Signature and Date)

NOTE: For proposals that require the use of nonhuman primates, companion animals, marine mammals, or for research deemed warranted by the USAMRMC, a site visit shall be conducted as necessary by the USAMRMC Animal Care and Use Review Officer or designees.

Appendix L

Safety Program

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Safety Program

1. Introduction

This appendix contains a description of the requirements, forms, approvals, and assurances relating to safety in the research environment.

NOTE: The Safety Program requirements now consist of two parts: a Facility Safety Plan (Institution-Based) and a Proposal Safety Plan (Proposal-Based) .

Approval of the Facility Safety Plan is granted on an institution basis rather than on a proposal basis. The Facility Safety Plan shall be institution-based, consist of six parts as outlined on pages L-3 to L-4, and be prepared by the Facility Safety Director/Manager of the institution. **Each institution is required to submit only one Facility Safety Plan.**

Approval of the Proposal Safety Plan is granted on an individual proposal basis. The Proposal Safety Plan shall be related to a specific proposal, consist of two parts as outlined on pages L-5 to L-6, and be prepared by the Principal Investigator (PI). **Each proposal is required to have an accompanying Proposal Safety Plan.**

Facility Safety Plan approvals are granted for a 5-year period with annual updates required (see Facility Safety Plan Status Report, pages L-7 to L-8). To determine if your organization has an approved Facility Safety Plan, contact http://mrmc-army.mil (select the Regulatory Compliance and Quality icon, the Facility Safety Plan icon, and then the Institutional Safety Plan Database).

a. If your organization's name appears on this Institutional Safety Plan Database **and** approval of the Facility Safety Plan has not expired, then your institution's Facility Safety Plan is not required. Note, however, that the PI is required to provide a Proposal Safety Plan that provides both information specific to the proposal and a signed assurance (see Proposal Safety Plan, pages L-5 to L-6).

b. If either your organization's name does not appear on this Institutional Safety Plan Database **or** the approval of your institution's Facility Safety Plan has expired, your Facility Safety Manager/Director must provide the U.S. Army Medical Research and Materiel Command's (USAMRMC's) Safety Office with a Facility Safety Plan and a signed assurance, as outlined below (see Facility Safety Plan, pages L-3 to L-4). In addition, the PI is required to provide a Proposal Safety Plan that provides both information specific to the proposal and a signed assurance (see Proposal Safety Plan, pages L-5 to L-6).

2. Facility Safety Plan (Institution-Based)

The Facility Safety Director/Manager must provide information from the institutional perspective, as appropriate, for each of the six parts listed below. A list of the first five components with a brief description of each is acceptable. **Do not send** institution safety manuals, although they may be referenced in your submission (a web site address is also acceptable). **Those parts that do not apply should be listed and labeled as "Not Applicable" or "N/A."**

a. Research Operations/Standard Operating Procedures (SOPs)
Provide a brief description of the safety procedures relating to the medical research operation of the facility. These should include (a) a description of any special skills, training, and SOPs that assure safe research operations (Bio-Safety Committee, Radiation Committee, HAZCOM, Blood-borne Pathogens, Chemical Hygiene Plan, etc.) and (b) a description of medical surveillance and support.

b. Facility Equipment and Description (Related to the Research Environment)
Provide (a) a description of the facility; (b) a description of personal protective equipment used within the facility; and (c) a list of specialized safety equipment such as bio-safety cabinets, hoods, exhausts, and ventilation systems.

c. Radioactive Materials
Provide a copy of the Nuclear Regulatory Commission or state-approved license.

d. Hazard Analysis (Related to the Research Environment)
Provide a description of each hazard identified, the hazard analysis performed based on maximum credible event and the plan to minimize or eliminate each hazard and control risk to laboratory personnel.

e. Biological Defense Research Program Requirements
(*Only applicable to the Biological Defense Research Program*)
For those institutions where PIs are supported by the USAMRMC and are conducting research with **Bio-safety Levels 3 and 4** material, a Facility Safety Plan must be prepared in accordance with 32 Code of Federal Regulations (CFR) 626.18. See the following URL: http://www.access.gpo.gov/nara/cfr/waisidx_99/32cfr626_99.html for a copy of the 32 CFR 626.18, Biological Defense Safety Program.

f. Facility Safety Director/Manager Assurance
The Facility Safety Director/Manager must provide the following signed assurance:

Facility Safety Director/Manager Assurance

- I assure that this institution has an existing institutional safety and occupational health program that meets appropriate federal, state, and local regulations as required by law.

- I assure that all hazards associated with the research laboratories have been identified, eliminated, and/or controlled in such a manner as to provide for a safe research laboratory environment.

- I accept full responsibility for submitting the Annual Facility Safety Plan Status Report including significant changes in facility, safety equipment, and safety procedures by fax to 301-619-4165, by e-mail to kenneth.sung@det.amedd.army.mil, or by mail to Commanding General, U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RCQ-S, 504 Scott Street, Fort Detrick, MD 21702-5012.

- I assure that I have consulted with all current PIs holding USAMRMC awards concerning this institution's safety policies and procedures and will consult with all future PIs holding USAMRMC awards concerning this institution's safety policies and procedures.

_____

Name of Institution's Safety Director/Manager (print)

_____ _____

Signature Date

Mailing Address: _____

Street

_____

City State Zip Code

Phone Number: _____

Fax: _____

E-mail Address: _____

Web Site: _____

3. Proposal Safety Plan (Proposal-Based)

The PI must provide one Proposal Safety Plan for each proposal recommended for funding. Provide information specific for the proposal for each of the three parts listed below. Please be concise and brief (one to two pages).

a. List of Hazards

Identify potential health hazards such as infectious material, toxic substances, radiation, hazardous chemicals, biological hazards, and other hazardous materials used in the proposed research.

b. Recombinant DNA

(*Only applicable if research involves Recombinant DNA; otherwise, label as N/A.*)
Research involving recombinant DNA must meet or exceed National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules, May 1999 edition. Provide a written approval letter from the organization's Institutional Bio-safety Committee. If DNA experiments are exempt under the NIH Guidelines, provide a copy of the written exemption notification.

Copies of the above NIH Guidelines are available at:

Fax:	301-496-9839
Phone:	301-496-9838
Web Site:	http://www4.od.nih.gov/oba
Mail:	Office of Recombinant DNA Activities National Institutes of Health 6705 Rockledge Drive, Suite 750, MSC 7985 Bethesda, MD 20892-7985

c. Principal Investigator Assurance

The PI must provide the following signed assurance:

Principal Investigator Assurance

- I assure that I have involved the Facility Safety Director/Manager in the planning of this research proposal, discussed with him/her all aspects of the proposal that relate to occupational health and safety, and will help him/her prepare the annual Facility Safety Plan Status Report.

- I assure that I will comply with my institution's safety program and its requirements.

- I understand that I am directly responsible for all aspects of safety and occupational health specific to my research protocol.

- I assure that I will report to the Facility Safety Director/Manager any changes in the safety or occupational health practices due to changes in my originally planned research.

- I assure that hazards associated with my research have been identified, eliminated and/or controlled.

- I assure that all Safety Plan requirements are in compliance with 32 CFR 626 and 627, "Biological Defense Safety Program and Biological Defense Safety Program, Technical Safety Requirements" (*if applicable*).

_____

Name of Principal Investigator (print)

_____ _____

Signature Date

Mailing Address: _____

Street

_____

City State Zip Code

Phone Number: _____

Fax: _____

E-mail Address: _____

4. Facility Safety Plan Status Report

A Facility Safety Plan Status Report must be submitted annually starting no later than 1 year after obtaining the initial approval of the institution's Facility Safety Plan. The Facility Safety Director/Manager must provide a brief description of any parts of the Facility Safety Plan that may have changed during the past 12 months. (Additional pages may be attached.)

During the past 12 months:

1. Have any change(s) in Research Operation Safety Procedure(s) been made?
   Yes _____ No _____
   If yes, briefly describe:

2. Have any modifications to the facility, equipment, and description (e.g., new equipment purchased, hood ventilation certification) been made?
   Yes _____ No _____
   If yes, briefly describe:

3. Hazard Analysis: Have any new hazards been identified for any of the awards supported by the USAMRMC?
   Yes _____ No _____
   If yes, provide a hazard analysis for each new hazard.

4. Radioactive Materials: Have any significant change(s) occurred in the use of the radioactive materials?
   Yes _____ No _____
   If yes, briefly describe:

   Are there any additional radioactive materials in use?
   Yes _____ No _____
   If yes, list additional material(s).

   Is the radioactive material licensure current?
   Yes _____ No _____
   If no, please explain.

I certify that all of the above elements are true and correct to the best of my knowledge, and I assure that this institution provides a safe environment for its employees working in research laboratories in accordance with federal, state, and local government regulations. This safety office provides employee safety training and periodic laboratory inspections in an effort to minimize, eliminate, or control potential hazards to the employees and the public.

I understand that the Safety Office, USAMRMC, may conduct periodic site visits in order to ensure the indicated elements are in compliance with regulatory requirements.

Name of the Institution: _____

Name of Safety Director/Manager: _____

Signature: _____ Date: _____
Safety Director/Manager

E-mail Address: _____

Phone Number: _____

Fax Number: _____

Facility Safety Plan approved by USAMRMC Safety Office: _____ Date _____