

**Appendix A
FY01 BCRP
Program Announcement II
Letter of Intent**

Please fill out one form for each proposal you intend to submit in response to the Department of Defense Breast Cancer Research Program Fiscal Year 2001 Program Announcement II. 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 (BCRP01)
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:

- | | |
|----------------------------------------------------------------------|-------------------------------------------------------------|
| <input type="checkbox"/> Innovator Award | <input type="checkbox"/> Predoctoral Traineeship Award |
| <input type="checkbox"/> Clinical Bridge Award | <input type="checkbox"/> Postdoctoral Traineeship Award |
| <input type="checkbox"/> Idea Award | <input type="checkbox"/> Career Development Award |
| <input type="checkbox"/> Undergraduate Summer Training Program Award | <input type="checkbox"/> HBCU/MI Partnership Training Award |

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

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

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.

Please send me the following:

- Copies of the Proposal Cover Booklet - How many? _____

Appendix A

Appendix B

Proposal Preparation

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Proposal Preparation

1. Who May Apply

Eligible institutions include for-profit, nonprofit, public, or 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/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/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 Orders¹ 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

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 by the Government 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. If color figures are submitted, they must be provided in all copies.
- Printing: The original proposal must be single-sided. (Double-sided pages are not acceptable, with the exception of article reprints.). Copies of the proposal may be single-sided or double-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.
- Paper Size: 8.5 x 11.0 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 Breast Cancer Research Program (BCRP) 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 BCRP under different award mechanisms will not be allowed. This includes submission of the identical research project to both a Research and Training award mechanism. All such duplicate submissions may be administratively withdrawn by the Government. The Government reserves the right to reject any proposal. The following two exceptions apply:

- a. An Idea Award proposal (Section IV) may address the same research question proposed in a Career Development Award (CDA) proposal (see Section IX). Both proposals must specify the same PI.
- b. A Clinical Bridge Award proposal (Section V) may address the same research question proposed in a CDA proposal (Section IX). Both proposals must specify the same PI.

4. Proposal Cover Booklet (Bubble Sheet)

Complete this form as described in Appendix C, Proposal Cover Booklet Instructions.

- a. Each proposal should include one original plus three photocopies of the Proposal Cover Booklet.
- b. Proposal Cover Booklets can be requested via phone, fax, e-mail, or mail at the addresses/ numbers in the Foreword. Please allow sufficient time for delivery by regular mail.

5. Title/Referral Page – No page limit

Please complete the Title/Referral Page, which can be found on page B-7 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. PI's full name (first, middle initial, last).
- c. Award mechanism.
- d. PI's phone number, fax number, and e-mail address.
- e. Organization name and location (including city, state, zip or postal code, and country).
- f. Name of administrative representative authorized to conduct negotiations.
- g. Phone number, fax number, and e-mail address of administrative representative authorized to conduct negotiations.
- h. 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).
- i. 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.

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Title/Referral Page
No Page Limit

Proposal title (up to 160 characters)

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

Appendix B

Keyword descriptive technical terms

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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 the PI name (last name, first name, middle initial).

7. Checklist for Proposal Submission (Instructions)

Choose the appropriate checklist for the award mechanism being submitted (see Table B-1 below). Complete the checklist and insert it immediately after the Table of Contents.

Table B-1: Checklists

Award Type/Mechanism	Page
Innovator Award	B-11
Research Awards Idea Award Clinical Bridge Award	B-13
Training/Recruitment Awards Undergraduate Summer Training Program Award Predoctoral Traineeship Award Postdoctoral Traineeship Award Career Development Award HBCU/MI Partnership Training Award	B-15

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Complete and submit with your proposal immediately after the Table of Contents to confirm that all components are included in your application.

**Innovator Award Checklist for FY01 BCRP Program Announcement II
Application Submission**

- | Yes | No | |
|--------------------------|--------------------------|-----------------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | Cover Booklet (original plus 3 copies) |
| <input type="checkbox"/> | <input type="checkbox"/> | Application (original plus 30 copies) |

Original plus 30 copies includes:

- | | | |
|--------------------------|--------------------------|--------------------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | Title/Referral Page |
| <input type="checkbox"/> | <input type="checkbox"/> | Table of Contents |
| <input type="checkbox"/> | <input type="checkbox"/> | Checklist for FY01 BCRP Application Submission |
| <input type="checkbox"/> | <input type="checkbox"/> | Technical Abstract (1-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Lay Abstract (1-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Essay (5-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Abbreviations (1-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | References (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Curriculum Vitae (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Existing/Pending Support (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Facilities/Equipment Description (no page limit) |

Administrative Documentation:

- | | | |
|--------------------------|--------------------------|-----------------------------------------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | List of items included in this section |
| <input type="checkbox"/> | <input type="checkbox"/> | Letter of institutional support |
| <input type="checkbox"/> | <input type="checkbox"/> | Letters of nomination |
| <input type="checkbox"/> | <input type="checkbox"/> | Letters of support from collaborating individuals and/or institutions |
| <input type="checkbox"/> | <input type="checkbox"/> | Cost Estimate (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Total cost estimate matches Proposal Cover Booklet, item 4 |
| <input type="checkbox"/> | <input type="checkbox"/> | Instruments (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | List of documents included in Instruments Section |
| <input type="checkbox"/> | <input type="checkbox"/> | Publications and Patent Abstracts (5-document limit) |

Additional Materials: Submit together in a manila clasp envelope.

- | | | |
|--------------------------|--------------------------|---------------------------------------------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | 3½" disk, zip disk, or CD containing files of technical and lay abstracts |
|--------------------------|--------------------------|---------------------------------------------------------------------------|

By signing below, you confirm that your application contains the information requested above.

Signature of Applicant

Date

NOTE: Exceeding page limits may result in application 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.

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Appendix B

Complete and submit with your proposal immediately after the Table of Contents to confirm that all components are included in your application.

Research Award Checklist for FY01 BCRP Program Announcement II Proposal Submission
(Idea and Clinical Bridge Awards)

- | Yes | No | |
|--------------------------|--------------------------|--------------------------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | Proposal Cover Booklet (original plus 3 copies) |
| <input type="checkbox"/> | <input type="checkbox"/> | Proposal (original plus 30 copies) |

Original plus 30 copies includes:

- | | | |
|--------------------------|--------------------------|-----------------------------------------------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | Title/Referral Page |
| <input type="checkbox"/> | <input type="checkbox"/> | Table of Contents |
| <input type="checkbox"/> | <input type="checkbox"/> | Checklist for FY01 BCRP Proposal Submission |
| <input type="checkbox"/> | <input type="checkbox"/> | Structured Technical Abstract (1-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Lay Abstract (1-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Statement of Work (2-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Proposal Relevance Statement (1-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Proposal Body (adhere to page limits for the individual mechanism) |
| <input type="checkbox"/> | <input type="checkbox"/> | Abbreviations (1-page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | References (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Biographical Sketches (3-page limit per individual) |
| <input type="checkbox"/> | <input type="checkbox"/> | Principal Investigator |
| <input type="checkbox"/> | <input type="checkbox"/> | Collaborating investigators and other key personnel |
| <input type="checkbox"/> | <input type="checkbox"/> | Existing/Pending Support (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Facilities/Equipment Description (no page limit) |

Administrative Documentation:

- | | | |
|--------------------------|--------------------------|-----------------------------------------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | List of items included in this section |
| <input type="checkbox"/> | <input type="checkbox"/> | Letters of support from collaborating individuals and/or institutions |
| <input type="checkbox"/> | <input type="checkbox"/> | Detailed Cost Estimate (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | Total cost estimate matches Proposal Cover Booklet, item 4 |
| <input type="checkbox"/> | <input type="checkbox"/> | Instruments (no page limit) |
| <input type="checkbox"/> | <input type="checkbox"/> | List of documents included in Instruments Section |
| <input type="checkbox"/> | <input type="checkbox"/> | Publications and Patent Abstracts (5-document limit) |

Additional Materials: Submit together in a manila clasp envelope.

- | | | |
|--------------------------|--------------------------|-------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | 3½" disk, zip disk, or CD containing files of technical and lay abstracts and Statement of Work |
|--------------------------|--------------------------|-------------------------------------------------------------------------------------------------|

By signing below, 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.

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Appendix B

Complete and submit with your proposal immediately after the table of contents to confirm that all components are included in your application.

Training/Recruitment Award Checklist for FY00 BCRP Proposal Submission
(Undergraduate Summer Training Program, Predoctoral Traineeship, Postdoctoral Traineeship, Career Development, and HBCU/MI Partnership Training Awards)

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	Proposal Cover Booklet (original plus 3 copies)
<input type="checkbox"/>	<input type="checkbox"/>	Proposal (original plus 30 copies)
<i>Original plus 30 copies includes:</i>		
<input type="checkbox"/>	<input type="checkbox"/>	Title/Referral Page
<input type="checkbox"/>	<input type="checkbox"/>	Table of Contents
<input type="checkbox"/>	<input type="checkbox"/>	Checklist for FY01 BCRP Proposal Submission
<input type="checkbox"/>	<input type="checkbox"/>	Structured Technical Abstract (1-page limit)
<input type="checkbox"/>	<input type="checkbox"/>	Lay Abstract (1-page limit)
<input type="checkbox"/>	<input type="checkbox"/>	Statement of Work (2-page limit)
<input type="checkbox"/>	<input type="checkbox"/>	Proposal Relevance Statement (1-page limit)
<input type="checkbox"/>	<input type="checkbox"/>	Proposal Body (adhere to page limits for the individual mechanism)
<input type="checkbox"/>	<input type="checkbox"/>	Abbreviations (1-page limit)
<input type="checkbox"/>	<input type="checkbox"/>	References (no page limit)
 <i>Biographical Sketches (3-page limit per individual):</i>		
<input type="checkbox"/>	<input type="checkbox"/>	Principal Investigator
<input type="checkbox"/>	<input type="checkbox"/>	Mentor (for Predoctoral and Postdoctoral)
<input type="checkbox"/>	<input type="checkbox"/>	Participating Training Program Staff and Named Trainees (for Undergraduate)
<input type="checkbox"/>	<input type="checkbox"/>	Participating Investigators at HBCU/MI and Collaborating Institution (for HBCU/MI Partnership)
<input type="checkbox"/>	<input type="checkbox"/>	Collaborating Investigators
<input type="checkbox"/>	<input type="checkbox"/>	Other Key Personnel
<input type="checkbox"/>	<input type="checkbox"/>	Existing/Pending Support (no page limit)
<input type="checkbox"/>	<input type="checkbox"/>	Facilities/Equipment Description (no page limit)
 <i>Administrative Documentation:</i>		
<input type="checkbox"/>	<input type="checkbox"/>	List of items included in this section
<input type="checkbox"/>	<input type="checkbox"/>	Transcripts (for Predoctoral and Postdoctoral)
<input type="checkbox"/>	<input type="checkbox"/>	Statement of Eligibility Form (for Postdoctoral and CDA)
<input type="checkbox"/>	<input type="checkbox"/>	Description by mentor of training environment (for Predoctoral and Postdoctoral)
<input type="checkbox"/>	<input type="checkbox"/>	Letters of support from the mentor (for Predoctoral and Postdoctoral)
<input type="checkbox"/>	<input type="checkbox"/>	Letters of recommendation (for Predoctoral and Postdoctoral)
<input type="checkbox"/>	<input type="checkbox"/>	Letters from collaborating individuals
<input type="checkbox"/>	<input type="checkbox"/>	Letters of institutional commitment (for Undergraduate, CDA, HBCU/MI Partnership (2) and others if applicable)
<input type="checkbox"/>	<input type="checkbox"/>	Detailed Cost Estimate (no page limit)
<input type="checkbox"/>	<input type="checkbox"/>	Total cost estimate matches Proposal Cover Booklet, item 4
<input type="checkbox"/>	<input type="checkbox"/>	Instruments (no page limit)
<input type="checkbox"/>	<input type="checkbox"/>	List of documents included in Instruments Section
<input type="checkbox"/>	<input type="checkbox"/>	Publications and Patent Abstracts (5-document limit)
 <i>Additional Materials: Submit together in a manila clasp envelope.</i>		
<input type="checkbox"/>	<input type="checkbox"/>	3½" disk, zip disk, or CD containing files of technical and lay abstracts and Statement of Work

By signing below, you confirm that your proposal contains the information requested above.

Signature of Applicant

Date

NOTE: Exceeding page limits may result in application 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.

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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 and on disk. **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 the disk versions 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, and that are identical to the versions contained in the proposal.** 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.
- f. Training Plan (for Training/Recruitment Awards): Briefly describe the training plan.

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.

In addition to the abstract pages contained within the proposal, submit a 3½" disk, zip disk, or CD containing the abstract files (clearly labeled with the name of the PI, institution, and word processing program). Submit abstracts in Word, WordPerfect, or ASCII format.

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 – Start section on a new page – 2-page limit

The Statement of Work 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 Statement of Work.

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

In addition to the Statement of Work pages contained within the proposal, submit a separate electronic file of the Statement of Work on the same disc that contains the electronic abstracts (see part 8 above).

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 is 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. Figures, tables, graphs, and photographs, if used, must be included within this section.

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. **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. If more than five such items are included in the submission, **the extra items will not be forwarded to scientific peer review.** Every copy of your proposal must include the same reprints and patent abstracts that are submitted with the original proposal. **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

Submit the following documentation to the address listed in the Foreword under Proposal Submission:

Proposal: **ONE** clearly labeled original (binder-clipped) and **THIRTY** collated photocopies (stapled or binder-clipped) of the **entire package. Every copy must match the original, including reprints of any publications.** Do not use rubber bands, or spiral or three-ring binders.

- Proposal Cover Booklet(s):** **ONE** original (binder-clipped to the original proposal) and **THREE** photocopies (**not** binder-clipped to proposal copies).
- Additional Material:** Place in a manila clasp envelope a 3½" disk, zip disk, or CD containing separately named files of the abstract and Statement of Work (clearly labeled with the name of the PI, institution, and word processing program). Format the electronic files in Word, WordPerfect, or ASCII.
- Letters of Recommendation:** Ensure that letters of recommendation are submitted with the proposal and included in the Administrative Documentation section.
- Packaging:** Package **ONE** complete proposal submission (original plus all materials requested above) per box. If acknowledgment of proposal receipt is desired, enclose a self-addressed, stamped postcard with each submission. This postcard should state the proposal title and PI's name.
- Noncompliance:** Noncompliance to established guidelines may be perceived as an attempt to gain an unfair competitive advantage and therefore may result in proposal rejection. Administrative reasons for **rejection** of all or part of proposals most frequently result from **failure to adhere to timelines, page limits, and font requirements.**
- Submit the Proposal to:** Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-PLF (BCRP01)
1076 Patchel Street (Building 1076)
Fort Detrick, MD 21702-5024

22. Receipt Deadline

The receipt deadline for all proposals requested in this program announcement (Program Announcement II) is June 13, 2001 at 4:00 p.m. Eastern Time.

Any proposal received by the USAMRMC after the exact date and time specified for receipt shall **not** be considered unless it is received before FY01 award negotiations have been completed, and:

- a. It was sent by mail, and it is determined by the Government that late receipt was due solely to mishandling by the Government after receipt at the Government installation, or

- b. It was sent by U.S. Postal Service Express Mail Next Day Delivery (**do not use Second Day Delivery**) to the address listed in Section 21 (Proposal Submission) above and postmarked no later than 8:00 p.m. (local time at point of origination) the day before the proposal receipt deadline, or
- c. It was placed into the control of a commercial courier service no later than 8:00 p.m. (local time at point of origination) the day before the proposal receipt deadline and guaranteed for delivery by 4:00 p.m. Eastern Time on the due date by the courier service. (**International Applicants: Please be advised that NEXT DAY DELIVERY MAY NOT BE AVAILABLE from your location; check with your commercial courier service.**), or
- d. The Government, at its sole discretion, decides to accept the late proposal if it determines that no competitive advantage has been conferred and that the integrity of the competitive grants process will not be compromised.

Investigators are advised that documentation of the time of receipt by the delivery agent may be necessary if a problem should occur.

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.

Appendix C

Proposal Cover Booklet Instructions

You must submit an original Proposal Cover Booklet and three photocopies. Additional Proposal Cover Booklets and instructions can be requested via phone, fax, e-mail, or mail at the addresses/numbers listed below. Please allow sufficient time for delivery by regular mail.

Phone: 301-682-5501 (8:00 a.m.-5:00 p.m. Eastern Time)
Fax: 301-682-5521
E-mail: prequest@unitedis.com
Mail: Commander
U.S. Army Medical Research and Materiel Command
ATTN: MCMR-PLF (BCRP01)
1077 Patchel Street (Building 1077)
Fort Detrick, MD 21702-5024

ATTENTION: To facilitate the processing of the proposal, it is extremely important that you read and follow the instructions completely as you are filling out the Proposal Cover Booklet. Take special care to see that the written and bubbled figures match exactly.

Marking Instructions

- Type or print in block letters in the “nonbubble” areas. (Ink is acceptable.)
- Make solid marks that fill the circle completely.
- Make no stray marks on this form.
- Do not fold or tear form.

Specific Instructions for Completing the Proposal Cover Booklet

1. **Proposal Log Number.** (Leave blank.)
2. **Program Identifier and Award Mechanism.** Fill out with “BCRP-01” and award mechanism abbreviation selected from the list below (e.g., BCRP-01, Idea). The mechanism must be filled out with careful consideration because it will determine, in part, how your proposal will be assigned and evaluated for funding.

<u>Award Mechanism</u>	<u>Mechanism Abbreviation</u>
Innovator Award.....	Innovator
Idea Award.....	Idea
Clinical Bridge Award:	
Pre-Clinical Lead-Up.....	Pre-Bridge
Post-Clinical Trial Follow-Up.....	Post-Bridge
Undergraduate Summer Training Award.....	Undergrad
Predoctoral Traineeship Award.....	Predoc

Postdoctoral Traineeship Award.....	Postdoc
Career Development Award	CDA
HBCU/MI Partnership Award	HBCU/MI Partner

3. **Award Mechanism Code.** Select one of the codes listed below. This must agree with the award mechanism listed in question 2.

<u>Award Mechanism</u>	<u>Mechanism Code</u>
Innovator Award	24
Idea Award.....	25
Clinical Bridge Award:	
Pre-Clinical Lead-Up	26
Post-Clinical Trial Follow-Up	27
Undergraduate Summer Training Award.....	28
Predoctoral Traineeship Award	29
Postdoctoral Traineeship Award.....	30
Career Development Award	31
HBCU/MI Partnership Award	32

4. **Total Funding Requested from the Government.** Fill in the total dollar amount requested. This figure is inclusive of all direct and indirect costs for the entire proposed period of the research as indicated on the last line of page 2 of the Detailed Cost Estimate form. **Please be sure to include only the costs requested from the Government.** Enter the amount in whole U.S. dollar figures only, and enter the numbers **flush** with the right-hand margin.
5. **Proposal Title.** Enter the title of the proposal, which may contain up to 160 characters. Capitalize the initial word and the first letter of each subsequent word, with the exception of prepositions, conjunctions, and articles. Please count each blank space as equivalent to one character.
6. **Principal Investigator (PI) Last Name, First Name, and Middle Initial.** The PI is the individual who is primarily responsible for the proposed research/services.
7. **Title.** Select the appropriate title for the PI.
8. **Degree(s) of Principal Investigator.** Select all that apply.
- 9-16. **Principal Investigator’s Mailing Address.** This is the primary address used to contact the PI. This is the address where the work will be performed. **Do not use the PI’s home address, and if possible, avoid the use of PO Boxes.** If applicable, indicate the PI’s organization (question 9), department (question 10), then street address (questions 11 and 12). Do not use abbreviations or acronyms of any kind in the address with the exception of state. Do not use formal terms such as “The” or “The Trustees of” when indicating the

organization. **When an organization or department name is not applicable, leave these sections blank and then fill out the PI’s address, city, state, country, and zip code in the designated sections.** Applicants should use the appropriate country code listed below for question 15. International applicants should enter the international postal code in the space provided in question 16.

<u>Country</u>	<u>Code</u>	<u>Country</u>	<u>Code</u>	<u>Country</u>	<u>Code</u>
Argentina	AR	India	IN	Senegal	SN
Australia	AU	Indonesia	ID	Singapore	SG
Austria	AT	Ireland	IE	Slovakia	SL
Belgium	BE	Israel	IS	South Africa	ZU
Brazil	BR	Italy	IT	Spain	ES
Canada	CA	Jamaica	JM	Sri Lanka	CE
Chile	CL	Japan	JP	Sudan	SD
China	CN	Kenya	KE	Sweden	SE
Colombia	CO	Korea	KR	Switzerland	CH
Congo	CG	Korea, P.D.R.	KP	Taiwan	TW
Costa Rica	CR	Lebanon	LB	Thailand	TH
Czech Rep	CS	Malaysia	MY	Trinidad/Tobago...	TD
Denmark	DK	Mexico	MX	Turkey	TR
Egypt	EG	Netherlands	NL	Uganda	UG
Finland	FI	New Zealand	NZ	United Kingdom ..	GB
France	FR	Norway	NO	United States	US
Germany	GY	Peru	PE	Uruguay	UY
Ghana	GH	Philippines	PH	Venezuela	VE
Greece	GR	Portugal	PT	Virgin Islands	VI
Guatemala	GT	Puerto Rico	RQ	West Africa	ZW
Iceland	IL	Russia	RU		

17-18. **Principal Investigator’s Phone and Fax Numbers.** U.S. and Canada phone and fax numbers must be filled in completely. International phone and fax numbers, including city code and country code, should be indicated in the spaces provided.

19. **Principal Investigator’s E-mail Address.** If the PI has access to e-mail, write the address in the space provided.

20. **Principal Investigator Demographics.** (Optional.) Indicate the PI’s gender, ethnicity, and U.S. military affiliation.

21. **Key Personnel Demographics.** (Optional.) Select all that apply for key personnel’s gender, ethnicity, and U.S. military affiliation.

Note: The data in questions 20 and 21 are being collected for demographic purposes and will be reported outside the Department of Defense (DOD) only as grouped data without personal identifiers. Disclosure of this information is voluntary.

22. **Work Performed in a U.S. Military Facility.** Please indicate yes, if some or all of the work will be performed at a DOD, Department of Veterans Affairs, a U.S. Uniformed Health Service institute, or other similar facility.
23. **Human Subjects.** Indicate all human subjects that will be used in this study. If no human subjects will be used, mark the appropriate bubble.
24. **Human Anatomical Substances.** Indicate all human anatomical substances that will be used in this study. If no human anatomical substances will be used, mark the appropriate bubble.
25. **Human Anatomical Substances Traceable to Donors.** Indicate whether human anatomical substances can be traced to a specific donor.
26. **Data Collection from Human Subjects.** Indicate all methods of all data collection on human subjects that will be used in this study. If no data collection from human subjects will be used, mark the appropriate bubble.
27. **Clinical Trials.** Indicate all of the types of clinical trials that are in the proposed work. If no clinical trials are proposed in this study, mark the appropriate bubble.
28. **Animal Subjects.** Indicate if animal subjects will be used in the proposed work and if animal subjects will be used by a subcontractor.
29. **Safety Provisions.** Select all that apply.
- 30-35. **Demographics of Human Test Subjects/Study Population of Interest.** If human subjects are being used, you **must** complete all these questions. If human subjects are **not** being used, leave questions 30 to 35 blank. For gender (question 30), demographics (question 31), ethnicity (question 32), age (question 33), general income (question 34), and U.S. military affiliation (question 35), indicate the appropriate descriptors for the human test subjects/study population that is being **specifically** targeted in the proposed research.
36. **Mentor Name.** Traineeship Awards only.
37. **Proposal Descriptors - Research Classification.** Choose **ONE** research classification from the following list that best describes the proposed work.

<u>Research Classification</u>	<u>Code</u>
Behavioral/Psychosocial Research	10
Clinical Research	20
Clinical Trials	30
Epidemiology/Public Health Research	40
Laboratory Research	50

38. **Proposal Descriptors – Congressionally Directed Medical Research Programs (CDMRP) Research Classification.** Select **ONE** primary four-digit code that best describes the proposed research from the CDMRP Research Classification list that begins on page C-8.
39. **Proposal Descriptors - CDMRP Research Classification.** Select **ONE** secondary fourdigit code that best describes the proposed research from the CDMRP Research Classification list that begins on page C-8. If no other code applies, please use code “0000.”
40. **Proposal Descriptors - Common Scientific Outline.** Select **ONE** primary four-digit code that best describes the proposed research from the Common Scientific Outline that begins on page C-16.
41. **Proposal Descriptors - Common Scientific Outline.** Select **ONE** secondary four-digit code that best describes the proposed research from the Common Scientific Outline that begins on page C-16. If no code applies, please use code “0000.”
- 42-46. **Proposal Descriptors.** (Leave blank.)
47. **Administrative Representative Authorized to Conduct Negotiations.** Indicate the primary and secondary administrative contacts authorized to conduct negotiations on the PI’s behalf. The organization, address, and appropriate contact information should be provided. The organization listed is the organization that is submitting the proposal on the PI’s behalf. If the organization has a grants/contracts/business official, this is the individual authorized to negotiate potential awards. The signature of an institutional representative certifies that the institution has examined the PI’s credentials and verifies that the PI is qualified to conduct the proposed study and to use humans or animals as research subjects, if appropriate. **This signature is mandatory.** For Certifications and Assurances, refer to the U.S. Army Medical Research Acquisition Activity web site located at <http://www-usamraa.army.mil>; under the “Contract & Assistance Information” sidebar, click on “Regulatory Information.”
48. **Organization Code.** (Leave blank.)
49. **Type of Organization.** Choose one organization code that best describes your institution from the list on the following page. Refer to the updated list of Department of Education recognized Historically Black Colleges and Universities/Minority Institutions (HBCU/MI) to determine HBCU/MI status. This list can be accessed on the CDMRP web site at

<u>Type of Organization</u>	<u>Organization Code</u>
Business-Large	A
Business-Small/Disadvantaged	B
Business-Small/Woman-Owned	C
Business-Small/Other	D
Educational Institution-HBCU	E
Educational Institution-MI	F
Educational Institution-Other	G
Federal Government-Air Force	H
Federal Government-Army	I
Federal Government-Navy	J
Federal Government-Veterans Affairs	K
Federal Government-DOD	L
Federal Government-Other	M
Foreign (non-U.S.)	N
Nonprofit	O
Other Organization	P
State Government	Q

50. **Institution’s Official Proposal Control Number.** This is the number that the institution uses to track the proposal. This number, if available, should be provided by the institution’s grants/contracts/business office listed in question 47.
51. **Principal Investigator.** The PI must fill out this information and sign in the space indicated. **This signature is mandatory.**
52. **How Did You Hear about This Announcement?** Please indicate all sources from the following list that apply to this announcement.

<u>Source</u>	<u>Code</u>
CDMRP web site	A
CDMRP e-mail	B
CDMRP postcard mailing.....	C
Previously applied/watched for release date	D
Information from a colleague	E
<i>Science</i> Advertisement.....	F
<i>Commerce Business Daily</i> Advertisement	G
Advertisement in another technical journal.....	H
Advertisement in a technical meeting’s proceedings.....	I
Display at American Association of Cancer Research meeting	J
Display at Society of Behavioral Medicine meeting	K
Display at Federation of American Society of Experimental Medicine meeting	L
Display at Minority Health Professionals meeting	M
Display at American Urological Association meeting.....	N
Display at American Society of Clinical Oncology meeting	O

Appendix C

Display at Complementary and Alternative Medicine meeting	P
Display at Endocrine Society meeting	Q
Display at Gynecology Oncology Group meeting	R
Display at American Society of Human Genetics meeting	S
Display at the Society for the Advancement of Chicanos and Native Americans in Science meeting	T
Display at American Society for Therapeutic Radiology and Oncology meeting	U
Display at Association of Military Surgeons of the United States meeting	V
<i>Chronicle of Higher Education</i> Advertisement	W

CDMRP Research Classification
(for questions 38 and 39)

Cell Biology: Covers the study of the cell and its structure, including cellular organization, regulation, composition, and function of normal and transformed cells.

- 0101 Cell cycle: Covers studies on the sequence and regulation of cellular events between mitotic divisions.
- 0102 Cellular structure: Covers the study of proteins and other macromolecules that are involved in mediating the recognition and adhesion of cells to their substrates and to other cells to include adhesion, integrins, matrix, membrane bound proteins, and cytoskeletal components.
- 0103 Growth factors/Cytokines: Covers studies on polypeptides and their receptors that control the ontogeny and maintenance of tissue form and function.
- 0104 Oncogenes: Covers studies on genes whose mutation or overexpression promotes tumor development/malignant phenotype.
- 0105 Tumor suppressor genes: Covers studies on genes whose mutation or inactivation leads to tumor development/malignant phenotype.
- 0106 Metabolism: Covers studies on the sum of all physical and chemical processes by which an organism is produced and maintained as well as the transformations by which energy is made available for use by the organism.
- 0107 Signal transduction: Covers studies on the activation of intracellular response pathways.
- 0108 Structural chemistry: Covers studies to determine the structure of biological compounds such as x-ray crystallography, nuclear magnetic resonance, and computer modeling.
- 0109 Functional study of biological molecules: Covers studies that determine the function of newly identified biological molecules or novel functions of previously studied molecules.
- 0199 Not otherwise specified: Covers studies in cell biology not otherwise specified in the other research areas.

Genetics and Molecular Biology: Covers studies on the molecular structures and events underlying biological processes, especially the relation between genes and the functional characteristics they determine.

- 0201 Chromosome structure: Covers studies on the organization of the DNA into a chromosome and the accompanying chromosomal elements and staining and sequencing techniques.
- 0202 DNA damage and repair: Covers studies on the mechanisms of DNA damage as well as the enzymatic correction of errors in DNA structure and sequence.

CDMRP Research Classification (for questions 38 and 39) - continued

- 0203 Genomic instability: Covers studies on genetic changes that result in new combinations of alleles and/or chromosomal modifications such as crossing over, deletions, translocations, and loss of heterozygosity.
- 0204 Familial and hereditary carcinogenesis: Covers studies of genes and their products that cause initiation, progression, and hereditary transmission of cancer in familial or hereditary clusters.
- 0205 Transcription, translation, and modification: Covers studies on the process by which genetic information encoded in a gene is converted into RNA and protein and subsequent post-translational modifications.
- 0206 Genomics and Proteomics: Covers study of a set or subset of genes or proteins expressed in a cell.
- 0299 Not otherwise specified: Covers studies in molecular biology and genetics not otherwise specified in the other research areas.

Endocrinology: Covers studies on structure and function of endocrine glands, their products, and their control to include hormones and their receptors.

- 0301 Clinical endocrinology: Covers studies of hormonal functions, ligand interactions, and metabolism as they relate to bedside and clinical applications.
- 0302 Endocrine carcinogenesis: Covers studies on the role of hormones in the initiation and support of cancer growth.
- 0303 Hormone metabolism: Covers studies of the biosynthesis, degradation, and enzymatic interconversions of hormones and structural analogs.
- 0304 Hormone receptors: Covers studies related to membrane-bound or intracellular molecules that bind with high affinity to, or respond to, hormones.
- 0305 Mechanism of hormone action: Covers studies of interactions between a ligand, its receptor, and co-activators in targeted metabolic processes and the downstream consequences of these interactions.
- 0399 Not otherwise specified: Covers studies in endocrinology not otherwise specified in the other research areas.

Pathobiology: Covers studies on the pathobiology of cells and tissues specifically related to the development of cancer.

- 0401 Angiogenesis: Covers studies on the neovascularization associated with tumor growth and the factors that mediate this phenomenon.
- 0402 Apoptosis: Covers studies on the process of a particular form of a cell death, programmed cell death, that is characterized by specific morphologic and biochemical properties.

CDMRP Research Classification (for questions 38 and 39) - continued

- 0403 Biomarkers: Covers studies on cellular constituents whose presence and/or concentration might serve as an indicator of the predisposition, presence, or progression of cancer. Includes the study of detection agents for uncharacterized biomarkers.
- 0404 Chemical/physical carcinogenesis: Covers studies on the influence of chemicals and other environmental factors on carcinogenesis.
- 0405 Progression/invasion/metastasis: Covers studies on cell proliferation from the time of initial transformation to metastasis.
- 0406 Stromal-epithelial interactions: Covers studies on the role of the interaction of the stromal and epithelial elements in the initiation of cancer.
- 0499 Not otherwise specified: Covers studies in pathobiology not otherwise specified in the other research areas.

Immunology: Covers studies of the cell-mediated and humoral aspects of immunity and immune responses excluding therapeutic manipulations of the immune system.

- 0501 Molecular immunology: Covers studies to identify immune markers and characterize antibody structures as well as genetic engineering and progressive cloning studies.
- 0502 Tumor immunology: Covers studies of interactions between the immune system and tumor(s).
- 0503 Regulation of the immune response: Covers studies of mechanisms that up- or downregulate the immune system, including psychoneuroimmunology.
- 0504 Immunodeficiency: Covers studies of inadequacies in the cell-mediated or humoral aspects of immune response or its regulation.
- 0505 Autoimmunity and autoimmune disease: Covers studies of specific immunity to constituents of self.
- 0599 Not otherwise specified: Covers studies in immunology not otherwise specified in the other research areas.

Primary Prevention: Covers studies that prevent the occurrence of disease.

- 0601 Lifestyle: Covers studies of the contributions and consequences of lifestyle and behavioral factors on disease risk, as well as studies to test educational and lifestyle interventions to reduce disease risk.
- 0602 Chemoprevention: Covers studies on the effect(s) of drugs to prevent occurrence of disease.
- 0603 Nutrition: Covers studies on the contributions and consequences of diet and/or nutrition on disease risk, as well as to test educational and diet and/or nutritional interventions intended to prevent the occurrence of disease.

CDMRP Research Classification (for questions 38 and 39) - continued

- 0604 Genetic risk: Covers studies among individuals with defined gene composition and genetic mutations to test interventions intended to prevent the occurrence of disease.
- 0605 Surgical prevention: Covers studies on the effects of prophylactic surgical interventions to prevent occurrence of disease.
- 0699 Not otherwise specified: Covers primary prevention studies not otherwise specified in the other research areas.

Detection and Diagnosis: Covers the study of improved detection, diagnostic, and prognostic techniques. Includes studies investigating disease presence and potential response to prevention and treatment strategies.

- 0701 Clinical Biomarkers: Covers the study of the use of compounds detectable in blood, body fluids, or tissues, whose detection can be used for screening, diagnosis, or prognosis.
- 0702 Cell/tissue/body fluid sampling: Covers the study of methods for collecting biological samples and studies on the most effective testing of these specimens for the detection, diagnosis, or prognosis of disease.
- 0703 Computer-aided diagnosis: Covers the study of computer programs and artificial intelligence systems to assist in the evaluation of radiographic or other diagnostic information.
- 0704 Digital imaging: Covers the study of capturing, storing, viewing, and analyzing radiographic or other images in a digital format.
- 0705 Magnetic resonance imaging: Covers the study of visualization of structures in the body by use of oscillating magnetic fields and analysis of the resulting radio frequencies produced.
- 0706 Nuclear medicine imaging: Covers the study of image production or count acquisition after the administration of a radionuclide.
- 0707 Ultrasonography: Covers the study of visualization of structures in the body by recording the reflections of high frequency sound waves directed into the tissues.
- 0708 X-ray imaging: Covers the study of visualization of structures in the body by externally applied ionizing radiation.
- 0709 Other imaging: Covers the study of imaging modalities not otherwise specified in the other research areas.
- 0799 Not otherwise specified: Covers studies in detection, diagnostic, or prognostic modalities not otherwise specified in the other research areas.

CDMRP Research Classification (for questions 38 and 39) - continued

Clinical and Experimental Therapeutics: Covers studies on agents to assess their use in treatment. Includes model systems ranging from cell cultures to animals and humans.

- 0801 Drug development: Covers the discovery, screening, synthesis, development, and formulation of drugs and the modification of existing agents.
- 0802 Pharmacology: Covers studies of the pharmacokinetics, toxicity, routes of administration, and mechanisms of action of treatment agents. This may include drugs that modify the effectiveness of other drugs.
- 0803 Chemotherapy: Covers the study of using drugs or a combination of drugs to kill or halt the growth of cancer cells. This may include drugs that modify the effectiveness of other drugs.
- 0804 Drug resistance/multidrug resistance: Covers the study of the mechanisms, treatments, and prevention of classical MDR and other forms of drug resistance.
- 0805 Targeted therapies (conjugated toxins): Covers the development, testing, and study of agents that combine a targeting component with a toxic or therapeutic component, including chimeric molecules incorporating a conjugated toxin, sequentially administered compounds one of which acts as a targeting agent, and targeted drug delivery vehicles.
- 0806 Vaccines: Covers the study of treatment of disease with agents designed to elicit immune responses to specific antigens.
- 0807 Immunotherapies: Covers the study of treatment of disease by passive immunization or by the use of agents designed to potentiate or suppress actions of leukocytes. Excludes vaccines.
- 0808 Radiotherapy: Covers the study of using ionizing radiation to treat disease or kill cells.
- 0809 Hormonal therapy: Covers the study of the treatment of disease by potentiating or blocking the effects of hormones.
- 0810 Gene therapy (includes vector development): Covers the study of treatment that modifies or inserts genes into cells to improve the body's natural ability to fight disease or to make the tumor more sensitive to other therapies. Includes gene vector development and antisense technologies.
- 0811 Photodynamic therapy: Covers the study of light-activated substances in treating disease.
- 0812 Antiangiogenics: Covers the study of using substances that inhibit blood vessel formation accompanying tumor growth.
- 0813 Surgery: Covers studies on procedures designed to remove or repair tissue cells.
- 0814 Hyperthermia: Covers the study of localized or systemic temperature increases for either direct therapeutic effect or enhancing the effectiveness of other therapies.

CDMRP Research Classification (for questions 38 and 39) - continued

- 0815 Rehabilitation: Covers the study of interventions to improve functional status and/or appearance related to disease or treatment. Examples would include prosthetic devices, plastic/reconstructive surgery, and occupational/physical/speech therapy.
- 0816 Symptom management: Covers studies of the factors or interventions that influence disease-specific symptoms and/or reduce treatment side effects. Symptom management may be medically or psychosocially based.
- 0899 Not otherwise specified: Covers studies in clinical and experimental therapeutics not otherwise specified in the other research areas.

Complementary and Alternative Medicine: Covers studies of treatments and practices that reflect nontraditional forms of intervention or supportive methods that complement or add to mainstream treatments.

- 0901 Neutraceuticals: Covers studies of nutritional, vitamin and/or dietary supplements and/or applications of nutritional, vitamin, and/or dietary supplements that reflect nontraditional forms of intervention or supportive methods that complement or add to mainstream treatments.
- 0999 Not otherwise specified: Covers studies of the application of non-neutraceutical approaches (e.g., meditation, biofeedback, massage) that reflect nontraditional forms of treatment or supportive methods that complement or add to mainstream treatments.

Health Care Delivery: Covers studies assessing the delivery of disease prevention, detection, treatment, and rehabilitation services.

- 1001 Health care settings: Covers studies describing and/or assessing interventions or policies to enhance the delivery of disease prevention, detection, treatment, and rehabilitation services in medical systems and medical care settings, including, for example, patterns of care assessments and cost effectiveness studies in a medical care setting.
- 1002 Communities: Covers studies describing and/or assessing interventions and/or policies for reaching and/or influencing populations in community and other nonmedical settings in order to improve the delivery of disease prevention, detection, treatment, and rehabilitation services. Studies include, for example, community outreach interventions.
- 1099 Not otherwise specified: Covers health care delivery studies not otherwise specified in the other research areas.

Biobehavioral Sciences: Covers studies describing knowledge, attitudes, and behavior in defined populations and assessing the relationship(s) between behavioral and social functioning and disease initiation, progression, detection, treatment, and rehabilitation.

- 1101 Basic behavioral: Covers descriptive studies of knowledge, attitudes, and behavior in defined populations or studies of the basic relationships between biology and behavioral factors and disease.

CDMRP Research Classification (for questions 38 and 39) - continued

- 1102 Quality of life: Covers studies of factors that contribute to quality of life (QOL), interventions designed to enhance QOL, or the QOL consequences that result from actions of patients, caregivers, and/or providers among individuals with or at risk for disease.
- 1103 Decision making: Covers studies of factors that contribute to patient, caregiver, or provider decision making regarding diagnosis, treatment, and/or rehabilitation, such as participation in clinical trials, risk assessment, genetic counseling, and adherence to treatment.
- 1104 Communication and education: Exploration of health communications theories and their application to cancer and cancer control issues, studies to fill gaps in understanding how patients, caregivers, health care providers, and the general population use health information, and development and testing of educational interventions.
- 1199 Not otherwise specified: Covers biobehavioral science studies not otherwise specified in the other research areas.

Epidemiology: Covers population-based observational research studies of the distribution of disease as well as the behavioral and/or biological determinants of disease risk, initiation, progression, detection, and/or prognosis.

- 1201 Descriptive epidemiology/surveillance: Covers population-based observational research studies of the distribution and characteristics of disease.
- 1202 Behavioral epidemiology: Covers population-based observational studies assessing the nature of associations between lifestyle and host factors and disease risk, initiation, progression, detection, prognosis, and/or treatment.
- 1203 Gene and/or environmental epidemiology: Covers population-based observational studies assessing the nature of associations and effect modification, including molecular changes between genetic susceptibility, polymorphic genes, and environmental or host factors and disease risk, initiation, progression, and/or intermediate disease endpoints.
- 1204 Nutritional epidemiology: Covers population-based observational studies assessing the nature of associations and effect modification between nutritional factors and disease risk, initiation, progression, detection, and prognosis.
- 1299 Not otherwise specified: Covers epidemiological studies not otherwise specified in the other research areas.

Research Resources: Covers support for the development and/or maintenance of institutional, regional, or national facilities to sustain biomedical research.

- 1301 Cancer training program: Covers support for extramural programs to train investigators.
- 1302 Registries: Covers support for development and maintenance of registries (i.e., central agencies for the collection of pathologic material and related clinical, laboratory, x-ray, and other data in a specified field of pathology, organized so that the data can be properly processed and made available for study).

CDMRP Research Classification (for questions 38 and 39) - continued

- 1303 Animal models: Covers support for development of animal models of human diseases.
- 1304 Computer models: Covers support for the development and maintenance of computer modeling and information management systems and novel uses of information technology.
- 1305 Cancer centers, clinical centers, or consortia: Covers support for the development of core-supported, multiproject research programs integrated around a common theme.
- 1306 Statistical models: Covers support for the development of models for data analysis.
- 1307 Cell lines: Covers the development of immortalized cell lines.
- 1399 Not otherwise specified: Covers studies in research resources not otherwise specified in the other research areas.

Common Scientific Outline
(for questions 40 and 41)

Biology

- 0011 Cancer-related biology: Biology of the organism, organs, tissues, cells, and subcellular organelles. Developmental biology from conception to adulthood and the biology of aging. Study of normal functioning genes, their localization, identification, and expression patterns, and functional studies of gene products. Studies of the immune system including cells, products, and functions. Extracellular matrix formation and interactions, cell-cell interactions. General mechanisms of carcinogen metabolism and DNA damage, DNA repair pathways, and mutation fixation. Epigenetic mechanisms in the regulation of cell proliferation and behavior. Progression, including clonal evolution, tumor-immune system interactions; factors which influence clonal expansion or regression, tumor promotion. Metastasis, including studies involving cell-cell interaction, tumor-host interactions, cell motility, remodeling of cellular matrix, cell migration, and clonal expansion at distant sites. Biology of tumor regression.
- 0012 Resources and infrastructure related to biology: Infrastructures related to discovery; for example, the Cancer Genome Anatomy Project. Informatics and informatics networks. Specimen resources (serum, tissue, etc.). Reagents, chemical standards, pharmaceuticals. Centers, consortia, and/or networks. Education and training of investigators.

Etiology

- 0021 Exogenous factors in the origin and cause of cancer: Lifestyle factors such as smoking, chewing tobacco, alcohol consumption, parity, diet, sunbathing, and exercise. Environmental and occupational exposures such as radiation, secondhand smoke, radon, asbestos, organic vapors, pesticides, and other chemical or physical agents. Infectious agents associated with cancer etiology, including viruses (human papilloma virus, etc.) and bacteria (*helicobacter pylori*, etc.). Viral oncogenes and viral regulatory genes associated with cancer causation.
- 0022 Endogenous factors in the origin and cause of cancer: Free radicals such superoxide and hydroxide radicals. Genes known to be involved or suspected of being mechanistically involved in familial cancer syndromes, e.g., BRCA1, Ataxia Telangiectasia, and APC. Genes and signals involved in growth stimulation or repression, including oncogenes (RAS, etc.), and tumor suppressor genes (p53, etc.) and hormones and growth factors such as estrogens, androgens, TGF-beta, GM-CSF, etc. Genes suspected or known to be involved in “sporadic” cancer events, for example, polymorphisms and/or mutations that may affect carcinogen metabolism (e.g., CYP, NAT, glutathione transferase).
- 0023 Interactions of genes and/or genetic polymorphisms with exogenous and/or endogenous factors: Gene-environment interactions. Interactions of genes with lifestyle factors, environmental and/or occupational exposures such as variations in carcinogen metabolism associated with genetic polymorphisms. Interactions of genes and endogenous factors such as DNA repair deficiencies and endogenous DNA damaging agents such as oxygen radicals or exogenous radiation exposure.
- 0024 Resources and infrastructure related to etiology: Informatics and informatics networks; for example, patient databanks. Specimen resources (serum, tissue, etc.). Reagents and chemical standards. Epidemiological studies pertaining to etiology. Statistical methodology or biostatistical methods. Centers, consortia, and/or networks. Education and training of investigators.

Common Scientific Outline (for questions 40 and 41) - continued

Prevention

- 0031 Interventions to prevent cancer: Personal behaviors that affect cancer risk: Research on determinants of personal behaviors, such as diet, physical activity, sun exposure, and tobacco use, which affect cancer risk. Interventions to change personal behaviors that affect cancer risk.
- 0032 Nutritional science in cancer prevention: Quantification of nutrients and micronutrients. Studies on the effect(s) of nutrients or nutritional status on cancer incidence. Dietary assessment efforts, including dietary questionnaires and surveys. Development, characterization, and validation of dietary/nutritional assessment instruments.
- 0033 Chemoprevention: Chemopreventive agents and their discovery, mechanism of action, development, testing in model systems, and clinical testing.
- 0034 Vaccines: Vaccines for prevention, their discovery, mechanism of action, development, testing in model systems, and clinical testing.
- 0035 Complementary and alternative prevention approaches: Discovery, development, and testing of complementary/alternative prevention approaches such as diet, herbs, supplements, or other interventions that are not widely used in conventional medicine or are being applied in different ways as compared to conventional medical uses. Hypnotherapy, relaxation, transcendental meditation, imagery, spiritual healing, massage, biofeedback, etc., used as a preventive measure.
- 0036 Resources and infrastructure related to prevention: Informatics and informatics networks; for example, patient databanks. Specimen resources (serum, tissue, etc.). Epidemiological studies pertaining to prevention. Clinical trials infrastructure. Statistical methodology or biostatistical methods. Centers, consortia, and/or networks. Education and training of investigators.

Early Detection, Diagnosis, and Prognosis

- 0041 Technology development and/or marker discovery: Discovery of markers (e.g., proteins, genes) and/or imaging methods that are potential candidates for use in cancer detection, diagnosis, and/or prognosis.
- 0042 Technology and/or marker evaluation with respect to fundamental parameters of method: Preliminary evaluation with respect to laboratory sensitivity, laboratory specificity, reproducibility, and accuracy.
- 0043 Technology and/or marker testing in a clinical setting: Evaluation of clinical sensitivity, clinical specificity, and predictive value. Quality assurance and quality control. Inter- and intra-laboratory reproducibility. Testing of the method with respect to effects on morbidity and/or mortality. Study of screening methods including compliance, acceptability to potential screenees, receiver-operator characteristics.

Common Scientific Outline (for questions 40 and 41) - continued

0044 Resources and infrastructure related to detection, diagnosis, or prognosis: Informatics and informatics networks; for example, patient databanks. Specimen resources (serum, tissue, images, etc.). Clinical trials infrastructure. Epidemiological studies pertaining to risk assessment, detection, diagnosis, or prognosis. Statistical methodology or biostatistical methods. Centers, consortia, and/or networks. Education and training of investigators.

Treatment

0051 Localized therapies - discovery and development: Discovery and development of treatments administered locally that target the organ and/or neighboring tissue directly, including but not limited to surgical interventions and radiotherapy. Therapies with a component administered systemically but that act locally (e.g., photodynamic therapy and radiosensitizers).

0052 Localized therapies - clinical applications: Clinical testing and application of treatments administered locally that target the organ and/or neighboring tissue directly, including but not limited to surgical interventions and radiotherapy. Clinical testing and application of therapies with a component administered systemically but that act locally (e.g., photodynamic therapy and radiosensitizers). Phase I, II, or III clinical trials of promising therapies that are administered locally.

0053 Systemic therapies - discovery and development: Discovery and development of treatments administered systemically such as cytotoxic or hormonal agents, novel systemic therapies such as immunologically directed therapies (vaccines, antibodies), gene therapy, angiogenesis inhibitors, apoptosis inhibitors and differentiating agents. Defining molecular signatures of cancer cells. Identifying molecular targets for drug discovery. Includes mechanistic studies of cellular metabolism, combinatorial chemical synthesis, drug screening, development of high throughput assays, and testing in model systems.

0054 Systemic therapies - clinical applications: Clinical testing and application of treatments administered systemically such as cytotoxic or hormonal agents, novel systemic therapies such as immunologically directed therapies (vaccines, antibodies), gene therapy, angiogenesis inhibitors, apoptosis inhibitors, and differentiating agents. Phase I, II, or III clinical trials of promising therapies administered systemically.

0055 Combinations of localized and systemic therapies: Development and testing of combined approaches to treatment. Clinical application of combined approaches to treatment such as systemic cytotoxic therapy and radiation therapy.

0056 Complementary and alternative treatment approaches: Discovery, development, and clinical application of complementary/alternative treatment approaches such as herbs, supplements, natural substances or other interventions that are not widely used in conventional medicine or are being applied in different ways as compared to conventional medical uses.

0057 Resources and infrastructure related to treatment: Informatics and informatics networks; for example, clinical trial networks and databanks. Mathematical and computer simulations. Specimen resources (serum, tissue, etc.). Clinical trial groups. Statistical methodology or biostatistical methods. Drugs and reagents for distribution and drug screening infrastructures. Centers, consortia, and/or networks. Education and training of investigators.

Common Scientific Outline (for questions 40 and 41) - continued

Cancer Control, Survivorship, and Outcomes Research

- 0061 Patient care and survivorship issues: Quality of life. Pain management. Psychological impacts of cancer survivorship. Rehabilitation. Reproductive issues. Long-term morbidity. Symptom management, including nausea, vomiting, lymphedema, neuropathies etc. Prevention of treatment-related toxicities and sequelae including symptom management, prevention of mucosities, prevention of cardiotoxicities, etc.
- 0062 Surveillance: Epidemiology and End Results Reporting (e.g., SEER). Surveillance of cancer risk factors such as diet, body weight, physical activity, sun exposure, tobacco use. Analysis of variations in risk factor exposure by demographic or other factors. Registries that track incidence, morbidity and/or mortality related to cancer. Trends in use of interventional strategies. Method development for risk factor surveillance.
- 0063 Behavior related to cancer control: Behavior medicine research and interventions. Influence of social factors, such as community, policy, education, and legislation, on behaviors related to cancer control. Attitudes and belief systems and their influence on psychological health and on behaviors related to cancer control. For example, how beliefs can alter attempts to seek screening, detection, and treatment. Interventions to change attitudes and beliefs that affect behavior related to cancer control and cancer outcomes. Influences of attitudes and beliefs on compliance to treatment and prevention protocols. Psychological or educational interventions to promote behaviors that lessen treatment-related morbidity and promote psychological adjustment to the diagnosis of cancer and to treatment effects. Burdens of cancer on family members/caregivers and psychological/behavior issues.
- 0064 Cost analyses and health care delivery: Analyses of cost effectiveness of methods used in cancer prevention, detection, diagnosis, prognosis, treatment, and survivor care/support. Studies of providers, such as geographical or care-setting variations in outcomes. Effect of reimbursement and/or insurance on cancer control, outcomes, and survivorship support. Access to care issues.
- 0065 Education and communication: Education of patients, health care providers, at-risk populations, and general population about cancer. Communication to patients regarding therapeutic options. Educational interventions to promote self-care and symptom management. Communicating cancer risk to underserved populations, at-risk populations, and the general public. Alternative teaching methods to communicate therapeutic options and risk reduction behavior to patients or the general public. Communication of lifestyle models that reduce cancer risk, such as communication of nutrition interventions. Communicating smoking and tobacco cessation interventions. Special approaches and considerations for underserved and at-risk populations. Education, information, prevention/screening/assessment systems for the general public or primary care professionals. Training, predictive cancer models, pain management, and surveillance systems for primary care professionals, telehealth/telemedicine applications. Communication regarding cancer genetics, managed oncology care, communicating with survivors. Barriers to successful health communication.

Common Scientific Outline (for questions 40 and 41) - continued

- 0066 End-of-life care: End-of-life care issues including palliative care, psychological interventions with families at end of life, hospice care, pain management for terminally ill patients, etc.
- 0067 Ethics and confidentiality in cancer research. Informed consent modeling and development. Quality of Institutional Review Boards. Protecting patient confidentiality and privacy. Research ethics.
- 0068 Complementary and alternative approaches for supportive care of patients and survivors: Hypnotherapy, relaxation, transcendental meditation, imagery, spiritual healing, massage, biofeedback, etc., as used for the supportive care of patients and survivors. Discovery, development, and testing of complementary/alternative approaches such as diet, herbs, supplements or other interventions that are not widely used in conventional medicine or are being applied in different ways as compared to conventional medical uses.
- 0069 Resources and infrastructure related to cancer control, survivorship, and outcomes research: Informatics and informatics networks. Clinical trial groups related to cancer control, survivorship, and outcomes research. Statistical methodology or biostatistical methods. Surveillance infrastructures. Centers, consortia, and/or networks. Education and training of investigators.

Scientific Model Systems

- 0071 Development and characterization of model systems: Development and characterization of model systems, including but not limited to: Computer simulation model systems and computer software development. In vitro model systems. Cell culture model systems. Organ and tissue model systems. Animal model systems such as drosophila and *C. elegans*, zebra fish, mouse, etc.
- 0072 Application of model systems: Application of model systems, including but not limited to: Computer simulation model systems and computer software development. In vitro model systems. Cell culture model systems. Organ and tissue model systems. Animal model systems such as drosophila and *C. elegans*, zebra fish, mouse, etc.
- 0073 Resources and infrastructure related to scientific model systems: Models made available for distribution to the scientific community. Centers, consortia, and/or networks. Education and training of investigators.

Appendix D

Sample Abstracts and Statements of Work

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TECHNICAL ABSTRACT

Prediction of Chemotherapy Response by Magnetic Resonance Spectroscopy

Michael G. Garwood, Ph.D., Idea Award Recipient

Background: While adjuvant doxorubicin and cyclophosphamide (AC) chemotherapy clearly prolongs overall survival for women, the relative risk reduction is small. Since new agents, particularly the taxanes, have substantial activity in breast cancer, it is important to learn how to best employ these drugs and maximize benefit of adjuvant chemotherapy. A complete pathologic response (pCR) to neoadjuvant AC is associated with the best overall survival. Thus, discovering methods to predict a pCR to specific chemotherapy regimens in individual patients should have clinical importance.

Objective/Hypothesis: Because chemotherapy induces apoptosis in breast cancer cells, we hypothesize that magnetic resonance spectroscopy (MRS) can identify metabolites associated with apoptosis. MRS can detect these early changes rapidly and noninvasively.

Specific Aims: (1) Measure MRS changes in primary human breast cancers treated with AC neoadjuvant chemotherapy, and (2) determine how MRS changes correlate with tumor response detected by magnetic resonance imaging (MRI) and with complete pathology response at time of surgery. Our long-term goal is to develop MRS as a technique to individualize treatment decisions and maximize treatment benefit for women with breast cancer.

Study Design: Concentrations of cellular compounds in primary breast lesions will be measured noninvasively by proton (^1H) MRS. Patients will undergo MRI and MRS scanning prior to AC treatment and at 24 hours after the first treatment. Changes in the molecular concentrations measured by MRS after the first treatment will be correlated with pathologic complete response. Patients will also undergo an additional MRI scan after their fourth cycle of treatment for the purpose of judging whether anatomic depiction by MRI correlates with pCR determined at surgery.

Relevance: A major challenge in breast cancer treatment is to determine which chemotherapeutic agent will provide the most benefit for an individual patient. This project will establish whether in vivo MRS is a powerful tool to individualize treatment decisions and to maximize treatment benefit for women with breast cancer.

LAY ABSTRACT

Prediction of Chemotherapy Response by Magnetic Resonance Spectroscopy
Michael G. Garwood, Ph.D., Idea Award Recipient

Chemotherapy given after surgical treatment of breast cancer saves lives by killing residual breast cancer cells left after surgery. Chemotherapy given before or after surgery is equally effective. Chemotherapy given before surgery has one major advantage, the response to treatment can be measured. A minority of women treated in this way will have complete disappearance of the tumor at surgery. Perhaps not unexpectedly, these women have the lowest relapse rates and best survival. Therefore, response to chemotherapy prior to surgery can identify women who receive the most benefit from treatment. Since many drugs can effectively kill breast cancer cells, a major challenge in breast cancer treatment is to determine which chemotherapeutic agent will provide the most benefit for an individual patient. The purpose of this proposal is to use magnetic resonance spectroscopy (MRS) to measure chemotherapy induced cell death. MRS can directly measure metabolites in tumors, and we hope to show that changes in metabolite levels measured immediately after chemotherapy treatment will identify tumors that will completely disappear with chemotherapy treatment. By performing these studies, we hope to develop a new technique that will be used to individualize and maximize the benefits of chemotherapy for breast cancer patients.

TECHNICAL ABSTRACT

Characterization of the Role of Hepatocyte Growth Factor in Genetically Defined Human Breast Cancer Cell Metastasis

Sendurai A. Mani, Ph.D., Postdoctoral Fellowship Award Recipient

Background: Hepatocyte growth factor (HGF), also known as scatter factor, is a multifunctional cytokine mainly produced by cells of mesenchymal origin. It elicits a variety of cellular responses in a paracrine fashion on neighboring epithelial cells expressing the Met tyrosine kinase receptor. HGF-Met signaling is essential during mouse development since inactivation of either the ligand or the receptor in mice leads to embryonic lethality. HGF-Met signaling has also been shown to be essential for wound healing, tissue regeneration, and the mammary gland development. The Met receptor was first identified as a constitutively active tpr-met oncoprotein in a human osteogenic sarcoma cell line that has the ability to transform NIH3T3 cells. Additionally, Met and HGF have also been found to be overexpressed or amplified in a variety of metastatic tumors, including human breast cancers. Also, the creation of an autocrine loop by co-expressing the unaltered form of Met and HGF in NIH3T3 cells has been shown to be oncogenic. Finally, overexpression of HGF in the non-metastatic cell line MDA MB 435 and other cancer cell lines enhanced the metastatic potential of these cells.

Objective/Hypothesis: I propose to study the role of HGF-Met signaling in inducing metastasis in genetically defined non-metastatic and angiogenic human breast cancer cells (HMLER), developed in our laboratory. These cells are transformed by introducing SV40 Large T antigen, the Val 12 *H-ras* oncogene, and the catalytic subunit of the human telomerase enzyme to the primary human mammary epithelial cells. Studies on HGF-mediated metastasis were performed in cell lines derived from tumor patients having several unknown genetic mutations; therefore, it is very difficult to predict the exact role played by HGF in inducing metastases in those genetically ill defined cells. HGF might have cooperated with other genes in order to induce metastases. HMLER cells will serve as a good model system to understand the role of HGF in inducing metastasis since we know the exact genetic changes introduced into these cells.

Specific Aims: (1) Determine the role of HGF in motility and invasion in genetically defined human breast cancer cells in vitro, and (2) determine the role of HGF in metastasis in genetically defined human breast cancer cells in vivo.

Study Design: HMLER cells express the met receptor but not HGF. I will therefore test whether the HMLER cells can respond to externally added HGF regarding cell scattering, cell motility, and tubule formation. I then will create an autocrine loop in HMLER cells by stably expressing the HGF gene using a retrovirus and analyze these cells for their ability to respond to the autocrine loop using the above assays. I will further characterize the HMLER-HGF cells for metastasis. If I find metastases, then I will try to understand the role of downstream signaling pathway in inducing metastases. If I do not find metastatic behavior in HMLER-HGF cells, then I will look for cooperating genes to induce metastases. For this, I will introduce a retroviral library made from MDA-MB 435 cells into HMLER-HGF cells and assay for metastasis.

Relevance: The HGF and c-Met are overexpressed and/or amplified in a variety of metastatic tumors. HGF and c-Met have been implicated in human tumor development and metastasis. Blocking HGF signaling was shown to inhibit invasion in a variety of tumors cell lines. Similar results were obtained upon downregulating Met expression. HGF-Met signaling thus serves as a promising target for therapeutic intervention in malignant diseases.

LAY ABSTRACT

Characterization of the Role of Hepatocyte Growth Factor in Genetically Defined Human Breast Cancer Cell Metastasis

Sendurai A. Mani, Ph.D., Postdoctoral Fellowship Award Recipient

Spreading of cancer cells from the primary tumor to other parts of the body is known as metastasis and is often the ultimate life-threatening stage of this disease. However, very little is known about the underlying genetic and cellular mechanisms of metastasis, and it is essential that we understand these mechanisms to develop a therapeutic intervention strategy. Most of the organs in the human body are made up of two types of cells, epithelial cells and mesenchymal cells, whereby more than 90% of human tumors arise from epithelial cells. Both epithelial cells and mesenchymal cells communicate with each other through small messenger molecules. Growth of these cells is normally kept under tight control. Also, epithelial cells are connected with one another, so they cannot move freely.

A small messenger molecule normally secreted by mesenchymal cells, called hepatocyte growth factor (HGF), has been shown to be present at abnormally high levels in the serum of metastatic breast cancer patients. This factor is also found elevated in other types of metastatic cancers. Under normal conditions, this factor is involved in breast development in the adult and also in embryonic organ development.

During cancer progression, this small messenger helps tumor cells to detach from their neighbor, stimulate the production of proteases, and induce tumor cell movement. During later stages of cancer development, the epithelial tumor cell starts producing this factor instead of depending on the mesenchymal cells.

To study the role of HGF in cancer metastasis, scientists normally use epithelial tumor cells derived from patients, which would have had much unknown damage in the genome. But recently, in our laboratory, Dr. William Hahn has converted a normal cell to a tumor cell by altering the function of few known genes. Most importantly, these cells form tumor in mice but they are not metastatic. These genetically defined cancer cells as opposed to genetically undefined cancer patient's tumor cells will serve as a good experimental model system to study metastasis. Since HGF is thought to induce metastasis in the tumor cells, I would like to develop a model system to study the role of HGF in inducing metastases by introducing the HGF gene into the non-metastatic human cancer cells. Development of this defined model system could be useful for the development of strategies specifically to block tumor cell invasion and metastasis.

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.

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 D

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.**

Appendix E

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

Appendix E

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

Appendix E

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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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.

Appendix F

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 G

Appendix H

Acronym List

AR	Army Regulation
BCRP	Breast Cancer Research Program
C-CTR	Collaborative-Clinical Translational Research Awards
CDA	Career Development Awards
CDMRP	Congressionally Directed Medical Research Programs
CEQ	Council on Environmental Quality
CFR	Code of Federal Regulations
CR	Cancer Receptor
CTR	Clinical Translational Research
CV	Curriculum Vitae
DHHS	Department of Health and Human Services
DOD	Department of Defense
DOEd	Department of Education
EPI	Environmental Process Interview
ET	Eastern Time
FDA	Food and Drug Administration
FY	Fiscal Year
GMP	Good Manufacturing Practice
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
IND	Investigational New Drug
IP	Integration Panel
IRB	Institutional Review Board
MPA	Multiple Project Assurance
N/A	Not Applicable
NIH	National Institutes of Health
OTSG	Office of The Surgeon General
PI	Principal Investigator
RAID	Rapid Access to Intervention Development
RCQ	Regulatory Compliance and Quality
SEER	Surveillance Epidemiology and End Results Report
SOPs	Standard Operating Procedures
SPA	Single Project Assurance
TBN	To Be Named
TSG	The Surgeon General
USAMRAA	U.S. Army Medical Research Acquisition Activity

Appendix H

USAMRMC
USC
USDA

U.S. Army Medical Research and Materiel Command
United States Code
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 or 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 stationery 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/psychotropic 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

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.

Appendix L

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 _____