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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES **PHS 2005-1**

SOLICITATION OF

THE PUBLIC HEALTH SERVICE

FOR

SMALL BUSINESS INNOVATION RESEARCH CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE

NOVEMBER 5, 2004

Internet: http://grants.nih.gov/grants/funding/sbir.htm

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The Appendices noted above are in Microsoft Word and Adobe Acrobat Reader fillable format.

NOTE: Other software packages for completing these proposals may be available from other sources; however, it is essential that the type size and format specifications are met or the proposal may be returned without review.

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF THE PUBLIC HEALTH SERVICE FOR SMALL BUSINESS INNOVATION RESEARCH (SBIR) CONTRACT PROPOSALS

I. GENERAL PROGRAM DESCRIPTION

The Small Business Innovation Research Program was reauthorized by the enactment of the Small Business Reauthorization Act of 2000, (Public Law 106-554) through Fiscal Year 2008. The authorizing SBIR legislation requires two significant programmatic changes:

- Commercialization Plan. All Phase II proposals must include a succinct commercialization plan. See instructions in *Section V.3*. for specific details.
- Data Collection Requirement. Each Phase II offeror will be required to provide information for the Small Business Administration (SBA) Tech-Net Database System. See SBA's Tech-Net website (http://tech-net.sba.gov/) for specific details.

The Public Health Service (PHS), Department of Health and Human Services (HHS), and certain other Federal agencies must reserve 2.5 percent of their current fiscal year extramural budgets for research or research and development (R/R&D) for a Small Business Innovation Research (SBIR) program. The objectives of the SBIR Program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal R/R&D needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D, increasing small business participation in Federal R&D, and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The SBIR program consists of three separate phases:

Phase I: Feasibility
$100,000
6 months

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further Federal support in Phase II. Phase I awards normally may not exceed $100,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed 6 months.

Phase II: Full R/R&D Effort
$750,000
2 years

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. Phase II awards normally may not exceed $750,000 for direct costs, indirect costs, and negotiated fees for a period normally not to exceed two years. That is, generally, a two-year Phase II project may not cost more than $750,000 for that project. *Phase II proposals may only be submitted upon the request of the Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section V). Only one Phase II award may result from a single Phase I SBIR contract.*

Phase III: Commercialization stage without SBIR funds

The objective of Phase III, where appropriate, is for the small business concern to pursue with non-SBIR funds the commercialization objectives resulting from the results of the research or R&D funded in Phases I and II. In some Federal agencies, Phase III may involve follow-on, non-SBIR funded R&D or production contracts for products or processes intended for use by the U.S. Government.

The competition for SBIR Phase I and Phase II awards satisfies any competition requirement of the Armed Services Procurement Act, the Federal Property and Administrative Services Act, and the competition in Contracting Act. Therefore, an agency that wishes to fund an SBIR Phase III project is not required to conduct another competition in order to satisfy those statutory provisions. As a result, in conducting actions relative to a Phase III SBIR

award, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5 that the project is a SBIR Phase III award that is derived from, extends, or logically concludes efforts performed under prior SBIR funding agreements and is authorized under 10 U.S.C. 2304(b)(2) or 41 U.S.C. 253(b)(2).

The NIH is interested in developing products and services via the SBIR/STTR program that would improve the health of the American people. In its commitment to also support President Bush's Executive Order 13329, encouraging innovation in manufacturing-related research and development, NIH will expand the focus of our SBIR/STTR program to encourage biomedical research related to advanced processing, manufacturing processes, equipment and systems; or manufacturing workforce skills and protection. This solicitation includes some topic areas that are considered relevant to manufacturing-related R&D. Additional information will be posted on the NIH SBIR/STTR website (http://grants1.nih.gov/grants/funding/sbir.htm) and in the NIH Guide for Grants and Contracts as it becomes available. Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers."

A. PURPOSE OF SOLICITATION

The purpose of this Solicitation is to *invite Phase I contract proposals from small business* concerns that have the expertise to contribute to the mission of the awarding components identified below and to provide the opportunity for the submission of Phase II contract proposals concurrently with Phase I (see specific topics listed in Section XII and identified as accepting Fast-Track proposals).

Included are instructions for offerors to prepare contract proposals, a description of the proposal review process, and some conditions of a contract award. *Contract proposals will be accepted only if they respond specifically to a research topic within this Solicitation (see* Section XII "Research Topics"*).* Otherwise, proposals will be returned to the offeror(s) without evaluation.

To apply for an SBIR grant rather than a contract, use the *Omnibus Solicitation of the Public Health Service for Small Business Innovation Research Grant Applications*. *(http://grants1.nih.gov/grants/funding/sbir.htm#sol)*.

B. AWARDING COMPONENTS

The following awarding components of the PHS are participating in this SBIR Solicitation for Contract Proposals.

National Institutes of Health (NIH)

- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Cancer Institute (NCI)
- National Institute on Drug Abuse (NIDA)
- National Institute of Mental Health (NIMH)
- National Heart, Lung, and Blood Institute (NHLBI)

Centers for Disease Control and Prevention (CDC)

- National Center for HIV, STD, and TB Prevention (NCHSTP)
- National Center for Environmental Health (NCEH)
- National Immunization Program (NIP)
- National Center for Infectious Diseases (NCID)
- National Center on Birth Defects and Developmental Disabilities (NCBDDD)

C. SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern (defined in Section III). In determining whether an offeror is a small business concern, an assessment will be made of several factors, including whether or not it is independently owned and operated and whether or not it is an affiliate of a larger organization whose employees, when added to those of the offeror organization, exceed 500. In conducting this assessment, all appropriate factors will be considered, including common ownership, common management, and contractual relationships.

In accordance with 13 CFR 121.3, affiliation exists when "… one concern controls or has the power to control the other … control may be affirmative or negative and it is immaterial whether it is exercised so long as the power to control exists." One of the

circumstances that would lead to a finding that an organization is controlling or has the power to control another organization involves sharing common office space and/or employees and/or other facilities (e.g., laboratory space). 13 CFR 121.3 also states that control or the power to control exists when "key employees of one concern organize a new concern … and serve as its officers, directors, principal stockholders, and/or key employees; and one concern is furnishing or will furnish the other concern with subcontracts, financial or technical assistance, and/or other facilities, whether for a fee or otherwise."

Access to special facilities or equipment in another organization is permitted (as in cases where the SBIR awardee has entered into a subcontractual agreement with another institution for a specific, limited portion of the research project). However, *research space occupied by an SBIR contractor organization must be space that is available to and under the control of the SBIR contractor for the conduct of its portion of the project*. Where there is indication of sharing of common employees, a determination will be made on a case-by-case basis of whether or not such sharing constitutes control or the power to control.

Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted *with* the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).

This letter must be signed by an *authorized official of the organization whose facilities are to be used for the SBIR project.* It also must include a description of the facilities and, if appropriate, equipment that will be leased/rented to the offeror organization.

All SBIR contract proposals will be reviewed with the above considerations in mind. *If it appears that an offeror does not meet eligibility requirements, the PHS will request an eligibility determination of the organization from the cognizant Small Business Administration (SBA) regional office. The evaluation of the proposal for scientific merit will be deferred until the SBA provides a determination*.

Principal Investigator Criteria. The primary employment of the Principal Investigator must be with the offeror at the time of contract award and during the conduct of the proposed project. PHS policy defines a Principal Investigator as the single individual designated in the proposal with responsibility for the scientific and technical direction of the project. Primary employment means that *more than one half of the Principal Investigator's time* is spent in the employ of the small business concern. Employ means that more than one half of the Principal Investigator's salary and benefits are paid by the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization*.

In the event that the Principal Investigator: (1) is a less-than-full-time employee of the small business, (2) is concurrently employed by another organization, or (3) gives the appearance of being concurrently employed by another organization, whether for a paid or unpaid position, at the time of submission of the proposal, *it is essential that documentation be submitted with the proposal to verify his/her eligibility*. If the Principal Investigator also is employed or appears to be employed by an organization other than the offeror (e.g., a university, a nonprofit research institute, or another company), a letter must be provided by the *non-offeror organization* confirming that the Principal Investigator will, if awarded an SBIR contract, become a less-than-half-time employee of such organization and will remain so for the duration of the SBIR project. If the Principal Investigator is employed by a university, the Dean's Office must provide such a letter. If the Principal Investigator is employed by another for-profit organization, the corporate official must sign the letter. This documentation is required for every proposal that is submitted, even one that is a revision of a previously submitted proposal.

Performance Site Criteria. For both Phase I and Phase II, the research or R&D project activity *must be performed in its entirety in the United States (see* Section III. Definitions*)*.

Market Research. *The PHS will not support any market research under its SBIR program*. Neither will it support studies of the literature that will lead to a new or expanded statement of work. Literature searches where the commercial product is a database are acceptable. For purposes of the SBIR program, "market research" is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, "market

research" does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

II. AGENCY CONTACT FOR INFORMATION

Questions on the administration of an SBIR contract should be directed to the contracting officers listed in Section X. Contracting Officers and Addresses for Mailing and Delivery of Proposals.

Please direct questions of a general nature about the NIH SBIR Program to:

Ms. Jo Anne Goodnight
NIH SBIR/STTR Program Coordinator
6705 Rockledge Drive
Rockledge I, Room 3534
Bethesda, MD 20892
Phone: (301) 435-2688 Fax: (301) 480-0146
Email: sbir@od.nih.gov

or

Ms. Kay Etzler
NIH SBIR/STTR Program Analyst
6705 Rockledge Drive
Rockledge I, Room 3522
Bethesda, MD 20892
Phone: (301) 435-2713 Fax: (301) 480-0146
Email: sbir@od.nih.gov

The PHS SBIR Contract Solicitation ***is available in electronic format*** on the NIH "Small Business Funding Opportunities" home page at http://grants.nih.gov/grants/funding/sbir.htm#sol. The Table of Contents includes direct links and cross-references to specific sections of the document. Text searches in the PDF files are possible using the "binocular" icon. The Phase I and Phase II forms have been modified to enable the fields to be filled in directly using Microsoft Word, or Adobe Acrobat Reader software, which is free.

HELP AND INSTRUCTIONS are available for printing and viewing Acrobat files. Information on Fillable PDF Forms is also available.

NOTE: Other software packages for completing an SBIR proposal may be available from other sources.

DISCLAIMER: Reference to these software packages neither constitutes nor should be inferred to be an endorsement or recommendation of any product, service, or enterprise by the National Institutes of Health, any other agency of the United States Government, or any employee of the United States Government. No warranties are stated or implied.

III. DEFINITIONS

Affiliate. This term has the same meaning as set forth in 13 CFR Part 121 – Small Business Size Regulations, §121.103, *"What is affiliation?"*

Child. NIH defines a child as an individual under the age of 21 years. It should be noted that the definition of child described above will pertain notwithstanding the FDA definition of a child as an individual from infancy to 16 years of age, and varying definitions employed by some states. Generally, state laws define what constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a research study. However, state laws vary, and many do not address the age at which a child can consent to participate in research. Federal Regulations (45 CFR 46, subpart D, Sec.401-409) address DHHS protections for children who participate in research, and rely on state definitions of "child" for consent purposes. Consequently, the children included in this policy (persons under the age of 21) may differ in the age at which their own consent is required and sufficient to participate in research under state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as: *(1)* Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies. *(2)* Epidemiologic and behavioral studies. *(3)* Outcomes research and health services research.

Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

Clinical Trial. The NIH defines a clinical trial as a prospective biomedical or behavioral research study

of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).

- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

- *NIH-Defined Phase III Clinical Trial*. For the purpose of the Guidelines an NIH-defined Phase III "clinical trial" is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Commercialization. The process of developing markets and producing and delivering products for sale (whether by the originating party or by others); as used here, commercialization includes both government and private sector markets.

Consultant. An individual hired to give professional advice or services for a fee, normally not as an employee of the hiring party. Consultants may also include firms that provide paid professional advice or services.

Contract. A mutually binding legal relationship obligating the seller to furnish the supplies or services (including construction) and the buyer to pay for them. It includes all types of commitments that obligate the Government to an expenditure of appropriated funds and that, except as otherwise authorized, are in writing. In addition to bilateral instruments, contracts include (but are not limited to) awards and notices of awards; job orders or task letters issued under basic ordering agreements; letter contracts; orders, such as purchase orders, under which the contract becomes effective by written acceptance or performance; and bilateral contract modifications. Contracts do not include grants and cooperative agreements covered by 31 U.S.C. 6301, et seq.

Essentially Equivalent Work. This term is meant to identify "scientific overlap," which occurs when: (1) substantially the same research is proposed for funding in more than one proposal (contract proposal or grant application) submitted to the same Federal agency; OR (2) substantially the same research is submitted to two or more different Federal agencies for review and funding consideration; OR (3) a specific research objective and the research design for accomplishing that objective are the same or closely related in two or more proposals or awards, regardless of the funding source.

Feasibility. The practical extent to which a project is capable of being successfully performed.

Funding Agreement. Any contract, grant, cooperative agreement, or other transaction entered into between a Federal agency and any small business concern for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government.

Human Subjects. A living individual about whom an investigator (whether professional or student) obtains for research purposes (1) data through intervention or interaction with the individual, or (2) identifiable private information. The regulations governing the inclusion of human subjects in research extend to the use of human organs, tissues, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

The use of autopsy materials is governed by applicable state and local law and is not directly regulated by 45 CFR Part 46.

Innovation. Something new or improved, including research for: (1) development for new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For purposes of PHS programs, an example of "innovation" would be new medical or biological products, for improved value, efficiency, or costs.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as "intellectual property," including but not limited to: patents, trademarks, copyrights, trade secrets, SBIR technical data (as defined in this section), ideas, designs, know-how, business, technical and research methods, and other types of intangible business assets, and including all types of intangible assets either proposed or generated by an SBC as a result of its participation in the SBIR Program.

Joint Venture. An association of persons or concerns with interests in any degree or proportion by way of contract, express or implied, consorting to engage in and carry out a single specific business venture for joint profit, for which purpose they combine their efforts, property, money, skill, or knowledge, but not on a continuing or permanent basis for conducting business generally. A joint venture is viewed as a business entity in determining power to control its management, has been assigned its own Employer Identification Number by the Internal Revenue Service, and is eligible under the SBIR Program provided that the entity created qualifies as an "SBC" as defined in this section.

Key Personnel Engaged on Project. This term is meant to identify those individuals who contribute in a substantive way to the scientific development or execution of the project, whether or not salaries are requested.

Principal Investigator. The one individual designated by the offeror to direct the project or program to be supported by the contract. The Principal Investigator is responsible and accountable for the proper conduct of the project or program.

Prototype. A model of something to be further developed that includes designs, protocols, questionnaires, software, devices, etc.

Research or Research and Development (R/R&D). Any activity that is:

1. A systematic, intensive study directed toward greater knowledge or understanding of the subject studied.
2. A systematic study directed specifically toward applying new knowledge to meet a recognized need.

3. A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

SBIR Technical Data. All data generated during the performance of an SBIR award.

SBIR Technical Data Rights. The rights a small business concern obtains in data generated during the performance of any SBIR Phase I, Phase II, or Phase III award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

Small Business Concern. A small business concern is one that, *on the date of award* for both Phase I and Phase II contracts, meets all of the following criteria:

1. Is organized for profit, with a place of business located in the United States, which operates primarily within the United States or which makes a significant contribution to the United States economy through payment of taxes or use of American products, materials or labor;
2. Is in the legal form of an individual proprietorship, partnership, limited liability company, corporation, joint venture, association, trust or cooperative, except that where the form is a joint venture, there can be no more than 49 percent participation by foreign business entities in the joint venture;
3. Is at least 51 percent owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States, except in the case of a joint venture, where each entity to the venture must be 51 percent owned and controlled by one or more individuals who are citizens of, or permanent resident aliens in, the United States; and
4. Has, including its affiliates, not more than 500 employees.

In the case of a publicly owned business, at least 51% of the small business voting stock must be owned by U.S. citizens or lawfully admitted permanent resident aliens.

Business concerns, other than investment companies licensed, or state development companies qualifying under the Small Business Investment Act of 1958, 15 U.S.C. 661, et seq., are affiliates of one another when either directly or indirectly, (a) one concern controls or has the power to control the other; or (b) a third-party/parties controls or has the power to control both. Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 CFR 121.3-2(a). The term "number of employees" is defined in 13 CFR 121.3-2(t).

Further information may be obtained by contacting the Small Business Administration Size District Office at http://www.sba.gov/size/.

Socially and Economically Disadvantaged Individual. A member of any of the following groups:

1. Black Americans.
2. Hispanic Americans.
3. Native Americans.
4. Asian Pacific Americans.
5. Subcontinent Asian Americans.
6. Other groups designated from time to time by SBA to be socially disadvantaged; or any other individual found to be socially and economically disadvantaged by SBA pursuant to Section 8(a) of the Small Business Act, 15 U.S.C. 637(a).

Socially and Economically Disadvantaged Small Business Concern. See 13 CFR Part 124 – 8(A) Business Development/Small Disadvantaged Business Status Determinations, §§124.103 ("Who is socially disadvantaged?") and 124.104 ("Who is economically disadvantaged?").

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by a Federal Government prime contractor calling for supplies or services required solely for the performance of the prime contract or another subcontract.

United States. The 50 states, the territories and possessions of the Federal Government, the Commonwealth of Puerto Rico, the District of Columbia, the Republic of the Marshall Islands, the Federated States of Micronesia, and the Republic of Palau.

Women-Owned Small Business Concern. A small business concern that is at least 51% owned by one or more women, or in the case of any publicly owned

business, at least 51% of the stock is owned by women, and women control the management and daily business operations. "Control" in this context means exercising the power to make policy decisions. "Operate" in this context means being actively involved in the day-to-day management.

IV. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals generally should not exceed 25 single-spaced pages, including the cover sheet, abstract, cost breakdown, and all enclosures or attachments. Pages should be of standard size (8 l/2" X 11"), and the font should be Arial or Helvetica 11-point. Excluded from the 25-pages are cover letters, Human Subjects Research and Vertebrate Animal information, letters of commitment from collaborators and consultants and letters to determine eligibility. Unless specifically solicited by a Contracting Officer, no other appendices may be submitted, and if submitted, they will not be considered in the evaluation of scientific and technical merit.

B. PROPOSAL COVER SHEET

Complete the form identified as Appendix A (MS Word | PDF), and use it as the first page of the proposal. *No other cover sheet should be used*.

- ***Topic Number.*** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted. If your proposal is responsive to a subtopic, provide both the topic and subtopic numbers. (A numerical or alphabetical designator precedes each topic and subtopic.)

- ***Project Title.*** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the Solicitation.

C. ABSTRACT OF RESEARCH PLAN

Complete the form identified as Appendix B (MS Word | PDF), and insert it as the second page of each proposal. Abstracts of successful proposals will be published by NIH and, therefore, should not contain proprietary information. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Summarize anticipated results and potential commercial applications of the proposed research.

D. RESEARCH PLAN

Any research proposal involving the collection of information, such as surveys or interviews, of more than nine respondents will require clearance by the U.S. Office of Management and Budget. Therefore, it is not practical to propose such an activity for Phase I, which normally has only a six-month duration.

Beginning on page three of the proposal, discuss in the order indicated the following elements:

1. ***Identification and Significance of the Problem or Opportunity.*** Provide a clear statement of the specific technical problem or opportunity addressed.

2. ***Technical Objectives.*** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.

3. ***Work Plan.*** Provide a detailed plan for the R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address the objectives and the questions stated in *Item 2* above. Discuss in detail the methods to be used to achieve each objective or task. For specific guidance and instructions related to Human Subjects research, please see the section entitled, "Human Subjects Research and Protection from Risk" and the "Human Subjects Research Guidance and Information Supplement."

4. ***Related Research or R&D.*** Describe significant research or R&D that is directly related to the proposal, including any conducted by the Principal Investigator/Project Manager or by the proposing firm. Describe how it relates to the proposed effort and any planned coordination with outside sources. *The Principal Investigator/Project Manager must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field*.

5. ***Relationship with Future R&D.***

   a. State the results expected from the proposed approach.

b. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.

6. ***Potential Commercial Applications.*** Describe why the proposed project appears to have potential commercial applications, and whether and by what means the proposed project appears to have potential use by the Federal Government.

7. ***Key Personnel and Bibliography of Directly Related Work.*** Identify key personnel, including their directly related education, experience, and bibliographic information. Where vitae are extensive, focus on summaries of the most relevant experience or publications. *Provide dates and places of employment* and some information about the nature of each position or professional experience. Curriculum vitae must identify the current or most recent position.

8. ***Salary Rate Limitation.*** Fiscal Year (FY) 2004 is the fifteenth consecutive year for which there is a legislatively mandated provision for the limitation of salary. Specifically, the Department of Health and Human Services (HHS) Appropriation Act for FY 2004, Public Law 108-7, restricts the amount of direct salary of an individual under an NIH grant or cooperative agreement (hereafter referred to as a grant) or applicable contract to Executive Level I of the Federal Executive Pay scale. Effective January 1, 2004, the Executive Level I salary level increased to $175,700 per year. It is anticipated that this same limit will apply in FY 2005.

9. ***Consultants.*** Involvement of consultants in the planning and/or research stages of the project is permitted. However, such use must be described in detail and supported by appropriate letters from each individual confirming his/her role in the project.

10. ***Facilities and Equipment.*** Indicate where the proposed research will be conducted. *One of the performance sites must be the offeror organization*. Describe the facilities to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project.

    List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

    Any equipment and products purchased with Government funds shall be American-made, to the extent possible.

    Title to Equipment. Title to equipment purchased with Government funding by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, the Government may transfer such title to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property.

E. CURRENT AWARDS AND PENDING PROPOSALS/APPLICATIONS

As the PHS uses both contracts and grants in its SBIR program, a small business concern may not submit both a contract proposal and a grant application for essentially the same project to the same or different awarding component(s) of the PHS. The only exception would be the submission of a grant application after a contract proposal has been evaluated and is no longer being considered for award.

While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work (as defined in this Solicitation) for consideration under numerous Federal program solicitations, it is unlawful to enter into contracts or grants requiring essentially equivalent effort.

If there is any question concerning this, it must be disclosed to the soliciting agency or agencies before award.

If a firm elects to submit identical proposals or proposals containing a significant amount of essentially equivalent work under other Federal program solicitations, include a statement in each such proposal indicating the information requested in items 1-10 set forth below.

In addition, provide the information requested in items 1-10 on (a) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (b) contract proposals and grant and cooperative agreement applications pending review or funding; and (c) contract proposals and

grant and cooperative agreement applications about to be submitted.

1. Name and address of the funding source.
2. Type of award (contract, grant, cooperative agreement) and identifying number.
3. Title of research project.
4. Name and title of Principal Investigator or Project Manager.
5. Hours per week on the project by the Principal Investigator or Project Manager.
6. Annual costs proposed or awarded.
7. Entire period of support.
8. Date of proposal/application submission or date of award.
9. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.
10. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR*.

F. PRIOR SBIR PHASE II AWARDS

If the small business concern has received more than 15 Phase II awards in the prior 5 fiscal years, submit name of awarding agency, date of award, funding agreement number, amount, topic or subtopic title, follow-on agreement amount, source, and date of commitment and current commercialization status for each Phase II. This required proposal information will not be counted toward the proposal page limitations.

G. PROPOSED COST BREAKDOWN

Complete the form identified as Appendix C (Contract Pricing Proposal) (MS Word | PDF). The cost breakdown should appear as the last section of the proposal. *If some items on this form do not apply to the proposed project, they need not be completed*.

- Under "Government Solicitation No.," enter "PHS 2005-1."
- If supplies are proposed, provide the quantities and the price per unit.
- Under "Direct Labor," *list all key personnel by name*. Support personnel may be consolidated into categories or labor classes, e.g., research assistants or data processing clerks.
- If travel is proposed, provide the following details on "Exhibit A – Supporting Schedule": destination(s); duration of trip(s); number of travelers; and cost per trip, broken down by cost elements, e.g., airfare, lodging, and meals.
- If consultants are proposed, provide name(s), rate(s), and number of hours/days.
- If a subcontract is proposed, provide the same type of detailed cost breakdown as required for Appendix C. *Also provide a copy of the subcontractual agreement*.
- Use "Exhibit A – Supporting Schedule" to itemize and justify all major cost elements. If more space is needed, use Page 3 of Appendix C.
- *Normally, at least two-thirds or 67% of the entire research or analytical effort must be carried out by the offeror*, i.e., subcontracts for portions of the scientific/technical effort and consultant fees normally may not exceed 33% of the total cost breakdown.

H. STREAMLINING THE CONTRACTING PROCESS

With the Federal Acquisition Streamlining Act of 1994 and the Federal Acquisition Reform Act of 1996, a number of terms and conditions that previously applied to contracts under $100,000 are no longer applicable. Under the SBIR program, Phase I awards, which normally may not exceed $100,000, will reflect the streamlined contract document.

The NIH has initiated special *"just in time" procedures* that are designed to reduce the administrative burden on offerors without compromising the information needed during the initial evaluation of proposals. Certain documents that would previously have been required for submission with the Phase II proposal will be requested at a later stage in the evaluation process. The following documentation is part of the "just in time" procedures and offerors who elect to submit proposals under the *"Fast-Track" initiative* below are not required to submit this documentation with their initial Phase II business proposal:

- ***Travel Policy.*** The offeror's written travel policy.
- ***Annual Financial Report.*** The offeror's most recent annual financial report.
- ***Total Compensation Plan.*** Salary and fringe benefits of professional employees under service contracts.
- ***Data Substantiating the Costs and Prices Proposed.*** That is, payroll documentation, vendor quotes, invoice prices, etc.

I. REQUIREMENT FOR ADEQUATE ASSURANCE OF PROTECTION OF HUMAN SUBJECTS

The HHS regulations for the Protection of Human Subjects, 45 CFR 46 (as amended), provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS. **The requirement is that an approved assurance of compliance with the regulations must be on file with the Office for Human Research Protections (OHRP), DHHS (http://www.hhs.gov/ohrp) before an HHS award can be made.**

Neither an Institutional Review Board (IRB) review nor an OHRP-approved Assurance is required at the time the proposal is submitted or at the time that the proposals are peer reviewed.

Human Subjects Research and Protection from Risk

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

Provided below is a table that presents six possible research scenarios, and links to the instructions for providing information on human subjects protection information and the inclusion of women, minorities, and children specific to each scenario. All research will fall into one of these six scenarios. Which scenario best matches your proposed research depends on your answers to the following five questions:

Question 1: Does your proposed research involve human subjects?

Question 2: Is your proposed research described by one or more of the exemptions in the Department of Health and Human Services (HHS) Regulations (45 CFR Part 46)?

Question 3: Does your proposed research include clinical research?

Question 4: Does your proposed research include a clinical trial?

Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

If you can answer the five questions, proceed to the table below, select the scenario that best matches your responses and then follow the instructions located on the scenario pages.

If you need additional guidance then click on the questions or the column heading in the table below and you will be provided additional information and guidance.

Much of the information on the protection of human subjects that you are required to provide in this section is identical to information that will be required to provide for IRB review.

DECISION TABLE FOR HUMAN SUBJECTS RESEARCH, PROTECTION AND THE INCLUSION OF WOMEN, MINORITIES, AND CHILDREN

	Criteria and Answers to Questions 1 thru 5				
Scenarios with linked instructions	1. Human Subjects Research	2. Exempt from HHS Human Subjects Regulations	3. Clinical Research	4. Clinical Trial	5. NIH-Defined Phase III Clinical Trial
A No Human Subjects	No	N/A	N/A	N/A	N/A
Requirements for Scenario A: - Indicate "No Human Subjects Research"					
B Human Subjects/E-4	Yes	Yes Exemption: 4	No	N/A	N/A
Requirements for Scenario B: - Indicate Exemption 4 (E-4) and include justification that E-4 is appropriate. - Address “Inclusion of Children” if known					
C Human Subjects/ Other Exemptions	Yes	Yes Exemptions: 1, 2, 3, 5, 6	Yes	N/A	N/A
Requirements for Scenario C: - Indicate Exemption number(s) and include justification that the designated exemption(s) is appropriate. - Address “Inclusion of Women and Minorities” - Address “Inclusion of Children”					
D Clinical Research	Yes	No	Yes	No	N/A
Requirements for Scenario D: - Address Protection of Human Subjects - Address “Inclusion of Women and Minorities” - Address “Inclusion of Children” “Targeted/Planned Enrollment Table(s)” for each new study/ protocol (New proposals; Competing Continuation proposals; Competing Supplements) - “Inclusion Enrollment Report Table(s)” (Competing Continuations; Competing Supplements)					
E Clinical Trials	Yes	No	Yes	Yes	No
Requirements for Scenario E: - All requirements in Scenario D - Data and Safety Monitoring Plan - Note: Some trials may require a Data and Safety Monitoring Board, based on risk					
F NIH-Defined Phase III Clinical Trial	Yes	No	Yes	Yes	Yes
Requirements for Scenario F: - All requirements in Scenario E Increased requirements for Inclusion of Women and Minorities in Clinical Research					

J. REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified as "key personnel" before funds are awarded for contract proposals involving human subjects. For information relating to this requirement, see the following notice (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html), which was published June 5, 2000 in the *NIH Guide for Grants and Contracts*. Prior to award, the selected contractor will be required to provide a description of education completed in the protection of human subjects for all key personnel. While NIH does not endorse programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See http://ohsr.od.nih.gov/ for computer-based training developed for NIH that can be downloaded at no charge. For information on facilitating education and developing curricula, see http://www.nih.gov/sigs/bioethics.

K. REQUIREMENT FOR ADEQUATE ASSURANCE OF COMPLIANCE WITH THE PHS POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS

Instructions and Required Information

This information must be submitted with the proposal, but is excluded from the 25-page limitation.

Create a section heading entitled **"Vertebrate Animals."** Place it immediately following the "Research Plan" section of the proposal (or after Human Subjects Research section, if applicable).

Under the Vertebrate Animals heading, address the following five points. In addition, when research involving vertebrate animals will take place at collaborating site(s) or other performance site(s), provide this information before discussing the five points. Although no specific page limitation applies to this section of the proposal, be succinct.

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.

2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.

3. Provide information on the veterinary care of the animals involved.

4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.

5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Guidance and Additional Instructions

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal (http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-02-064.html).

In August, 2002 NIH announced an IACUC "just-in-time" process for applications submitted for the October 1, 2002 deadline or other deadlines where the applications had a May/June 2003 Council review. The PHS policy requirement that no award may be made without an approved Assurance and without verification of IACUC approval remains in effect. The new policy gave institutions flexibility in the timing of IACUC review relative to the submission of a proposal and the verification of IACUC review. The policy does not require that IACUC approval be deferred. Institutional officials retain the discretion to require IACUC approval prior to NIH peer review in circumstances of their choosing if deemed necessary. As part of the NIH peer review process, the scientific review group will

continue to address the adequacy of animal usage and protections in the review of a proposal and will continue to raise any concerns about animal welfare issues. Verification of IACUC approval will be required in a "just-in-time" fashion prior to award.

The PHS *Policy on Humane Care and Use of Laboratory Animals* requires that offeror organizations proposing to use vertebrate animals file a written Animal Welfare Assurance with the Office of Laboratory Animal Welfare (OLAW), establishing appropriate policies and procedures to ensure the humane care and use of live vertebrate animals involved in research activities supported by the PHS. The PHS policy stipulates that an offeror organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. This policy implements and supplements the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* and requires that institutions use the *Guide for the Care and Use of Laboratory Animals* as a basis for developing and implementing an institutional animal care and use program. This policy does not affect applicable state or local laws or regulations that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 USC 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

The PHS Policy defines "animal" as "any live, vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes."

No PHS award for research involving vertebrate animals will be made to an offeror organization unless that organization is operating in accordance with an approved Animal Welfare Assurance and provides verification that the IACUC has reviewed and approved the proposed activity in accordance with the PHS policy. Proposals may be referred by the PHS back to the IACUC for further review in the case of apparent or potential violations of the PHS policy. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the PHS policy. Foreign offeror organizations applying for PHS awards for activities involving vertebrate animals are required to comply with PHS policy or provide evidence that acceptable standards for the humane care and use of animals will be met.

L. NEEDLE EXCHANGE

It is anticipated that the HHS Fiscal Year 2005 Appropriations Act will continue a restriction on using contract funds to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.

M. BAN ON HUMAN EMBRYO RESEARCH

It is anticipated that the HHS Fiscal Year 2005 Appropriations Act will continue the ban on funding of human embryo research. Currently, contract funds may not be used for: (1) the creation of a human embryo or embryos for research purposes, or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). The term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells. Additionally, Federal funds may not be used for cloning of human beings.

N. RESEARCH USING HUMAN EMBRYONIC STEM CELLS

http://stemcells.nih.gov/index.asp

In signing the proposal Cover Sheet, the duly authorized representative of the offeror certifies that if research using human embryonic stem cells is proposed, the offeror will be in compliance with the "Notice of Extended Receipt Date and Supplemental Information Guidance for Applications Requesting Funding that Proposes Research with Human Embryonic Stem Cells" (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-006.html).

V. "FAST-TRACK" INITIATIVE

(Applicable Only to Proposals Submitted to NIH)

The "Fast-Track" initiative is a parallel review option available to those small business concerns (offeror organizations) whose proposals satisfy additional

criteria that enhance the probability of the project's commercial success. This initiative is applicable only to NIH and only if an awarding component indicates it is accepting Fast-Track proposals for a particular topic. (Refer to Section XII, "Research Topics," for notation.)

The Fast-Track initiative is an opportunity for small business concerns to submit both a Phase I and Phase II proposal for concurrent peer review. This initiative also has the potential to minimize any funding gap between Phase I and Phase II.

Fast-Track Proposal Process

To identify the proposals as Fast-Track, check the box marked "Yes" next to the words "Fast-Track Proposal" shown on the Phase I Proposal Cover Sheet, Appendix A (MS Word | PDF).

The small business concern must submit both a Phase I and a Phase II proposal for concurrent initial peer review and evaluation. The Fast-Track proposal must consist of the following parts:

1. ***Phase I Proposal.*** Prepared in accordance with Section IV. Phase I Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section VII) for Phase I proposals.
2. ***Phase II Proposal.*** Prepared in accordance with Section VI, Fast-Track Phase II Proposal Preparation Instructions and Requirements and addressing all factors stated in the evaluation criteria (Section VII) for Phase II proposals.
3. **Commercialization Plan**
   (formerly Product Development Plan [PDP])

(*Applicable to all Phase II proposals and Phase I/ Phase II Fast-Track proposals*.)

All Phase II proposals *and* Fast-Track proposals must include a succinct Commercialization Plan, formerly referenced as a "Product Development Plan (PDP)." The Commercialization Plan is limited to *15 pages*. Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan.

Create a section entitled, "Commercialization Plan," and provide a description in each of the following areas:

a. ***Value of the SBIR Project, Expected Outcomes, and Impact.*** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.

b. ***Company.*** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales. Include a short description of the origins of the company. Indicate your vision for the future, how you will grow/maintain a sustainable business entity, and how you will meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.

c. ***Market, Customer, and Competition.*** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.

   Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product.

   Briefly describe your marketing and sales strategy. Give an overview of the current competitive landscape and any potential competitors over the next several years. *(It is very important that you understand and know the competition.)*

d. ***Intellectual Property (IP) Protection.*** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.

e. ***Finance Plan.*** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:

- Letter of commitment of funding.
- Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
- Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
- Specific steps you are going to take to secure Phase III funding.

f. ***Production and Marketing Plan.*** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.

g. ***Revenue Stream.*** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.

Offerors are *encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization* of the product(s) or service(s) resulting from the SBIR contract.

Your Phase III funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or "angels"; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

Fast-Track proposals that do not contain all parts described above will be redirected for Phase I consideration only.

The Phase I and Phase II proposals will be scored individually.

Fast-Track Phase II proposals may be funded following submission of the Phase I final report, and a determination that the Phase I objectives were met, feasibility was demonstrated, and funds are available.

VI. FAST-TRACK PHASE II PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

A. LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase II proposals generally should not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8 1/2" x 11") and the font should be Arial or Helvetica 11-point. Excluded from the page limitation are cover letters and letters from collaborators and consultants.

B. TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D (MS Word | PDF).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B (MS Word | PDF). State the broad, long-term objectives and specific aims. Do not include any proprietary information. Briefly and concisely describe the research design and methods for achieving these goals.
4. **Anticipated Results of Phase I Effort** - Briefly discuss and summarize the objectives of your Phase I effort, the research activities to be carried out, and the anticipated results.
5. **Research Plan**
   a. *Detailed Approach and Methodology* - provide an explicit detail description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe

what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor work progress under the contract. Offerors using Human Subjects or Vertebrate Animals in their research should refer to the specific instructions provided in this Solicitation.

b. *Personnel* - List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. ***Provide curricula vitae for all key staff members,*** describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and ***provide curriculae vitae for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.***

c. *Resources* - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. (***Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)***

d. *Other considerations* - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects, etc. Note: If the research plan includes the use of human subjects or animals, refer to paragraphs IV. I-N of this solicitation for further guidance.

e. *Appendices*

(1) **Work Statement** – The Contracting Officer may require the offeror to develop a Statement of Work similar in format to the sample in Appendix E (MS Word | PDF). Create this from your detailed approach and methodology. It will be incorporated into the final contract document. Do not include proprietary information.

(2) **Commercialization Plan** – Required for ALL Phase II and Fast-Track proposals. Comply with requirements referred to in *Section V.3.*

6. **Summary of Related Activities** - Use Appendix F (MS Word | PDF).

7. **Technical Proposal Cost Information** - Use Appendix C (MS Word | PDF). Delete the fringe benefit costs, indirect costs and fee. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.

8. **Number of Copies** - Submit an original and 9 copies.

C. BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Cover Page** - Use NIH Form 2043, Proposal Summary and Data Record, Appendix G (MS Word | PDF).

2. **Proposed Cost Breakdown** - Use Appendix C (MS Word | PDF). Explain the basis for all costs and submit documentation to support all proposed costs. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.

3. **Number of Copies** - Submit an original and 4 copies.

VII. METHOD OF SELECTION AND EVALUATION CRITERIA

Proposals will be initially screened to determine their compliance with the administrative requirements of this Solicitation and their applicability to the research topic selected by the offeror. Using the technical evaluation factors described below in Section VII.B., a peer review panel will evaluate proposals passing the initial screening for technical merit and scientific acceptability, to determine the most promising approaches.

A. EVALUATION PROCESS

Your proposal will be peer reviewed by a panel of scientists selected for their competence in relevant

scientific and technical fields. Each peer review panel will be responsible for evaluating proposals for scientific and technical merit. The peer review panel provides a rating, makes specific recommendations related to the scope, direction and/or conduct of the proposed research, and for those proposals recommended for award, may provide a commentary about the funding level, labor mix, duration of the proposed contract project, vertebrate animal and human subject research issues. The Institute program staff of the awarding component will conduct a second level of review. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component. A Phase I or Phase II contract may be awarded only if the corresponding proposal has been recommended as technically acceptable by the peer review panel. ***Funding for any/all acceptable proposals is not guaranteed.***

B. TECHNICAL EVALUATION CRITERIA

In considering the technical merit of each proposal, the following factors will be assessed:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach and identification of clear measurable goals (milestones) to be achieved during Phase I. (*Preliminary data are not required for Phase I proposals*.)	40%
2. The qualifications of the proposed Principal Investigator, supporting staff, and consultants.	20%
3. The potential of the proposed research for technological innovation.	15%
4. The potential of the proposed research for commercial application.	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS	WEIGHT
1. The scientific/technical merit of the proposed research, including adequacy of the approach and methodology, and identification of clear, measurable goals to be achieved during Phase II.	30%
2. The potential of the proposed research for commercialization and the adequacy of the Commercialization Plan.	30%
3. The qualifications of the proposed Principal Investigator, supporting staff and consultants.	25%
4. The adequacy and suitability of the facilities and research environment.	15%

C. PROPOSAL DEBRIEFING

Offerors will be notified when they are no longer being considered for award. Offerors are entitled to one debriefing, which can be requested within three days of the receipt of the notification.

D. AWARD DECISIONS

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research); and
4. Availability of funds.

The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area. The SBIR contract projects do not require establishing a competitive range or requesting final proposal revisions before reaching source selection decisions.

VIII. CONSIDERATIONS

A. AWARDS

1. The award instrument will be a contract.
2. A profit or fixed fee may be included in the proposal, as specified in Federal Acquisition Regulation (FAR) Part 15.404-4. The fee will be negotiated as an element of the potential total contract amount over and above allowable costs.
3. Phase I awards will be firm fixed price contracts. Normally, Phase II awards will be cost-plus-fixed-fee contracts.
4. Normally, Phase I contracts may not exceed $100,000. Phase II contracts normally may not exceed $750,000—including direct costs, indirect costs, and negotiated fixed fee.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS		NO. OF AWARDS	ESTIMATED TIME OF AWARD
National Institutes of Health (NIH)	National Institute on Alcohol Abuse and Alcoholism (NIAAA)	3	Scientific and Technical Merit Review: March 2005 Anticipated Award Date: June 2005
	National Cancer Institute (NCI)	27 - 50	Scientific and Technical Merit Review: May 2005 Anticipated Award Date: July 2005
	National Institute on Drug Abuse (NIDA)	11	Scientific and Technical Merit Review: March 2005 Anticipated Award Date: August 2005
	National Institute of Mental Health (NIMH)	3	Scientific and Technical Merit Review: February - March 2005 Anticipated Award Date: June – July 2005
	National Heart, Lung, and Blood Institute (NHLBI)	3	Scientific and Technical Merit Review: February 2005 Anticipated Award Date: August 2005
Centers for Disease Control and Prevention (CDC)	National Center for HIV, STD, and TB Prevention (NCHSTP)	7	Scientific and Technical Merit Review: February 2005 Anticipated Award Date: August 2005
	National Center for Environmental Health (NCEH)	2	Scientific and Technical Merit Review: February 2005 Anticipated Award Date: August 2005
	National Immunization Program (NIP)	2	Scientific and Technical Merit Review: February 2005 Anticipated Award Date: June 2005
	National Center for Infectious Diseases (NCID)	7	Scientific and Technical Merit Review: February 2005 Anticipated Award Date: August 2005
	National Center on Birth Defects and Developmental Disabilities (NCBDDD)	5	Scientific and Technical Merit Review: February 2005 Anticipated Award Date: July 2005

B. FINAL REPORT

Original plus 2 copies

A final report is required of all Phase I and Phase II contractors. It should include a detailed description of the project objectives, the activities that were carried out, and the results obtained. An original and two copies of this report must be submitted as directed by the Contracting Officer not later than the expiration date of the Phase I contract.

Each Phase II "Fast-Track" contractor must submit semi-annual progress reports. A final report is required no later than the expiration date of the Phase II contract. *All reports (original plus two copies) must be submitted as directed by the Contracting Officer or as specified in the contract.*

C. PAYMENT

The Government shall make payments, including invoice and contract financing payments, by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to register in the Central Contractor Registration (CCR) database on or before the award of a contract. The registration site for the CCR is http://www.ccr.dlis.dla.mil.

Payments on Phase I contracts may be made on a monthly advance basis. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be on a monthly basis unless otherwise authorized by the contracting officer.

D. LIMITED RIGHTS INFORMATION AND DATA

Proprietary Information. Information contained in unsuccessful proposals will remain the property of the offeror. The Government, however, may retain copies of all proposals. Public release of information in any proposal will be subject to existing statutory and regulatory requirements.

The Department of Health and Human Services (HHS) recognizes that, in responding to this Solicitation, offerors may submit information that they do not want used or disclosed for any purpose other than for evaluation. Such data might include trade secrets, technical data, and business data (such as commercial information, financial information, and cost and pricing data). The use or disclosure of such information may be restricted if offerors identify it and the Freedom of Information Act (FOIA) does not require its release. For information to be protected, offerors must identify in the Notice of Proprietary Information (on the Proposal Cover Sheet) the page(s) on which such information appears. Any other Notice may be unacceptable to the Government and may constitute grounds for removing the proposal from further consideration without assuming any liability for inadvertent disclosure.

Unless disclosure is required by the FOIA, as determined by FOI officials of the HHS, data contained in those portions of a proposal that have been identified as containing restricted information, in accordance with the Notice of Proprietary Information, shall not be used or disclosed except for evaluation purposes.

The HHS may not be able to withhold data that has been requested pursuant to the FOIA, and the HHS FOI officials must make that determination. The Government is not liable for disclosure if the HHS has determined that disclosure is required by the FOIA.

If a contract is awarded to the offeror as a result of, or in connection with, the submission of a proposal, the Government shall have the right to use or disclose the data to the extent provided by law. Proposals not resulting in a contract remain subject to the FOIA.

Rights to Data Developed Under SBIR Funding Agreement. Rights to data, including software developed under the terms of any funding agreement resulting from a contract proposal submitted in response to this Solicitation, shall remain with the awardee. However, the Government shall have the limited right to use such data for internal Government purposes.

(1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the Small Business Concern (SBC), or from using the information to produce future technical procurement specifications that could harm the SBC that discovered and developed the innovation.

(2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical

data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or Federally-funded SBIR Phase III) unless, subject to (b)(3)of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR offeror. Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a Phase III award is issued within or after the Phase II data rights protection period and the Phase III award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the Phase III protection period. Agencies have discretion to adopt a protection period longer than four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.

(3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, II, or III of the SBIR Program, as described in Section 4 of this Policy Directive. The scope and extent of the SBIR technical data rights applicable to Federally-funded Phase III awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only: (i) Upon expiration of the protection period applicable to the SBIR award, or (ii) by agreement between the awardee and the agency.

(4) Agencies must insert the provisions of (1), (2), and (3) immediately above as SBIR data rights clauses into all SBIR Phase I, Phase II, and Phase III awards. These data rights clauses are non-negotiable and must not be the subject of negotiations pertaining to an SBIR Phase III award, or diminished or removed during award administration. An agency must not, in any way, make issuance of an SBIR Phase III award conditional on data rights. If the SBIR awardee wishes to transfer its SBIR data rights to the awarding agency or to a third party, it must do so in writing under a separate agreement. A decision by the awardee to relinquish, transfer, or modify in any way its SBIR data rights must be made without pressure or coercion by the agency or any other party. Following issuance of an SBIR Phase III award, the awardee may enter into an agreement with the awarding agency to transfer or modify the data rights contained in that SBIR Phase III award. Such a bilateral data rights agreement must be entered into only after the SBIR Phase III award, which includes the appropriate SBIR data rights clause, has been signed. SBA must immediately report to the Congress any attempt or action by an agency to condition an SBIR award on data rights, to exclude the appropriate data rights clause from the award, or to diminish such rights.

Copyrights. The awardee may normally copyright and publish (consistent with appropriate national security considerations, if any) material developed with PHS support. The awarding component receives a royalty-free license for the Federal Government and requires that each publication contain an acknowledgement of agency support and disclaimer statement, as appropriate. An acknowledgement shall be to the effect that: “This publication was made possible by contract number _____ from (*PHS awarding component*)” or “The project described was supported by contract number _____ from (*PHS awarding component*).”

Patents. Small business concerns normally retain the principal worldwide patent rights to any invention developed with Government support. Under existing regulations, 37 CFR 401, the Government receives a royalty-free license for Federal Government use, reserves the right to require the patent-holder to license others in certain circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it substantially in the United States.

To the extent authorized by 35 U.S.C. 205, the Government will not make public any information disclosing a Government-supported invention for a four-year period to allow the awardee a reasonable time to file a patent application, nor will the Government release any information that is part of that application.

Information about additional requirements imposed by 37 CFR 401 should be obtained from local counsel or from:

Office of Policy for Extramural Research Administration,
Extramural Inventions and Technology Resources Branch,
National Institutes of Health (NIH)
6705 Rockledge Dr., Rm. 1175, MSC 7980
Bethesda, MD 20892-7980
(301) 435-0679 (v)
(301) 480-0272 (fax)
george.stone@nih.gov

Inventions must be reported promptly—within two months of the inventor's initial report to the contractor organization—to the Division of Extramural Inventions and Technology Resources, NIH, at the address above. This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 USC 202, and may result in loss of the rights of the small business concern, inventor, and Federal Government in the invention. All foreign patent rights are immediately lost upon publication or other public disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

The reporting of inventions can be accomplished by submitting paper documentation, including fax, or electronically through the NIH Edison Invention Reporting System. Use of the Edison system satisfies all mandated invention reporting requirements and access to the system is through a secure interactive Web site (https://s-edison.info.nih.gov/iEdison) to ensure that all information submitted is protected. In addition to fulfilling reporting requirements, Edison notifies the user of future time sensitive deadlines with enough lead-time to avoid the possibility of loss of patent rights due to administrative oversight. Edison can accommodate the invention reporting need of all organizations. For additional information about this invention reporting and tracking system, visit the Edison home page cited above or contact Edison via email at Edison@od.nih.gov.

Sharing Biomedical Research Resources. It is the policy of the NIH that unique research resources developed with NIH funding must be shared with the research community. Restricted availability of these resources can impede the advancement of research. Principles and Guidelines for Recipients of NIH Research Grants and Contracts, as published in the Federal Register Notice on December 23, 1999 [http://ott.od.nih.gov/NewPages/RTguide_final.html], provide assistance to determine reasonable terms and conditions for acquiring and disseminating research tools, consistent with the objectives of furthering biomedical research and adhering to the Bayh-Dole Act.

(1) Sharing Research Data. See http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html. Offerors submitting proposals that exceed $500,000 per year shall include in the proposal a plan for data sharing or state why data sharing is not possible.

Reviewers will not factor the proposed data-sharing plan into the determination of scientific merit or score. Program staff will be responsible for overseeing the data sharing policy and for assessing the appropriateness and adequacy of the proposed data-sharing plan.

NIH recognizes that data sharing may be complicated or limited, in some cases, by institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule. As NIH stated in the March 1, 2002 draft data sharing statement (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-035.html), the rights and privacy of people who participate in NIH-sponsored research must be protected at all times. Thus, data intended for broader use should be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual subjects. When data sharing is limited, offerors should explain such limitations in their data sharing plans.

For more information on data sharing, please see our website at http://grants.nih.gov/grants/policy/data_sharing/.

(2) Sharing Model Organisms. All proposals where the development of model organisms is anticipated are to include a description of a specific plan for sharing and distributing unique model organism research resources or state appropriate reasons why such sharing is restricted or not possible. Unlike the NIH Data Sharing Policy, the submission of a model organism sharing plan is not subject to a cost threshold of $500,000 or more in direct costs in any one year. The adequacy of plans

for sharing model organisms will be considered by the reviewers when a competing proposal is evaluated. Reviewers will be asked to describe their assessment of the sharing plan in an administrative note and will not include their assessment in the overall score. For additional information on this policy, see the NIH Model Organism for Biomedical Research Website at: http://www.nih.gov/science/models/ and NIH GUIDE Notice OD-04-042: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html.

Royalties. If royalties exceed $1,500, you must provide the following information on a separate page for each separate royalty or license fee:

1. Name and address of licensor.
2. Date of license agreement.
3. Patent numbers.
4. Patent application serial numbers, or other basis on which the royalty is payable.
5. Brief description (including any part or model number of each contract item or component on which the royalty is payable).
6. Percentage or dollar rate of royalty per unit.
7. Unit price of contract item.
8. Number of units.
9. Total dollar amount of royalties.
10. If specifically requested by the Contracting Officer, a copy of the current license agreement and identification of applicable claims of specific patents (see FAR 27.204 and 31.205-37).

E. PERFORMANCE OF RESEARCH AND ANALYTICAL WORK

In Phase I projects, normally a minimum of two-thirds or 67% of the research or analytical effort must be performed by the small business concern.

In Phase II projects, normally a minimum of one-half or 50% of the research or analytical effort must be performed by the small business concern.

The Contracting Officer must approve deviations from these requirements in writing.

Contractor Commitments. Upon entering into a contract, the contractor agrees, in accordance with the terms and conditions of the contract, to accept certain legal commitments embodied in the clauses of Phase I and Phase II contracts. The following list illustrates the types of clauses to which a contractor is bound. This list is not exhaustive. Copies of complete terms and conditions are available upon request.

Clauses That Apply to Contracts *NOT* Exceeding $100,000

1. ***Standards of Work.*** Work performed under the contract must conform to high professional standards.
2. ***Inspection.*** Work performed under the contract is subject to Government inspection and evaluation at all times.
3. ***Termination for Convenience.*** The Government may terminate the contract at any time for convenience if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.
4. ***Disputes.*** Any dispute concerning the contract that cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
5. ***Equal Opportunity.*** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
6. ***Affirmative Action for Veterans.*** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran or veteran of the Vietnam era.
7. ***Affirmative Action for Handicapped.*** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
8. ***Gratuities.*** The Government may terminate the contract if any gratuities have been offered to any representative of the Government to secure the contract.
9. ***American-made Equipment and Products.*** When purchasing equipment or products under an SBIR contract award, the contractor shall purchase only American-made items whenever possible.

Clauses That Apply to Contracts Exceeding $100,000

In addition to the foregoing clauses, the following clauses apply to contracts expected to exceed $100,000.

10. ***Examination of Records.*** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.

11. ***Default.*** The Government may terminate the contract for default if the contractor fails to perform the work described in the contract and such failure is not the result of excusable delays.

12. ***Contract Work Hours.*** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).

13. ***Covenant Against Contingent Fees.*** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.

14. ***Patent Infringement.*** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

F. ADDITIONAL INFORMATION

1. This Solicitation is intended for informational purposes and reflects current planning. If there is any inconsistency between the information contained herein and the terms of any resulting SBIR contract, the terms of the contract are controlling.

2. Prior to award of an SBIR contract, the Government may request the offeror to submit certain organizational, management, personnel and financial information to assure responsibility of the offeror to receive an award.

3. The Government is not responsible for any expenditures of the offeror in advance and in anticipation of an award. In a cost reimbursement contract, reimbursement of costs by the Government may be made only on the basis of costs incurred by the contractor after award and during performance.

4. This Solicitation is not an offer by the Government and does not obligate the Government to make any specific number of awards. Awards under this program are contingent upon the scientific/technical merit of proposals and the availability of funds.

5. The SBIR contract program is not intended as a mechanism to invite unsolicited proposals. Unsolicited SBIR contract proposals shall not be accepted under the SBIR program in either Phase I or Phase II.

6. If an award is made pursuant to a proposal submitted in response to this SBIR Solicitation, the contractor will be required to certify that he or she has not previously been, nor is currently being, paid for essentially equivalent work by any agency of the Federal Government.

7. Prior to award of a contract, the contractor will be required to provide a Data Universal Numbering System (DUNS) number. A DUNS number may be obtained immediately, at no charge, by calling Dun and Bradstreet on (800) 333-0505.

IX. INSTRUCTIONS FOR PROPOSAL SUBMISSION

A. RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this Solicitation is:
5:00 p.m., Eastern Standard Time
Friday, November 5, 2004

Any proposal received at the offices designated below after the exact time specified for receipt will not be considered unless it is received before award is made and:

1. It was sent by registered or certified mail not later than the fifth calendar day prior to the date specified for receipt of proposals;

2. It was sent by mail or hand-delivered and it is determined by the Government that the late receipt was due primarily to mishandling by the Government after receipt at the Government installation;

3. It was transmitted through an electronic commerce method authorized by the Solicitation and was received at the initial point of entry to the Government infrastructure not

later than 5:00 p.m. one working day prior to the date specified for receipt of proposals;

4. It is the only proposal received, or;

5. It is received in the office designated for receipt of proposals on the first workday on which normal Government processes are resumed following an emergency or anticipated event that interrupts normal Government processes so that proposals cannot be received by the exact time specified in the Solicitation.

Despite the specified receipt date above, a proposal received after that date may be considered if it offers significant costs or technical advantages to the Government and it was received before proposals were distributed for evaluation, or within 5 calendar days after the exact time specified for receipt, whichever is earlier.

B. NUMBER OF COPIES

For Phase I, submit the original and 5 copies of each proposal. The Principal Investigator and a corporate official authorized to bind the offeror must sign the original. The 5 copies of the proposal may be photocopies of the original.

For Phase II, see instructions under paragraph VI.

C. BINDING AND PACKAGING OF PROPOSAL

Send all copies of a proposal in the same package. Do not use special bindings or covers. Staple the pages in the upper left corner of each proposal.

X. CONTRACTING OFFICERS AND ADDRESSES FOR MAILING OR DELIVERY OF PROPOSALS

Any small business concern that intends to submit an SBIR contract proposal under this Solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, and topic number(s). If a topic is modified or canceled before this Solicitation closes, only those companies that have expressed such intent will be notified.

A. NATIONAL INSTITUTES OF HEALTH (NIH)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Ms. Roberta Wilhelm
Phone: (301) 443-1191
Fax: (301) 443-3891
Email: rwilhelm@niaaa.nih.gov

Proposals to the NIAAA must be mailed or delivered to:

Ms. Roberta Wilhelm
Contracting Officer
Contracts Management Branch
National Institute on Alcohol Abuse and Alcoholism
5635 Fishers Lane, Room 3016
Bethesda, MD 20892-9304 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIAAA.*

National Cancer Institute (NCI)

Mr. Joseph Bowe
Phone: (301) 435-3810
Fax: (301) 480-0309
Email: jb166i@nih.gov

Proposals to the NCI, if mailed through the U.S. Postal Service, must be addressed as follows:

Mr. Joseph Bowe
Contracting Officer
Research Contracts Branch,
National Cancer Institute
6120 Executive Blvd., EPS Room 6038
Bethesda, MD 20892-7222 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NCI*.

National Institute on Drug Abuse (NIDA)

Ms. Nancy A. Hurd
Phone: (301) 443-6677
Fax: (301) 443-7595
Email: nhurd@nida.nih.gov

Proposals to the NIDA must be mailed or delivered to:

Ms. Nancy A. Hurd
Contracting Officer, Contracts Management Branch
National Institute on Drug Abuse
6101 Executive Boulevard
Room 260, MSC 8402
Bethesda, Maryland 20892-8402 *

**Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIDA*.

National Institute of Mental Health (NIMH)

Mr. David Eskenazi
Phone: (301) 443-2696
Fax: (301) 443-0501
Email: de5d@nih.gov

Proposals mailed to the NIMH must be addressed to:

Mr. David Eskenazi
Contracting Officer
Chief, Contracts Management Branch
National Institute of Mental Health
6001 Executive Boulevard
Room 8154, MSC 9661
Bethesda, Maryland 20892-9661*

*_Change the city to Rockville and the zip code to 20852 if hand-delivered or delivered by an overnight service to the NIMH_.

National Heart, Lung, and Blood Institute (NHLBI)

Mr. Robert Best
Phone: (301) 435-0330
Fax: (301) 480-3338
E-mail: bestr@nhlbi.nih.gov

Proposals to the NHLBI, if mailed through the U.S. Postal Service, must be addressed as follows:

Review Branch
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
6701 Rockledge Drive
Room 7091
Bethesda, MD 20892-7924*

*Change the zip code to 20817 if hand-delivered or delivered by an express or other courier service to the NHLBI.

B. CENTERS FOR DISEASE CONTROL AND PREVENTION

Mr. Curt Bryant
Phone: (770) 488-2806
Fax: (770) 488-2828
Email: ckb9@cdc.gov

Proposals to the NCHSTP, NCEH, NIP, NCID, and NCBDDD must be mailed or delivered to:

Mr. Curt Bryant
CDC Small Business Program Manager
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

XI. SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit http://nnlm.gov/ or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service
1-800-553-6847
http://www.ntis.gov

National Technology Transfer Center
Wheeling Jesuit College
1-800-678-6882
http://www.nttc.edu/

Regional Technology Transfer Centers
1-800-472-6785
http://www.ctc.org/NewFiles/RTTCs.html

XII. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

The NIAAA supports research on the causes, prevention, control, and treatment of the major health problems of alcohol abuse, alcoholism, and alcohol-related problems. Through its extramural research programs, the NIAAA funds a wide range of basic and applied research to develop new and/or improved technologies and approaches for increasing the effectiveness of diagnosis, treatment, and prevention. The NIAAA also is concerned with strengthening research dissemination, scientific communications, public education, and data collection activities in the areas of its research programs.

This solicitation invites proposals in the following area:

017 Development of Methodology for Measuring Compliance for Medications

(Fast-Track proposals will be accepted)

Currently, NIAAA is funding over 25 human pharmacotherapy studies. It appears that the efficacy of medications is dependent, in part, on patient compliance. Measurement of patient compliance in pharmacotherapy trials and medical practice, however, is difficult. Current methods employed include pill counts, electronic pillboxes, riboflavin, and plasma levels of the medication. The purpose of this contract is to develop innovative methods for measuring patient compliance in administering medications. Women and minorities should be included in the study.

Phase I should entail development and early, pre-clinical testing of the technique for measuring compliance. Phase II would involve larger-scale evaluations to determine the validity of the technique. This would involve measuring compliance using a double-blind, placebo-controlled pharmacologic trial.

026 Science Education Materials Development for Kindergarten through 12th Grade

(Fast-Track proposals will be accepted)

Approximately one million youth, ages 12-17, are consuming alcohol. Experimentation with alcohol is beginning at ever-younger ages. Moreover, research suggests that the earlier the onset of drinking, the more likely it is that an individual will develop drinking-related problems in adulthood. Nearly 14 million American adults develop problems from drinking. Specific problems include health deterioration (including death) from damage to the brain, liver, gastrointestinal tract, and/or heart; injuries such as automobile crashes and household/workplace accidents; domestic and other forms of violence; neglect of work and family, and costs to society associated with police, courts, jails, and unemployment. Problems of adolescent drinking include poor school performance, absenteeism and dropping out; use/abuse of other drugs; psychological and social maladjustment; and criminal involvement.

Nevertheless, alcohol use is part of the American culture, and most adults who drink do so with a minimum of risk. Thus, despite what young people are taught in health education or physical education about the potential for alcohol use to cause them problems, many take drinking for granted--regarding it as a common “rite of passage” to adulthood, especially for boys.

Few curricular materials about substance abuse generally, and alcohol abuse specifically, are science-based. Rather, they focus on substance abuse awareness and on social influence--the importance of personal self-esteem, and on building refusal skills. This health education approach is indeed valuable, but it is not enough. For example, being told in a health education class that alcohol use by underage drinkers can cause cognitive damage is very different from learning the *science*, or the *why* behind this finding. Moreover, “telling” is not always “teaching”. The critical thinking skills involved in the methodology of doing science are learned in science education, not in health education. Critical thinking is an invaluable asset in personal decision-making.

The purpose of the NIAAA science education program is to support the infusion of research findings into supplementary, interdisciplinary, curriculum materials and educational technology-based activities that help make the represented disciplines (science, math, social studies, English composition, and/or more) relevant to an issue in the student’s life. Specifically, the NIAAA science education program is designed to support middle-school and high school teachers help students to enjoy the process of discovery in accordance with the National Science Education Standards (NSES-1996), and to appreciate how medical science generally, and alcohol science specifically, addresses public health issues.

The overall objective is to reinforce and complement the social influence model of substance abuse prevention with scientific knowledge to support student decision-making processes and skills. Because fact-based information on alcohol and how it affects the human body (and other living organisms) is available and objective, it should be readily teachable and able to be integrated into existing school curricula.

The supplementary curriculum materials developed must be both scientifically valid and age- or grade-appropriate. Project design must also address performance objectives in relation to the chosen grade level(s) and subject(s)/discipline(s). Specifically, applicants must link proposed content to NSES standards (and Project 2061: Benchmarks

for Science Literacy, preferably) in physiology, biochemistry, genetics, general science (i.e. the scientific method and science skills) or other areas that can be supplemented by alcohol-related science instruction.

The materials developed should include both background information and instructional guidance for teachers, recognizing that many teachers, especially at the middle-school level, may lack sufficient education in science, mathematics, or technology themselves, and may be uncomfortable and unprepared to teach science concepts, statistical methods, and related disciplines. At the same time, applicants must make every effort to ensure that the potential exists (or is embedded within the design itself) for interdisciplinary approaches to be developed. In today's classroom, teachers' time is increasingly prescribed by state, local and national objectives. Thus, it becomes imperative to make connections with other subject areas and to address these instructional objectives and standardized test questions in the project design. The materials should be "teacher-friendly" while promoting active, teacher-guided, student-conducted scientific inquiry.

Discovery-based activities focused upon case studies to guide classroom discussion; active engagement in laboratory work; use of the 5E's Instructional Model; cooperative learning activities in small groups with access to resource materials and with group presentation of findings/information are all encouraged. Resulting materials should utilize/reflect current educational technologies, while ensuring that a core curriculum and associated materials are print-based for the benefit of under-resourced schools. Similarly, hands-on laboratory activities should require only commonly available supplies. Streaming video, computer simulations, and other venues for conveying more complex laboratory activities may be included--if transferable to other media for under-resourced schools, e.g. videotape in lieu of streaming video. Project design should address the selection of instructional technologies/media.

Evaluation components -- whether embedded or separate -- to assess student learning, age-appropriate relevance, and teacher satisfactions or instructional difficulties (such as which activities work well and which do not) shall be included. As part of this, the evaluation design should insure that controlled testing is both fair and accurate (i.e. control group classrooms must have at least adequate supplies, materials or references).

Evidence of plans to ensure focus group(s), a scientific advisory board, and/or field testing, as appropriate, should be included in the project design. Consultation from science teachers and related educators must be included.

027 Development and Clinical Testing of Biochemical Markers

(Fast-Track proposals will be accepted)

The development of effective biochemical markers represents a powerful means for early diagnosis and treatment of alcohol dependent/abuse patients and for the identification of individuals who have a predisposition for alcoholism. There are two different types of biochemical markers: trait markers and state markers.

Trait biomarkers have the ability to detect inborn characteristics of individuals who are vulnerable for alcoholism. This type of marker would be invaluable for screening of high-risk individuals (e.g., children of alcoholics) and targeting them with preventive or early treatment interventions. In addition, trait markers might assist practitioners in identifying subpopulations of alcoholics who may need different treatment strategies. An ideal trait marker should have several features. First, it should display validity in detecting people susceptible to alcoholism, particularly before the onset of alcoholism or during periods of stable abstinence. Second, it should be easily and reliably measured. Third, it should be specific for alcoholism only and not affected by other medical or psychiatric disorders or drugs. Since alcoholism is a complex disease, it is likely that more than one type of gene and protein exist as trait marker.

State markers or markers of alcohol consumption serve several important purposes. First, they can assist physicians in diagnosing individuals with chronic drinking problems, particularly patients who deny excessive drinking. Moreover, they may also identify individuals in early stages of heavy drinking, thus avoiding the long-term medical, psychological, and social consequences of chronic alcoholism. Second, state biomarkers can aid in the diagnosis and treatment of other diseases (liver diseases, pancreatitis, and cardiovascular diseases) that were, at least, caused by excessive drinking. Third, they are useful in alcohol treatment and prevention programs. Since the goal of many of programs is abstinence, monitoring relapse is important in gauging success. Last, state biomarkers are important in clinical alcohol trials. Although self-

reports have become more sophisticated and valid (e.g., Timeline Followback), they still rely on accurate reporting. These new and reliable biomarkers could then be used to confirm the self-report. Several biomarkers with certain limitations are currently in use including carbohydrate-deficient transferrin (CDT), gamma glutamy transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and mean corpuscular volume (MCV). New state markers need to be developed that incorporate the following attributes: validity, reliability, stability, cost, practicability, acceptability, and transportability.

Areas that may be of interest to small businesses include, but are not limited to:

1. Develop and evaluate clinically alcohol-sensitive biomarkers to identify individuals who are predisposed to alcoholism; determine relapse; measure levels of drinking; and determine alcohol-induced tissue damage.
2. Identify genes, and proteins that are expressed during the development of alcohol dependence for biomarker development.
3. Develop methodologies for high throughput identification of alcohol metabolites and other signaling molecules that are expressed during alcohol intake.
4. Use knowledge of genetic and molecular mechanisms underlying alcohol-induced organ damage (including alcohol-related liver, pancreas, heart disease and FAS) to develop new biomarkers of tissue and cell damage.
5. Evaluate clinically innovative alcohol-sensitive biomarkers (trait, relapse, organ damage) for sensitivity and specificity.

NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, treatment, rehabilitation from cancer, and the continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread applications, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management.

Total costs for the following NCI contract topics are capped at a maximum of $100,000 for Phase I and $750,000 total costs for Phase II.

This Solicitation invites proposals in the following areas:

195 Virtual Microscopy for the Early Detection of Cancer

(Fast-Track proposals will be accepted)

The purpose of this proposal is to facilitate the development and application of novel digital microscopic imaging modalities that are applicable to early detection and screening. Virtual microscopy provides high-resolution images in three dimensions and facilitates the visualization of tissue biopsy specimens that can be manipulated by the computer and specific tissues can be selected and displayed. Using this technique in combination with differential staining characteristics, it is possible to visualize only the specific anatomical details of interest without having to look at the complex tissue structures.

As a new form of microscopy, virtual microscopic imaging requires the development of new methods of tissue processing and visualization. Potentially this technology can be applied to clinical scenario for the detection of biomarkers and the determination of their spatial localization in the biological samples for the accurate differentiation of pre-neoplastic lesions from malignant tumors thereby facilitating early detection of cancer.

The specific goals are:

a) Development of novel methods in digital virtual imaging at the microscopic level using conventional methods of tissue processing,

b) Application of digital microscopy for biomarker identification, micro-anatomical analysis, and for the molecular classification of early lesions,

c) Development of novel methods of tissue processing for virtual examination.

Virtual microscopy is a novel means of detecting biological abnormalities, which still needs to be refined and improved. Its potential applications in research and clinic have to be explored. Virtual microscopy will offer new advantages in the visualization of biological tissues, enabling accurate

determination of pre-malignant and malignant tumors. Currently, there are very few grants funded by NIH on virtual microscopy, addressing the above-mentioned objectives. Encouraging, research in this area will be very promising and a timely approach for the early detection of cancer.

Phase I Activities and Expected Deliverables: Phase I will involve novel inventions related to improvements in the tissue processing and microscopic techniques to facilitate virtual microscopy, which can be subsequently tested in a larger research environment for its robustness and clinical applications.

Phase II Activities and Deliverables: Phase II will involve validation of novel techniques in a larger research or clinical setting for the robustness and sensitivity of virtual microscopy that can potentially lead to more versatile and promising commercial implications.

196 Antibody Array for Cancer Detection

(Fast-Track proposals will not be accepted)

Detection of cancers in a late stage significantly and adversely affects survival of cancer patients. The major obstacles in improving earlier detection are the inaccessibility of the sites of tumor origin and the multiplicity of sites from which tumors may arise. To overcome these obstacles and to improve diagnosis of subjects who might harbor clinically inapparent tumors, researchers are applying a variety of strategies, including application of new imaging technologies (e.g., helical CT), identification and monitoring of high-risk cohorts, and the development of new biomarkers based on differences in gene and protein expression of preneoplastic, neoplastic, and normal cells from the same origin. Molecules that are uniquely or differentially expressed in neoplastic or prenoplastic cells, which may be also secreted into accessible body fluids, such as blood, urine, nipple aspirate, or sputum may be useful as markers for risk assessment and early detection of cancer. Furthermore, the identification of biomarkers in body fluids is minimally invasive and may further enhance the current imaging, pathology and cytology diagnostic methods.

The purpose of this initiative is to develop an antibody array in collaboration with the NCI Early Detection Research Network (EDRN). It is anticipated that the collaboration will provide sets of antigens by the EDRN investigators and permit the development, production and dissemination of antibody microarray technologies for the research community engaged in research focused on early detection and risk assessment of cancer. The specific objectives are, but are not limited to:

a) Prepare and purify biomarkers as recombinant tagged proteins.

b) Prepare and purify biomarker-specific antibodies in the form of single chain fragment of variable region (scFv) antibodies and or monoclonal antibodies (mAb).

c) Validate the specificity of the antibodies.

d) Optimize antibody microarrays using different matrices.

e) Develop and/or improve methodologies for quantitative measurements of the bound antigens.

f) Perform initial validation studies in collaboration with EDRN using the antibody microarrays.

Currently there is no single marker or a combination of a limited number of biomarkers that has a sufficient sensitivity and specificity to diagnose asymptomatic cancer or early stage cancer. However, recent developments in gene and proteomic profiling of precancerous and cancerous lesions suggest that patterns of markers may be used to distinguish cancer and non-cancer with high sensitivity and specificity (95-100%). Antibody microarrays will provide a fast, reliable, high-throughput, sensitive, and quantitative detection tool of multiple differentially expressed antigens (annotated proteins and post-translational modified proteins) from a limited amount of sample (e.g. 20ul of serum) obtained through a minimally invasive method. Furthermore, this methodology is likely to become the next step in conversion of MS proteomic patterns to well defined diagnostic targets. Involvement of biotech, via SBIR mechanism, with high-throughput technologies will further strengthen the EDRN efforts in early detection and in dissemination of these technologies to improve early detection.

Phase I Activities and Expected Deliverable: Production of antibody against antigens provided by EDRN.

Phase II Activities: Fabrication and Validation of Antibody Arrays.

197 Early Detection Research Network Bioinformatics Research Program (EDRN-BRP)

(Fast-Track proposals will be accepted)

The purpose of this initiative is to support the development of software for analysis and evaluation of cellular signatures for earlier cancer detection in prevention research. The work will be performed in collaboration with the NCI Early Detection Research Network (EDRN) (http://www.cancer.gov/edrn). The objectives are:

a) Develop analytical methods for proteomic and genomic data analysis

- pre-analytical data processing algorithms for time-of-flight (TO) Mass Spectrometer (MS) data and genomic expression data
- protein biomarker identification via innovative data mining and pattern recognition methods such as the classification tree, boosting, support vector machines, artificial neural networks, cluster analysis, etc.

b) Development of algorithms to improve diagnostics by applying:

- algorithms for longitudinal or cross-sectional data in order to classify patients according to the relevant disease states using surface-enhanced laser diffraction/ Matrics-Assisted (SELDI/MALDI) profiling data; gene expression analysis;
- algorithms to patient data for early detection of cancer;
- validating the clinical utility of algorithms to differentiate cancer types;
- validation of the algorithms through the analysis of simulated data and comparison with well established results.

c) Development of bio-computational approaches to automated calibration, normalization and synchronization of SELDI/MALDI instruments.

- Development of methods to assess and quantify the reproducibility of high-throughput proteomic and genomic technologies.

The data for both the development and validation of algorithms will come from the various laboratories of the Early Detection Research Network. The EDRN is comprised of 18 biomarker development laboratories (BDLs), nine clinical and epidemiology centers (CECs), three biomarker validation laboratories (BVLs), and a central data management and coordinating center (DMCC). The successful awardees will become Associate Members of EDRN and serve on its committees and subcommittees. The awardees will closely work with the DMCC and follow the policies and procedures of the EDRN.

The proposed initiative fulfills the needs of and provides a unique opportunity for the awardees to collaborate with investigators of the Early Detection Research Network, a NCI flagship program. This type of mechanism is particularly suited to an area such as informatics which can assist in analyzing some important research questions in new emerging proteomics and genomics data arising from study on precancerous and cancerous lesions. Data mining and bioinformatics tools developed through the initiative have the potential for commercialization, a major objective of the SBIR mechanism.

Phase I Activity and Expected Deliverables: Development of data mining, algorithms and analytical tools.

Phase II Activity and Expected Deliverables: Cross-comparison and Validation of data mining, algorithms and analytical tools.

198 Chemical Optimization and Structure-Activity Relationships

(Fast-Track proposals will be accepted)

The goal of this initiative is clinical development candidate identification through synthesis, analog development and structure-activity relationship studies of screening leads.

High throughput screening campaigns of more than 140,000 samples from the NCI repository addressing a number of molecular targets of potential therapeutic significance in cancer, HIV and opportunistic infections routinely identify lead compounds with potent and selective activity. While preliminary structure-activity studies can sometimes be performed with available analogs in the repository, much additional work is needed to optimize the screening leads for potency and pharmaceutical properties (bioavailability, pharmacokinetics, metabolism, formulation) consistent with clinical development.

The Screening Technology Branch of the Developmental Therapeutics Program has attempted to develop and will continue to pursue CRADA partnerships for this need, but efforts to date indicate that the companies most capable of and disposed toward conducting this type of research are small, frequently startup, entities with minimal to no resources to commit to such a project, despite their intrinsic interest and expertise. A current example is the arylstibonic acid class of HIV nucleopcapsid-p7 protein-nucleic acid antagonists. Two companies expressed a strong interest in working with STB to conduct these medicinal chemistry studies, but had no available funds to invest in the project.

The SBIR mechanism would provide the initial seed funds to move such a project from concept (screening lead) to something with considerably more commercial potential (preclinical development candidate).

Phase I Activity and Expected Deliverables: The lead compound will be synthesized, if necessary, to provide sufficient material for secondary testing and preliminary in vivo evaluation. At the same time, a series of analogs will be prepared, with the goal of defining the critical structural elements necessary for activity. The net result of Phase I research should be a confirmed lead compound with good potency and pharmaceutical properties.

Phase II Activity and Expected Deliverables: Additional synthetic work will be undertaken to refine the previously identified lead structure, with the goal of maximizing potency and other desirable attributes while minimizing toxicity and other undesirable attributes. Here, a larger series of more closely related analogs would likely be prepared and evaluated in primary and, as appropriate, secondary screens. Sufficient quantities of the lead compound(s) will be necessary for detailed pharmacological evaluation. The net result of Phase II research should be identification of a clinical development candidate.

Some areas likely to be covered in successful proposals include:

a) Analog synthesis/medicinal chemistry

b) Structure-activity relationships

c) ADME (absorption, distribution, metabolism) and formulation

d) Efficient synthesis of selected lead compound(s)

e) Scale up synthesis of clinical development candidate

203 Development of a Database and Candidate Gene, Protein, and Biochemical Pathway Nomination Software for Tobacco-Related Disease and Tobacco Addiction Investigations

(Fast-Track proposals will not be accepted)

The purpose of this initiative is to develop a database and associated software that will permit users to identify candidate genes, proteins, and biochemical pathways that may be associated with tobacco-related diseases or tobacco addiction for further epidemiological investigation.

There is a substantial and growing body of evidence in the scientific literature concerning the increased risk of disease attributable to tobacco use, including studies of tobacco-related cancers, metabolic, cardiovascular, and addictive diseases (“tobacco related diseases”). The increasing number of studies that include tobacco-related variables, e.g., tobacco metabolites, pack-year history, and measures of nicotine dependence, along with the number and complexity of the epidemiologic, pharmacologic, behavioral, genomic, and biochemical findings, makes it increasingly challenging for interested investigators to evaluate the entire body of tobacco-related disease literature for promising leads. This SBIR proposal seeks an offeror to develop a database and associated tools to aggregate information across tobacco-related disease studies. The resulting database and tools would be used to identify and nominate human genes, proteins, or biochemical pathways for further investigations in molecular epidemiology, behavioral science, or other areas of research.

The offeror will assemble an expert review group to compile a list of keywords commonly associated with tobacco-related diseases or addiction studies in the scientific literature (“tobacco-related keywords”) as well as terms associated with biochemical, pharmacologic, and genomic investigations (“biological terms”). Tobacco-related keywords should be those derived from the National Cancer Institute’s Enterprise Vocabulary Services (NCI EVS) and biological terms should be those available at NCBI (http://www.ncbi.nlm.nih.gov/About/tools/restable_data.html). The offeror will develop or adapt software with text-searching capability and will use this software to search public datasets (PubMed, U.S. Surgeon General reports, NCI and other NIH institute monographs and reports) in order

to identify the subset of studies focused on the biochemical, pharmacologic, and genomic aspects of tobacco-related diseases or tobacco addiction, that also contain specific biochemical pathway, pharmacologic, or genomic terms. The subset of identified abstracts/texts and associated tobacco-related keywords, biological terms and analytical results will be imported into a database. The offeror should attempt to utilize data models that can be semantically related to publicly available data models capable of storing tobacco-related keywords and biological objects, such as caCore (http://ncicb.nci.nih.gov/core). These tobacco-related keywords will identify all relevant studies that contain either the specific keyword or other synonymous terms.

The offeror will reassemble the expert review group to define a threshold sample size and establish statistical significance criteria. These criteria will be applied to identify a subset of relevant studies from those identified from the public literature, and the analytical results of the biochemical, pharmacologic, or genomic association will be imported into the database. The offeror will develop or adapt software to permit users to query the database and to refine the scope of the search using tobacco-related keywords, biological terms, or data attributes related to the analytical results. The data model should be available for the adept user to review for the development of more sophisticated queries using structured query language (SQL).

The offeror will develop or adapt software with the capability to export, in defined formats, results of queries for review and subsequent analysis. The software will provide complex visualization of query results beyond flat text files of defined formats.

The need to analyze the growing number of clinical, population-based, and laboratory-based tobacco-related disease datasets with associated biochemical, pharmacologic and genomic information poses substantial integration and analysis challenges. Software that is capable of identifying specific tobacco-related key words in the public literature, importing identified text and associated biological terms into a database, and providing user query features for export, visualization, and nomination of candidate biological objects for future investigation requires professional programming expertise. Such software would readily find a large market in the basic, clinical, epidemiologic, and pharmaceutical research fields.

Phase I Activities and Expected Deliverables: 1) Expert curation performed to identify tobacco related disease terms from the NCI EVS. 2) Development of a first draft data ontology of tobacco-related disease terms and of a meta-ontology capable of aggregating tobacco related disease and existing gene, protein and biochemical pathway data ontologies. 3) Identification of a single epidemiological study (case:control or family based) for a tobacco-related disease or for tobacco addiction where the peer-reviewed literature or other sources contain clinical data (e.g., lung cancer or nicotine dependence diagnosis), anthropometric/environmental/lifestyle/behavioral data (e.g., sex, age, BMI, smoking history, alcohol consumption, depression index), and associated genomic findings (e.g., linkage or association results). The offeror will identify, search and import literature describing this data into a prototype version of the database and demonstrate query capabilities using this single study for the dataset of associated candidate genes, proteins or biochemical pathways.

Phase II Activities and Expected Deliverables: 1) Searching of literature and genomic databases. 2) Data basing of aggregated literature and genomic information. 3) Expert curation performed to abstract analytical results. 4) Import of analytical results into the database. 5) Development of query, export and visualization features. 6) Testing, debugging and optimization of database ontology relationships, aggregated and curated data, query, export and visualization features of the software.

204 Plant Genomic Models for Establishing Physiological Relevance of Bioactive Components as Cancer Protectants

(Fast-Track proposals will not be accepted)

Although considerable evidence points to enhanced consumption of whole grains, fruits and vegetables as deterrents to cancer, there are numerous conflicting results. Part of the discrepancies about the health benefits of foods may arise from variation in the content and/or bioavailability of specific bioactive components. While the scientific community lumps foods by classes, there is recognized variation within individual species and varieties of grains, fruits and vegetables. Recent advances in plant genomics provide an exceptional opportunity to evaluate the physiological significance of bioactive components and the food matrix for their overall influence on cancer prevention and tumor behavior. Using these technologies, products of

individual genes can be eliminated or enhanced. For example, the content and availability of specific carbohydrates, flavonoids, carotenoids, polyphenols, etc., can be increased or decreased by genomic manipulation. This would allow content, speciation, and molecular targets involved in cancer processes to be examined.

The purpose of this initiative is to develop and market new plant genomic and genetic resources for evaluating food bioactive components and for evaluating the food matrix in cancer prevention. It is anticipated that these resource foods will simultaneously facilitate collaborative research among plant biologists, cancer biologists, and nutrition scientists to evaluate specific foods for their health benefits.

Objectives are:

- Develop plant mutants, transgenics, or other genetically modified food plants with deficient or elevated levels of potential bioactive compounds involved with cancer prevention. Examples might include deletion and over expression mutants for altered starch or antioxidants.
- Evaluate specific bioactive food components or the food matrix as modifiers of cancer risk and tumor prevention.
- Evaluate the food matrix as a modifier of the overall effectiveness of individual bioactive food components.

The proposed initiative will provide new resources to define the physiological role of bioactive components within foods as opposed to isolated components for cancer prevention. The resources will help clarify Inconsistencies among basic, clinical and epidemiological findings about the relationship between diet and cancer. Currently, there is a dearth of NIH awards exploiting plant genomics to test the scientific basis of bioactive compounds in foods as cancer protectants. Consumers are confused about whether food or dietary supplements are the best source of bioactive compounds for health promotion including cancer prevention. The proposed SBIR will assist in providing fundamental information for evaluating the health benefits attributed to specific foods and their components.

Phase I Activities and Expected Deliverables:
Phase I will involve development and screening of new plant genetic resources (transgenics, mutants, etc.) with modified levels of bioactive compounds. Development of food resources with both low (deficient) and high (overexpression) levels of bioactive compounds is desired to test model hypotheses and for comparative assessments.

Phase II Activities and Expected Deliverables:
Scale-up of plant development and validation of the modified food resources as cancer protectants in either preclinical or clinical studies. It is anticipated that these studies will focus on the ability of these modified foods to modulate genetic pathways involved with cancer processes such as DNA repair, cell proliferation, apoptosis, cell differentiation, carcinogen metabolism, inflammatory response and/or hormone regulation.

205 Metabolomics for Early Cancer Detection

(Fast-Track proposals will be accepted)

Metabolomics is the study of small molecules, or metabolites present in cells, tissues, and bodily fluids. Representative small molecules include compounds like glucose, cholesterol, ATP, and lipid signaling molecules. The identities, concentrations, and fluxes of these molecules are the final products of interactions between gene expression, protein expression, and the cellular environment. When compared to DNA, RNA, and proteins, the limited numbers of small molecules make them suitable for analysis by high throughput methods.

Metabolomics researchers concentrate on biofluids, including blood, urine, and spinal fluid, and attempt to identify and quantify all the small molecules within a sample to find new markers for disease or drug toxicity, or indicators of nutritional status. Currently a number of researchers are using high throughput metabolomic technologies to identify early signatures of diseases, especially central nervous system disorders. However, while a number of cancers have been shown to alter metabolites levels in bodily fluids, there is little research on application of this technology to early cancer detection or risk assessment.

The purpose of this solicitation is to stimulate research to determine whether metabolomics can be used to distinguish patients with cancer from healthy individuals, to develop and optimize metabolomics methods for use with bodily fluids from cancer patients, and to assess the potential usefulness of these technologies for early cancer detection and risk assessment.

Although the NCI provides significant support for research on cancer biomarker discovery and

validation using both genomic and proteomic approaches, there is currently no single genetic or protein biomarker or a combination of biomarkers that has sufficient sensitivity and specificity to reliably diagnose early stage cancers. Metabolomics offers an alternate method for cancer biomarker discovery but is currently receiving very limited support from the NCI; three grants listed in the CRISP database directly concern metabolomics and cancer detection.

Phase I Activities and Expected Deliverables: Phase I proposals should either determine whether metabolomics can be used to distinguish patients with cancer from healthy individuals using body fluids or improve existing metabolomics technologies for use in early cancer detection or risk assessment.

Phase II Activities and Expected Deliverables: Phase II proposals will involve validation of the sensitivity and specificity of metabolomics for early cancer detection or risk assessment as well as the in robustness of the technology that can potentially lead to commercial applications.

206 Methods for Innovative Pharmaceutical Manufacturing and Quality Assurance

(Fast-Track proposals will be accepted)

Effective use of science and engineering principles during the development of a drug can improve both the efficiency and reliability of the manufacturing process and the quality of the final product. The purpose of this initiative is to facilitate the development of innovative methods that improve and modernize the medical product manufacturing process for biologic drugs for cancer treatment. The focus of this research includes:

1) Development of innovative methods for more rapid and efficient production of biologics by designing, optimizing and monitoring the manufacturing process including new applications of in-line or on-line process analyzers providing multi-variate data to improve the efficiency of process controls and determination of production end-points.

2) Development of formulation design and stability testing strategies that collect information on multiple attributes with minimal sample preparation.

3) Development of methods and reagents to more efficiently assess factors related to the ultimate product quality, safety and efficacy of biologics.

These projects may include but are not limited to development of new or improved manufacturing methods for recombinant protein products, monoclonal antibodies or virus-based therapeutics (herpes simplex, adenovirus or vaccinia) including 1) application of new technologies for monitoring and improving process efficiency 2) development and standardization of new methods to predict and detect safety problems during manufacturing 3) development of tools for product testing including development of in vitro assays and new animal models 4) development and production of reference standards and reagents required for GMP manufacturing of a specific product type. The proposed projects must be conducted in compliance with FDA Guidelines for manufacturing biotherapeutics (http://www. FDA.gov). The long-term goal of this initiative is to provide the tools necessary for efficient and high-quality manufacturing of novel therapies in the emerging field of cancer biologics.

The FDA recently released a report identifying a gap between the rapid advances in the discovery of potential new therapies and actual medical product development (challenge and opportunity on the critical path to new medical products, FDA, DHHS, March 2004). This report has identified an urgent need for applied research to guide technology development in the production of safe and effective drugs. The potential of recent advances in basic and translational research cannot be fully realized without research targeting the process of creating safe and effective drugs. To address this issue, the FDA has launched a new initiative to encourage development and implementation of innovative approaches to pharmaceutical manufacturing and quality assurance (Guidance for Industry, PAT-A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance, www. FDA.gov).

Significant opportunities exist for improving the efficiency of pharmaceutical manufacturing and quality assurance through the innovative application of novel product and process development controls and modern analytical chemistry. The mission of the Biological Resources Branch of the NCI is to provide resources necessary for evaluation of new therapeutics in a Phase I clinical trial, including drug manufacture (http://web.ncifcrf.gov/research/brb). Consistent with this mission, the NCI seeks to fund projects that focus on the application of novel approaches to the medical product development pathway for cancer therapeutics.

Phase I Activities and Expected Deliverables:
Phase I will involve novel inventions related to improvements in manufacturing processes, in vitro or in vivo assay systems for evaluating the safety and efficacy of a product or class of products, or development of reference standards and reagents required for GMP production of a class of products.

Phase II Activities and Expected Deliverables:
Phase II activities will include validation of novel process improvements in manufacturing or production of reference standards, reagents and novel assays systems identified in Phase I. The deliverable for a Phase II project will be a process or product that applies new technology to medical product development.

207 Synthesis Modules for Radiopharmaceutical Production

(Fast-Track proposals will be accepted)

The purpose of this initiative is to increase the availability and diversity of radiopharmaceutical synthesis modules for research and production activity. There is an increasing and unmet need for synthesis modules that allow for diverse sequences of chemical reactions. This SBIR RFP will encourage small businesses to enter and continue research in development of synthesis modules for radiopharmaceutical production and establish a business producing synthesis modules.

New radioactive compounds (radiopharmaceuticals) are needed to push the frontiers of molecular medicine, both for diagnosis and therapy. In order for new, targeted radiopharmaceuticals to become widespread there must be standardized synthesis procedures that meet GMP requirements. In practice this is usually accomplished by means of synthesis modules that are placed in chemistry hoods with appropriate shielding for radioactivity. These automated, robotic systems ensure that radiopharmaceuticals are synthesized on site to meet QA and regulatory requirements. Synthesis modules make possible the production of the compounds routinely and efficiently, with low personnel radiation dose. Investing in synthesis module research currently for an uncertain market is a high risk activity for small businesses.

Phase I Activities and Expected Deliverables:

- Choice of synthetic method or pathway to pursue; literature search and market research
- Become familiar with FDA regulations governing synthesis modules and the adiopharmaceuticals they produce
- Choice of partner(s) to work with, medical advice and a source of radioactive materials
- Preliminary design for synthesis module based on bench-top methods
- A materials list for the production of synthesis module
- Deliverables: Literature search, design, materials list

Phase II Activities and Expected Deliverables:

- Produce one or more working synthesis modules
- Show production capability and reproducibility with 10 runs
- Analyze the resulting product
- Standard operating procedures for the use of synthesis module
- Demonstration of commercial potential

208 Targetry Systems for Production of Research Radionuclides

(Fast-Track proposals will be accepted)

The purpose of this initiative is to make available for research (in diagnosis or therapy) radionuclides (radioisotopes) that are either not currently available or not reliably available from any private or public source. Research and development of targetry and production and processing methods are needed to provide a supply of non-standard radionuclides to investigators at reasonable prices. National laboratories and academic centers have been the traditional sources of research radionuclides. However, it is now increasingly feasible for small businesses to enter and continue research in target production for radionuclides and establish a business producing the targets. This is especially true for cyclotron-produced isotopes, but by forming partnerships with a National Lab or other entity it is also possible for a small business to become involved in the production of reactor-produced isotopes. Examples of radionuclides for which there is a need include, but are not limited to, I-124, Br-76, Cu-64, Y-86, and At-211.

Radioactive elements that are not in commercial production are needed to expand the frontiers of molecular medicine, both for diagnosis and therapy.

Each radionuclide (radioisotope) has the chemical signature of its element which permits certain kinds of reactions not available with other elements, and allows the labeling of particular diagnostic or therapeutic drugs. Efficient production of the radionuclides, i.e. production that is not wasteful of expensive bombarding time or expensive enriched target material, requires careful engineering both of the stable target (starting material) and of the handling of the radioactive target after irradiation. Targetry is engineered for the particular circumstances of the irradiating system, both to conform to physical dimensional requirements and to the strength of the irradiating beam.

Phase I Activities and Expected Deliverables:

- Choice of radionuclides to pursue; literature search and survey of current needs
- Choice of partner(s) to work with
- Choice of bombarding system
- Research into starting materials appropriate for available beam energy, bombarding system, and specific activity to be produced
- Plan for investigating target systems and target processing, including a preliminary design
- Materials list for the production of research targets
- Literature search

Phase II Activities and Expected Deliverables:

- Produce one or more working target systems and show production with 10 runs
- Produce standard operating procedures for the targetry system
- Demonstration of commercial potential

209 Establishment of Benchmark Data Sets for Radiotherapy Quality Assurance

(Fast-Track proposals will be accepted)

The goal of this work is to improve the quality of radiotherapy treatments by providing datasets and methods for verification of treatment planning calculations that will be usable in the typical clinic. Short term, the goal is to collect and test a representative set of benchmark treatment planning data to verify that it can be obtained in a consistent and usable fashion and that it can improve the efficiency and consistency of treatment planning algorithms. Long term the goal is to expand this process to encompass large enough datasets to cover the large majority of commercially available treatment planning systems in the United States.

Currently most radiotherapy treatments are given in non-academic radiotherapy clinics and the quality of these treatments is greatly dependent upon the ability of the clinical physicist to model and plan the radiation treatments. This is even more the case with the new and growing use of intensity modulated radiation (IMRT) therapy treatments that are critically dependant on computer calculations and can no longer be verified by hand computations. In addition, many more departments, including smaller facilities, are being recruited into the clinical trials mechanisms of the NCI in order to expedite the safe and efficacious use of radiotherapy, which is used in over half of the patients treated for cancer.

Thus the NCI wishes to promote the development new methods that can be made available for establishing consistent and accurate planning and delivery of radiation treatments.

Proposals should describe the creation of benchmark datasets to provide the basis for algorithm validation in the computation of radiation therapy plans. The work should outline such datasets and methods for measuring a series of test cases for validation of photon beam dose calculation algorithms. This proposed work should reflect the concepts stated in Task Group Report -53 from the American Association of Physicists in Medicine for the generation of specific data sets for the validation of treatment planning systems. The proposals should also enumerate a plan that validates the widespread ability to implement these methods and the capability of these datasets and methods to improve the consistency and accuracy of clinical treatment plans.

Phase I Activities and Expected Deliverables: 1) Written requirements for the benchmark data sets that are compatible with commercially available treatment planning systems; 2) design of the phantoms required for the benchmark data sets; 3) written measurement methods and procedures, 4) implementation of these procedures and phantoms in 3 clinics of differing capabilities; 5) written assessment of the impact of these benchmark data sets on the accuracy and consistency of the treatment plans; 6) written estimate of the scope of data required to fully implement the benchmark approach to radiotherapy QA in clinics throughout the Country; 7) written strategy for gathering full datasets, including oversight by a national review

group such as the NCI funded effort at the Radiological Physics Center.

Phase II Activities and Expected Deliverables: 1) Implementation of the strategy (from Phase I items 6 and 7.) for gathering full datasets that will be adequate for widespread distribution to therapy centers throughout the Country; 2) implementation of data review, validation and collation (Phase I items 5 and 7) so that the data can be made available for down-loading from the web or distribution on CD-ROM to all clinics; 3) production for distribution of the benchmark datasets.

210 Using Social Marketing to Disseminate Evidence-based Energy Balance Intervention Approaches to Worksites

(Fast-Track proposals will be accepted)

The NCI seeks to use social marketing to promote widespread adoption of evidence-based energy balance promotion (i.e., obesity reduction) approaches within worksites. The short-term goals of this solicitation are: (1) to conduct innovative focus groups with employers and employees for the purpose of translating evidence-based approaches into prototype programs that minimize barriers and enhance benefits both for overweight employees and their employers; and (2) to use the research findings to develop and test an implementation plan for disseminating evidence-based approaches in worksites that employ a high proportion of overweight/obese individuals. The focus should be on employees who could benefit most from increased physical activity and reduced caloric consumption participate, and employers who can be motivated to offer them evidence-based energy balance programs in or through their worksites. The final product will be a tested “how to” kit which incorporates evidence- and consumer-based strategies along with procedures for implementation and use within worksites. The long-term goal of this solicitation is to support the effective dissemination of evidence-based energy balance intervention approaches in the workplace via an affordable “how to” kit that promotes energy balance and helps reduce overweight and obesity.

NCI, in its Plan and Budget Proposal for Fiscal Year 2005 and as part of the overall NIH comprehensive anti-obesity research strategy, has assigned top priority to optimizing energy balance to reduce the cancer burden. Substantial research already has been conducted on the prevention and treatment of obesity through behavioral and environmental approaches to modifying lifestyles, and evidence-based approaches have been identified (for example, see http://thecommunityguide.org). Dissemination of these promising evidence-based energy balance intervention approaches is critical, but effective dissemination has been hampered by a lack of systematic attention to the perceived benefits and barriers associated with these approaches among people who could benefit from them, and among intermediary organizations who are potential users of evidence-based programs.

As noted in the NIH strategic plan on obesity, social marketing can strengthen the dissemination of proven strategies through the identification of perceived benefits and barriers associated with each of the evidence-based approaches to energy balance among overweight/obese individuals and intermediary organizations that interact with them. This approach will help ensure that products and programs developed for intermediary organizations are evidence-based, easy to use, and address infrastructure barriers, and are easy to access and attractive to the intended audiences (e.g., employees).

This solicitation fits into the larger NCI Energy Balance Dissemination Initiative (EBDI), which aims to identify evidence-based approaches to energy balance promotion (via individual- and environmental-level interventions that promote physical activity and/or reduce caloric consumption), and define opportunities to disseminate these approaches to intermediary organizations in the various sectors which could benefit from adopting them.

The NCI requires the offeror to:

1. Identify a worksite population of overweight/obese individuals who would benefit from, and are open to energy balance-related behavior changes.
2. Identify employment sectors, as well as specific employers, that have access to the employee segments identified, and have one or more compelling reasons for wanting to adopt evidence-based energy balance promotion programs.
3. Convene focus groups with the employers and employees to identify the perceived benefits and barriers (including infrastructure and administrative barriers) associated with, or potentially associated with (e.g., through the

use of incentives), evidence-based energy balance intervention approaches.

4. Use the research findings to develop a process and network for disseminating evidence-based intervention approaches in identified worksite organizations in a manner that helps ensure employer and employee participation (including the reduction of infrastructure barriers). The offeror's plan must specify how they will profit from implementation of the plan (e.g., by selling the "how to" kit and consulting services to employers).
5. Implement the social marketing plan developed in Step 4 (above) with employers (and other necessary intermediary organizations, for example, non-profit physical activity and/or nutrition service providers), alone or in partnership with other organizations.
    - Work with the targeted employers to resolve barriers and infrastructure problems and motivate end users to change weight-related behaviors.
    - Additional research may be conducted with employers and/or employees, if necessary.
6. Develop and implement a process evaluation to monitor and track the social marketing activities used, adoption of evidence-based programs by employers, and infrastructure adaptations made.

Phase I Activities and Expected Deliverables:

- Steps 1 through 4 as stated above.
- NCI requires a written deliverable for each step above. The deliverable must be approved before the applicant can proceed to the next step.
- The deliverable for step 4 should take the form of a document that can be used in Phase II.

Phase II Activities, Expected Deliverables and Final Product:

- Steps 5-6 as described above.
- Final deliverables include the products used in implementing and assessing Step 5 (e.g., research documents, electronic databases, "sales" brochures, etc.), and at least one article describing the development and evaluation of the program that is suitable for publication in appropriate scientific journals and/or books.
- The final product should be a tested "how to" kit which incorporates the evidence- and consumer-based strategies along with procedures for implementation and use by employers.

211 Developing Item Response Theory Software for Outcomes and Behavioral Measurement

(Fast-Track proposals will be accepted)

The goals of this topic are to develop and/or adapt software that employs both traditional and modern measurement methods [i.e., item response theory (IRT) modeling] to respond to the needs of cancer outcomes, health surveillance, and behavioral researchers. Software should be user-friendly, flexible, and inclusive of a variety of IRT models for both dichotomous and polytomous response data, with sophisticated graphic capabilities, tests of model fit, and extensions of the software for multi-dimensional modeling, testing for differential item functioning, linking questionnaires, and computerized-adaptive testing.

There is a great need in cancer outcomes, health surveillance, and behavioral research to develop instruments that are valid, reliable, and sensitive with minimal response burden. This need for psychometrically sound and clinically meaningful measures calls for better analytical tools beyond the methods available from traditional measurement theory. Applications of item response theory (IRT) modeling have increased considerably because of its utility for instrument development and evaluation, scale scoring, assessment of measurement equivalence, instrument linking, and computerized-adaptive testing (CAT). However, the powerful tools of IRT modeling have not been fully embraced by the health outcomes, surveillance, or the behavioral research community mainly because of the lack of user-friendly software that can respond effectively to the measurement issues that are encountered in these fields. In addition, most of the documentations associated with the current software do not provide examples that are relevant to these fields nor do they teach how these methods can be used.

IRT models the relationship, in probabilistic terms, between a person's response to a survey question and his or her standing on the construct being measured by the scale. These measured constructs may include any latent (unobservable) variable, such as depression, fatigue, pain, or physical functioning, which requires multiple items on a questionnaire to estimate a person's level or standing on the construct. Based on collected data, IRT assigns to

each scale item a set of properties that allows instrument developers to identify the most informative items for a researcher's study population. Consequentially, IRT offers researchers the ability to tailor questionnaires for individuals or groups, yet to maintain the ability to compare or combine scores among individuals or groups (notwithstanding the fact that each individual is responding to his/her most efficient item set). As a result, we enhance scale reliability with minimal response burden, which ultimately will improve the use of patient-reported outcomes in cancer research.

IRT modeling was developed in educational assessment where it is the dominant method of major testing programs, like the SAT, LSAT, and GRE, for evaluating item adequacy, scoring tests, equating scores from one test administration to another, and using CAT. This historical development is reflected in both the software and supporting documents that are still available today. For example, we read in the literature of examinees taking tests to measure their math abilities. Both the software and literature needs to be translated into terms that are palatable to health outcomes, surveillance, and behavioral researchers where illustrations use appropriate examples for these two fields.

The leading IRT software programs were developed before Windows operating systems; and despite recent software updates that provide Windows-based interactions, the remnants of IRT's DOS orientation are still present. This requires even highly educated users to study in detail today's long and confusing supporting manuals to know what information to enter in the command files. The software should be user-friendly and platform-independent, allowing one to move files from PCs to Macs to Unix platforms and should be flexible to accommodate new IRT models. Further, the software should allow users to have access both to instant on-line help for both input and output functions and to sophisticated graphics capabilities for modeling characteristic curves, information curves, and model fit indices.

Also, the software should be adapted for the measurement issues that are often encountered in health outcomes, surveillance, and behavioral research and provide extensions of the IRT applications bundled in the same software package. Researchers often work with polytomous response data collected over single or repeated measurements, and with smaller sample sizes than educational research. The need for minimal response burden and the correlation among measured domains make multi-dimensional IRT modeling an attractive alternative. Researchers need multiple measures of model-fit and person-fit, including graphical approaches. Currently, independent software exists for testing differential item functioning, linking questionnaires, and running computerized-adaptive testing, but value would be added to have these applications available as modules that are fully integrated with the IRT software.

Phase I Activities and Expected Deliverables: The contractor should consult with both leading psychometricians who have experience in IRT modeling and health outcomes, health surveillance, and behavioral researchers who have a range of training in measurement to help shape the functionality and presentation of the software and literature to be developed in Phase II. Deliverables should include: (1) a complete program design and specification, (2) an outline of the manual and primer, and (3) a prototype of the software that responds to the minimal changes recommended in this proposal. Offerors may request a one year Phase I.

Phase II Activities and Expected Deliverables: Develop the full IRT software and supporting documents based on Phase I findings including beta-testing of the software on a variety of datasets among healthcare researchers with a variety of measurement backgrounds. Also, develop a curriculum, evaluation measures, and other educational materials designed to integrate this software into the healthcare community. Deliverables will include: (1) the software, (2) the manual, primer, and other educational materials, and (3) at least one article describing the development and evaluation of the program that is suitable for publication in appropriate scientific journals and/or books.

212 Integrating Patient-Reported Outcomes in Clinical Oncology Practice

(Fast-Track proposals will be accepted)

Numerous reports have identified the need to improve the management of symptoms and quality of-life-problems in cancer patients whether these problems are related to treatment or the course of disease. Addressing this issue, the short-term goal of this project requires the offeror to develop integrated, ongoing patient-reported outcome (PRO)

measurements to provide timely, efficient, individualized information for monitoring patient progress and improving decision making in routine oncology patient care. The long-term goal is to develop computerized PRO data measurement and information systems for use by clinicians and patients that include cancer-specific symptoms and quality-of-life domains using well-validated instruments or item banks and computer adaptive testing administration to gather patient-reported data for use in clinical practice.

Such systems are intended to facilitate collection of information from patients via alternative delivery platforms, such as telephones, computers, handheld devices, and the Internet at selected or patient-determined intervals (not only at the time of a patient visit). Health status reports for both patients and clinicians need to be screened for urgency and tailored to their preferences and knowledge in a standardized format that can be integrated with medical records data, evidence-based guidelines, and resources for responding to patient needs. Data collection that meets privacy and confidentiality concerns will be used not only for patient care, but also to develop norms for clinician use and for research.

The systematic use of PRO information to guide care is accepted by clinicians in theory but does not occur in routine oncology practice in the U.S. (Donaldson, M.S., “Taking Stock of Health-Related Quality of Life Measurement [HRQOL] in Oncology Practice in the United States,” in press, JNCI). Although much methodological instrument development has occurred, and feasibility studies collecting data in conjunction with the patient visit have shown improved patient-clinician communication, many challenges to widespread adoption still exist. These challenges include general clinician belief that instruments are not adapted for efficient use at the individual (rather than clinical trial) level. The use of HRQOL in routine practice requires acceptance by clinicians, patients, and administrators, timely communication among all who provide care, efficient data collection, analysis, and reporting and resources for responding to identified patient problems. For patients, it will require addressing the acceptability of PRO assessment in light of response burden and possible concerns about confidentiality. Importantly, patients will expect that data they provide will help to improve their care. The way forward, however, does not lie simply in adding PRO measurement to other clinician tasks such as the occasional, time-limited patient visit. Rather, effective implementation will require new information infrastructures and technologies to embed the timely, routine use of PRO information in the care process. In particular, a key objective is to uncouple outcomes measurement from the strictures of the patient visit—an opportunity provided by information technologies.

The rapid deployment and public acceptance of information technologies and networks offer an opportunity for developers to incorporate information about cancer patient functioning with clinical records. Such systems would provide as-needed reports to patients and treating clinicians to assist in informed decision-making to improve cancer care. Health status reports can be tailored to the preferences and knowledge of the patient and clinician and may include graphical display of health status over time as well as identifying the need for clinical attention. Clinicians may wish to respond by e-mail, phone, or other means, rather than by patient visit only. Such tracking may help patients become more involved with their own care as do dieters who keep food records.

The NIH RoadMap initiative on Re-engineering the Clinical Research Enterprise has recognized the value added of advances in information technology and measurement theory to collect PROs by creating a 5-year $25 million RFA (RM-04-011) for the Dynamic Assessment of Patient-Reported Chronic Diseases Outcomes (http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-04-011.html). This RoadMap project will revolutionize the way PRO data are administered and collected. However the survey items used to measure HRQOL will not be specific to cancer, but rather, will be selected to address a range of chronic diseases. Further, the focus of the RFA is to improve the monitoring of PROs for clinical research with only brief mention of improving care in the clinical practice setting. The clinical setting would be addressed only in late phases of the project or as an extension beyond the five-year term. There is need to act now to work with patients and oncologists to develop integrated information systems that focus on cancer care and implementation in practice settings so that products of the RoadMap initiative can be successfully incorporated into practice.

The ideal system should be adaptable to integrate with other data systems and be platform-independent (work across Windows, Mac, Unix, and other operating systems). PRO administration should be device independent, allowing patients to self-report via devices such as telephone, Internet, or handhelds. A flexible self-report system gives

patients the freedom to choose a device that meets their preferences, schedule, or limitations.

PRO data can be integrated with clinical information and reports tailored to user preferences. For oncologists, the report can profile patient functioning over time with clinically meaningful changes in health status highlighted for their attention. Such reports can include links to guidelines and treatment recommendations adapted for the individual patient, local practice, and available resources. Reports for patients can be in a format that is easily understandable for them to monitor their own progress and to indicate when they may need immediate care. De-identified PRO and clinical data could foster a better understanding of patterns of care and treatment effectiveness as well as to track changes in special populations and across tumor sites. Further, data could be used to update the data collection instruments to improve questionnaire properties and suggest research to narrow knowledge gaps.

Phase I Activities and Expected Deliverables: 1) Conduct interviews, focus groups, clinical site visits and meetings among patients, clinicians, health care personnel, and information technology and PRO experts; 2) Perform literature reviews to determine the scientific and technical feasibility of creating and implementing such systems in practice settings; 3) A report detailing the program design and specification including a plan to integrate the PRO information system into a network of clinical practices; 4) a prototype of the PRO data monitoring, collection, and reporting infrastructure; and 5) agreements from cancer clinical settings to participate in testing and evaluation.

Phase II Activities and Expected Deliverables: 1) Develop and integrate the information systems in clinical practices; 2) Create evaluation measures; 3) Evaluate and refine the program based on user feedback; 4) Create a manual, tutorial, and other educational materials designed to integrate this system in other clinical practices including cancer centers and community care settings—addressing both technical implementation and social/cultural change management; 5) Developed software to run the full system and track outcomes; and 6) at least one article describing the development and evaluation of the system that is suitable for publication in appropriate scientific journals.

213 Portable e-Technology Tools For Real-Time Energy Balance Research

(Fast-Track proposals will not be accepted)

The short-term goal of this project is to develop a prototype of an innovative portable intervention and assessment tool for energy balance (integrative diet and physical activity) research and a web site prototype for monitoring the work accomplished with this tool. The research tool envisioned will incorporate both self-report and “objective” [e.g., motion detection, tracking vital signs, analysis of physiology, GPS, digital camera, etc.] indicators. The long-term goal is to 1) develop and evaluate the research tool and an interactive network platform that integrates the research tool, and eventually includes the outcome data contributed by the cancer prevention researchers using this tool, and 2) develop a tracking component for the network.

Rates of obesity in the United States have dramatically increased over the past 20 years to reach epidemic levels. Obesity, the result of energy imbalance (i.e., energy intake/energy expenditure), has been linked to several types of cancer (IARC, 2002). Energy balance and obesity have been designated as key areas of interest at NCI (e.g., 2005 Bypass Budget), NIH (e.g., trans-NIH obesity task force), and DHHS (Health People 2010). During an NCI-sponsored working group meeting, entitled “Capturing Physical Activity and Diet in Real Time”, the need for innovative tools to assess and modify obesity related health behaviors was highlighted by the expert panel.

Currently, research on interactive and/or simultaneous effects of energy intake and expenditure is sparse (IARC, 2002). Instead, research has focused on physical activity, diet, and weight separately in relation to cancer (as well as other health outcomes). As a result, research tools that adequately capture real-time energy balance in an integrated and verifiable manner have not been developed.

To better understand the influence of energy balance on cancer and cancer prevention, the development of portable e-technology tools to precisely measure and modify energy balance-related health behaviors (i.e., diet, physical activity) is critical. Current tools (e.g., surveys, handheld computers, cell phones, accelerometers, etc.) have not been developed with dynamic (i.e., real time) and integrative nature of energy balance in mind. Furthermore, there has been limited integration of

the self-report and “objective” methodologies to understand energy balance. Interdisciplinary collaborations (e.g., behavioral researchers, computer scientists, nutrition specialists, exercise physiologists, etc.) are required to move the field forward in an integrative manner.

In addition to the need to develop portable e-technology tools that integrates different aspects of energy balance, there is also a need to consolidate the information obtained from these tools into an interactive database that can be monitored and tracked over time. To date, researchers have typically used portable e-technology in isolation of a centralized database, which limits the potential dissemination and interdisciplinary use of the information. An interactive database can provide a centralized channel for individuals to self-monitor their health behaviors, for information to be analyzed and potentially send in appropriate form back to the individual, and for researchers to engage in creative interdisciplinary collaborations with multi-levels of longitudinal data collected in real-time.

Phase I Activities and Expected Deliverables: 1) Prototype of a portable research tool using e-technology that can assess diet and physical activity using both self-report and “objective” methods; 2) research tools should include an option to provide real-time information feedback to the user; 3) an outline of the operations manual and primer; 4) software designs and specifications, where applicable; and 5) a prototype of an interactive web-based platform for researchers.

The integrative research tool could enhance existing technology (e.g., handheld computers, cell phones, text message devices, accelerometers, heart rate monitors, etc.), merge existing technology, or develop a new platform. Consultation with leading behavioral researchers with expertise in diet, physical activity, and weight is required.

Phase II Activities and Expected Deliverables: 1) Development and beta-testing of the tool and web site on individuals from a variety of backgrounds is expected; 2) the final research tool, web site and related software, (where applicable); 3) The operations manual and primer, and 4) at least one article describing the development and evaluation of the research tool and web site that is suitable for publication in scientific venues.

214 Systems to Enhance Data Collection and Medication Compliance in Clinical Trials

(Fast-Track proposals will be accepted)

Numerous emerging technologies such as health informatics, cellular technology, and pharmacy automation now make it possible to develop a medication management system that enhances data collection and medication compliance in drug clinical trials to reduce the cost and enable accurate measurement of therapeutic effects. Poor patient compliance often makes it difficult to detect the therapeutic effect of drugs that have potential benefit to patients and can affect the ability to make a rational clinical decision about further therapy. Needed are cost-effective systems that accurately track dosing times, missed doses, eliminate costly uncertainty, and the need for data entry from patient diaries.

The short term goal of this project is to develop a prototype of such a system with detailed system specifications and concept testing, and demonstrate technical feasibility that would logically lead to a Phase II. The long term goal is to evaluate the effectiveness of the system on medication compliance in a sample of clinical trial subjects, cost effectiveness, and the overall acceptability of the system among the stakeholders in the drug development value chain: pharmaceutical companies, federal agencies (e.g., NCI), regulatory bodies (e.g., FDA), clinical monitoring companies, clinical software companies, patients, and healthcare providers.

The pharmaceutical industry is estimated to spend over $45 billion a year on research and development. Within the R&D process, clinical trials form the largest single cost center for new drug development. The clinical-trial process required by the food & drug administration to ensure product safety is both lengthy and costly. According to a recent report from the tufts center for the study of drug development, it costs $802 million to develop a prescription drug. Peter Tollman, vice president of the Boston consulting group, said modeling done by his firm put the average development cost at $818 million. Only one in five drugs is approved for sale in the United States, according to several experts, which has a direct impact on the return on investment for drug manufacturers. In order to maintain profitability, companies need to take measures to improve the efficiency and effectiveness of the clinical trial process.

The author of the Tuft study, Joseph DiMasi, said that high failure rates, the exorbitant cost of clinical trials, and the average time needed to win government approval of about 12 years were the primary reasons drug development has become so costly. Ten drug companies provided confidential data for the study. Tufts began tracking drug development costs in 1976. The last survey, published a decade ago, put the average development cost at $231 million in 1987 dollars. If those expenses had merely kept pace with inflation, new drugs would cost about $318 million today.

It would appear that drug clinical trial costs are spiraling out of control. Thirty percent of these costs are associated with handling patient records, and the cost of noncompliance can be as high as $2000 to $10,000 per patient over the course of a study. For example, double data entry of compliance records costs $4.00 per page. Each compliance data query costs $20 per page. The typical clinical trial involves 4,000 people today, compared with 1,300 in the 1980s, according to Raymond V. Gilmartin, president of Merck. These figures suggest costs associated with noncompliance on the order of $8 to $40 million per trial. These costs should decrease with an effective medication compliance system in place, reducing the cost to market for new cancer drugs or other drugs.

Phase I Activities and Expected Deliverables: 1) Development of a conceptual prototype; 2) Feasibility testing via qualitative research from focus groups with stakeholders; 3) technical feasibility demonstration of the proposed system; 4) development of detailed system specifications; 5) cost analysis.

Phase II Activities and Expected Deliverables: 1) Development of a functional prototype, 2) Implementation of the system in a clinical trial to demonstrate system efficacy, and medication compliance; 3) Conduct cost analysis to assess potential savings including analysis of production costs and ROI (return on investment) by comparing current monitoring costs to monitoring costs for patients using the proposed system; 4) Assess overall user acceptability of the system among the stakeholders in the drug development value chain: pharmaceutical companies, federal agencies (e.g., NCI), regulatory bodies (e.g., FDA), clinical monitoring companies, clinical software companies, patients, and healthcare providers; and 5) Produce at least one article describing the development and evaluation of the program that is suitable for publication in appropriate scientific journals and/or books.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This Solicitation invites proposals in the following areas:

028 Prevention Training

(Fast-Track proposals will be accepted)

Prevention research has established a significant wealth of information regarding effective substance abuse prevention programs. Previous PRB SBIR contracts have focused on prevention research dissemination (mechanisms which are utilized to transfer drug abuse prevention information to practitioners, policy makers, and the public) and measurement modules for prevention interventions (aiding various groups to identify existing or develop new measures of the antecedents, mediators and outcomes thought to be associated with the interventions). This solicitation seeks development of materials and methods for training trainers and prevention intervention delivery personnel in ways that ensure the program is implemented with fidelity.

The purpose of Phase I would be to identify effective ways to package substance abuse prevention training materials and to develop effective methods for training trainers and prevention delivery personnel. Key concepts of program delivery such as recruitment and retention and fidelity of implementation would be addressed. Development of innovative models and methods for training and implementation, such as the infusion model, are encouraged.

Phase II would involve implementation development and effectiveness testing of training materials and modules at the trainer and intervention delivery levels in real world settings. Plans for marketing of training at both levels would be presented.

029 Development Of Science Education Materials Or Programs

(Fast-Track proposals will be accepted)

For many years students in the United States have scored poorly on standardized tests relative to their international peers. Furthermore, student interest in science has been declining. At the same time, public science literacy has remained low. Low science literacy among students and other groups has many implications. In order for NIDA to fulfill its mission, there is a need to ensure that adequate numbers of students are entering science education tracks and eventually pursuing careers in biomedical sciences. It is also important to the mission of NIDA that other groups, such as the general public, health care workers, etc. are scientifically literate. It is particularly important to NIDA that all members of society understand the role of science, biology, and technology as they relate to neuroscience and drug abuse and addiction research. There is a lack of public understanding of behaviors that increase the risk for drug abuse, the use of animals in drug abuse related behavioral and biomedical research, and the necessity for basic research to make progress toward improving health. Furthermore, there is a substantial misunderstanding about the nature of addiction as a biologically based brain disorder. To address all of these issues, it is imperative that efforts be made to educate our nation's school children, the general public, health care workers, members of the judicial system, and other groups about the science of addiction.

Therefore to address these issues this contract solicitation seeks innovative projects or programs that will substantially improve scientific literacy among one or more of the following groups: 1) students and teachers at the kindergarten through 12th grade levels; 2) the general public; 3) health care practitioners; 4) members of the judicial system; 5) other groups that have a need to be scientifically literate. Programs or projects must seek to improve general scientific literacy with a specific focus on drug abuse related research. For example, a project could teach basic neuroscience first and then subsequently teach how abused drugs act in the brain and body. Programs and projects aimed at school children should convey the scientific process in a way which makes learning science fun and interesting for the students and which captures their enthusiasm for science. Student programs and projects must also adhere to the National Science Education Standards. Programs or projects aimed at other groups should be directed to increasing their knowledge of scientific terms, concepts, reasoning, and their ability to understand scientific public policy issues. Regardless of the intended audience, all programs and projects must include an evaluation component that can provide useful and accurate information on the efficacy of the program or project.

Phase I should include studies to determine the best format for the chosen audience (e.g. focus groups), studies that demonstrate feasibility, and the development of a prototype.

Phase II should include continued formative evaluations to guide the development of the program or project, development of the program or project, and a summative evaluation to determine the project/program's efficacy in improving science education/literacy.

060 Develop New Technologies for Screening and Assessing Drug Abuse and Matching Patients with Appropriate Treatment Services

(Fast-Track proposals will be accepted)

Improved coordination of primary care and drug abuse treatment services can support the delivery of more holistic, integrated, and cost-effective approaches in the provision of health care for individuals with problem drug use, abuse, and related health problems. Primary care settings are important potential access points to drug use screening, assessment, referral, and treatment. New screening and assessment instruments that can be self-administered or administered by a variety of health care providers are needed to detect problem drug use and related health problems among patients in primary care settings. NIDA is interested only in screens and assessments that are—or can be—embedded into other more comprehensive behavioral health screening/assessment instruments, in order to maximize efficiency and likelihood of use. These instruments should have optimal levels of sensitivity and specificity for their proposed purposes within primary care settings.

New technologies, including CD-ROM, the Internet, videotape, videodisc, and other electronic means have great potential for helping treatment providers in specialty and non-specialty care settings (a) screen for problem drug use and associated health problems and risk behaviors, (b) assess the nature and degree of drug use and related disorders, and (c) identify appropriate types and levels of treatment services for patients based on their individual treatment needs. These new technologies potentially can provide a more cost effective way of identifying problem drug use and associated disorders in a variety of health care settings, speeding the

assessment process, and improving treatment placement decisions.

Phase I would explore the practicality of technological solutions to be used in primary care settings for patient screening, assessment, and placement. Selected technical approaches would be developed and pilot tested. Phase II would involve further development of those technologies that were successfully pilot tested in Phase I and the testing of those technologies in applied primary care settings.

065 Development of New Chemical Probes and Discovery of Alternate Drug Delivery Dosage Forms for Drug Abuse Studies

(Fast-Track proposals will be accepted)

This proposal invites proposals on design and development of alternate dosage forms of drugs that are not orally administered, such as nicotine, marijuana, heroin, and others for drug abuse research as well as on the discovery of new chemical probes for cannabinoids, neuropeptides, nicotinic acetylcholinergic receptors and others for studying the mechanisms of action of substances of abuse. The biological screening of these new compounds as potential ligands is also encouraged.

Phase I should demonstrate the feasibility of the proposed innovation and Phase II, the development, characterization, testing, and screening of innovation.

067 Development of Novel Approaches in Human Neuroscience

(Fast-Track proposals will be accepted)

In recent years, there has been an increase in studies employing functional magnetic resonance imaging (fMRI) to understand brain processes and functional neuronal systems. In particular, these neuroimaging techniques are being used to probe how drugs of abuse alter brain functioning. Consequently, there is a need for the development of stimulus generation hardware (e.g., non-paramagnetic goggles) to be used within an MRI magnet that can display stimuli important in drug studies. As the studies of brain function become more sophisticated, task-related assessments of brain activation are increasingly important. Shielded goggles or other types of stimulus-generating hardware and software are necessary for presentation, for example, of neurocognitive tasks, drug-related images for the induction of craving, or other “virtual reality” types of dynamic stimuli important in studies of drug abuse and addiction. Presently, these are being developed; however, the cost for these is prohibitive for many research applications. Therefore, development of lower cost stimulus hardware is critical for MRI research studies, particularly targeting substance abuse. Responses to this type of stimulation then could be correlated with brain measures using neuroimaging techniques. These types of studies will provide new insights into drug-brain-behavior interactions.

070 Develop Research Training Modules for International Application

(Fast-Track proposals will be accepted)

To facilitate research collaborations with scientists from other countries and to respond to the international demand for science-based drug abuse information, there is a need for the development of a series of information and training modules specially targeted to foreign trainees and investigators. These modules, which will be in English, will target non-native speakers and will therefore require preparation in clear, concise, non-colloquial language as well as attention to cultural factors. These modules will utilize new technologies, including CD-ROM, Internet and other electronic means to assist our research partners in other countries. These new technologies can provide a more cost-effective mode of implementing NIDA-sponsored workshops and training sessions oversees as well as to facilitate the preparation of collaborative proposals by providing non-U.S. researchers with enhanced research skills. Further, development of these materials will assist NIDA in responding to requests from international organizations, in particular the United Nations Office of Drugs and Crime (UNODC), the Organization of American States/Inter-American Drug Abuse Commission (OAS/CICAD) as well as the World Health Organization (WHO) to cooperate in the preparation of science-based information for prevention and treatment planners and providers.

Proposed topics for the modules include, but are not limited to: Drug Abuse Treatment Approaches; Understanding the Neuroscience of Addiction; Tools and Guidelines for Assessing and Evaluating Drug Abuse Treatment Programs; Treatment Approaches with HIV-Positive Drug Abusers.

Phase I would explore the practicality of technological solutions for international information and training modules. Selected technologies would be developed and pilot tested. Phase II would

involve further development of those technologies that were successfully pilot tested in Phase I.

071 Microarray Technology Applications in Drug Abuse and Addiction

(Fast-Track proposals will be accepted)

NIDA seeks to improve its ability to identify targets, understand better underlying mechanisms of action, and eventually predict which patients are most likely to respond positively to promising new therapeutic agents. The research agenda NIDA will pursue includes:

- Using microarray technology to examine the pharmacogenomics or pharmacogenetics of drugs used to treat addictions (ex. bupropion, nicotine patch, methadone, buprinorphine)
- Examining sets of gene expression profiles to predict responsiveness to drugs used to treat addictions

One limitation of NIDA's current genetics research effort is the lack of standardized open-source microarray technologies available across existing, and to be established, addiction science investigators. No research currently exists focused on sharing microarray data across a consortium with MIAME compliant metadata and associated clinical observations. The lack of a centralized resource to acquire microarray products, provide standardized management of genetic and allied metadata, and a suite of services for statistical analysis of large-scale datasets needed to investigate expression of addiction related genes and their products must be overcome for genomic discoveries to bear successively on addictive disorders.

Accordingly, NIDA seeks the development and application of a data warehouse solution that accommodates the Institute's needs for a comprehensive, flexible, and adaptable solution for the storage, indexing, and annotation of various high-throughput microarrays for genome-wide transcriptional profiling and polymorphism analysis. The solution sought will serve as a key component in support of pharmacogenomics analysis in investigational drug research. The requirements gathering will focus on needs for geographically dispersed researchers to load data remotely, specify experiments through user-friendly client interfaces, and preserve well-annotated experiments in an unsummarized raw data format that maintains data points obtainable from those microarrays. The warehouse should allow for the export of analyses in a number of common data formats, such as .csv and .txt, to facilitate further study of the data in third-party software tools. NIDA will consider deployed installations as well as application service provider solutions operated at contractor locations.

During Phase 2 a successful Phase 1 design will be developed and tested using studies to be undertaken under the NIDA Genetics Consortium or in clinical studies with genetic protocols conducted in a NIDA-sponsored clinical trial network. The contractor will be responsible for acquiring microarray chips as part of the solution developed in Phase 2 in addition to the establishment of the data warehouse and user interface products. The contractor will also identify and implement a number of standard ontologies and controlled vocabularies in order to fully model clinical data pertaining to tissue samples, the disease context, genetics, and specific pathologies under investigation in NIDA studies.

Due to the collaborative nature of this project, NIDA expects to quickly accumulate up to one thousand deposited microarrays. The eventual data warehouse must support analysis across sample batches upward from 100 to fully meet the demands of the intended users.

The intended product of the project ultimately will enable NIDA to examine and understand gene expression profiles in dependence and addiction, and how gene expression patterns determine drug response. The use of such a product on a wide scale basis is expected to increase the number of scientists actively exploring the neuroscience of addiction, and accelerate the number of studies investigating addiction and co-morbid conditions.

072 Medicinal Chemistry - Design and Synthesis of Novel Chemical Libraries for Treatment Agents for Drug Abuse

(Fast-Track proposals will be accepted)

The purpose of this contract is to design and synthesize novel compound libraries the goal of which is to produce compounds that moderate the effects of 1) cocaine and/or methamphetamine or 2) marijuana.

Examples of potential stimulant therapies are compounds which affect primarily dopaminergic systems and would either represent "agonist type" therapies for stimulants, antagonize stimulant effects, or prevent relapse. Compounds active at the D1 and D3 receptors are of special interest. Other

pharmacological areas of interest include CRF antagonist and mGluR ligands. Phase I would be used to design and synthesize novel chemical libraries through combinatorial or other high-throughput techniques and to screen these compounds in various pharmacological assays as possible treatment agents for cocaine or methamphetamine abuse. Phase II would be used to further develop compounds identified as screening "hits" into clinical candidates for the treatment of cocaine or methamphetamine abuse.

Examples of potential cannabis abuse therapies are compounds which are either agonist therapies (focusing on improving the bioavailability of existing therapeutics) or especially antagonist therapies for marijuana abuse. Phase I would be used to design and synthesize novel chemical libraries through combinatorial or other high-throughput techniques and to screen these compounds in various pharmacological assays as possible treatment agents for cannabis abuse. Phase II would be used to further develop compounds identified as screening "hits" into clinical candidates for the treatment of cannabis abuse.

For potential stimulant abuse therapies the Contractor may carry out their own in vitro and in vivo pharmacological screens, or collaborate with NIDA Treatment Discovery Program (in vitro binding studies, rodent locomotor activity studies, rodent and primate drug discrimination studies, and rodent and primate self-administration studies). For potential cannabis therapies the Contractor must independently carry out in vitro and in vivo pharmacological screens. During Phase II, the Contractor may independently develop identified compounds into new treatment entities, or may request to enter into a cooperative agreement with NIDA for the further development of a new drug with commercial promise as a treatment agent.

073 Internet-based Application of Existing/Proven Therapies

(Fast-Track proposals will be accepted)

Community treatment providers have demonstrated growing interest in and increased need for new technologies to assist in the translation of research on efficacious drug abuse treatment into community treatment settings with children, youth, and adults. Web-based technologies, have great potential for reaching new groups of patients. However, the application and development of such technologies has lagged behind their use in other settings and contexts. These new technologies potentially can provide a more cost effective way of speeding the translation of research-based drug abuse treatment services into community settings.

Previous SBIR contracts supported by the Services Research Branch have focused on the dissemination of research findings on treatment services to practitioners, policy makers, and the public; assessment instruments for needs assessment, diagnosis and treatment planning; and measurement tools for identifying the antecedents, mediators, and outcomes associated with treatment services. This solicitation seeks to advance these previous efforts by encouraging the development of web-based treatment technologies for translating treatment strategies and services with proven efficacy into effective community practice.

Phase I would explore the practicality of web-based application of evidence-based drug abuse treatment services into community practice. Selected technical approaches would be developed and pilot tested. Phase II would involve further development of those technologies that were successfully pilot tested in Phase I and the testing and evaluation of those technologies in applied clinical settings.

074 Development of Cell-Based Assays to Identify Therapeutic Targets for Substance Abuse and Addiction

(Fast-Track proposals will be accepted)

The purpose of this announcement is to solicit proposals for the development of assays that can be used in high-throughput (HTP) approaches to identify therapeutic targets for substance abuse and addiction. These HTP approaches include, but are not limited to, the screening of small molecule libraries or RNAi libraries. Some of the assays to develop include but are not limited to:

- Assays for modifying multi-protein signaling complexes, regulatory networks and synaptic transmission associated with addiction
- Assays to identify highly specific molecular markers that might be useful for identifying a function (e.g. TH production)
- Biochemical or cell-based assays of activity, behavior or interaction of proteins and other molecules of interest

- Assays to identify changes in immediate early gene (IEG) expression, as well as sensitization and tolerance

- Assays to identify changes in expression of genes critical for distinct aspects of addiction and withdrawal

075 Real-time Data Collection Paired with Ecological Momentary Assessment (EMA)

(Fast-Track proposals will be accepted)

Paper and electronic diaries have long been used as tools to record events, environment, mood and experiences. Recent technological advancements have made it possible to use a PDA-like device to record EMAs. These devices are carried by the subject, and prompt the completion of a series of questions throughout the day. They also provide a time/date stamp. Additionally, questions can be tailored to the time of day, such that they can be morning, afternoon and/or evening relevant (e.g., drug craving upon awakening).

Although PDA devices that are used to collect EMAs have great potential as research and therapeutic tools, they are limited to manual data downloads. NIDA is looking for proposals that develop a PDA-like device that performs EMAs, collects data, then has a “real-time”, automatic download capability, such that researchers or therapists are able to track performance during the day. This is especially important in a therapeutic setting. For example, if the level of craving is monitored in real-time, and passes above a certain level, it would allow a therapist to intervene in a timely manner and may prevent a relapse event.

The Phase I proposal should demonstrate the feasibility, reliability and validity of real-time monitoring of EMA data.

The Phase II proposal should demonstrate its utility as a research tool and as a tool for drug treatment therapy.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

The mission of the National Institute of Mental Health (NIMH) is to diminish the burden of mental illness through research. To achieve this goal, the NIMH funds basic research, clinical studies, and services delivery research concerning any aspect of behavioral and mental disorders (including HIV prevention and neuro AIDS research). Ultimately, this research will lead to greater understanding, better treatment and rehabilitation or prevention of mental disorders. The NIMH is also concerned with the speedy dissemination and use of this knowledge through scientific communications and public education, and in its more effective implementation in practice and service delivery systems.

This solicitation invites proposals in the following areas:

DIVISION OF SERVICES AND INTERVENTION RESEARCH

045 Suicide Prevention Materials and Training for Criminal and Civil Court Systems (Adult/Geriatric/Child and Adolescent Populations)

(Fast-Track proposals will not be accepted)

The University of Rochester Center for the Study and Prevention of Suicide has held a series of conferences on suicide prevention under an NIMH R13 conference grant (Preventing Suicide: A Scientific Consensus Process). The most recent workshop, “Suicide Prevention for Men in their Middle Years” was held on June 11-12 at the L’Enfant Plaza Hotel in Washington, D.C. A major recommendation from this workshop was that a training curriculum on the risk factors for suicide and the identification of suicidal ideation be developed for all civil and criminal court personnel including: discretionary decision makers (police – prosecutors – judges); gate keepers (clerks – case managers); offender services (defense attorneys [private and public bar] and pre-trial services); and police and peace keeping officers. Although the workshop was dedicated to suicide prevention for men in their middle years, this recommendation encompasses a curriculum focused on risk factors; identification of suicidal ideation and understanding evidence based preventive interventions for both men and women, children and adolescents as well as older adults. This recommendation is consistent with the National Strategy for Suicide Prevention (see http://www.mentalhealth.org/suicideprevention/default.asp), Goal 6, "Implement Training for Recognition of At-Risk Behavior and Delivery of Effective Treatment," objective 6.6, "By 2005, increase the proportion of correctional workers who have received training on identifying and responding to persons at risk for suicide" and the objectives of the Suicide Prevention Resource Center (see http://www.sprc.org/), funded to help implement The National Strategy for Suicide Prevention. In addition, in order to lead to treatment and prevention of suicidal behavior, such training must include a

module to enable court personnel to not only identify but to effectively and expeditiously connect persons at risk to effective treatments and services. This requires the relevant court personnel to develop an understanding of: 1) the quality and focus of local treatment providing entities, 2) the pathways whereby effective interventions and treatments are available within the local jurisdiction and 3) the constraints or opportunities conferred by an individual's status within various systems. Such information will vary across localities. Key to making this endeavor successful is building a collaborative relationship across the court and mental health systems that can be sustained beyond the duration of the training activity. Phase I of this SBIR is to develop the prototype curriculum/modules and delivery approaches for the recommended training. Approaches may include web-sites, use of interactive media, training trainers and educators (for reaching individuals still engaged in training or early career development), conferences and seminars.

Curriculum/modules should be designed so they are appropriate for different disciplines, positions and levels of training. The curriculum should be evidence-based on current research findings applicable to the specific population or populations being considered. Attention should be given to the process of updating information, follow-up training and include a module to facilitate an understanding of available resources (e.g., such as mapping the system exercises). During Phase I the contractor will be expected to design a prototype course, module(s) and delivery system. While scientific content will be developed by individuals with considerable mental health research expertise in suicide risk and prevention, input from end users is critical through all phases of content and delivery development. End users are defined as civil and criminal court personnel including: discretionary decision makers (police – prosecutors – judges); gate keepers (clerks – case managers); offender services (defense attorneys [private and public bar] and pre-trial services). Additional expertise might include the following: adult educators; service providers; professional associations; community groups and individual and family stakeholders/consumers.

Phase I will also include a preliminary evaluation/usability study of the materials, curriculum and delivery system approaches. During Phase II different models and approaches will be tested for their effectiveness and usability with target audiences.

Background Information from Workshop: The criminal and civil court systems have unique opportunities to promote public health oriented efforts to prevent and reduce the psychiatric morbidity and the injurious or fatal outcomes associated with suicide. This is based on a fundamental recognition that 1) many critical life situations tend to present specifically for adjudication or resolution in the courts, and 2) civil and criminal court appearances often are overwhelming and life-altering experiences for litigants, defendants, and respondents. The courts thus can provide the opportunity to intervene by providing a mandate (for some cases) or a well-developed referral structure to facilitate access for litigants to an integrated array of selective and indicated preventive interventions to reduce suicidal behaviors and suicide, and their attendant psychiatric outcomes. In order to engage in any innovative prevention strategies, it will be imperative to foster an evolution in the understanding of the roles of courts and to systematically provide new options for preventive and therapeutic interventions. All recommended programmatic initiatives or new screening tools for use in the criminal justice system should be evaluated in a rigorous fashion prior to widespread or global dissemination.

To be responsive to this announcement the proposal must demonstrate an in-depth knowledge and experience with: (1) research on risk factors, identification of suicidal ideation and evidence based suicide preventive interventions; (2) research and knowledge of civil and criminal court systems and personnel; (3) assessing and understanding how individuals in a given jurisdiction move through the criminal justice and mental health service systems, as well as experience in building collaboration across systems; (4) knowledge and technical expertise in the design of adult education programs; (5) technical expertise in developing appropriate multiple approaches/strategies (e.g., WEB, CD-ROM, video, seminars, etc.); (6) plan to assure the accuracy of information and its update; and (7) demonstrated ability to recruit appropriate expertise.

Two or three meetings with NIMH staff may be proposed for orientation and presentation of draft prototypes. Since the degree of complexity of this project may require more than 6 months to complete, the offeror should clearly identify the amount of time and support needed to complete their proposed scope of work.

055 Development of Tools to Enhance Mental Health Interventions and Services Research Training: Executive Research Leadership or Science/Research Education Curriculum

(Fast-Track proposals will not be accepted)

The Division of Services and Intervention Research will support the development of tools to enhance research training in all areas of science supported by the Division. This will include a) development and evaluation of tools to enhance research and executive leadership in the mental health interventions and services sciences and b) the development of science/research education curriculum, materials, and methodologies relevant to new research knowledge and directions in mental health interventions and services research. Each of these areas of interest is described below:

a) Development and Evaluation of Tools to Enhance Research and Executive Leadership in the Mental Health Interventions and Services Sciences

Mental health interventions and services research has become increasingly more complex over the past five years. For example, interventions and services research more frequently involves large-scale multi-site trials with diverse settings and populations. In addition, it is not unusual for studies to involve large multi-disciplinary teams of researchers across different academic departments as well as interactions with different types of community/service organizations and systems, the public, policy makers and industry. In order to be successful in this new environment mental health interventions and services scientists need to blend specific scientific/technical knowledge and skills with a program of formal, empirically validated training in *research and executive leadership that is tailored to the specific needs of mental health interventions and services researchers.* Therefore, the focus of Phase I is on the planning and development of curricula, materials, methodologies and evaluation criteria that can be used in the deployment, evaluation and sustained operation of a blended research and executive leadership program.

Mastery of these blended skills is important at all phases of career development but is particularly critical for mid-level research faculty with single or multiple research grants (e.g., R01 or equivalent) and for newly funded junior researchers with career development or research awards. In developing research and executive leadership tracks for junior and mid-level scientists attention should be given to the very different needs of these two groups of researchers. For example, programs for junior researchers may focus more on the development of detailed “research executive leadership career development plans” and courses while a track for mid-level scientists should include a comprehensive and focused program of training with an identified and structured core curriculum.

Various universities and organizations offer effective programs for some components of this type of program (e.g., Executive Leadership in Academic Medicine). However, there are no existing programs that offer a combination of: (1) multidisciplinary training for researchers from diverse institutions and disciplines (social work, psychiatry, psychology, pharmacy etc.); (2) programs that are specifically tailored to the needs of mental health interventions and services scientists and; (3) offer both advanced scientific content and science leadership skills that integrated and specific to the needs of junior and mid-level researchers.

The purpose of this contract is to develop and evaluate a suite of tools and mentoring strategies (workshops, cd-rom, web-based approaches, networking etc.) to enhance the research and executive leadership capacity of mental health interventions and services researchers. During Phase I prototype training materials, curriculum, outcome measures and protocols will be developed and evaluated by relevant stakeholders. Since it is not known, a priori, what the best curriculum, materials and strategies are to enhance capacity, to be responsive to this request, the proposal must include multiple evidence-based alternatives/strategies. These strategies and materials, or different combinations of tools and approaches, will be fully developed and extensively beta tested and refined during Phase II.

Innovation should involve the careful blending of mental health interventions and services science research with executive and management training (negotiation skills, leadership, business, management and financial skills relative to academic mental health research careers). Additional areas to be included from the executive management side are presentation skills, financial projections, process issues, communication strategies, organizational psychology and structure, affect management, understanding legal issues related to managing a research enterprise, staff management/teams, and developing strategic /ideas. These leadership and management approaches must be developed and/or

adapted to the specific needs of the services and interventions scientific community and the organizational context where this research takes place.

The proposed, "Enhanced Research and Executive Leadership Program" may focus on women or other groups underrepresented as directors of advanced programmatic research grants. For example, over the past five to ten years the Division of Services and Interventions Research (DSIR) has seen an increase in the number of women and persons of color entering and remaining in research careers related to mental health clinical epidemiology, treatment and preventive interventions, and services research. Despite this increase in diversity among *trainees* (e.g., pre/post docs supported on institutional training grants, F31, F32, minority supplements and dissertation awards), *junior researchers* (e.g., K01, K08, K23) and investigators holding *individual research grants* (e.g., R01) there has been relatively little growth in the number of women and persons of color who are directors of advanced programmatic grants. For the purpose of this contract the term "advanced programmatic grants" includes, but is not limited to, institutional training grants (T32), short-term educational grants (R25), centers and multi-site studies (e.g., P20, 30, 50 and U types of mechanisms) and non-mentored K awards (K02, 24 and 05). Moreover, the number of women and persons of color in the mental health interventions and services sciences who hold executive academic positions, who have strong research backgrounds, is extremely limited. For example, currently there are only a handful of women who hold the position of chair of an academic department of psychiatry in the United States.

b) Development of Science/Research Education Curriculum, Materials, and Methodologies Relevant to New Research Knowledge and Directions in Mental Health Interventions and Services Research

The Division of Services and Interventions Research (DSIR), NIMH supports a broad range of research and training in mental health treatment and preventive interventions, services and clinical epidemiology (http://www.nimh.nih.gov/dsir/index.cfm). The number of individuals in the research "pipeline" remains limited compared to the public health challenges of the field. In addition, the development of empirically based, state-of-the-science curriculum, materials and methodologies relevant to the science supported by DSIR has been slow to emerge, be tested and disseminated by diverse strategies (training of educators, student workshops, web, telecommunications, cd-rom or combined strategies). Therefore, the primary focus of Phase I is on the development and usability testing of prototypes for new curriculum, educational materials, and methodologies (e.g., state-of-the-art educational technology such as standardized patient, interactive video, computer simulation, web-based learning) to educate undergraduate college students, graduate fellows, young investigators and clinicians (with the potential to participate in research activities) in areas relevant to DSIR's mission. This may also include mental health scientific literacy for individuals at all phases of the educational pipeline (e.g., elementary through high school, undergraduates) and professional development (post-baccalaureate, medical school, residents, clinical professional schools). Materials/curriculum may be developed in areas where new knowledge and methods are emerging but where few or very limited programs/resources exist. Examples of such areas might include, but are not limited to, the following: *Mental Health Pharmacoeconomics, Research on Mental Health and the Criminal Justice System, Research on the Homeless Mentally Ill, Mental Health Preventive Interventions, Geriatric Mental Health Interventions and Services Research, Research on Developing and Disseminating Treatment and Services Interventions, Mental Health Biostatistics and Research Methods, Suicide Prevention Research Methods, Subject Recruitment as well as topics related to interventions and services research for specific disorders such as autism spectrum disorder, anorexia, and bipolar disorder. Other areas might include principles of research ethics, innovative approaches to teaching basic brain and behavioral research to interventions and services research fellows to facilitate new paradigms (e.g.,) and mental health community engagement research (e.g. focus on methodology). In d*eveloping prototypes attention should be paid to issues of cultural diversity and research on community inclusion.

Curriculum materials may be developed as part of an interactive web-based networking tool for linking services and interventions research training and education programs specific to social work research. Areas of high priority might include: suicide, geriatrics, child or underserved populations.

During Phase I an array of prototype materials, curriculum and methodologies will be developed and undergo usability testing by relevant stakeholders.

Since it is not known, a priori, which strategies and methodologies are the most cost-effective, a strategy for evaluating the different approaches or combination of approaches must be developed during Phase I for implementation during Phase II.

(Innovations could include the linking of leading investigators and fellows/junior researchers in real time; an interactive archive; the capture and reformatting of workshops, seminars and grand rounds by leading investigators; online statistics and research design workshops in specific targeted areas; and interactive online career development support activities. For example, individuals with mid-level career awards, such as the K24, could host online consultations with mentees or groups of mentees. In addition, specific training programs could make course content available, link trainees, or provide “courses of excellence” via the site. Since there are several training and education programs that send fellows to diverse sites, the web-based tool should provide a structure to assure that program and fellows/junior faculty are routinely linked for scientific, mentoring and administrative activities. For example, an application that focuses on networking for the development of social work researchers might include *research content topics* (e.g., as stages of intervention development, testing and manualization of interventions, services research including cross-systems collaboration, community integration and rehabilitation, and development and adaptation of culturally appropriate interventions and services, social work practice research), *research process topics* (e.g., developing interdisciplinary research collaborations, community based research collaborations) and *research operational topics* (e.g., infrastructure development as it relates to training and development).

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts, fosters, and supports an integrated and coordinated program of basic research, clinical investigation, and trials, observational studies, and demonstration and education projects. The Institute’s mission includes studies related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, blood, sleep disorders, and blood resources management. Studies are conducted in its own laboratories and by other scientific institutions and individuals supported by research grants and contracts. The NHLBI SBIR program fosters basic, applied, and clinical research on all product and service development related to the mission of the NHLBI.

This solicitation invites proposals in the following areas.

031 New Technology Development for Global Assay of Blood Coagulation

(Fast-Track proposals will be accepted)

It is currently estimated that about half of the population in the US and Europe will die from diseases related to the formation of a blood clot in a vital organ. Depending on the organ affected, the clinical condition may be described as a heart attack, stroke or thromboembolic disorder, but the underlying source of the disease is a blood clot. Formation of a blood clot is a complex process. It involves a cascade of reactions between several plasma proteins called clotting factors. These interactions are controlled by activators and inhibitors. The cellular components - platelets, leukocytes and endothelial cells - intimately participate and regulate the coagulation process. There are also modifiers and significant redundancy in the system. Coagulation is complicated but it is a precisely regulated biological process; a shift in the equilibrium may cause thrombosis or bleeding with serious consequences.

There are excellent assays to measure the concentration or activity of a single coagulation protein. Similarly, there are laboratory and clinical procedures to determine the hemostatic status of parts of the clotting pathway. However, because of the complexity and multiple regulations, these assays have only limited values in predicting either thrombotic or bleeding risk in a patient. The emergence of novel technologies, and improved data handling capability, have created opportunities for developing instrumentation for the rapid measurement of a large number of parameters involved in coagulation utilizing a small volume of blood. It may now be possible to develop models that can accurately predict the thrombotic or bleeding risk in an individual and thus customize therapy based on patient profiles.

The goal of this proposal is to develop new instrumentation utilizing modern technology that can rapidly and accurately predict the hemostatic status of an individual. The ultimate market for this technology will be hospitals, clinical laboratories and medical centers.

Phase I should address the initial development of high throughput technology and data handling capability for a global assay of hemostatic factors.

Phase II should entail validation of the above technology in animal models e.g. in mice where many knockout variants are available. This step may or may not be needed and is optional. Responders may propose validation of the system by application to a patient population with established bleeding or thrombotic risk.

032 Bioreactor Production of Clinical Grade rAAV in Sf9 Cells for DMD

(Fast-Track proposals will be accepted)

The goals of this proposal are: 1. To develop "current Good Manufacturing Practice" (cGMP) protocols for the production of clinical grade recombinant adeno-associated virus (rAAV) in Sf9 cells. 2. To determine scale-up protocols for production and processing of rAAV in Sf9 cells. 3. To produce sufficient quantities of rAAV in Sf9 cells for a preclinical study for Duchenne muscular dystrophy (DMD).

AAV-BASED GENE THERAPY OF DMD

Recently, the Laboratory of Biochemical Genetics, National Heart, Lung, and Blood Institute (LBG/NHLBI) has developed a novel method of producing rAAV in the insect cell line, Sf9, using recombinant baculoviruses (Autographa californica nuclear polyhedrosis virus or AcNPV) to deliver the genetic components. This process results in robust AAV capsid protein expression as well as high levels of rAAV DNA replication. The vector genomes are then encapsidated in the Sf9 cells. Preliminary data show that Sf9 cells produce >1014 particles per liter. Therefore, large bioreactors (≥1000 liters) should allow large-scale production of rAAV up to commercial size batches. The major advantage of this system is that Sf9 cells grow in suspension cultures limited in size only by the volume of the vessel.

DMD represents a true challenge for gene therapy, requiring stable and systemic distribution of the therapeutic genetic information, including skeletal muscles, diaphragm and heart. To date, no gene delivery system, or vector, has demonstrated this at a clinically relevant scale. However, recent studies in mice indicate that vectors derived from adeno-associated viruses (AAV) could help reach this goal if made available in sufficient quantity and quality.

AAV vectors containing a shortened version of the dystrophin cDNA (micro-dystrophin, see below) has been evaluated in the mdx mouse model of Duchenne muscular dystrophy. This compact and functional variant of dystrophin can be accommodated into AAV vectors and muscle function can be recovered following gene transfer.

Phase I of the SBIR proposal is to develop a cGMP process for rAAV production in Sf9 cells. Five liter bioreactors of Sf9 cells have produced >1015 particles, or >1014 particles per liter, thus demonstrating that rAAV production is feasible in "stirred-tank" bioreactors. Adapting conditions for processing large amounts of rAAV and establishing cGMP compliant, standard operating procedures (SOPs) for bioreactor production and downstream processing is the objective of Phase I.

Phase II objectives are to produce sufficient rAAV for a preclinical study in large animal models of muscular dystrophy. Prior to a human clinical trial, the safety profile of the vector at therapeutic doses has to be established. The relatively large size of the muscular dystrophy dogs necessitates substantial vector preparations to achieve meaningful results. Extrapolating from the mdx mouse data, a single therapeutic dose for a dog may approach10^{14} particles; for toxicity studies, it is desirable to exceed the therapeutic dose by 10 to 100 fold. Ideally, the vector administered to the animals would be from a single preparation manufactured according to cGMP protocols. Thus, a well-designed study could require 10^{18} particles. This is feasible using Sf9 cells in a 1,000 to 5,000 liter bioreactor.

Duchenne Muscular Dystrophy (DMD) is the most frequent hereditary myopathy affecting about one in three and half thousand male births of all races. It is an X-linked recessive disorder where mutations in the DMD gene result in a failure to produce dystrophin in striated muscles. The muscle fibers are exquisitely fragile and are continuously destroyed from normal muscle activity. The muscles slowly degenerate leading to virtually complete fibrosis with fatty infiltration.

Clinical symptoms appear in children between 18 months and 3 years. Progression of the disease is characterized by ongoing muscle wasting, leading to the loss of walking ability at 9 to 12 years of age. Subsequent spine deformation, breathing difficulties and cardiomyopathy are eventually fatal, usually before 15 years of age. Even with improvements in patient care (e.g., arthrodesis and tracheotomy ventilation) the disease is always fatal before the age of 30. There are no cures or treatments for patients with the disease.

GENETICS

The DMD locus is on the X-chromosome (Xp21.2 – OMIMid: 310200) and corresponds to the dystrophin coding region. With nearly 2.5 million base pairs, it is the longest gene ever detected, but only about 14,000 base pairs contain coding sequences distributed over 79 exons. Full-length dystrophin (DP 427) is a 427 kDa cytoskeletal protein expressed in all muscles. A variety of protein isoforms (DP 260, DP 140, DP 116, DP 71) are generated through the differential usage of four internal promoters located in introns 29, 43, 55 and 62. These isoforms are found in retina, central nervous system, peripheral nervous system, and non-muscle tissues, respectively.

Approximately one-third of patients carry de novo mutations. Altogether, more than half of DMD boys bear large genomic deletions encompassing one to several exons. The extent of the mutations is not directly correlated with the severity of the phenotype. The “out-of-frame” deletions that elicit formation of premature stop codons and consequent abortive protein translation results in dystrophin deficiencies and severe phenotypes. In contrast, deletions that produce “in-frame” mRNAs leading to shorter proteins are responsible for a milder myopathy known as Becker Muscular Dystrophy (BMD).

RESEARCH CONSORTIUM

A consortium of government, academic and private institutions will interact to meet the Phase I and phase II goals of the SBIR. Conditions for producing microdystrophin rAAV at laboratory and pilot production scales will be established in the LBG/NHLBI. The respondent’s rAAV production facility will work with the NHLBI intramural lab and consortium to develop scale-up and cGMP processes. The consortium consists of Dr. Olivier Danos, Genethon (Evry, France), Dr. Richard C. Mulligan, Harvard Medical School (Boston, MA), and Dr. Robert M. Kotin, LBG/NHLBI (NIH, Bethesda, MD).

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER FOR HIV, STD AND TB PREVENTION (NCHSTP)

The mission of NCHSTP is to provide national leadership in preventing and controlling human immunodeficiency virus, other sexually transmitted diseases, and tuberculosis by working with community, state, national, and international partners in effective multi-disciplinary programs of surveillance, research, and evaluation.

This Solicitation invites proposals in the following areas:

DIVISION OF AIDS, STD, AND TB LABORATORY RESEARCH

This contract proposal solicitation has been amended to include the following 5 topics.

019 Development of Novel Genotyping Procedures for Mycobacterium Tuberculosis

The Institute of Medicine Report identified the need for better methods for genotyping of M. tuberculosis strains to facilitate and focus tuberculosis control efforts. Currently available methods are too costly, time consuming, technically demanding, or labor intensive to be applicable at the local level. This contract seeks to develop field-expedient genotyping technology including clinical laboratory tests and accompanying instrumentation. The technology should be readily usable by staff in State and Local Public Health Laboratories. The following are particular areas of interest:

a) Development and evaluation of instrumentation to facilitate genotyping by the spoligotyping or MIRU typing methods in a cost-efficient manner.

b) Development and evaluation of new methods for genotyping M. tuberculosis strains.

020 New Laboratory Tests for Tuberculosis and Detection of Drug Resistance

In order to accomplish the Healthy People 2010 goal of reducing the time required for the laboratory confirmation of the diagnosis of tuberculosis to 48 hours, rapid tests to detect Mycobacterium tuberculosis or its products are needed. In addition, rapid tests that can reduce the turnaround-time for detection of drug-resistance are needed. This contract seeks to develop field-expedient testing technology (including clinical laboratory tests and accompanying instrumentation) to detect M. tuberculosis or its products in patient specimens and/or to determine drug resistance of M. tuberculosis isolates. The technology should be readily usable by staff in clinical and public health laboratories. The following are particular areas of interest:

a) Development and evaluation of procedures and instrumentation to facilitate nucleic acid

amplification testing methods for M. tuberculosis and optimize the ease-of-use and cost-efficiency of nucleic acid amplification testing.

b) Development of rapid cost-efficient methods to detect and identify Mycobacterium tuberculosis or its products in patient specimens suitable for use in clinical laboratories.

c) Development of rapid cost-efficient methods and accompanying instrumentation to determine drug resistance of M. tuberculosis isolates suitable for use in clinical laboratories.

022 Technology to develop handheld amplification test for sexually transmitted infections

There is an increasing use of amplification tests for the detection of sexually transmitted infections. More recently, conventional nucleic acid amplification tests are being replaced by updated by more recent methods such as real time PCR. Additionally, there is also a trend to develop tests that are easily useable in on-site field conditions. The Division of AIDS, STD, and TB Laboratory Research, National Center for HIV, STD, and TB Prevention, CDC is interested in funding developmental research to produce a handheld multiplex nucleic acid amplification test for the rapid diagnosis of sexually transmitted infections, on-site in clinical settings, with a high degree of specificity and sensitivity. The multiplex detection would be for two subsets of microorganisms: 1) Genital ulcer disease to include *Haemophilus ducreyi*, *Treponema pallidum*, and Herpes Simplex Virus and 2) Genital discharge disease to include *Neisseria gonorrhoeae*, *Clamydia trachomatis, Trichomonas vaginalis*, and *Mycoplasma genitalium*. The system developed needs to be rapid, inexpensive and require minimum technical experience.

023 Technology to develop an ambient temperature specimen transport system

There is an increasing use of amplification tests for the detection of sexually transmitted infections. Therefore, an increasing problem for many local laboratories is the issue of specimen transportation. Many nucleic acid amplification tests require that a specimen be tested within 24 to 48 hours after collection or otherwise the specimen needs to be frozen. Many private or small community providers are unable to meet these guidelines. Due to this expanding problem, the Division of AIDS, STD, and TB Laboratory Research, National Center for HIV, STD, and TB Prevention, CDC is interested in funding developmental research for the production of an ambient temperature specimen transport system for use in nucleic acid amplification tests. Such a system should be able to provide a stable and adequate specimen for nucleic acid amplification tests for a time period of four to seven days. Additionally, since there are growing opportunities for specimen self-collecting, the system must also be inconspicuous and convenient for patients to transport, by mail or otherwise, to the testing laboratory. It must also meet all state and federal guidelines for the shipment of hazardous/infectious materials. The system developed must also be inexpensive and require minimum technical experience.

024 System to concentrate and purify nucleic acids from whole blood

Nucleic acid amplification tests are increasingly becoming the method of choice for the detection of sexually transmitted infections. The use of whole blood as the specimen for detection of blood-borne infections such as syphilis has been hampered by the presence of amplification inhibitors and the low number of organisms/ml of blood at various stages of the disease. Attempts to concentrate the DNA present in blood specimens has also led to concentration of amplification inhibitors. Conversely, standard purification techniques often lead to inadequate nucleic acid targets. To address this issue, the Division of AIDS, STD, and TB Laboratory Research, National Center for HIV, STD, and TB Prevention, CDC is interested in funding developmental research of a system for both the concentration and purification of nucleic acid targets from whole blood to enable nucleic acid amplification. The system developed needs to be rapid, consistent, inexpensive and require minimum technical experience.

DIVISION OF TUBERCULOSIS (TB) ELIMINATION (DTBE)

021 Development of a Novel Internet-Based Information System for Remote TB Control and Prevention Programs

As noted in CDC's response to the IOM TB report, goal one reflects activities related to maintaining control of TB. While remarkable advances have been accomplished on the US mainland, appropriate and effective infrastructure and TB information systems to support surveillance, reporting, and patient-centric interventions have been challenging to implement and maintain in the US-affiliated Pacific Island Jurisdictions (PIJ). The PIJs are very remotely situated from the US mainland and they

grapple with tremendous geographical distances within jurisdictions creating an environment which does not readily support reliable information systems.

This contract seeks to develop a secure internet-based information system using established standards which will enable PIJs to overcome unique conditions such as (1) the lack of standardization throughout the current paper-based management and reporting systems, (2) the lack of data communication between rural and urban health centers, (3) the inadequate internet connectivity.

- Development of a system to provide the ability to monitor and evaluate program processes and outcomes which are useful for surveillance, reporting, prevention and control activities to ensure that patient-centered case management and monitoring of treatment outcomes are the standard of care for all TB patients in the PIJs
- Development of a system which builds the capacity of PIJ TB control programs to conduct systematic and comprehensive reviews of TB patients
- Development of a system which improves and enhances TB laboratory capabilities
- Development of a system which must work on the current foundation of dial-up Internet access
- Development of a system which addresses the challenges of intermittent Internet access so that data can be entered “off-line” and is able to synchronize over the Internet
- Development of a system which captures necessary patient and laboratory information yet is optimized for querying large amounts of data to support program evaluation activities and CDC reporting and monitoring requirements
- Development of a system which supports access by multiple users across multiple PIJs.

DIVISION OF STD PREVENTION

This contract proposal solicitation has been amended to include the following topic.

025 A Delivery System for Patient-Delivered Partner Treatment for Sexually Transmitted Disease Control

Sexually transmitted diseases (STDs) like gonorrhea and chlamydia are a major public health concern in the United States (US). These infections are of concern because of the negative sequelae, e.g., pelvic inflammatory disease, ectopic pregnancy, and infertility, they can produce and because of evidence that they can facilitate the transmission of Human Immunodeficiency Virus (HIV).

Efforts to control STDs in the US have focused on partner notification, the practice of eliciting sex partner locating information from persons diagnosed with STDs and following up with sex partners; these efforts are usually conducted by Health Departments. The burden of STDs and a shift of STD care in the US from the public to the private sector have forced health care professionals to develop alternate strategies for STD control. One of these strategies is patient-delivered partner therapy (PDPT), a provider’s practice of prescribing or dispensing medication to patients diagnosed with an STD to be administered to their sex partners. PDPT research has shown promising findings for reduced reinfection and is clinically practiced. There are, however, no widely used or standardized PDPT delivery systems available that can provide the medication in appropriate packaging that includes labeling and educational material for patients and their partners.

Phase I goals are to develop a portable, inexpensive, user-friendly delivery system that health care professionals may use to dispense medications to patients diagnosed with an STD for their sex partners. The system should meet child-proofing requirements; provide the correct storage environment for medications; and provide labeling, i.e., name of medication, dose, number of doses contained in the system, contraindications for use, follow-up instructions and major side effects. The system should also contain easily understandable STD educational material for the patient and partner and sources where the patient and/or partner may obtain additional educational information if needed, e.g., links to STD websites. The system should focus on, but not be limited to, treatments for gonorrhea and Chlamydia. The Phase I end-product will be a model of the physical delivery system.

In Phase II, the product will be piloted in clinic settings. Results from the pilot testing will be used to edit and revise the product.

NATIONAL CENTER FOR ENVIRONMENTAL HEALTH (NCEH)

The mission of NCEH is to provide national leadership, through science and service, that

promotes health and quality of life by preventing or controlling those diseases, birth defects, disabilities, or deaths that result from interactions between people and their environment.

Main activities within NCEH include national leadership in prevention programs, global health, and the use of human genetic knowledge, tests, and services; public health surveillance; applied research; epidemiologic studies; laboratory analyses; statistical analyses; behavioral interventions; operations and systems research; communication and education; standards, guidelines, and recommendations; and training and technical assistance of officials of state and local health agencies in preventing and responding to public health challenges.

Emergency Services: NCEH helps local, state, federal, and international agencies plan their responses to emergency situations. NCEH responds to requests for emergency and recovery assistance after technologic disasters (e.g., radiation, chemical, or biological releases) and after natural disasters (e.g., hurricanes, wind storms, earthquakes, volcanic eruptions, or floods). NCEH established and now maintains the National Pharmaceutical Stockpile, which is designed to ensure the rapid deployment of life-saving pharmaceuticals for treating victims of terrorist attacks. NCEH also provides technical support for public health activities during international emergencies, including civil strife, disasters, and famine.

Environmental Health Services: NCEH provides a number of environmental health services that help other agencies, environmental health programs, and professionals better anticipate, identify, and respond to environmental problems and their consequences on human health. NCEH's services include helping to protect the public's health within U.S. national parks and on international cruise vessels that enter U.S. ports, ensuring the health of the public and workers during disposal of chemical weapons, and providing information and consultation on a wide range of environmental health issues.

This Solicitation invites proposals in the following areas:

014 Unmanned Aerial Vehicle and Imagery for Humanitarian Response

The lack of rapid, real-time imagery is one of the greatest obstacles to emergency health planning and response in complex humanitarian emergencies. The inability of emergency responders to gain a full picture of villages, towns, water points, settlements and communities frequently impedes the efficient distribution of essential humanitarian services and supplies. Recent advances in small unmanned aerial vehicles (UAV) present an opportunity to collect real-time fixed and video images of areas affected by complex humanitarian emergencies.

There is an urgent need for a small UAV that can be used by emergency health staff to gather information and images of refugees and others affected by conflict. NCEH is interested in funding developmental work to produce a UAV that can be rapidly deployed, is durable and lightweight, requires minimal technical skill, is man-portable, and has a significant flight duration. The UAV should incorporate daylight, low-light, and infrared surveillance equipment. Images should be both fixed and video, referenced to global-position system grids, and of a size that can be transmitted over CDC email systems. Imagery from the UAV would be used to more efficiently allocate resources and plan health-related response activities.

015 Automated User Defined Tool for Emergency Planning and Quality Control

There is a need for a standardized public health planning process to address emergencies that may involve a wide range of hazards: natural, technological and terrorism. Public health officials face many challenges to efficient and effective planning. These include limitations on time and the background knowledge necessary for evidence based decision-making. In addition, public health emergency plans must address a wide range of possible contingencies, yet remain user friendly and widely accessible.

An automated software tool is needed in order to guide public health officials in the process of integrating national and international standards of disaster response into an objective-based and measurable plan format. The resultant "paperless plan" must then be tested and validated according to widely held methods for continuous quality improvement as defined and applied by the user. The resultant interactive plan must also be widely accessible from a variety of IT platforms including desktops, laptops, LAN-based Internet and remote wireless PDA's.

NATIONAL IMMUNIZATION PROGRAM (NIP)

The National Immunization Program (NIP) of CDC, plans, coordinates, directs, and participates in efforts to prevent and reduce illness and premature death through immunization against disease. Activities include: (1) conducting epidemiology, national surveillance, research and technical consultation on designated diseases for which effective immunizing agents are available, and on the safety of vaccines; (2) assessing immunization levels at national, state, and local levels; (3) guiding the development of recommendations, guidelines, technologies, and policies for effective, safe, efficient, and economical use of existing vaccines, and for the development and incorporation of new and improved vaccines and associated technologies into disease control programs; (4) providing technical, epidemiologic, scientific, statistical, financial, programmatic, and administrative assistance to state and local health departments in support of their immunization programs to prevent diseases recommended for vaccination; (5) implementing national outreach, mobilization, and public information activities to increase understanding about the benefits and risks of vaccines, to promote the demand for them, and to improve immunization practices among health care providers; (6) designing, developing, and implementing information systems to ensure that persons are properly immunized with the recommended vaccines for them; (7) collaborating with the World Health Organization (WHO) and its regional offices and with other CDC Centers/Institutes/Offices (CIOs) in worldwide eradication efforts for polio, and in planning for eradication of other diseases.

This solicitation invites proposals for the following topic areas:

016 Develop Methods to Enhance Administration of Vaccines, Including Live Virus Vaccines, Through the Respiratory Tract

Because of the drawbacks associated with injection of vaccines using syringes and needles, the National Immunization Program has established development of alternate methods of vaccine administration as a research priority. We are requesting proposals for methods to enhance the delivery of measles, rubella and mumps vaccines through the respiratory tract. Proposals should address 1) Respiratory delivery methods for vaccines, including but not limited to aerosols, dry powders and nasal sprays, or 2) Methods for improving the uptake or effectiveness of vaccines delivered through the respiratory tract 3) Methods for evaluating deposition of vaccines in the respiratory tract, including but not limited to computer simulation models and in vitro models, or 4) Methods for facilitating study of vaccines delivered through the respiratory tract in animal models.

019 Disposable-Cartridge Jet Injector Technology

The National Immunization Program invites proposals for disposable-cartridge jet injector technology for affordable use in developing and developed countries for slow-speed, routine vaccinations, and for high-speed mass campaigns. Proposals may be for new or improved injectors themselves or for associated technology, such as filling systems or accessories, auto-reconstitution of lyophilized vaccines, and other related components.

Proposals that promote standardization of cartridge-injector interfaces among different companies through appropriate licensing arrangements will be given priority consideration because of the public interest in universal standards for cartridges.

NATIONAL CENTER FOR INFECTIOUS DISEASES (NCID)

The mission of the National Center for Infectious Diseases (NCID) is to prevent illness, disability, and death caused by infectious diseases in the United States and around the world.

To accomplish this goal, our staff members work in partnership with local and state public health officials, other federal agencies, medical and public health professional associations, infectious disease experts from academic and clinical practice, and international and public service organizations.

We accomplish our mission by conducting surveillance, epidemic investigations, epidemiologic and laboratory research, training, and public education programs to develop, evaluate, and promote prevention and control strategies for infectious diseases.

The NCID plans, directs, and coordinates a national program to improve the identification, investigation, diagnosis, prevention, and control of infectious diseases. Emerging and reemerging infectious diseases are rising due to demographic and ecological conditions that include rapid population growth, increasing poverty and urban migration, more frequent movement of people across

international boundaries, changes in the habitats of animals and insects that transmit disease, increasing numbers of people with impaired immune systems, and changes in the way food is processed and distributed. The Centers for Disease Control and Prevention (CDC) published an updated emerging infectious disease plan, *Preventing Emerging Infectious Diseases: A Strategy for the 21st Century.* This plan provides a detailed description of NCID's planned effort to understand, detect, control, and prevent national and international emerging infectious diseases. The plan builds upon new technologies, public health lessons learned in recent years, and the needs of the global public health community. The aim of the plan is to build a stronger, more flexible United States public health system that can rapidly respond to known diseases as well as be prepared for unexpected diseases and public health events as they arise. The plan is built upon four major goals: (a) surveillance and response; (b) applied research; (c) infrastructure and training; and (d) prevention and control. The plan also addresses seven emerging disease issues that affect human suffering and place a burden on society as well as three special populations. These include antimicrobial resistance, foodborne and waterborne diseases, diseases transmitted through animals and insects, disease transmitted through blood products, chronic diseases caused by infectious agents, vaccine development and use, people with immunesuppressed health conditions, pregnant women and newborns, and people crossing international boundaries. Achievement of the goals and objectives described in this plan can only be attained through collaboration and partnerships between CDC and other agencies, organizations, and individuals in public health and health-care communities worldwide.

This solicitation invites proposals for the following topic areas:

033 Development of Serologic Assays to Measure Immune Responses in Anthrax

CDC is seeking organizations for a research project that would result in identification of major immunogenic antigens that induce immune responses in anthrax, and then modification and/or development and validation of sensitive and specific assays for diagnostic use. This would include standardization of the antigen preparation, development of reference reagents, including reference sera, and standardization of assays, that could lead to validated, FDA-cleared products for in vitro diagnostic use. CDC has particular interest in assays to detect antibodies to *B. anthracis* lethal factor, spore proteins and spore antigens in clinical samples. CDC is not interested in assay development for detection of antibodies to *B. anthracis* protective antigen.

The CDC goal is to establish and maintain assays for detection of antigens and immune responses to *Bacillus anthracis* that would be widely available and effectively utilized in clinical and State and local Public Health Laboratories.

Submitted proposals should focus on previous experience and current capabilities in the relevant areas. Only those organizations with a strong background and experience in developing immunologic assays should respond

Phase I deliverables:

- Proof that identified antigens/antibodies are useful in diagnosis of anthrax and present in clinically relevant samples.
- Identification for sourcing and procurement of suitable, sustainable reference materials.
- Identification for sourcing and procurement of suitable, sustainable clinical samples for test development and validation
- Development of an easy-to-use assay format to detect identified antigens/antibodies that is suitable for use in clinical and State and local Public Health Laboratories.
- Proof that assay endpoints can be interpreted as 'positive' and 'negative' read-outs for diagnosis of anthrax.

Phase II deliverables

- FDA clearance of the assay for in vitro diagnostic use for diagnosis of anthrax.

034 Biological Control of Lyme Disease Spirochete Vector Ticks

Novel control methodologies for killing the primary vector of Lyme disease spirochetes in the eastern United States (*Ixodes scapularis*) are urgently needed. Biological control of ticks holds great promise as part of an integrated pest management campaign. Biological control methods include the use of parasitoid wasps, predators, fungi, nematodes, and other life forms to destroy ticks. The use of naturally derived chemicals (extracted from

plants) can also be a component of biological control of ticks. A plan to test a novel biological control method against *Ixodes scapularis* should be tested in the laboratory, modified for maximal efficiency and tried against field populations of ticks.

035 Oral Vaccines that Target Peridomiciliary Lyme Disease Reservoirs

A licensed vaccine against Lyme disease in humans, while demonstrating efficacy, nevertheless failed to serve as a successful disease prevention measure for various reasons. Rodent-targeted bait boxes have been shown to be an effective way to deliver acaricides to these animals for control of tick vectors of Lyme disease. This baited system could also be used to deliver an oral vaccine to rodents, as an alternative method for preventing reservoir infection and subsequent transmission to humans. Research aimed at the development and testing of oral vaccines in delivery systems that target zoonotic reservoirs of Lyme disease should be encouraged for use in preventing Lyme disease.

036 Murine Monoclonal Antibody/Human IgM Chimeric Antibody Construction and Expression

Human IgM positive control sera are required for standard serological assays (IgM capture ELISA and a duplex microsphere-based immunoassay) employed by the Diagnostic and Reference Lab, Division of Vector-Borne Infectious Diseases (DVBID), Ft. Collins, CO, to meet current CLIA human diagnostic testing standards. Positive controls are used to establish assay performance and as an indicator of reagent integrity. The availability of antiviral human IgM sera for the panel of arboviruses that are screened by the DVBID Diagnostic Lab is often problematic. It can be difficult or costly to locate large volumes of plasma or serum of high titer and specificity as well as challenging to deal with lot-to-lot variability in antibody reactivity and affinity. It would be advantageous to have a consistent supply of well-characterized human positive control sera. It would be possible to develop such a supply of control antibodies by using virus-group reactive murine monoclonal antibody (MAb)-producing hybridomas developed at DVBID for three groups of viruses: Alphaviruses (2A2C-3), Flaviviruses (6B6C-1) and California group Bunyaviruses (10G5.4). Using recombinant DNA technology, MAb hybrids (chimeras) could be constructed and would consist of murine light and heavy chain variable regions, which encode antigen binding specificity, combined with human kappa and IgM constant regions. Such chimeric antibodies could be reproducibly expressed in virtually unlimited quantities and would also be homogeneous in affinity and specificity.

The contractor would acquire appropriate hybridoma cells from DVBID and isolate the immunoglobulin V regions using PCR cloning. Sequencing of multiple clones of V gene product should be performed to monitor for Taq DNA polymerase-induced errors. The contractor would also develop an immunoglobulin expression vector with a human IgM constant region (C_K and C_μ) into which would be inserted the V_H and V_L gene fragments isolated by PCR cloning to produce chimeric mouse-human IgM antibodies. The chimeric antibody constructs would be transfected into appropriate cells and the transfectant supernatants monitored for expression of chimeric antibody. The final steps would be to establish stable cell lines secreting desired chimeric antibodies and purification of a lot of each chimeric antibody. The chimeric antibodies will be tested at DVBID for reactivity in the standard applicable serological assays.

037 Vaccination of Birds for West Nile Virus Using Recombinant Seeds

Wild birds are the amplifying hosts of West Nile virus, a mosquito-borne pathogen of significant public and veterinary health importance. The transmission cycle could potentially be interrupted by immunizing large numbers of passerine and other granivorous birds. Oral vaccination could be achieved either by delivering recombinant seeds to birds through traditional backyard birdfeeders, or through fields grown with recombinant seed-bearing crops. Oral vaccination of crows using a DNA plasmid was unsuccessful. Success should require successful transformation of plant cells, and expression of immunogenic viral cDNA within edible portions of the plant, ideally the seeds. Phase I would entail transformation of plant germ cells using the cDNA plasmid that carries the WNV envelope gene (available from Dr. Jeff Chang at CDC), and expression of viral protein in a form that reacts with anti-WNV antibodies. Phase II would entail demonstration of immunity of plant-derived WNV E protein in an avian model, such as chicks, as well as field testing of delivery systems (*e.g.*, commercially produced seeds or agricultural crops, such as corn or wheat). Phase III would entail field testing of a large-scale crop production system.

038 Development of Novel Reagents for Poxvirus Research and Diagnostics

The development of reagents, diagnostic reagents and test kits for the detection of orthopoxviruses (OPX) or exposure to OPX, as well as reagents able to discriminate other poxviruses has regained interest in the past several years due to concerns of bioterrorism events as well as recognition of zoonotic transmission of OPX in North America. Use of reagents for existing diagnostic tests and for test development continues to be of high interest for public health, bioterrorism preparedness and research related to these viruses. The development of high quality and standardized reagents such as species-specific monocolonal antibodies, polyclonal antibodies, viral antigen preparations (including recombinants) as well as unique reagents and methods for serology and antigen detection are sought. In addition, reagents for diagnosis or detection of confounding viral agents such as parapox are also desired. Commercial development of test kits would be of high interest utilizing novel detection formats as well as traditional methods.

039 North American Orthopoxviruses as Vaccine Vectors; Safety, Efficacy and Feasibility

Several orthopoxviruses have been utilized as vaccines or as vaccine vectors expressing recombinant proteins. Vaccinia (smallpox vaccine) remains the only OPX routinely used in humans. However, adverse events associated with smallpox vaccine have impaired it's acceptance as a vaccine and potentially as a vaccine vector. There are several North American OPX isolates that were isolated in wildlife but are not recognized to result in serious clinical manifestations in wildlife or humans. Interest in utilization of these isolates for vaccine vectors is based on several assumptions. One; that these isolates are not associated with human or serious animal disease, two; that they are relatively safe for use in animal populations, and three; that they would parallel vaccinia in their ability to elicit a powerful immune response against recombinant proteins by the host.

Research on the characterization of these viruses is desirable and proposals should include characterization of the viruses as compared to vaccinia or other well characterized OPX regarding host range (actual and predicted), disease potential, utility for engineering, and efficacy in immune induction using a model system(s).

040 Assay Development for Taenia solium Cysticercosis and Taeniasis

Each year neurocysticercosis affects ~50 million people in Latin America, Africa, and Asia, often causing severe disability or death. This infection, acquired by ingestion of eggs through fecal-oral contact with a carrier of the pork tapeworm, *Taenia solium*, is responsible for rates of epilepsy that are three to six times higher than in areas that are disease free. Transmission is associated with free-roaming pig-rearing practices, inadequate sanitation, ignorance, and poverty. Highly conservative estimates for Peru alone have put the yearly loss due to cysticercosis in pigs at ~$4 million and that for human treatment at ~$32 million. Epidemiologic surveys of rural areas of Peru, Mexico, Bolivia, China, Rwanda, and Ecuador, done by CDC have put the prevalence of this disease between 10% to 23%. Increasing immigration and travel has resulted in the importation of this disease to developed countries. This is exemplified by a 1.37% prevalence of this disease in an orthodox Jewish community in Brooklyn, New York, traceable to domestic workers from South America who harbored adult tapeworms and a 4 to10% rate of cysticercosis related seizure admissions in emergency departments of Latino-prominent states (NM, AZ, CA) in the U.S. The WHO and other public health agencies consider the cysticercosis/taeniasis disease complex eradicable. A large-scale disease elimination project has been initiated in an area in Northern Peru with a population of ~100,000. Immunoblot diagnostic tests (EITB) for cysticercosis and taeniasis invented by CDC scientists have revolutionized patient identification, epidemiology, and control of this disease complex. Chemically synthesized and recombinant antigens for these tests, covered under U.S. patents, assigned to the CDC, were developed and their sequences registered with GeneBank:

GeneBank registry number	*Antigen name*	*Application*
AF098073	Ts18 var1	Human/porcine cysticercosis
AF082830	TsRS1	Human/porcine cysticercosis
AF082829	Ts14	Human/porcine cysticercosis

GeneBank registry number	*Antigen name*	*Application*
AF356343	TsRS2 var1	Human/porcine cysticercosis
AY212944	GP50a	Human/porcine cysticercosis
AY212945	GP50b	Human/porcine cysticercosis
AY212946	GP50c	Human/porcine cysticercosis
AY211879	T24	Human/porcine cysticercosis
AY183761	TSES33	Human taeniasis
AY128681	TSES38	Human taeniasis

We solicit proposals for the development of commercially viable, rapid, robust, and field-application assay formats and test kits based on these antigens. These tests must be applicable for both human/porcine cysticercosis, and human taeniasis. The assays must be functional with minimal equipment and amenable to large-scale surveys or control programs.

NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

NCBDDD provides national leadership for preventing birth defects and developmental disabilities and for improving the health and wellness of people with disabilities.

This solicitation invites proposals for the following topic areas:

001 Development of Materials for "Birth Defects Prevention Month"

Design, test, and produce low-budget campaign materials for "January is Birth Defects Prevention Month" that can be replicated at state and local levels.

002 Development of Health Communication Materials to Prevent Alcohol-Exposed Pregnancies in Underserved Populations

Research indicates a need for health communication materials targeting specific audiences, including underserved populations, to prevent alcohol-exposed pregnancies. The National Center on Birth Defects and Developmental Disabilities invites proposals to develop, produce and evaluate innovative health communication materials to reach underserved audiences who are at risk of alcohol-exposed pregnancies. Target audiences will include, but are not limited to, Hispanic and American Indian women of child-bearing age. Target audiences, content, and methods of delivery will be determined through audience segmentation and formative research. These materials will be culturally and linguistically appropriate for each segmented audience (not translations of previously existing materials).

003 Development, Production, and Evaluation of a Folic Acid Educational Tool for Use with a Variety of Audiences

Develop, produce and evaluate the effectiveness of an educational video/CD-Rom/instructional module about the importance of pre-conceptional folic acid. Target audiences include but are not limited to: engaged couples; high school and college students, beauty spa and salon employees, health professionals such as nurses and nutritionists, newly married couples, Hispanic women, and all women of reproductive age.

004 Teratogen Symbol Testing among Diverse Audiences

Preliminary drafts of teratogenic symbols have been tested among groups of adult women of childbearing age from different race/ethnic backgrounds. The results from this preliminary research have been fruitful in identifying specific design elements from the various drafts that can communicate clearly and effectively that a medication has teratogenic properties. These design elements need to be incorporated into a new symbol design and re-tested among both adolescent and adult women of childbearing age from different race/ethnic backgrounds with differing literacy levels, and with different language preferences. The goal is to ensure that a symbol is developed that is accurately interpreted by all women of reproductive age.

005 Development of Health Education Materials to Promote Pre-Pregnancy Health Visits

A variety of health messages are important for women prior to pregnancy and in the earliest weeks of pregnancy. Research indicates that many women do not feel that a doctor's visit is necessary prior to conception. The National Center on Birth Defects and Developmental Disabilities invites proposals to develop, test, produce and evaluate communication materials designed to make women aware of the importance of obtaining health care prior to pregnancy. The health communication module (in any format) should include concepts such as maintaining a healthy weight prior to pregnancy, not smoking, drinking alcohol or using street drugs, being up-to-date on vaccinations, explain the concept of medication teratogenicity, and other topics.

HUMAN SUBJECTS RESEARCH

GUIDANCE AND INFORMATION SUPPLEMENT

SCENARIO A: NO HUMAN SUBJECT RESEARCH PROPOSED

CRITERION

If you are uncertain as to whether your research involves Human Subjects please read: Question 1: Does your proposed research involve human subjects?

INSTRUCTIONS

In your proposal narrative, create a heading labeled “Human Subjects Research” and place it immediately after the last entry in the Research Plan section. Include the following statement below the heading: “No Human Subjects Research is proposed in this proposal.”

If your research involves human specimens, cell lines and/or data from subjects, please provide a justification for your claim that no human subjects are involved.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

Do not follow the instructions for Scenario A if research activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution. You will need to consider an alternative scenario.

If you need to consider an alternative Scenario return to the Decision Table.

SCENARIO B: HUMAN SUBJECTS RESEARCH CLAIMING EXEMPTION 4

CRITERIA

Human Subjects Research	Yes
Exemption	4
Clinical Research	No
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

INSTRUCTIONS AND REQUIRED INFORMATION

Check the box marked "This proposed project involves human subjects" on the face page.

Create a "**Human Subjects Research**" section heading and place it immediately following the last entry in the Research Plan section.

Indicate that you are claiming Exemption 4 and provide a justification that explains why you believe your research meets this exemption.

Although your research may be exempt from the IRB oversight provisions, it is still Human Subjects research and you will need to address the following three items:

1. Human Subjects Involvement and Characteristics:

a. Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.

b. Describe the characteristics of the subject population, including their anticipated number, age range, and health status. If the characteristics of the population are not available, then the applicant should indicate that the information is unknown.

c. Identify the criteria for inclusion or exclusion of any subpopulation.

d. Explain the rationale for the involvement of vulnerable populations, such as fetuses, neonates, pregnant women, children, institutionalized individuals, or others who may be considered vulnerable populations. Exemptions 1-6 do not apply to research involving prisoners or subjects who become prisoners (see 45 CFR Part 46 Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see 45 CFR Part 46 Subpart D), Exemption 2 can only be used for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

e. List any collaborating sites where human subjects research will be performed and describe the role of those sites in performing the proposed research.

2. Sources of Materials:

a. Describe the research material obtained from living human subjects in the form of specimens, records, or data.

b. Describe any data that will be recorded on the human subjects involved in the project.

c. Describe the linkages to subjects, and indicate who will have access to subject identities.

d. Provide information about when the specimens, records, or data were collected and whether new material or data will need to be collected specifically for your proposed research project.

3. Justification:

a. Indicate that you are claiming Exemption 4.

b. Provide a justification for why your research meets the criteria for Exemption 4. Note: Even if your research is appropriate for Exemption 4, you are required to address the inclusion of children, if known.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

The material that you provide will be used by reviewers as part of their evaluations on the research approach and methodology.

What types of research meet the criteria for Exemption 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. Determining the appropriateness of Exemption 4 for research using specimens and data can be complex.

Note: Prospective collection of additional specimens does not meet the criteria for Exemption 4.

If you are uncertain as to whether your research qualifies for exemption please read: Question 2: Does your proposed research qualify for an exemption from IRB review?

If you are uncertain as to whether your research qualifies for Exemption 4 please refer to: Exemption 4 Guidance and Information

or

If you need to consider an alternative Scenario return to the Decision Table.

SCENARIO C: HUMAN SUBJECTS RESEARCH CLAIMING EXEMPTION 1,2,3,5, OR 6

CRITERIA

Human Subjects Research	Yes
Exemption	1, 2, 3, 5, 6
Clinical Research	Yes
Clinical Trial	N/A
NIH-Defined Phase III Clinical Trial	N/A

INSTRUCTIONS AND REQUIRED INFORMATION

Check the box marked "This proposed project involves human subjects" on the face page.

Create a section entitled "**Human Subjects Research**" immediately following the last entry in the Research Plan section. In this section, identify which exemption (1,2,3,5,6) you are claiming. Provide a justification that explains why you believe your research meets this exemption. (If you are claiming Exemption 4 please refer to Scenario B and the appropriate instructions.)

Although your research may be exempt from the IRB oversight provisions, it is still Human Subjects Research and you will need follow the instructions that are identified for each of the following five topics and provide the information that is requested:

1. Human Subjects Involvement and Characteristics:

a. Describe the proposed involvement of human subjects in the work outlined in the Research Design and Methods section.

b. Describe the characteristics of the subject population, including their anticipated number, age range, and health status.

c. Identify the criteria for inclusion or exclusion of any subpopulation (e.g., men, women, children).

d. Explain the rationale for the involvement of vulnerable populations, such as fetuses, neonates, pregnant women, children, institutionalized individuals. Please note that research involving prisoners is not exempt under any category (see 45 CFR Part 46 Subpart C).

e. List any collaborating sites where human subjects research will be performed and describe the role of those sites in performing the proposed research.

2. Sources of Materials:

a. Describe the sources of the research material obtained from living human subjects in the form of specimens, records, or data.

b. Describe any data that will be recorded on the human subjects involved in the project.

c. Describe the linkages to subjects and indicate who will have access to subject identities.

d. Provide information about when the specimens, records, or data were collected and whether new material or data will need to be collected specifically for your proposed research project.

3. Justification:

In this section, identify which exemption (1, 2, 3, 5, or 6) you are claiming. (If you are claiming Exemption 4 please refer to Scenario B and the appropriate instructions.) Justify why your research is appropriate for the exemption that you have claimed.

4. Inclusion of Women and Minorities (click and follow instructions)

The inclusion of women and members of minority groups and their subpopulations must be addressed in developing a research design appropriate to the scientific objectives of the study.

Create a section entitled “Inclusion of Women and Minorities” and place it immediately following the last entry in the “Human Subjects Research” section.

Describe the composition of the proposed study population in terms of sex/gender and racial/ethnic group, and provide a rationale for selection of such subjects. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants. See http://grants.nih.gov/grants/funding/women_min/women_min.htm.

5. Inclusion of Children (click and follow instructions)

For the purpose of implementing these guidelines, a **child** is defined as an individual under the age of 21 years. (For additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html.)

GUIDANCE AND ADDITIONAL INSTRUCTIONS

The material that you provide will be used by reviewers as part of their evaluations on the approach and methodology of your proposed research.

If you are uncertain as to whether your research qualifies for exemption please read: Question 2: Does your proposed research qualify for an exemption from IRB review?

If you are uncertain as to whether your research qualifies for exemption 4 please refer to: Exemption 4 Guidance and Information

or

If you need to consider an alternative Scenario return to the Decision Table.

SCENARIO D: HUMAN SUBJECTS AND CLINICAL RESEARCH

CRITERIA

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	No
NIH-Defined Phase III Clinical Trial	No

INSTRUCTIONS AND REQUIRED INFORMATION:

Check the box marked “This proposed project involves human subjects” on the face page.

Create a section entitled “**Human Subjects Research**” immediately following the last entry in the Research Plan section.

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

1. Human Subjects Research (click and follow instructions)

2. Inclusion of Women and Minorities (click and follow instructions)

3. Inclusion of Children (click and follow instructions)

If your proposal utilizes Collaborating Sites provide the information identified above for each participating site.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

The material that you provide will be used by reviewers as part of their evaluations on the approach and methodology of your proposed research.

Research that meets the criteria for Exemption 4 is not considered clinical research.

Research that uses **existing (archived)** specimens that **can** be linked to living individuals must address the inclusion of women, minorities and children as identified above, unless the investigator does not have access to the information. The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

If you are uncertain as to whether your research qualifies as clinical research please read: Question 3: Does your proposed research include Clinical Research?

or

If you need to consider an alternative Scenario return to the Decision Table.

SCENARIO E: HUMAN SUBJECTS AND CLINICAL TRIAL

CRITERIA

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	No

INSTRUCTIONS AND REQUIRED INFORMATION:

Check the box marked, “This proposed project involves human subjects” on the face page.

Create a section entitled “**Human Subjects Research**” immediately following the last entry in the Research Plan section.

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

1. Human Subjects Research (click and follow instructions)

2. Data and Safety Monitoring Plan (click and follow instructions)

3. Inclusion of Women and Minorities (click and follow instructions)

4. Inclusion of Children (click and follow instructions)

If you proposal utilizes Collaborating Sites provide information for each of the issues identified above for each participating site.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

The material that you provide will be used by reviewers as part of their evaluations on the research design and methods of your proposed research.

If you are uncertain as to whether your research qualifies as clinical trial please read: Question 4: Does your proposed research include a clinical trial?

or

If you need to consider an alternative Scenario return to the Decision Table.

SCENARIO F: HUMAN SUBJECTS AND NIH DEFINED PHASE III CLINICAL TRIAL

CRITERIA

Human Subjects Research	Yes
Exemption	No
Clinical Research	Yes
Clinical Trial	Yes
NIH-Defined Phase III Clinical Trial	Yes

INSTRUCTIONS AND REQUIRED INFORMATION:

Check the box marked “This proposed project involves human subjects” on the face page.

Create a section entitled “**Human Subjects Research**” immediately following the last entry in the Research Plan section.

Follow the instructions that are identified for each of the following topics and provide the information that is requested:

1. Human Subjects Research (click and follow instructions)

2. Data and Safety Monitoring Plan (click and follow instructions)

3. Inclusion of Women and Minorities (including information requirement for NIH-Defined Phase III Clinical Trial) (click and follow instructions)

4. Inclusion of Children (click and follow instructions)

If your proposal utilizes Collaborating Sites provide the information identified above for each participating site.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

The material that you provide will be used by reviewers as part of their evaluations on the research approach and methodology.

If you are uncertain as to whether your research qualifies as clinical research please read: Question 5: Does your proposed research meet criteria for an NIH-Defined Phase III Clinical Trial?

or

If you need to consider an alternative Scenario return to the Decision Table.

HUMAN SUBJECTS RESEARCH

QUESTION 1: DOES YOUR PROPOSED RESEARCH INVOLVE HUMAN SUBJECTS?

The first thing you must determine is whether or not your research involves human subjects.

Federal regulations (45 CFR Part 46) define a **human subject** as a living individual about whom an investigator conducting research obtains:

- data through intervention or interaction with the individual or
- identifiable private information

The definition of human subjects includes the use of human organs, tissues, and body fluids, as well as graphic, written, or recorded information, from living individuals if the identity of the subjects can be readily ascertained by the investigator or other members of the research team.

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Regulatory requirements (Federal and state) to protect human subjects apply to a much broader range of research than many investigators realize, and researchers using human tissue specimens are often unsure about how regulations apply to their research. Regulatory obligations to protect human subjects *may* apply, for example, to research that uses –

- Bodily materials, such as cells, blood or urine, tissues, organs, hair or nail clippings, from identifiable living individuals, even if you did not collect these materials
- Residual diagnostic specimens, from identifiable living individuals, including specimens obtained for routine patient care that would have been discarded if not used for research
- Private information, such as medical information, that can be readily identified with living individuals, even if the information was not specifically collected for the study in question. This includes research on cell lines or DNA samples that can be readily associated by the investigator or others engaged in the research with the identity of living individuals.

Cadaver Specimens: If your research proposes the use of cadaver specimens, then the answer to question 1 is "No" because human subjects are defined as "living individuals." The use of cadaver specimens is governed by applicable state and local law and is not directly regulated by 45 CFR Part 46.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

If you answered No to question 1 then refer to Scenario A.

If activities involving human subjects are planned at any time during the proposed project period, either at the applicant organization or at any other performance site or collaborating institution, then your answer is "Yes" even if the research is exempt from regulations for the protection of human subjects.

If you answered Yes to question 1 then you need to determine whether your research qualifies for an exemption from the Human Subjects Protection requirements. Proceed to Question 2

or

If you need to consider an alternative Scenario return to the Decision Table.

EXEMPT RESEARCH

QUESTION 2: IS YOUR PROPOSED RESEARCH DESCRIBED BY ONE OR MORE OF THE EXEMPTIONS IN THE HHS REGULATIONS (45 CFR PART 46)?

Some human subjects research is exempt from the HHS regulations (45 CFR Part 46). Read descriptions of the following six exemptions to determine if your research meets the criteria for one or more of the following exemptions. In order to be exempt, the involvement of human subjects in the research activities must be limited to only one or more of the categories of exempt research.

OHRP advises that the IRB (or some authority other than the investigator) determines whether proposed research is exempt from the HHS human subjects regulations.

Research involving individuals who are or who become prisoners cannot be exempt under any exemption categories (see 45 CFR Part 46 Subpart C).

Exemption 1: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

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

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

Exemption 2 for research involving survey or interview procedures or observation of public behavior, does not apply to research involving children (see 45 CFR Part 46, Subpart D), except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

Exemption 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 (b)(2) of this section if: (i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

Exemption 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.

Research that meets the criteria for Exemption 4 is not considered “clinical research.”

Evaluating what does and does not fall under Exemption 4 can be complex. The NIH brochure, Research on Human Specimens, contains information that is helpful in making this determination. See http://www.cancerdiagnosis.nci.nih.gov/specimens/brochure.html and also the information contained at: Exemption 4 Guidance and Information.

Exemption 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: (i) public benefit or service programs (ii) procedures for obtaining benefits or services under those programs (iii) possible changes in

or alternatives to those programs or procedures or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

Exemption 6: Taste and food quality evaluation and consumer acceptance studies (i) if wholesome foods without additives are consumed or (ii) 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 Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

If you answered Yes to question 2 then your research qualifies for an exemption.

If you answered No to Question 2 then your research does not qualify for one of the exemption your research is not exempt from IRB Review. Return to the Decision Table and choose another option or proceed to Question 3.

If your research qualifies for Exemption 4 follow the instructions for Scenario B and read the information contained in Exemption 4 Guidance and Information.

If your research qualifies for any of the other five exemptions follow the instruction for Scenario C.

Remember that you need to identify which exemption you believe is applicable to your research, provide a justification for exemption with sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that a claimed exemption is appropriate.

Proceed to Question 3

or

Return to Decision Table

CLINICAL RESEARCH

QUESTION 3: DOES YOUR PROPOSED RESEARCH MEET THE DEFINITION FOR CLINICAL RESEARCH?

The NIH defines Clinical Research as:

(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes: (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, or (d) development of new technologies.

(2) Epidemiologic and behavioral studies.

(3) Outcomes research and health services research.

Clinical research that does not meet the criteria for a clinical trial or an NIH-defined Phase III clinical trial must follow the instructions in Scenario D.

Research that meets the criteria for Exemption 4 is not considered "clinical research." Investigators with research that meets the criteria for Exemption 4 must follow the instructions provided in Scenario B.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

If your answered yes to Question 3 then proceed to Question 4 and Question 5 to determine whether your research meets the criteria for a clinical trial or an NIH-defined Phase III clinical trial.

or

Return to Decision Table

CLINICAL TRIAL

QUESTION 4: DOES YOUR PROPOSED RESEARCH INCLUDE A CLINICAL TRIAL?

The NIH defines a Clinical Trial as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices).

Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious and effective.

Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits these criteria of a clinical trial.

Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision-making for the subject or the test itself imposes more than minimal risk for subjects.

Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases:

Phase I clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range, and to identify side effects).

Phase II clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.

Phase III studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.

Phase IV studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

If you answered “Yes” to Question 4, then you will need to provide a general description of a Data and Safety Monitoring Plan. See Scenario E.

Also continue to Question 5 to determine whether your research meets the criteria for an NIH-defined Phase III clinical trial.

If you answered “Yes” to Question 3 (Clinical Research) and “No” to Question 4 (Clinical Trial), then follow the instructions for Scenario D.

or

Return to Decision Table.

NIH-DEFINED PHASE III CLINICAL TRIAL

QUESTION 5: DOES YOUR PROPOSED RESEARCH MEET CRITERIA FOR AN NIH-DEFINED PHASE III CLINICAL TRIAL?

An *NIH-Defined Phase III Clinical Trial* is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of either evaluating an experimental intervention in comparison with a standard or control intervention or of comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

If your research meets the above criteria, then in addition to providing a Data and Safety Monitoring Plan, you will be expected to address whether you expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology, and other relevant studies.

You will be expected to provide a research plan that must include one of the following plans:

- Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, OR
- Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups is not required as subject selection criteria, but inclusion is encouraged.), OR
- Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

If you answered yes to Question 5 then proceed to Scenario F.

If you answered No then

Return to Decision Table to choose another Scenario.

EXEMPTION 4 GUIDANCE AND INFORMATION

Research that meets the criteria for Exemption 4 is Human Subjects Research, but it is not considered clinical research. Evaluating what does and does not fall under Exemption 4 can be complex. The NIH Brochure, "Research on Human Specimens," (http://www.cancerdiagnosis.nci.nih.gov/specimens/ brochure.html) is helpful in making this determination.

Exemption 4 includes 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.

NOTE: Some researchers mistakenly believe that any studies on existing pathology specimens are exempt. Exemption 4 does not apply to specimens that are linked to patient identity, even if the subject identifiers are locked up or kept by someone other than the researcher. It does not matter if the tissue would otherwise have been discarded. OHRP strongly recommends that investigators should not have the authority to make an independent determination that research involving human subjects is exempt. Investigators should check with the IRB or other designated authorities to determine institutional policies and procedures for the designation of any exemptions claimed for the proposed research (see http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc95-02.htm).

WHAT IS MEANT BY "EXISTING" DATA OR SPECIMENS?

Exemption 4 applies to retrospective studies of specimens that have already been collected. The materials must be "on the shelf" (or in the freezer) at the time the protocol is submitted to the IRB or other designated officials at your institution to determine whether the research is indeed exempt. Prospective collection of additional specimens does not meet the criteria for Exemption 4.

WHAT ABOUT SPECIMENS OBTAINED FROM A TISSUE BANK?

OHRP offers guidance about the requirements for establishing tissue banks and repositories to collect, store, and distribute human tissue materials for research purposes (see current guidance at http://www.hhs.gov/ohrp/policy/index.html). There are many kinds of tissue banks that operate in different ways. Use of tissue specimens obtained from an established tissue repository may be exempt under certain circumstances. You should check with your IRB or other designated authorities at your institution to determine how the exemption applies to your research.

WHAT IS MEANT BY "PUBLICLY AVAILABLE SOURCES"?

This language in the regulation was intended to apply to public sources of data, such as census data. Its meaning with respect to human tissue specimens is widely debated. Although there are organizations that make human cells and tissues broadly accessible at reasonable cost to the research community, these materials are not usually available to the public at large.

WHAT IS MEANT BY "IDENTIFIERS LINKED TO THE SUBJECTS"?

Identifiers, such as names, social security numbers, medical record numbers, or pathology accession numbers, permit specimens to be linked to living individuals and perhaps also to associated medical information.

Exemption 4 may apply to specimens provided by a tissue bank or other repository, so long as the specimens are provided without identifiers and the repository has firm policies and procedures, approved by its own IRB, to prevent the release of personal information.

Exemption 4 does not apply in situations where a researcher receives "coded" specimens from a collaborator if the collaborator retains the key to the code, even though the researcher may have no access to patient identities.

HOW CAN I DETERMINE WHETHER MY RESEARCH MEETS THE CRITERIA FOR EXEMPTION 4?

The humans subjects regulations decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) from the Office of Human Research Protection (OHRP) will help you to see whether your research falls under the human subjects regulations and if so, whether it meets the criteria for Exemption 4. OHRP advises that investigators should not have the authority to make an independent determination that research involving human subjects is exempt. Investigators should check with the IRB or other designated authorities to determine institutional policies and procedures for the designation of any exemptions claimed for the proposed research (see http://www.hhs.gov/ohrp/humansubjects/guidance/hsdc95-02.htm).

GUIDANCE AND ADDITIONAL INSTRUCTIONS

Return to Scenario B

or

Return to Decision Table

HUMAN SUBJECTS RESEARCH

Create a section entitled "**Human Subjects Research**" immediately following the last entry in the Research Plan section. Provide information to address the following issues:

1. RISKS TO THE SUBJECTS

a. Human Subjects Involvement and Characteristics:

Describe the proposed involvement of human subjects in the work outlined in the Research Plan section.

Describe the characteristics of the subject population, including their anticipated number, age range, and health status.

Identify the criteria for inclusion or exclusion of any subpopulation.

Explain the rationale for the involvement of special classes of subjects, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.

List any collaborating sites where human subjects research will be performed, and describe the role of those sites in performing the proposed research.

b. Sources of Materials:

Describe the research material obtained from living human subjects in the form of specimens, records, or data.

Describe any data that will be recorded on the human subjects involved in the project.

Describe the linkages to subjects, and indicate who will have access to subject identities.

Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for your proposed research project.

c. Potential Risks:

Describe the potential risks to subjects (physical, psychological, social, legal, or other) and assess their likelihood and seriousness to the subjects.

Where appropriate, describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent:

Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.

Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. The informed consent document need not be submitted to the PHS unless requested.

b. Protection Against Risk:

Describe planned procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.

Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies), must include a description of the plan for data and safety monitoring of the research to ensure the safety of subjects.

3. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Discuss the potential benefits of the research to the subjects and others.

Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

4. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.

Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologicals) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the Food and Drug Administration, and/or the status of requests for an IND or IDE covering the proposed use of the test article in the research plan.

5. DATA AND SAFETY MONITORING PLAN

Create a section heading entitled "**Data and Safety Monitoring Plan**." If your research includes a clinical trial.

Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring, and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB),the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (http://www.fda.gov/) and also see the following websites for more information related to IND and IDE requirements:
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)
http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)

The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:

Principal Investigator (required)

Independent individual/Safety Officer

Designated medical monitor

Internal Committee or Board with explicit guidelines

Data and Safety Monitoring Board (DSMB - required for multi-site trials involving interventions that entail potential risk to the participants)

Institutional Review Board (IRB - required)

A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html).

6. NOTE: DATA AND SAFETY MONITORING BOARD

NIH specifically requires the establishment of **Data and Safety Monitoring Boards** (DSMBs) for **multisite** clinical trials involving **interventions that entail potential risk to the participants**, and **generally** for Phase III clinical trials. Although Phase I and Phase II clinical trials may also use DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.

GUIDANCE AND ADDITIONAL INSTRUCTIONS

Proceed to Inclusion of Women and Minorities

INCLUSION OF WOMEN AND MINORITIES

Instructions:

Create a section heading entitled "**Inclusion of Women and Minorities**" and place it immediately following the "Human Subjects Research" section. Although no specific page limitation applies to this section of the proposal, be succinct.

This section of the research plan must include and address, at a minimum, the following four points:

1. The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups for each proposed study or protocol using the format in the Targeted/Planned Enrollment Table. (Instructions for completing this table are provided below.) If you are using existing specimens and/or data that does not meet the criteria for Exemption 4 and you do not have access to information on the distribution of women and minorities, so state and explain the impact on the goals of the research as part of the rationale that inclusion is inappropriate (item 3 below). Alternatively, you may describe the women and minority composition of the population base from whom the specimens and/or data will be obtained.

2. A description of the subject selection criteria and rationale for selection of sex/gender and racial/ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.

3. A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group (see examples below).

4. A description of proposed outreach programs for recruiting sex/gender and racial/ethnic group members as subjects.

Examples of acceptable justifications for exclusion of:

A. One gender:

    1. One gender is excluded from the study because:
        - inclusion of these individuals would be inappropriate with respect to their health;
        - the research question addressed is relevant to only one gender;
        - evidence from prior research strongly demonstrates no difference between genders;
        - sufficient data already exist with regard to the outcome of comparable studies in the excluded gender, and duplication is not needed in this study.
    2. One gender is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects by gender (e.g., uniquely valuable stored specimens or existing datasets are single gender; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens).
    3. Gender representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete gender documentation are used), and this does not compromise the scientific objectives of the research.

B. Minority groups or subgroups:

    1. Some or all minority groups or subgroups are excluded from the study because:
        - Inclusion of these individuals would be inappropriate with respect to their health;
        - The research question addressed is relevant to only one racial or ethnic group;
        - Evidence from prior research strongly demonstrates no differences between racial or ethnic groups on the outcome variables;

- A single minority group study is proposed to fill a research gap;
- Sufficient data already exists with regard to the outcome of comparable studies in the excluded racial or ethnic groups and duplication is not needed in this study.

2. Some minority groups or subgroups are excluded or poorly represented because the geographical location of the study has only limited numbers of these minority groups who would be eligible for the study, and the investigator has satisfactorily addressed this issue in terms of:
   - The size of the study;
   - The relevant characteristics of the disease, disorder or condition;
   - The feasibility of making a collaboration or consortium or other arrangements to include representation.
3. Some minority groups or subgroups are excluded or poorly represented because the purpose of the research constrains the applicant's selection of study subjects by race or ethnicity (e.g., uniquely valuable cohorts, stored specimens or existing datasets are of limited minority representation, very small numbers of subjects are involved, or overriding factors dictate selection of subjects, such as matching of transplant recipients or availability of rare surgical specimens).
4. Racial or ethnic origin of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens or data sets with incomplete racial or ethnic documentation are used) and this does not compromise the scientific objectives of the

ADDITIONAL INSTRUCTIONS AND REQUIREMENTS WHEN NIH-DEFINED PHASE III CLINICAL TRIALS ARE PROPOSED

If your proposed research includes an NIH-Defined Phase III Clinical Trial, the section on Inclusion of Women and Minorities also must address whether you expect to find clinically important sex/gender and/or race/ethnicity differences in the intervention effect. The discussion may include supporting evidence and/or data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. Your discussion of expected sex/gender and/or race/ethnicity differences in intervention effect must include selection and discussion of one of the following analysis plans:

A. Plans to conduct valid analyses to detect significant differences in intervention effect among sex/gender and/or racial/ethnic subgroups when prior studies strongly support these significant differences among subgroups, **OR**

B. Plans to include and analyze sex/gender and/or racial/ethnic subgroups when prior studies strongly support no significant differences in intervention effect between subgroups. (Representation of sex/gender and racial/ethnic groups in not required as subject selection criteria, but inclusion is encouraged.), **OR**

C. Plans to conduct valid analyses of the intervention effect in sex/gender and/or racial/ethnic subgroups (without requiring high statistical power for each subgroup) when the prior studies neither support nor negate significant differences in intervention effect between subgroups.

INSTRUCTIONS FOR COMPLETING THE TARGETED/PLANNED ENROLLMENT TABLES FOR REPORTING RACE AND ETHNICITY DATA FOR SUBJECTS IN CLINICAL RESEARCH

A. New Proposals and Clinical Research Studies begun after January 10, 2002:

All new clinical research studies should collect and report information on participants with respect to two categories of ethnicity and five categories of race. The new Inclusion Enrollment Report Table (MS Word or PDF) for reporting summary data on participants to NIH includes two categories of ethnicity and five categories of race and is based on recent changes by the Office of Management and Budget (OMB) regarding standards for data on race and ethnicity. Investigators should review the instructions and Frequently Asked Questions about using the new Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

For new proposals and clinical research studies begun after January 10, 2002, use the Targeted/Planned Enrollment Table format (MS Word or PDF).

Provide the study title.

The ‘”Total Planned Enrollment” means the number of subjects that are expected to be enrolled during the entire period of the study and are needed to evaluate the research question The “Total Planned Enrollment” will be reported in two ways in the table: by “Ethnic Category” and by “Racial Categories.”

“Ethnic Category”: Provide the numeric distribution of the Total Planned Enrollment according to ethnicity and sex/gender in the top part of the table.

“Racial Categories”: Provide the numeric distribution of the Total Planned Enrollment, this time by racial categories and sex/gender, in the bottom part of the table. Note that Hispanic is not a racial category.

If there is more than one study/protocol, provide a separate table for each.

List any proposed racial/ethnic subpopulations below the table.

How should I report race and ethnicity data when my research involves a foreign population?

Investigators are encouraged to design their data collection instruments in ways that allow respondent self-identification of their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the required categories. Also, the investigator can report on any racial/ethnic subpopulations by listing this information in an attachment to the required table. This may be particularly useful when distinctive subpopulations are relevant to the scientific hypotheses being studied.

When completing the tables, investigators should asterisk and footnote the table indicating that data includes foreign participants. If the aggregated data only includes foreign participants, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign participants, we suggest the investigator complete two separate tables – one for domestic data and one for foreign data, with an asterisk and footnote accompanying the table with foreign data.

B. Clinical Research Studies begun before January 10, 2002:

If the proposed research uses existing data, then use the formats below for competing continuations and competing supplements.

Competing Continuations and Competing Supplements:

For competing continuations involving the collection of new/additional clinical data, use the "Targeted/Planned Enrollment Table (MS Word or PDF)" and the instructions above. **Note:** If you choose to report information with the new Targeted/Planned Enrollment Table, you must continue to use this format for the remaining years of the project.

For competing continuations involving studies begun before January 10, 2002 that do not involve the collection of new/additional clinical data, the data on ethnicity/race and sex/gender may be presented in EITHER the Targeted/Planned Enrollment Table (MS Word or PDF) OR the 4/98 Version of the Inclusion Table (MS Word or PDF). If data were originally collected from study subjects using two questions (one about ethnicity and one about race) and subjects were given the option of selecting more than one race, then use the Targeted/Planned Enrollment Table. Otherwise, use the 4/98 Version of the Inclusion Table, which uses a combined race/ethnicity format with five categories.

For competing supplemental proposals involving studies begun before January 10, 2002, investigators may report ethnicity/race and sex/gender composition using EITHER the Inclusion Enrollment Report (MS Word or PDF) OR the 4/98 Version of the Inclusion Table (MS Word or PDF). If data are being collected using two questions (one about ethnicity and one about race) and subjects were given the option of selecting more than one race, then use the Targeted/Planned Enrollment Table. **Note:** If you choose to report information with the new Targeted/Planned Enrollment Table, you must continue to use this format for the remaining years of the project.

If data are being collected using one question that combines ethnicity and race, use the 4/98 Version of the Inclusion Table. For previously funded studies that used the 4/98 Version of the Inclusion Table the earlier reporting format is NOT directly transferable to the format.

Investigators should review the instructions and Frequently Asked Questions about using the new Enrollment Table format at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

C. What Inclusion/Enrollment Table Should Principal Investigators Use for Reporting Accrual Data to NIH? (New versus Old Table)

The following instructions apply to progress reports, whether submitted as part of a non-competing or competing proposal.

Guidelines for choosing the new Inclusion Enrollment Report Table versus the old Inclusion Table are as follows:

New Inclusion Enrollment Report (MS Word or PDF)

- Studies begun after January 10, 2002, must be designed to ask participants two questions, one about their ethnicity and one about their race, and investigators must use the new Inclusion Enrollment Report table format for reporting summary data to NIH.
- Principal investigators who started a study prior to January 10, 2002 using the old Inclusion Table format for reporting summary data to NIH may switch to the new Inclusion Enrollment Report format if they choose to do so, but they must also change their data collection methods to ask two questions (one about ethnicity and another about race) rather than one question (that combined race and ethnicity) for all participants enrolled in the study from that point on.
- For studies that began prior to January 10, 2002: When the study is submitted for competing continuation (Type 2) and plans to collect new/additional data, the principal investigator is required to change to the new standards for collecting data and use the new Inclusion Enrollment Report format for reporting data to NIH. In some cases, this will mean that principal investigators will need to re-ask study participants about their race and ethnicity using the new two-question format. Note: principal investigators should not ask again about race and ethnicity if the subjects are no longer participating in the study.

Old Inclusion Table (4/98 Version) MS Word or PDF

- Studies begun prior to January 10, 2002 (and now in their non-competing Type 5 period) that were structured with one question about race and ethnicity may continue to report enrollment/accrual data to NIH based on the old form, i.e., using five categories of race/ethnicity. However, when they come in for competitive renewal (Type 2), they will need to change to the new standards/new form for any additional data collection.

- Principal investigators should not switch to the new form if only one question about race and ethnicity is used in data collection.
- Sample of old "Inclusion Table: format: http://grants.nih.gov/grants/funding/women_min/InclusionOld_Form.pdf

Investigators who have questions about these choices should contact NIH program staff for advice.

NEXT SECTION: INSTRUCTIONS

When you have completed this section proceed to Inclusion of Children

INCLUSION OF CHILDREN

Create a section entitled "**Inclusion of Children**" and place it immediately following the last entry in the Inclusion of Minorities" section.

For the purpose of implementing these guidelines, a child is defined as an individual under the age of 21 years (for additional information see http://grants.nih.gov/grants/funding/children/children.htm and http://grants.nih.gov/grants/guide/notice-files/not98-024.html).

Provide either a description of the plans to include children or, if children will be excluded from the proposed research, application or proposal, then you must present an acceptable justification (see below) for the exclusion.

If children are included, the description of the plan should include a rationale for selecting a specific age range of children. The plan also must include a description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.

Scientific Review Groups will assess each proposal with regard to the age-appropriate inclusion or exclusion of children in the research project.

When children are involved in research, the Additional Protections for Children Involved as Subjects in Research (45 CFR Part 46 Subpart D) apply and must be addressed in the "Human Subjects Research and Protection from Risks" subheading.

JUSTIFICATIONS FOR EXCLUSION OF CHILDREN

For the purposes of this policy, all individuals under 21 are considered children; however, exclusion of any specific age group, such as individuals under 18, should be justified in this section.

It is expected that children will be included in all research involving human subjects unless one or more of the following exclusionary circumstances can be fully justified:

1. The research topic to be studied is not relevant to children.

2. There are laws or regulations barring the inclusion of children in the research.

3. The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.

4. A separate, age-specific study in children is warranted and preferable. Examples include:

   a. The relative rarity of the condition in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or

   b. The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or

   c. Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances,

consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions, to allow children to be included rather than excluding them.

5. Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.

6. Study designs aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).

7. Other special cases justified by the investigator and found acceptable to the review group and the Institute Director.