

SOLICITATION OF
THE NATIONAL INSTITUTES OF HEALTH AND
THE CENTERS FOR DISEASE CONTROL
AND PREVENTION
FOR

SMALL
BUSINESS
INNOVATION
RESEARCH
CONTRACT PROPOSALS

PROPOSAL RECEIPT DATE NOVEMBER 9, 2009

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APPENDIX A — PROPOSAL COVER SHEET - USE FOR PHASE I PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc)
[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)

APPENDIX B — ABSTRACT OF RESEARCH PLAN - USE FOR PHASE I, PHASE II, AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc)
[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)

APPENDIX C — PRICING PROPOSAL - USE FOR PHASE I, PHASE II AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc)
[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf)

APPENDIX D — PHASE II TECHNICAL PROPOSAL COVER SHEET - USE FOR PHASE II AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc)
[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf)

APPENDIX E — STATEMENT OF WORK SAMPLE FORMAT - USE FOR PHASE II AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc)
[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf)

APPENDIX F — SUMMARY OF RELATED ACTIVITIES - USE FOR PHASE II AND FAST- TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc)
[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf)

APPENDIX G — PROPOSAL SUMMARY AND DATA RECORD - USE FOR PHASE II AND FAST-TRACK PROPOSALS

[MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc)
[PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf)

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 NATIONAL INSTITUTES OF HEALTH AND THE
CENTERS FOR DISEASE CONTROL AND PREVENTION FOR
SMALL BUSINESS INNOVATION RESEARCH
CONTRACT PROPOSALS****PART I INSTRUCTIONS FOR PREPARING AND SUBMITTING A PROPOSAL****1. PROGRAM DESCRIPTION**

1.1 PURPOSE OF SOLICITATION

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) invite small business concerns to submit research proposals under this Small Business Innovation Research (SBIR) Contract Solicitation. Firms with the capability to conduct research and development (R&D) in any of the health related topic areas described in [Section 12](#), and to commercialize the results of that R&D, are encouraged to participate.

This solicitation is for Phase I contract proposals and also for Phase I/Phase II Fast-Track contract proposals (see specific topics listed in [Section 12](#) and awarding components 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 12 “Research Topics”).** Otherwise, proposals will be returned to the offeror(s) without evaluation.

To apply for an SBIR GRANT rather than an SBIR CONTRACT, use the Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Applications (<http://grants.nih.gov/grants/guide/pa-files/PA-09-080.html>).

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 Federal SBIR program is authorized under Public Laws 97-219, 99-443, 102-564, and 106-554. The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive, 2002. This SBIR Contract solicitation strives to encourage scientific and technical innovation in areas specifically identified by the NIH/CDC awarding components shown in Section I.3. The guidelines presented in this solicitation reflect the flexibility provided in the Policy Directive to encourage proposals based on scientific and technical approaches most likely to yield results important to the NIH/CDC and to the private sector.

1.2 THREE PHASE 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 profit (fixed fee) for a period normally not to exceed two years. *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 5). 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 outcomes of the research or R&D funded in Phases I and II. 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 program that improve the health of the American people. In its commitment to also support President Bush's [Executive Order 13329](http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2004/pdf/04-4436.pdf) (<http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/2004/pdf/04-4436.pdf>), encouraging innovation in manufacturing-related research and development, NIH seeks, through the SBIR program, 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 Small Business Research Funding Opportunities Web site](http://grants.nih.gov/grants/funding/sbir.htm) (<http://grants.nih.gov/grants/funding/sbir.htm>) and in the [NIH Guide for Grants and Contracts](http://grants.nih.gov/grants/guide/index.html) (<http://grants.nih.gov/grants/guide/index.html>) 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](http://www.commerce.gov/opa/press/Secretary_Evans/2004_Releases/ManufacturingReport/DOC_MFG_Report_Complete.pdf)" (http://www.commerce.gov/opa/press/Secretary_Evans/2004_Releases/ManufacturingReport/DOC_MFG_Report_Complete.pdf).

1.3 AWARDING COMPONENTS

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

National Institutes of Health (NIH)

- National Cancer Institute (NCI)
- National Center for Research Resources (NCRR)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute on Drug Abuse (NIDA)
- National Institute of Environmental Health Sciences (NIEHS)

Centers for Disease Control and Prevention (CDC)

- National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
- National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)
- National Center for Immunization and Respiratory Diseases (NCIRD)
- National Center for Zoonotic, Vector-Borne & Enteric Diseases (NCZVED)
- Coordinating Center for Terrorism Preparedness and Emergency Response (COTPER)

1.4 SBIR PROGRAM ELIGIBILITY

Organizational Criteria: Each organization submitting a proposal under the SBIR program must qualify as a small business concern as defined in [Section 3](#). 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 C.F.R. 121.103, affiliation exists when "... one concern controls or has the power to control the other ... control may be affirmative or negative, ...it does not matter whether control 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 C.F.R. 121.103 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."

Joint ventures and limited partnerships are eligible provided the entity created qualifies as a small business concern as defined in [Section 3](#) of this solicitation.

If it appears that an offeror does not meet eligibility requirements, the NIH/CDC will request an eligibility determination of the organization from the cognizant SBA Government Contracting Area Office. The evaluation of the proposal for scientific merit will be deferred until the SBA provides a determination.

Project Director/Principal Investigator Criteria. The primary employment of the Project Director/Principal Investigator (PD/PI) must be with the offeror at the time of contract award and during the conduct of the proposed project. The PD/PI is 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 PD/PI's time* is spent in the employ of the small business concern. *Primary employment with a small business concern precludes full-time employment at another organization.*

In the event that the PD/PI: (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 PD/PI 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 PD/PI 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 PD/PI is employed by a university, the Dean's Office must provide such a letter. If the PD/PI 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.

Multiple Principal Investigators. Offerors may propose a multiple Project Director/Principal Investigator (PD/PI) model to direct the project or program to be supported by the contract. The multiple PD/PI model is intended to

supplement, and not replace, the traditional single PI model. Ultimately, the decision to submit a proposal using the multiple PD/PI versus single PD/PI is the decision of the investigators and their organizations. The decision whether to employ multiple PDs/Pis should be consistent with and justified by the scientific goals of the project.

The offeror organization may designate multiple individuals as principal investigators (PD/Pis) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple principal investigators are named, each is responsible and accountable to the offeror organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on a proposal or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

For Multiple PD/PI proposals: The first PI listed must be affiliated with the small business concern organization submitting the proposal and will serve as the **Contact PD/PI**. For both SBIR Phase I and SBIR Phase II, the *primary employment of the "Contact PD/PI" must be with the small business concern at the time of award and during the conduct of the proposed project.*

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 [Part I, Section 3. Definitions](#)).

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.

Market Research. *The NIH/CDC will not support any market research under the 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.

2. AGENCY CONTACT FOR INFORMATION

Web Site. The NIH SBIR/STTR Web Site at <http://grants.nih.gov/grants/funding/sbir.htm> offers electronic access to SBIR solicitations, abstracts of ongoing SBIR projects, the latest updates on the SBIR program, hyperlinks to sources of business assistance, and other useful information.

Technical Questions about Solicitation Topics or Contract Administration. Technical questions about a particular contract topic and general questions on the administration of an SBIR contract should be directed to the appropriate contracting officer listed in [Section 10. Contracting Officers and Addresses for Mailing and Delivery of Proposals](#).

General Questions about the NIH SBIR Program

Ms. Jo Anne Goodnight
NIH SBIR/STTR Program Coordinator
6705 Rockledge Drive
Rockledge I, Room 3540
Bethesda, MD 20892-7963
Phone: 301-435-2688 Fax: 301-480-0146
Email: sbir@od.nih.gov

Ms. Kay Etzler
NIH SBIR/STTR Program Analyst
6705 Rockledge Drive
Rockledge I, Room 3535
Bethesda, MD 20892-7963
Phone: 301-435-2713 Fax: 301-480-0146
Email: sbir@od.nih.gov

General Questions about the CDC SBIR Program

Dr. Paul Smutz
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: 404-639-4783
Fax: 404-639-4903
Email: wsmutz@cdc.gov

Listserv. The NIH maintains a ListServ e-mail broadcast service. To stay in touch with SBIR opportunities and receive notices about upcoming conferences and solicitations, subscribe by sending an email to LISTSERV@LIST.NIH.GOV with the following text in the message body: subscribe listname your name, where listname is the name of the list you wish to subscribe to, and your name is your name. (LISTSERV will get your e-mail address from the "From:" address of your e-mail message.)

3. DEFINITIONS

Affiliate. This term has the same meaning as set forth in 13 C.F.R. Part 121 – Small Business Size Regulations, §121.103, “What is affiliation?”

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

Child. The NIH Policy on Inclusion of Children defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific or ethical reasons not to include them.

DHHS Regulations (45 C.F.R. Part 46, Subpart D, Sec.401-409 (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd>)) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a “child.” Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to 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 research with human subjects that is:

(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 studies, 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.
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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 controlled 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.

Coded. With respect to private information or human biological specimens, *coded* means that:

- (1) identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and
- (2) a key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

Research that involves only coded private information/data or coded human biological specimens may not constitute human subjects research under the DHHS human subjects regulations (45 CFR 46) if:

- the specimens and/or information/data are not obtained from an interaction/intervention with the subject specifically for the research; and
- the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited).

Individuals who provide coded information or specimens for proposed research and who also collaborate on the research involving such information or specimens are considered to be involved in the conduct of human subjects research.

(See the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf>.)

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 who provides professional advice or services for a fee, but normally not as an employee of the engaging party. In unusual situations, an individual may be both a consultant and an employee of the same party, receiving compensation for some services as a consultant and for other work as a salaried employee. To prevent apparent or actual conflicts of interest, grantees and consultants must establish written guidelines indicating the conditions of payment of consulting fees. Consultants may also include firms that provide paid professional advice or services.

Contract. An award instrument establishing a binding legal procurement relationship between a funding agency and the recipient, obligating the latter to furnish an end product or service and binding the agency to provide payment therefore.

Data and Safety Monitoring Plan. NIH requires a data and safety monitoring plan for each clinical trial that will provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the contractor's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. The reporting of Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by 45 CFR Part 46 (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>).

Data and Safety Monitoring Board (DSMB). NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, *and generally for Phase III clinical trials*.

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 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.

Exemptions. The six categories of research exempt from the DHHS human subject regulations are:

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 with children (see 45 CFR Part 46, Subpart D (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd>)), 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.

The human subjects regulations decision charts

(<http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm>) of the Office of Human Research Protection (OHRP) will determine whether the research falls under the human subjects regulations and if so, whether it meets the criteria for Exemption 4. The NIH Office of Extramural Research website also contains information that is helpful for determining whether human subjects research meets the criteria for Exemption 4. See <http://grants.nih.gov/grants/policy/hs/index.htm>.

Research that meets the criteria for Exemption 4 is not considered "clinical research" as defined by NIH. Therefore the NIH policies for inclusion of women, minorities and children in clinical research, and targeted/planned enrollment tables, do not apply to research projects covered by Exemption 4.

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.

Feasibility. The extent to which a study or project may be done practically and successfully.

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

Gender. Refers to the classification of research subjects into either or both of two categories: women and men. In some cases, representation is unknown, because gender composition cannot be accurately determined (e.g., pooled blood samples or stored specimens without gender designation).

Human Subjects. The DHHS regulations “Protection of Human Subjects” ([45 CFR Part 46](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>), administered by OHRP) 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*

Individually Identifiable Private Information. According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

Innovation. Something new or improved, including research for: (1) development of new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies. For the 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.

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. (45 CFR 46.102(f)).

Interaction includes communication or interpersonal contact between investigator and subject. (45 CFR 46.102(f)).

Investigator. The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. (See OHRP's [2004 Coded Specimen Guidance](http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm) (<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm>).)

Joint Venture. An association of 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.

For additional information, see <http://www.sba.gov/library/cfrs/13cfr121.html>.

Manufacturing-related R&D as a result of Executive Order 13329. Encompasses improvements in existing methods or processes, or wholly new processes, machines or systems. Four main areas include:

1. *Unit process level technologies* that create or improve manufacturing processes including:
 - fundamental improvements in existing manufacturing processes that deliver substantial productivity, quality, or environmental benefits.
 - development of new manufacturing processes, including new materials, coatings, methods, and associated practices.
2. *Machine level technologies* that create or improve manufacturing equipment, including:
 - improvements in capital equipment that create increased capability (such as accuracy or repeatability), increased capacity (through productivity improvements or cost reduction), or increased environmental efficiency (safety, energy efficiency, environmental impact).
 - new apparatus and equipment for manufacturing, including additive and subtractive manufacturing, deformation and molding, assembly and test, semiconductor fabrication, and nanotechnology.
3. *Systems level technologies* for innovation in the manufacturing enterprise, including:
 - advances in controls, sensors, networks, and other information technologies that improve the quality and productivity of manufacturing cells, lines, systems, and facilities.
 - innovation in extended enterprise functions critical to manufacturing, such as quality systems, resource management, supply change integration, and distribution, scheduling and tracking.
 - technologies that enable integrated and collaborative product and process development, including computer-aided and expert systems for design, tolerancing, process and materials selection, life-cycle cost estimation, rapid prototyping, and tooling.
4. *Environment or societal level technologies* that improve workforce abilities, productivity, and manufacturing competitiveness, including:
 - technologies for improved workforce health and safety, such as human factors and ergonomics.
 - technologies that aid and improve workforce manufacturing skill and technical excellence, such as educational systems incorporating improved manufacturing knowledge and instructional methods.

Obtains. In its guidance for use of coded specimens, OHRP has determined that under the definition of human subject at 45 CFR 46.102(f), *obtaining* identifiable private information or identifiable specimens for research purposes constitutes human subjects research. *Obtaining* means receiving or accessing identifiable private information or identifiable specimens for research purposes. OHRP interprets *obtaining* to include an investigator's use, study, or analysis for research purposes of *identifiable private information* or identifiable specimens already in the possession of the investigator.

Principal Investigator, Program Director, or Project Director (PD/PI). The individual(s) designated by the applicant organization to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award. The applicant organization may designate multiple individuals as principal investigators (PDs/Pis) who share the authority and responsibility for leading and directing the project, intellectually and logistically. When multiple principal investigators are named, each is responsible and accountable to the applicant organization, or as appropriate, to a collaborating organization for the proper conduct of the project or program including the submission of all required reports. The presence of more than one PD/PI on an application or award diminishes neither the responsibility nor the accountability of any individual PD/PI.

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 that has been provided for specific purposes by an individual and that 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. (45 CFR 46.102(f))

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

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

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

Senior/Key Personnel. The PD/PI and other individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries or compensation are requested under the contract.

Typically these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of Senior/Key Personnel. Consultants should also be included if they meet the definition of Senior/Key Personnel. Senior/Key Personnel must devote measurable effort to the project whether or not salaries or compensation are requested--"zero percent" effort or "as needed" are not acceptable levels for those designated as Senior/Key Personnel.

Significant Difference. For purposes of NIH policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

Small Business Concern. A concern that, on the date of award for both Phase I and Phase II funding agreements:

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 business entities in the joint venture;
3. is (i) at least 51 percent owned and controlled by one or more individuals who are citizens of the United States or permanent resident aliens in the United States, (ii) at least 51% owned and controlled by another business concern that is itself at least 51% owned and controlled by individuals who are citizens of, or permanent resident aliens in the United States; or (iii) a joint venture in which each entity to the venture must meet the requirements of either (i) or (ii) of this section;

4. has, including its affiliates, not more than 500 employees.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 C.F.R. 121, as is the process for calculating "number of employees."

Business concerns include, but are not limited to, any individual (sole proprietorship), partnership, corporation, joint venture, association, or cooperative. Further information may be obtained by contacting the Small Business Administration Size District Office at <http://sba.gov/size>.

Socially and Economically Disadvantaged Individual. A member of any of the following groups: Black Americans; Hispanic Americans; Native Americans; Asian-Pacific Americans; Subcontinent Asian Americans; other groups designated from time to time by the Small Business Administration (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. A socially and economically disadvantaged small business concern is one that is at least 51% owned by (a) an Indian tribe or a native Hawaiian organization, or (b) one or more socially and economically disadvantaged individuals; **and** whose management and daily business operations are controlled by one or more socially and economically disadvantaged individuals.

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, territories and possessions of the U.S., Commonwealth of Puerto Rico, Trust Territory of the Pacific Islands, and District of Columbia.

Women-Owned Small Business Concern. A small business concern that is at least 51% owned by a woman or women who also control and operate it. "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.

4. PHASE I PROPOSAL PREPARATION INSTRUCTIONS AND REQUIREMENTS

4.1 LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase I proposals shall not exceed 50 single-sided, single-spaced pages for the entire proposal, all inclusive [including all pages, cover sheet(s), tables, CVs, resumes, references, pictures/graphics, and all enclosures, appendices or attachments, etc.]. Proposal pages shall be numbered "Page 1 of 50," "Page 2 of 50," and so on. Pages shall be of standard size (8.5" X 11") with a font size of 11 points (or larger). Two sided pages count as two pages. There are NO exclusions to the page limit – the complete proposal shall not exceed 50 pages. Pages in excess of the page limitation will be removed from the proposal and will not be read, considered, or evaluated.

4.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

4.2.1 Technical Proposal Cover Sheet - Complete the form identified as Appendix A ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf)), and use it as the first page of the proposal. *No other cover sheet should be used.*

If submitting a proposal reflecting Multiple Project Directors/Principal Investigators (PDs/PIs), the individual designated as the Contact PI should be entered here.

- **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.

4.2.2 Abstract of Research Plan - Complete the form identified as Appendix B ([MS Word](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc)

(<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc>) | [PDF](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf)

(<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf>), and insert it as the second page of each proposal. Do not include any proprietary information as abstracts of successful proposals will be published by NIH. 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.

Include at the end of the Abstract a brief description (two or three sentences) of the relevance of this research to **public** health. In this description, be succinct and use plain language that can be understood by a general, lay audience.

4.2.3 Research Plan

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

- a. **Identification and Significance of the Problem or Opportunity.** Provide a clear statement of the specific technical problem or opportunity addressed.
- b. **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.
- c. **Work Plan.** Provide an explicit, detailed plan for the Phase I R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address how the objectives will be met and the questions stated in Item b above. Discuss in detail the methods to be used to achieve each objective or task. The plan should indicate what is planned, how, when, and where the work will be carried out, a schedule of major events, the final product to be delivered, and the completion date of the effort. The Phase I effort should determine the technical feasibility of the proposed concept. 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](#)."
- d. **Related Research or R&D.** Describe significant research activities directly related to the proposed effort, including any conducted by the Project Director/Principal Investigator (PD/PI), the proposing firm, consultants, or others. Describe how these activities interface with the proposed project and discuss any planned coordination with outside sources. *The PD/PI must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field.*
- e. **Relationship with Future R&D.**
 1. State the anticipated results of the proposed approach, assuming project success.
 2. Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.
- f. **Potential Commercial Applications.** Describe why the proposed project is deemed to have potential commercial applications (for use by the Federal Government and/or private sector markets.) Describe the market as it currently exists and how your product may enter and compete in this market. Include the potential barriers to market entry and how you expect to overcome them.
- g. **Key Personnel and Bibliography of Directly Related Work.** Identify key personnel, including their directly related education, experience, and bibliographic information. Where resumes 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. Resumes must identify the current or most recent position.

Multiple PD/PI Leadership Plan. For proposals designating multiple PDs/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

- h. **Subcontractors/Consultants.** Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail and identified in the cost proposal. In addition, supported by appropriate letters from each individual confirming his/her role in the project must be included. Small business concerns must perform a minimum of two-thirds for Phase I of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.
- i. **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.

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.

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.

Any research proposal involving the collection of information, such as surveys or interviews, of 10 or more public 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.

4.2.4 Current Awards and Pending Proposals/Applications

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 NIH/CDC. 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. A firm that receives a Phase I SBIR contract may submit a Phase II grant application and vice versa.

A Phase I contractor may submit a Phase II contract proposal only if invited by an NIH Contracting Officer.

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 a-j set forth below.

In addition, provide the information requested in items a-j on (1) active funding through contracts, grants, and cooperative agreements from public or private sponsors; (2) contract proposals and grant and cooperative agreement applications pending review or funding; and (3) contract proposals and grant and cooperative agreement applications about to be submitted.

- a. Name and address of the funding source.
- b. Type of award (contract, grant, cooperative agreement) and identifying number.
- c. Title of research project.
- d. Name and title of Principal Investigator(s) or Project Manager(s).
- e. Hours per week on the project by the Principal Investigator(s) or Project Manager(s).
- f. Annual costs proposed or awarded.
- g. Entire period of support.
- h. Date of proposal/application submission or date of award.
- i. Title, number, and date of solicitations under which proposals or applications were submitted or awards received.
- j. The specific applicable research topic for each SBIR proposal or application submitted or award received. *Specifically identify those projects that are SBIR.*

4.2.5 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 information must be submitted with the proposal.

4.2.6 Proposed Cost Breakdown

Complete the form identified as Appendix C (Contract Pricing Proposal) ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.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 2010-1."
- 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.

- Cost for travel funds must be justified and related to the needs of the project. 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.
- Small business concerns must perform a minimum of two-thirds of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

4.2.7 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 uses 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.

4.2.8 Requirement for Adequate Assurance of Protection of Human Subjects

The DHHS regulations for the Protection of Human Subjects, 45 C.F.R. 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 DHHS. *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 a DHHS 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

Instructions and Required Information

This information must be submitted with the proposal.

Create a section heading entitled “**Human Subjects Research.**” Place it immediately following the “Research Plan” section of the proposal.

In the Human Subjects Research section, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks ([45 CFR Part 46 \(http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm\)](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm)), (2) the requirements of NIH policies for data and safety monitoring of clinical trials, and (3) the requirements of NIH policies on inclusion of women, minorities, and children.

Provided in the [Human Subjects Research Guidance and Information Supplement](#) are 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. Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in Section 3 of the Supplement. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Targeted/Planned Enrollment Table, and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part I, Section 3, Definitions. Section 5 of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

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 for IRB review.

4.2.9 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.

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://grants.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 seq.) 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.

4.3 LIMITATIONS ON USE OF APPROPRIATED FUNDS

The Department of Health and Human Services Appropriation Act for Fiscal Year 2009 (Public Law 111-8), limits the use of appropriated funds on NIH grant, cooperative agreement, and contract awards for Fiscal Year 2009, as specified below. It is anticipated that these statutory provisions will continue in subsequent fiscal years.

Salary Rate Limitation

Public Law 111-8, Division F, Title II, Section 203 restricts the use of Federal funds to pay the direct salary of an individual under an NIH grant, cooperative agreement, or applicable contract, at a rate in excess of Executive Schedule, Level I of the Federal Executive Pay scale. Direct salary is exclusive of fringe benefits, overhead and general and administrative expenses (also referred to as "indirect cost" or "facilities and administrative (F&A) costs"). Direct salary has the same meaning as the term "institutional base salary." An individual's direct salary (or institutional base salary) is the annual compensation that the Contractor pays for an individual's appointment whether that individual's time is spent on research, teaching, patient care or other activities. Direct salary (or institutional base salary) excludes any income that an individual may be permitted to earn outside of duties to the Contractor. The salary rate limitation also applies to individuals proposed under subcontracts; however, it does not apply to consultants. The legislation also does not apply to firm fixed price contracts. Effective January 1, 2009, the Executive Level I salary is \$196,700 per year.

Anti-Lobbying (for contracts exceeding \$100,000)

"(a) No part of any appropriation contained in this Act shall be used, other than for normal and recognized executive-legislative relationships, for publicity or propaganda purposes, for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself. (b) No part of any appropriation contained in this Act shall be used to pay the salary or expenses of any grant or contract recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature."

Restriction on Distribution of Sterile Needles

"Notwithstanding any other provision of this Act, no funds appropriated under this Act shall be used to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug."

Acknowledgment of Federal Funding

"When issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money, all grantees receiving Federal funds included in this Act, including but not limited to State and local governments and recipients of Federal research grants, shall clearly state: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) percentage and dollar amount of the total costs of the project or program that will be financed by non-governmental sources."

Restriction on Abortions

"(a) None of the funds appropriated under this Act, and none of the funds in any trust fund to which funds are appropriated in this Act, shall be expended for any abortion."

Ban on Funding of Human Embryo Research

"(a) None of the funds made available in this Act may 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 46.204(b) (2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). (b) For purposes of this section, 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 enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells."

Limitation on Use of Funds for Promotion of Legalization of Controlled Substances

"(a) None of the funds made available in this Act may be used for any activity that promotes the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established by section 202 of the Controlled Substances Act (21 U.S.C.812). (b) The limitation in subsection (a) shall not apply when there is significant medical evidence of a therapeutic advantage to the use of such drug or other substance or that federally sponsored clinical trials are being conducted to determine therapeutic advantage."

NIH Public Access Requirement

"The Director of the National Institutes of Health shall require that all investigators funded by the NIH submit or have submitted for them to the National Library of Medicine's PubMed Central an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication: *Provided*, that the NIH shall implement the policy in a manner consistent with copyright law."

Further information on the implementation of NIH's Public Access Requirement is available in NIH Guide Notice [NOT-OD-08-033](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html) (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html>) published on January 11, 2008.

Dissemination of False or Deliberately Misleading Scientific Information

"None of the funds made available in this Act may be used to disseminate scientific information that is deliberately false or misleading."

While this mandate has not been included in past appropriations acts, it is similar to existing requirements concerning research integrity, fraud, and false claims, and as such, NIH does not expect this new requirement to impact significantly the business practices at most institutions. Grantees and contractors are advised to review their implementation of the PHS Policies on Research Misconduct contained in 42 CFR Part 93 and the Civil False Claims Act (31 U.S.C. 3729(a)), Criminal False Claims Act (18 U.S.C. 287 and 1001), and Program Fraud and Civil Remedies Act (31 U.S.C. 3801 et seq.).

Restriction on Employment of Unauthorized Alien Workers

"None of the funds in this Act may be used to employ workers described in section 274A(h)(3) of the Immigration and Nationality Act."

While this mandate has not been included in past appropriations acts, it is similar to existing requirements contained in the Immigration and Nationality Act (18 U.S.C. 1324a), and as such, NIH does not expect this new requirement to impact significantly the business practices at most institutions. Grantees and contractors are advised to review their current hiring and employment practices to ensure compliance.

5. "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 12. "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.

Phase I and Phase II are considered separate funding agreements under the Fast-Track Initiative. Therefore, Phase I Fast-Track awardees must recertify that they meet all of the eligibility criteria for an SBIR award prior to issuance of the Phase II award.

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 \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.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 4. Phase I Proposal Preparation Instructions and Requirements, and addressing all factors stated in the evaluation criteria (Section 7) for Phase I proposals.

2. **Phase II Proposal.** Prepared in accordance with Section 6, Fast-Track Phase II Proposal Preparation Instructions and Requirements and addressing all factors stated in the evaluation criteria (Section 7) for Phase II proposals.
3. **Commercialization Plan.** Prepared in accordance with instructions in Section 6.2.

The Phase I and Phase II proposals are separate proposals and 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.

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

6.1 LIMITATIONS ON LENGTH OF PROPOSAL

SBIR Phase II proposals shall not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8.5" x 11") with a font size of 11 points (or larger). Excluded from the page limitation are cover letters and letters from collaborators and consultants. Pages in excess of the page limitation will be removed from the proposal, and will not be read, considered, or evaluated.

6.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf)).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.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 detailed 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 resumes for all key staff members*, describing directly related education, experience, and relevant publications. Describe in detail any involvement of subcontractors or consultants, and *provide resumes 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 [Sections 4.2.8 and 4.2.9](#) of this solicitation for further guidance.

Multiple PD/PI Leadership Plan. For proposals designating multiple PDs/Pis, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/Pis and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/Pis should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

Resource Sharing Plan(s). NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing, this must be explained in the application. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.

1. *Data Sharing Plan:* Offerors seeking \$500,000 or more in direct costs in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible (for example human subject concerns, the Small Business Innovation Development Act provisions, etc.). See [Data-Sharing Policy \(http://grants.nih.gov/grants/policy/data_sharing/\)](http://grants.nih.gov/grants/policy/data_sharing/) or <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>.

2. *Sharing Model Organisms:* Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state appropriate reasons why such sharing is restricted or not possible. See [Sharing Model Organisms Policy \(http://grants.nih.gov/grants/policy/model_organism/index.htm\)](http://grants.nih.gov/grants/policy/model_organism/index.htm), and [NIH Guide NOT-OD-04-042 \(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html\)](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html).

3. *Genome Wide Association Studies (GWAS):* Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, [NIH Guide NOT-OD-07-088 \(http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html\)](http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html), and <http://grants.nih.gov/grants/gwas>.

- 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 \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.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 the Phase II portion of ALL Fast-Track proposals.

The Phase II portion of Fast-Track proposals must include a succinct Commercialization Plan. 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.

6. **Summary of Related Activities** - Use Appendix F ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf)).
7. **Number of Copies** - Submit an original and 9 copies.

6.3 BUSINESS PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Cover Page** - Use NIH Form 2043, Proposal Summary and Data Record, Appendix G ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf)).
2. **Proposed Cost Breakdown – For Phase I**, use Appendix C ([MS Word \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.doc) | [PDF \(http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf\)](http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.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. **For Phase II Fast-Track**, use Appendix C. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.
3. **NIH Policy on Threshold for Negotiation of Facilities and Administrative (F&A)/Indirect Costs (IDC) Rates for SBIR proposals** - Effectively immediately, SBIR offerors who propose in the contract an F&A/IDC rate of 40 percent of total direct costs or less will not be required to provide further justification at the time of award, and F&A/ID costs will be awarded at the requested rate. However, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for F&A/IDC rates on an *ad hoc* basis. If the SBC has a currently effective negotiated indirect cost rate(s) with a Federal agency, such rate(s) should be used when calculating proposed F&A/ID costs for an NIH proposal. (However, the rate(s) must be adjusted for IR&D expenses, which are not allowable under HHS awards.)

SBCs are reminded that only actual F&A/ID costs may be charged to projects. If awarded at a rate of 40 percent or less of total direct costs, the rate used to charge actual F&A/ID costs to projects cannot exceed the awarded rate unless the SBC negotiates an indirect cost rate(s) with DFAS. DFAS will negotiate F&A/IDC rates for SBCs receiving awards if the requested rate is greater than 40 percent of total direct costs.
4. **Number of Copies** - Submit an original and 4 copies.

7. METHOD OF SELECTION AND EVALUATION CRITERIA

All Phase I and Fast-Track proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria in Section 7.1, a panel of scientists, consisting primarily of nongovernment experts knowledgeable in the disciplines or fields under review, will evaluate proposals to determine the most promising technical and scientific approaches. Each proposal will be judged on its own merit. The Agency is under no obligation to fund any proposal or any specific number of proposals in a given topic. It also may elect to fund several or none of the proposed approaches to the same topic or subtopic.

7.1 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. When relevant, reviewers will be instructed to comment on the reasonableness of the following Resource Sharing Plans, or the rationale for not sharing the following types of resources. However, reviewers will not factor the proposed resource sharing plan(s) into the determination of scientific merit or priority score. Program staff within the funding organization will be responsible for monitoring the data sharing policy

- Data Sharing Plan [http://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm]
- Sharing Model Organisms [<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html>]
- Genome Wide Association Studies (GWAS) [<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html>].

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 and commercial potential. A Phase I or Fast-Track 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.*

7.2 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. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs? (Preliminary data are not required for Phase I proposals.)	40%
2. The qualifications of the proposed PDs/PIs, 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. The commercial potential of a proposal will be assessed using the following criteria: - Whether the outcome of the proposed research activity will likely lead to a marketable product or process. - The offeror's discussion of the potential barriers to entry and the competitive market landscape.	15%
5. The adequacy and suitability of the facilities and research environment.	10%

FACTORS FOR PHASE II PROPOSALS (FOR FAST-TRACK ONLY)	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. For proposals designating multiple PDs/PIs, is the leadership approach, including the designated roles and responsibilities, governance, and organizational structure, consistent with and justified by the aims of the project and the expertise of each of the PDs/PIs?	30%
2. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by (a) the offeror's record of successfully commercializing its prior SBIR/STTR or other research projects, (b) commitments of additional investment during Phase II and Phase III from private sector or other non-SBIR funding sources, and (c) any other indicators of commercial potential for the proposed research.	30%
3. The qualifications of the proposed PDs/PIs, supporting staff and consultants.	25%
4. The adequacy and suitability of the facilities and research environment.	15%

7.3 PROPOSAL DEBRIEFING

Offerors will be notified promptly in writing if their proposals are no longer being considered for award. Offerors may request a debriefing by submitting a written request to the Contracting Officer within three days of receipt of the notification. Untimely requests may be accommodated at the Government's discretion.

7.4 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.

8. CONSIDERATIONS

8.1 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.
5. Cost-sharing is permitted for proposals under this solicitation; however, cost sharing is not required nor will it be an evaluation factor in the consideration of your proposal. Cost-sharing is an explicit arrangement under which the contractor bears some of the burden of reasonable, allocable, and allowable contract cost. If cost-sharing is proposed, it should be reflected in your budget summary.

Approximate number of Phase I contract awards:

AWARDING COMPONENTS	NO. OF AWARDS	ESTIMATED TIME OF AWARD
National Institutes of Health (NIH) National Cancer Institute (NCI)	64	Scientific and Technical Merit Review: May 2010 Anticipated Award Date: Sept. 2010
National Institutes of Health (NIH) National Center for Research Resources (NCRR)	7	Scientific and Technical Merit Review: February 2010 Anticipated Award Date: July 2010
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	10-11	Scientific and Technical Merit Review: February-April 2010 Anticipated Award Date: July-Sept 2010
National Institutes of Health (NIH) National Institute on Alcohol Abuse and Alcoholism (NIAAA)	10-19	Scientific and Technical Merit Review: March 2010 Anticipated Award Date: July-Aug 2010
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	3-15	Scientific and Technical Merit Review: March 2010 Anticipated Award Date: June 2010
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	10	Scientific and Technical Merit Review: March 2010 Anticipated Award Date: August 2010
National Institutes of Health (NIH) National Institute of Environmental Health Sciences (NIEHS)	8-10	Scientific and Technical Merit Review: March 2010 Anticipated Award Date: May 2010
Centers for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	1	Scientific and Technical Merit Review: February 2010 Anticipated Award Date: May 2010

AWARDING COMPONENTS	NO. OF AWARDS	ESTIMATED TIME OF AWARD
Centers for Disease Control and Prevention (CDC) National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	1	Scientific and Technical Merit Review: February 2010 Anticipated Award Date: May 2010
Centers for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	1	Scientific and Technical Merit Review: February 2010 Anticipated Award Date: May 2010
Centers for Disease Control and Prevention (CDC) National Center for Zoonotic, Vector-Borne & Enteric Diseases (NCZVED)	1	Scientific and Technical Merit Review: February 2010 Anticipated Award Date: May 2010
Centers for Disease Control and Prevention (CDC) Coordinating Center for Terrorism Preparedness and Emergency Response (COTPER)	2-3	Scientific and Technical Merit Review: February 2010 Anticipated Award Date: May 2010

8.2 MONTHLY PROGRESS REPORT

Contractors will be required to submit a monthly progress report during Phase I along with their invoice. Phase II reports will be required at intervals stipulated in the terms and conditions of award.

8.3 FINAL REPORT

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 must be submitted as specified in the contract or as directed by the Contracting Officer.*

8.4 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 before the award of a contract. The registration site for the CCR is <http://www.ccr.gov>.

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.

8.5 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 (DHHS) 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 DHHS, 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 DHHS may not be able to withhold data that has been requested pursuant to the FOIA, and the DHHS FOI officials must make that determination. The Government is not liable for disclosure if the DHHS 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 Government purposes only.

- (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 paragraph (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 the SBIR Policy Directive, dated September 24, 2002. 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.

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 (DHHS awarding component)" or "The project described was supported by contract number _____ from (DHHS 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 a patent application.

Inquiries or information about additional requirements imposed by 37 C.F.R. 401 should be obtained from local counsel or from:

Office of Policy for Extramural
Research Administration,
Division of Extramural Inventions and
Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Drive, MSC 7980
Bethesda, MD 20892-7980
Phone: (301) 435-0679
Fax: (301) 480-0272
Email: jpkim@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.

Awardees are encouraged to submit reports electronically using Interagency Edison (<http://www.iedison.gov>). Information from these reports is retained by the NIH as confidential and submission does not constitute any public disclosure. Failure to report as described at 37 CFR Section 401.14 is a violation of 35 U.S.C. 202 and may result in loss of the rights of the recipient organization. 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.

Resource Sharing Plan(s). NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value of, and advance research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If

the final data/resources are not amenable to sharing, this must be explained in the Resource Sharing section of the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.

(a) *Data Sharing Plan*: Investigators seeking \$500,000 or more in direct costs in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible (for example human subject concerns, the Small Business Innovation Development Act provisions, etc.) Offerors are encouraged to discuss data-sharing plans with their program contact. See [Data-Sharing Policy \(http://grants.nih.gov/grants/policy/data_sharing/\)](http://grants.nih.gov/grants/policy/data_sharing/) or <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html>.

(b) *Sharing Model Organisms*: Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms and related resources, or state appropriate reasons why such sharing is restricted or not possible. See [Sharing Model Organisms Policy \(http://grants.nih.gov/grants/policy/model_organism/index.htm\)](http://grants.nih.gov/grants/policy/model_organism/index.htm), and [NIH Guide NOT-OD-04-042 \(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html\)](http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html).

(c) *Genome Wide Association Studies (GWAS)*: Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or provide an appropriate explanation why submission to the repository is not possible. A genome-wide association study is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies, [NIH Guide NOT-OD-07-088 \(http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html\)](http://www.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html), and <http://grants.nih.gov/grants/gwas/>.

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).

8.6 PERFORMANCE OF RESEARCH AND ANALYTICAL WORK

For Phase I projects, small business concerns must perform a minimum of two-thirds or 67% of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract.

For Phase II projects, small business concerns must perform a minimum of one-half or 50% of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract.

The Contracting Officer must approve deviations from these requirements in writing after consultation with the agency SBIR Program Manager/Coordinator

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.

8.7 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 at 1-866-705-5711 or via the Internet at <https://eupdate.dnb.com/requestoptions/government/ccrreg/>. The contractor must also be registered in the Central Contractor Registry (CCR) prior to award of a contract. Registration can be made via the Internet at <http://www.ccr.gov>.

9. INSTRUCTIONS FOR PROPOSAL SUBMISSION

9.1 RECEIPT DATE

The deadline for receipt of all contract proposals submitted in response to this solicitation is:

5:00 p.m., Eastern Time
Monday, November 9, 2009

Any proposal, modification or revision received at the offices designated below after the exact time specified for receipt is "late" and will not be considered unless it is received before award is made, and

1. There is acceptable evidence to establish that it was received at the Government installation designated for receipt of offers and was under the Government's control prior to the time set for receipt of offers; or
2. It is the only proposal received.

Acceptable evidence to establish the time of receipt at the Government installation includes the time/date stamp of that installation on the proposal wrapper, other documentary evidence of receipt maintained by the installation, or oral testimony or statements of Government personnel.

If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.

Proposals may be withdrawn by written notice received at any time before award. Notwithstanding above, a proposal received after the date and time specified for receipt may be considered if it offers significant cost 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.

Note: Modifications or revisions to proposals that result in the proposal exceeding the stated page limitations will not be considered.

9.2 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 Fast-Track Phase II, submit the original and 9 copies.

For Phase I and Fast-Track Phase II business proposals, submit an original and 4 copies.

9.3 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.

10. 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, email, 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.

10.1 NATIONAL INSTITUTES OF HEALTH (NIH)

National Cancer Institute (NCI)

Ms. Mary Landi-O'Leary
Phone: (301) 435-3807
Fax: (301) 480-0309
Email: ml186r@nih.gov

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

Ms. Mary Landi-O'Leary
Contracting Officer
Office of Acquisitions
National Cancer Institute
6120 Executive Blvd., EPS, Room 6044
Bethesda, MD 20892-7193 *

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

National Center for Research Resources (NCRR)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3430
E-mail: taylorjc@nhlbi.nih.gov

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

Office of Review
National Center for Research Resources
National Institutes of Health, DHHS

6701 Democracy Bl, Room 1072
Room 7091
Bethesda, MD 20892-4874 *

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

National Heart, Lung, and Blood Institute (NHLBI)

Mr. John Taylor
Phone: (301) 435-0327
Fax: (301) 480-3338
E-mail: taylorjc@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 Research Activities
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7195
6701 Rockledge Drive, MSC 7924
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.*

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Mr. Matthew Packard
Phone: (301) 443-3041
Fax: (301) 443-3891
Email: packardm@mail.nih.gov

Proposals to the NIAAA must be mailed or delivered to:

Mr. Matthew Packard
Chief, NIAAA Contracts Management Branch
NICHD Office of Acquisitions, NIH
5635 Fishers Lane, Room 3019
Bethesda, MD 20892-9304 *

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

National Institute of Allergy and Infectious Diseases (NIAID)

Mr. Peter Jackson
Phone: (301) 496-8426
Fax: (301) 480-2310
Email: pj8v@nh.gov

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

Mr. Peter Jackson
Contracting Officer
OA, DEA, NIAID
6007B Rockledge Dr., Room 3133
Bethesda, MD 20892-7612 *

**Change the city to North Bethesda, MD and the zip code to 20817 if hand-delivered or delivered by an overnight service to the NIAID.*

National Institute on Drug Abuse (NIDA)

Mr. Brian O'Laughlin
Phone: (301) 443-6677
Fax: (301) 443-7595
Email: bo50d@nih.gov

Proposals to the NIDA must be mailed or delivered to:

Mr. Brian O'Laughlin
NIDA R&D Contracts Management Branch
Neurosciences Office of Acquisition
6101 Executive Boulevard
Room 260, MSC 8402
Bethesda, MD 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 Environmental Health Sciences (NIEHS)

Ms. Velvet M. Torain
Phone: (919) 541-0400
Fax: (919) 541-2712
Email: torain@niehs.nih.gov

Proposals to the NIEHS must be mailed or delivered to:

Ms. Velvet M. Torain
Supervisory Contract Specialist
Office of Acquisitions, OM
National Institute of Environmental Health Sciences
P.O. Box 12874
Research Triangle Park, NC 27709

Proposals to the NIEHS, *if hand-delivered or delivered by an overnight service*, must be addressed as follows:

Ms. Velvet M. Torain
Supervisory Contract Specialist
Office of Acquisitions, OM
National Institute of Environmental Health Sciences
530 Davis Drive
Research Triangle Park, NC 27709

10.2 CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Dr. Paul Smutz
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: (404) 639-4783
Fax (404) 639-4903
Email: wsmutz@cdc.gov

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)

Mrs. Theresa Routh-Murphy
Contracting Officer
Phone: (770) 488-2713
Fax: (770) 488-2778
Email: TNR3@cdc.gov

Proposals to the NCCDPHP must be mailed or delivered to:

Mrs. Theresa Routh-Murphy
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road, MS-E09
Atlanta, GA 30341

National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)

Mr. Julio Lopez
Contracting Officer
Phone: (770) 488-2892
Fax: (770) 488-2868
Email: jlopez3@cdc.gov

Proposals to NCHHSTP must be mailed or delivered to:

Mr. Julio Lopez
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

National Center for Immunization and Respiratory Diseases (NCIRD)

Ms. Nancy Norton
Contracting Officer
Phone: (770) 488-2056
Fax: (404) 488-2777
Email: nnorton@cdc.gov

Proposals to NCIRD must be mailed or delivered to:

Nancy Norton
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road, MS-K14
Atlanta, GA 30341

National Center for Zoonotic, Vector-Borne & Enteric Diseases (NCZVED)

Ms. Nancy Norton
Contracting Officer
Phone: (770) 488-2056
Fax: (404) 488-2777
Email: nnorton@cdc.gov

Proposals to NCZVED must be mailed or delivered to:

Nancy Norton

Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road, MS-K14
Atlanta, GA 30341

Coordinating Center for Terrorism Preparedness and Emergency Response (COTPER)

Vivian Hubbs
Contracting Officer
Phone: (770) 488-2647
Fax: (770) 488-2670
Email: vhubbs@cdc.gov

Proposals to COTPER must be mailed or delivered to:

Vivian Hubbs
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road, MS-K69
Atlanta, GA 30341

11. 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>

12. RESEARCH TOPICS

NATIONAL INSTITUTES OF HEALTH

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.

SBIR Phase I and Phase II awards may not exceed the limits for total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

Phase II proposals may only be submitted upon the request of the NCI Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section 5). Unless the Fast-Track option is specifically allowed as stated within the topic areas below, applicants are requested to submit only Phase I proposals in response to this solicitation.

NCI Phase II Bridge Award

The National Cancer Institute would like to provide notice of a recent funding opportunity entitled the SBIR Phase II Bridge Award. This notice is for informational purposes only and is not a call for Phase II Bridge Award proposals. This informational notice does not commit the government to the development of a Phase II Bridge Award mechanism for, or making such awards to, contract awardees.

Successful transition of SBIR research and technology development into the commercial marketplace is difficult, and SBIR Phase II awardees often encounter significant challenges in navigating the regulatory approval process, raising capital, licensure and production, as they try to advance their projects towards commercialization. The NCI views the SBIR program as a long term effort; thus, in order to help address these difficult issues, the NCI has developed the SBIR Phase II Bridge Award under the grants mechanism. The previously-offered Phase II Bridge Award was designed to provide additional funding of up to \$3M and up to three additional years to assist promising small business concerns with the challenges of commercialization. The specific requirements for the previously-offered Phase IIB Bridge Award can be reviewed in the full RFA announcement (<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-021.html>).

The NCI anticipates expanding the Phase II Bridge Award program in the future to also include awardees funded under the SBIR contract mechanism. Pending its planned continuation, it is anticipated that the Phase II Bridge Award program will be open to contractors who successfully complete a Phase I award as a result of this solicitation, and who are subsequently awarded a Phase II contract (or have an exercised Phase II option under a Fast-Track contract). Provided it is available in the future, NIH SBIR Phase II contractors who satisfy the above requirements may be able to apply for a Phase II Bridge Award under a future Phase II Bridge Award grant/cooperative agreement funding opportunity announcement (FOA), if they meet the eligibility requirements detailed therein. Selection decisions for a Phase II award will be based both on scientific/technical merit as well as business/commercialization potential.

NCI Topics:

This solicitation invites Phase I (and in certain topics Fast-Track) proposals in the following areas:

255 Development of Anticancer Agents

Number of anticipated awards: 5

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget: Phase I: \$200,000; Phase II: \$1,500,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

The short term goal of this SBIR contract topic is to support small businesses that are developing candidate therapeutic agents of interest. Work scope may include animal efficacy testing, structure activity relationships (SAR), medicinal chemistry, formulation, production of GMP bulk drug and clinical product, as well as pharmacokinetic, pharmacodynamic, and toxicological studies. These data will establish the rationale for continued development of the experimental therapeutic agent to the point of filing an Investigational New Drug Application (IND) (http://www.fda.gov/cder/Regulatory/applications/ind_page_1.htm). Successful projects will also be eligible for further development at NCI, including early-stage clinical trials via the Joint DCTD-CCR Early Therapeutic Development Program. Companies should submit proposals for the development of agents that are in mid to late pre-clinical development (expected time to clinic 1-3 years). The development plan, targeted to oncologic indications, will be reviewed by NCI. Agents for rare cancers are of particular interest to the NCI.

Project goals:

The goal of the NCI SBIR program is to accelerate the development of products that benefit cancer patients. The NCI Strategic Plan identifies integrating clinical trial structures to expedite identification of the most promising treatment opportunities and rapid execution of the necessary clinical trials as a strategic priority (Strategy 4.5). Part of this strategy includes creating an integrated infrastructure to accelerate the implementation of high-priority clinical trials. The long term goal of this contract topic is to enable a small business to bring a fully developed cancer therapeutic agent to the clinic and eventually to the market.

Phase I activities and expected deliverables:

- Specific activities will range from SAR and medicinal chemistry to animal toxicology and pharmacology, depending on the agent selected for development.
- Development plan that describes in detail the experiments necessary to file an IND or an exploratory IND.
- Demonstrate ability to deliver results for the initial set of experiments (project-specific, according to the development plan above).

Phase II activities and expected deliverables:

- Complete all experiments according to the development plan (can be re-evaluated if needed).
- If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agent in question (oncologic indications).
- Demonstrate the ability to produce a sufficient amount of clinical grade materials suitable for an early clinical trial (according to FDA's Exploratory IND guidance) <http://www.fda.gov/cder/guidance/7086fnl.htm>.

257 Biopsy Instruments and Devices that Preserve Molecular Profiles in Tumors

Number of anticipated awards: 2

(Fast-Track proposals will be accepted.)

Budget (total costs): \$250,000 for Phase I; \$2,000,000 for Phase II

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Molecular medicine holds much promise for advancing cancer diagnosis and treatment, if biomarkers, molecular targets and drug effects on these targets can be accurately assessed in tumor nodules in the viscera. The amount

and function of molecular drug targets within signal transduction pathways are often regulated by rapid enzymatic reactions in response to physiological stimuli. Biopsies play a central role in assessing biomarkers and molecular targets in solid tumors, but conventional practices and medications used by surgeons and interventional radiologists necessarily perturb the tumor environment and thereby induce extraneous and confounding molecular responses to tissue trauma, vascular changes, hypoxia, anesthetics, etc. Expedient processing of the biopsy specimen using snap freezing or rapid fixation are ineffective for preventing many rapid enzymatic modifications, because time frames of biopsy procedures are much longer than that of the enzymatic reactions. Thus, there is a need to develop clinical devices, instruments and approaches suitable for clinical practice that stabilize molecular profiles in visceral tumor lesions during the procedure, and prevent molecular response to the procedure. The diagnostics market includes devices for needle cryobiopsy of breast lesions that freeze the tissue in situ before sampling, but the needle size is too large for percutaneous image-guided biopsy of visceral sites. Although unlikely to improve routine diagnostic biopsies, innovative approaches for tumor biopsy that preserve the molecular profile will create an entirely new diagnostic area and market in molecular therapeutics, which will not only facilitate pharmacodynamic assessment of targeted therapeutics but also enable individualized molecular therapy of solid tumors based on accurate information about signal transduction pathways, molecular drug targets and biomarkers.

Project goals:

The short-term goal of the project is the identification of technical strategies with potential for stabilizing the molecular profile of cancerous lesions in visceral tissue sites during clinical biopsy procedures. The long-term goals of the project are the design and development of operational prototype instruments/devices required to practice the innovative biopsy approach; the demonstration of the operational success of the innovative approach when applied to visceral lesions of solid tumors in model systems; and the evaluation of the potential superiority of the innovative biopsy approach over conventional surgical and radiological procedures for assessing highly dynamic molecular profiles that are associated with a high degree of instability during conventional biopsy procedures. The project scope includes advancements in biopsy technologies and approaches from any medical discipline performing biopsy procedures (surgery, radiology, dermatology, etc.) that improve the fidelity of molecular assessment of visceral tumor lesions. Reaching these goals on the basis of experimental evidence will mark a major advance in the ability to accurately assess the molecular profile of solid tumor lesions of the viscera and the functional status of their molecular targets during early clinical trials of experimental therapeutics. If successful, this project will improve the accuracy of biomarker assessment for diagnosis and prognosis and the information available about the pharmacodynamics and molecular efficacy of targeted drug therapy.

Phase I activities and expected deliverables:

Phase I proposal should identify a technical strategy for preventing changes in molecular status during solid tumor biopsy and articulate its rationale and critical principles of operation. It is expected that the company will demonstrate an understanding of the regulatory requirements for clearing the proposed instrument or device through the FDA. Research plan should contain quantifiable, testable feasibility milestones.

- Generate scientific data indicating that the innovative biopsy procedure stabilizes a biochemical process or reaction, or a functional molecular status, that is unstable during conventional surgical or needle biopsy procedures.
- Provide a description of the technical strategy underlying the innovative biopsy approach, the critical operating principles and the experimental design for testing if feasibility has been achieved.
- Provide a summary report of the results proving the feasibility of the innovative biopsy approach in tumor lesions of the viscera.
- Produce histochemical, biomarker, and/or other pharmacodynamic data that demonstrate that the innovative biopsy approach stabilizes a biochemical or molecular endpoint that is unstable during conventional biopsy procedures.
- Engage and obtain feedback from potential customers and users guiding the development of the product.

Phase II activities and expected deliverables:

- Design of clinic-ready device using FDA-compliant design processes.
- Production of a clinic-ready system and R&D activities to support integration of such system in clinical practice.
- Specify or develop assay for assessing molecular preservation which is suitable to be a general quality control indicator of molecular stabilization in clinical specimens.
- Design and conduct comparative studies of the innovative biopsy approach and instrument, and surgical and/or conventional needle biopsy of visceral lesions of a solid tumor model in animals, using validated assays.
- Provide results of the comparative study of the innovative and conventional biopsy approaches in the animal model, using validated assays
- Generate scientific publication regarding system performance oriented at the end user (surgeon, interventional radiologist, oncologist, pathologist, etc)
- Provide instrument data sheet and written instructions for the operation of any prototype biopsy device or instrument and the procedure for performing the innovative biopsy with quality control measures.

258 Innovative Devices to Protect Radiosensitive Organs and Structures During Radiation Therapy

Number of anticipated awards: 3

(Fast-Track proposals will be accepted.)

Budget (total costs): \$200,000 for Phase I; \$1,000,000 for Phase II

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Radiation therapy is an important tool in the cancer treatment arsenal. More than one million patients undergo radiation therapy in the US each year. Recent improvements in radiation therapy instrumentation increased the clinical utility of this treatment modality. Despite significant progress, there are still situations where patient/organ motion is limiting the dose that can be safely delivered to the tumor without damaging adjacent radiosensitive organs such as bladder, heart, spinal cord and others. There have been significant recent advances in this area, examples of which include development of implantable markers and electromagnetic localization systems, introduction of respiratory gating, advances in image-guided radiation therapy, growth in availability of proton/heavy ion radiotherapy, brachytherapy, and others. However, in certain clinical situations damage to the adjacent tissues, and resulting complications, could be further reduced and therapy efficacy could be enhanced, if better knowledge of radiation dose distribution could be obtained and organ motion during the radiation delivery could be better controlled. This contract topic seeks to stimulate research, development, and commercialization of innovative devices designed to protect radiosensitive organs and structures during radiation delivery.

It is expected that the proposed innovation is driven by clinical practice. Therefore, in addition to standard proposal components; the contract proposal must contain specific discussion of:

1. Evidence of an existing clinical problem which is addressed by the proposed method.
2. Analysis of competitive methods to address the same problem and explanation of competitive technical advantages of proposed system.

3. Quantitative estimate of the number of patient cases where the strategy will help to deliver better result per typical clinical site. This evaluation should be supported by literature, radiation oncologists, radiologist, medical physicist, or other qualified specialist.

Project goals:

The short-term goal of the project is to perform proof-of-principle technical feasibility demonstration of innovative strategy for protection of critical organs and structures through methods or procedures enacted prior to, during, or following the radiation delivery. These strategies may include, but are not limited to innovative devices, methods, phantoms, software, imaging systems, etc to assist in this goal. The long-term goal of the project is to generate scientific evidence regarding the safety and efficacy of the method and to bring the strategy to the clinic and to the market.

Phase I activities and expected deliverables:

Phase I activities should support the technical feasibility of the innovative approach. Specific activities and deliverables during Phase I should include:

- Design of a prototype system
- Development or procurement of an appropriate phantom necessary to evaluate the performance of the proposed system
- Validation of the prototype system with the phantom

Documentation providing a top-level description of the prototype system design, validation protocol, and testing results should be provided to NCI as part of Phase I progress report.

Phase II activities and expected deliverables:

Phase II activities should support introduction of the device into clinical practice. All Phase II or Fast-track proposals must contain a section entitled "Regulatory Plan" demonstrating an understanding of the regulatory requirements for clearing the device through the FDA, company's plan in meeting the requirements, and explanation of how the proposed work helps to meet these requirements. Where cooperation of other equipment manufacturers is critical for implementation of proposed methodology, company should provide evidence of such cooperation (through partnering arrangement, collaboration, or letters of intent).

Specific activities and deliverables during Phase II should include:

- Design of clinic-ready device using FDA-compliant design process
- Scientific studies of system performance as required by the FDA for submitting IDE, 510(k), PMA, or other appropriate regulatory pathway. (Studies may include phantom testing, animal testing, clinical testing, etc)
- Production of a clinic-ready system and R&D activities to support integration of such system in clinical practice
- Submission of scientific publication regarding system performance oriented at the end user (radiation oncologist, medical physicist, etc.).

Data sheet detailing performance of developed system should be provided to NCI as part of Phase II progress report.

271 Development of Molecular Pharmacodynamic Assays for Targeted Therapies

Number of anticipated awards: 3

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: \$150,000; Phase II: \$750,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

The NCI requests that qualified small businesses submit proposals to develop pharmacodynamic assays for measuring drug response of a number of high-priority molecular targets. A list of the targets of interest to NCI is shown below. The short term goal of this contract topic is to develop new robust, validated assays to measure molecular-level responses to treatment in conjunction with preclinical development of new candidate therapeutic agents. These assays should quantify the modulation of molecular targets upon treatment with investigational anticancer therapeutics and support pharmacodynamic studies in animal models and in human tumor and surrogate tissue samples. Real-time assays that could be used to rapidly assess response to treatment in the early clinical trial setting are highly desirable. Ideally, these assay measurements should have a correspondence to tumor modulation in animal efficacy models via the same target. Standard operating Procedures (SOPs) for these assays must be developed and be provided to the NCI along with all supporting data. (To view sample SOPs, please see: <http://sbir.cancer.gov/>.) Small businesses may also submit proposals for the development of assays that measure molecular targets relevant to oncology therapeutics development which have been identified by the small business.

It is envisioned that the NCI will assist SBIR contractors developing robust pharmacodiagnostic assays for immediate clinical needs via collaboration and partnership. An example of this collaboration would be the contribution of bulk critical reagents, calibrators, and positive and negative controls generated in NCI's laboratories and in GMP-grade contracting and manufacturing facilities. The provision of high quality assay kit components is essential for ensuring successful analytical validation of the assay. Furthermore, these assays will undergo "clinical proof of concept" studies in NCI Phase 0/I drug trials, which may lead to the generation of FDA-quality data. The clinical demonstration of assay performance is often critical to capture market share through widespread clinical adoption, as well as obtaining coverage by healthcare insurers. Although the type of partnership/collaboration will be unique for each assay, the NCI will be able to assist the company in defraying some of the costs and speed up the timeline for generating data required for CLIA laboratory adoption and/or 510K or PMA approval by leveraging the NCI's resources.

Project goals:

The long term goal of this contract topic is to provide a mechanism to develop a series of molecular pharmacodynamic assays to confirm clinical target modulation for a wide array of cancer therapeutics, to determine earlier in the drug development process if the target is modulated as intended, and whether this corresponds to either tumor stasis or regression. In addition to the assay itself, the contract recipient will develop and provide to the NCI SOPs that have been fully validated with human tumor/tissue samples.

The goal of the NCI SBIR program is to fund small businesses to develop commercially viable products that advance the research and development needs of the Institute. It is expected that companies will extend this work into developing research kits or diagnostic reagents to stratify patients for clinical trial selection or to evaluate response to new therapeutic agents. The NCI Strategic Plan identifies validating molecular targets for cancer prognosis, metastasis, treatment response and cancer progression as a strategic priority (Strategy 4.2). Part of this strategy includes creating a library of validated molecular target assays in order to advance broad development of targeted anti-tumor agents. Market analysis indicates that pharmacodynamic assay development is a valuable first step for eventual commercialization of cancer diagnostics and laboratory assays, in addition to serving the needs of cancer therapeutic development.

Phase I activities and expected deliverables:

- Develop a research pharmacodynamic assay for the molecular target described below (This list is also posted at <http://sbir.cancer.gov/>).

- Characterize assay reproducibility, variability and accuracy.
- Deliver to NCI the SOP of the research pharmacodynamic assay for the molecular target described.
- Make available to NCI sufficient critical reagents for test evaluation.

Phase II activities and expected deliverables:

- Develop a qualified or validated molecular pharmacodynamic assay for the target described. The assay should be applicable in the clinical setting.
- Perform studies to characterize the correlation between the resulting assay in tumor versus surrogate tissues (e.g. blood, serum), if applicable.
- Perform studies to characterize the correlation between the resulting assay in human versus animal tissues.
- Make available to NCI all SOPs for this assay.
- Make available to NCI sufficient critical reagents for test validation.

Molecular Pharmacodynamic Targets of Interest to NCI:

The following molecular pharmacodynamic targets have been identified as high priority for the NCI, based on the current pipeline of therapeutic agents under development. This list of molecular targets is being actively pursued by NCI's researchers; thus assays developed under this topic will be good candidates for beta testing at NCI laboratories and clinics. The NCI will determine and periodically re-prioritize the list of molecular targets to be addressed in subsequent years based on the needs of both intramural and extramural investigators:

1. Multiplexed assays for obtaining multiple, integrated PD readouts from tumor in a single biopsy specimen (any technology platform - microscopy, immunoassay of laser capture micro dissected tissue, etc), for example,
 - a. Interrogate multiple targets within a molecular pathway, such as PTEN/Akt/PI3K/mTORC1 & 2; Wnt/ Frizzled; Notch/Jagged/gamma-secretase; SHH/Smoothed/Gli, or NF-kB/IKK
 - b. Interrogate across multiple core signaling pathways of human cancer types identified by genome-wide analyses, pathway module signatures, or other types of global analyses of the cancer genome, such as, the twelve core pathways in pancreas cancer (see Jones et al, Science 321, 1801 [2008]) or the three core pathways in glioma (see The Cancer Genome Atlas Research Network, Nature 455, 1061 [2008])
 - c. Quantify the number of target molecules containing important combinations of post-translational modifications, for example, activating and suppressing modifications of individual Akt isoforms
2. Multichannel quantitative immuno-fluorescence, -infrared, -far infrared microscopy assays with companion image analysis methods, and other tissue visualization methods, for difficult PD evaluations in biopsy specimens, for example:
 - a. Identification of tumor stem cells using specific monoclonal antibodies to three or more stemness markers on a single slide, e.g., ALDH 1A1, SOX2, OCT 3/4, NANOG, CD44v6, CD133, CD166, CD49b, Olfm4 and/or innovative stemness markers already established scientifically by the company
 - b. Restricted PD evaluation of two or more PD endpoints to tumor stem cells identified by multiple markers
 - c. Restricted PD evaluation of cell surface receptor tyrosine kinases to the plasma membrane compartment
 - d. Restricted PD evaluation of nuclear markers to the inner nuclear membrane

- e. Quantitative evaluation of low prevalence molecular targets (~5,000-10,000 molecules per cell) against the backdrop of high prevalence targets (~100,000-1,000,000 molecules per cell)
3. Assays for quantifying important phosphorylated sites on members of the Met protooncogene family other than Met, and/or their specific enzymatic products (e.g., RON, STK, SEA)
4. Assays for quantifying new nuclear markers that are early indicators of apoptotic commitment of tumor cells, preferably immunofluorescence, although other assay formats will be considered

Sample Standard Operating Procedures (SOPs):

As mentioned above, sample Standard Operating Procedures (SOPs) are available at <http://sbir.cancer.gov/>. They demonstrate the level of rigor expected for pharmacodynamic assay development activities under this contract topic. They are not meant to indicate a preference for a particular technology platform.

272 Point of Care Analysis of Circulating Tumor Cells for Cancer Diagnostics, Prognosis and Treatment

Number of anticipated awards: 4

(Fast-Track proposals will be accepted.)

Budget: Phase I: \$200,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Circulating tumor cells (CTCs) are cancer cells that shed from either the primary tumor or its metastases and are circulating in the peripheral blood. While metastases are directly responsible for the majority of cancer deaths, CTCs may constitute seeds for metastases and are instrumental for the spread of the disease. Therefore the development of CTC-related applications is very important.

Analysis of CTCs may allow earlier detection of metastasis-capable malignancy when it is in a less invasive stage, and the ability to remove CTCs from circulation could potentially limit metastases after surgery. Many studies have shown that the presence of CTCs in peripheral blood and/or bone marrow is of prognostic significance in different types of solid tumors, and that CTC numbers also help monitor response to treatment. The current FDA-approved CTC analysis is based on immunological capture of CTC by magnetic beads. However, this method does not capture all types of CTCs and may be limited in its efficiency and accuracy. Hence it is important to develop improved methodologies for CTC detection, enumeration, isolation, and subsequent genetic or proteomic analysis. Moreover, the development of technologies that allow the efficient removal of CTCs from circulation could have therapeutic potential. This contract topic seeks to stimulate research, development, and commercialization of innovative devices and methodologies designed for Point of Care analysis of CTC-based diagnostics, prognosis and treatment.

Project Goals:

The long-term goal of the project is to develop Point of Care (POC) devices and methods of CTC detection, enumeration, isolation, removal and subsequent genetic and proteomic analysis for better cancer diagnosis, prognosis and treatment. The major focus is to develop clinical tools rather than tools for basic research. In the long term, these tools should be developed as POC devices and must perform at a lower cost than current methodology or offer significantly improved sensitivities/specificities or new features such as predictive diagnostics or treatment management tools not available with current technologies. The short term goal is to demonstrate the technical viability of the proposed approach to detect and/or isolate and/or eliminate CTCs in an experimental setting. Acceptable studies include but not limited to:

- CTC isolation and enrichment technologies such as magnetic separation, microfluidics, size separation and negative or positive selection.
- Surface antigen based CTC isolation and analysis
- Viable CTC cell isolation and/or culturing for treatment assessment
- CTC elimination from circulation
- Scanning, imaging, flow cytometry technologies for CTC
- Technologies to predict treatment and to monitor progress using CTCs
- Non-separation based technologies for CTC
- CTC detection, monitoring, or elimination using wireless devices
- Other tools for CTC detection, enumeration, isolation and analysis with clinical utilities.

Phase I activities and expected deliverables:

- Demonstrate the feasibility of the innovation (e.g. spiking relevant body fluids with CTCs and perform experiments with a bench-top device). Conduct benchmarking studies against current technologies (if available)
- Characterize the variation, reproducibility and accuracy of the method
- Provide NCI with detailed estimations of the cost of producing the proposed devices and/or reagents, including an analysis/breakdown of vendors and/or sources of raw materials

Phase II activities and expected deliverables:

- Develop a prototype of the POC device analytical tool incorporating the technology demonstrated in Phase I
- Test with a sufficient number of patient samples to demonstrate clinical utility and advantages, with an appropriate consideration of statistical significance
- If CTC elimination devices are developed, they should also be tested with *in vivo* animal models

273 Process Analytic Technologies (PAT) for Biologics: Innovative Methods for Monitoring and Analyzing Product Quality and Safety During Manufacture of Cancer Therapeutics

Number of anticipated awards: 2

(Fast-Track proposals will be accepted.)

Budget: Phase I: \$200,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

The NIH Roadmap Initiative for Medical Research emphasizes the importance of translational activities that bridge the gap between laboratory research and medical product development. In addition, the FDA has identified a growing gap between the rapid advances in drug discovery and the number of regulatory approvals for new drugs. One aspect of translational research that is frequently overlooked is the significance of the transition from a

lab-scale production process to an industrial-scale manufacturing process. Production lot failures that occur during manufacturing or product testing significantly increase production costs and time-to-market. Expensive toxicology studies and clinical trial results are often brought into question during regulatory review for failure to demonstrate reliable, reproducible methods of production or for inadequate characterization of the agent used in the study. A primary roadblock in the development of new cancer therapeutics is the lack of well-defined manufacturing processes for production of high quality, safe and effective biologics. Innovative, state-of-the art technologies are critical to cost-effective, regulatory compliant pharmaceutical manufacturing at the commercial-scale.

The FDA has 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 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 launched an 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.

Project Goals:

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 thus the quality and safety attributes of the final product. The focus of this research should include the development of innovative technologies for optimizing and monitoring the manufacturing process using in-line or in-process analyzers that can provide multi-variant data to improve the efficiency of process controls and determination of production end-points. Examples of such process innovations or improvements are:

- Innovation or improved in-line monitoring of lyophilization parameters.
- Innovation or improved in-line or in-process monitoring of endotoxin levels.
- Innovation or improved in-line or in-process monitoring of product quality attributes such as activity, glycosylation, aggregation, etc.
- Innovation or improved in-line or in-process monitoring of product yields for common biologics such as antibodies, DNA plasmids, viral vectors, and recombinant proteins

The contract proposal must contain specific discussion of:

1. Evidence of an existing problem which is addressed by the proposed method.
2. Analysis of competitive methods to address the same problem and explanation of the technical advantages of proposed system.

Phase I activities and expected deliverables: Phase I will involve the development of innovative methods or improvements related to the in-line or in-process monitoring of product quality and safety attributes during manufacturing. Examples of phase I activities and deliverables:

- Scientific data demonstrating the feasibility of the in-line or in-process production process innovation or improvement.

- Scientific data demonstrating the proposed scalability of the in-line or in-process production process innovation or improvement.
- Beta-testing of the in-line or in-process production process innovation or improvement.
- Engage and obtain feedback from potential customers and users guiding the development of the product.
- Provide the program and contract officers with a letter of commercial interest.

Phase II activities and expected deliverables: Phase II activities will include delivery of prototype with full validation of the novel technologies identified in Phase I. Examples of phase II activities and deliverables:

- Prototype with detailed specifications for hardware/software that supports the in-line or in-process production process innovation or improvement.
- Full validation of the in-line or in-process production process innovation or improvement.
- Install hardware/software at a pilot customer facility and provide NCI with a report summarizing system performance and whether it addresses customer needs.

274 Quantitative Cell-Based Imaging For Clinical Diagnosis and Treatment

Number of anticipated awards: 3

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: \$150,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

This SBIR announcement solicits proposals to develop semi-automated quantitative imaging assays to enumerate cells in tumor tissue. While genetic, epigenetic or proteomic profiles of tumors may predict therapeutic response, these methods are often slow, complicated and fail to assess small subsets such as cancer stem cells, host immune or stromal cells whose presence may determine the clinical outcome of a treatment. Additionally, this SBIR announcement seeks to standardize objective measurement of immunohistochemistry and in situ hybridization - two processes that have been difficult to standardize. A semi-automated assay also may improve the pathologist's throughput and accuracy compared to manual enumeration of rare cells. These objectives complement several NCI strategic goals in molecular medicine, nanotechnology and development of novel therapeutics.

SBIR respondents will develop a set of fluorophore-labeled secondary reagents that detect haptens conjugated to primary antibodies or nucleotide probes that react with specific cellular antigens, genes or gene transcripts. The secondary reagents will be used in standardized tissue-based immunofluorescence assays that can be measured with current state of the art image acquisition and quantitative analysis and that are independent of the antigens or genes being measured so long as the primary reagents bear the appropriate haptens. Preclinical models may be used in Phase I but ultimately the assay must be clinically useful. The multiplex reagents may be provided by a central laboratory in specific assays or distributed through kits. Small businesses may also submit proposals to measure cellular subsets relevant to oncology that they have identified.

Project Goals:

The short term goal is to develop multiplex reagents to facilitate performance of validated quantitative imaging assays to measure cell subsets within neoplastic tissue. This solicitation seeks to create stable mixtures of

fluorescent reagents that detect at least 3 separate and distinct haptens conjugated to primary antibodies or oligonucleotides that are used in immunohistochemistry and/or in situ hybridization. The aim is to create a mixture of three or more secondary reagents that can be used reproducibly in assays independent of the specific antigens or nucleic acids being detected by the primary antibodies or nucleotide probes. The fluorophores on the reagents must be chosen so as to maximize separation of signals by the three or more reagents as well as other reagents that may be used to identify such cell constituents as nuclei. Tissues used for assay development should be collected in accordance with guidelines provided by the NCI Office of Biorepositories and Biospecimen Research (OBBR, please see <http://biospecimens.cancer.gov/>). The assay can be envisioned as either a service by a central laboratory or as a kit with equipment and supplies, including calibrators and a SOP. SOPs for these assays must be developed and provided to the NCI. Also data using a second technology that confirms the quantitative measurements of the specified cell subsets (e.g., by flow cytometry, functional assay or laser capture microscopy and western blotting) must also be provided to the NCI. Small businesses may submit proposals for the development of assays that have been identified in the literature or by the small business to support development of oncologic therapeutics.

The long term goal of this contract topic is to develop imaging assays for cell-based markers that provide prognostic, predictive or therapeutic response information on clinical tissue biopsies that may be used in clinical practice. Achievement of this goal would support the goal of the NCI SBIR program to fund small businesses to develop commercially viable products that advance the research and development needs of the National Cancer Institute. Strategic priorities 4.1-.3 and 4.5 of the NCI Strategic Plan identify efforts to validate biomarkers and targets for cancer prognosis, metastasis, treatment response and cancer progression, then integrating these into clinical trials as being important.

Market analysis indicates that development of quantitative imaging assays is a valuable first step for eventual commercialization of cancer diagnostics and laboratory assays, as well as serving the needs of cancer therapeutic development. In addition to the assay itself, the contract recipient will develop and provide SOPs to the NCI that have been fully qualified or validated with human tumor/tissue samples. Finally, companies should extend this work into developing either services or kits with integrated equipment that will stratify patients for clinical trial selection or that predict or evaluate response to new therapeutic agents.

Phase I activities and expected deliverables:

1. Develop stable mixtures of at least three fluorophore-labeled reagents that stoichiometrically bind to such standard haptens as biotin, dioxygenin, DNP, fluorescein or other compounds conjugated to primary antibodies or nucleotides (please see list below for examples). These reagents should be used in a multiplex quantitative imaging assay that identifies and counts defined cellular subsets in a preclinical model or clinical specimens that is consistent with the current DICOM standard (<http://medical.nema.org/Dicom/>). The NCI is interested in quantitative multiplex fluorescent assays to enumerate and identify defined cellular subsets in tissue sections of tumors (please see <http://sbir.cancer.gov/> for this list of candidates). Each cell type may be identified by separate sets of primary antibodies or oligonucleotides that are individually labeled with one of the haptens that are recognized by the anti-hapten secondary reagents. The aim is to create a mixture of secondary reagents that can be used reproducibly in assays independent of the exact epitopes of the antigens or sequences of the nucleic acids being measured as well as being used in assays that simultaneously measure antigens and genes. The fluorophores on the reagents must be chosen so as to maximize separation of signals by the three reagents as well as other reagents that may be used to identify such cell constituents as nuclei. The imaging assay must demonstrate accuracy in formalin-fixed tissues. The SBIR recipient must deliver SOPs for specimen collection, processing and stability of the cell subset under the conditions of the imaging assay.
2. The SBIR recipient must demonstrate research assay reproducibility, variability and accuracy in a preclinical model or appropriate tissues for the intended clinical use of the assay. An important aspect of this is the development of reliable calibrators for the assay. The data demonstrating consistency with the current DICOM standard and assay SOPs must be provided to the NCI. The NCI can assist in acquisition of appropriate tissues.

3. The SBIR recipient must provide evidence of confirmation of the specificity of the assay's results by a second technology that assesses phenotype or function of the cell of interest.

Phase II activities and expected deliverables:

1. Report to NCI confirmation of the use of a stable set of at least three fluorophore-labeled secondary reagents in a semi-automated quantitative imaging assay as described and required in Phase I for a specified cell subset in clinical samples. In addition, a second technology must confirm the measurement of the specified cell subset phenotypically and/or functionally. NCI can assist in acquisition of appropriate specimens for this confirmation and testing. This is expected to require analysis of normal and malignant tissues that are both fresh and formalin-fixed to enable parallel confirmation of phenotype and/or function.
2. Provide to NCI the SOP for specimen collection and processing and of the imaging assay for the cell subset with the exception of proprietary information. This SOP should describe the characteristics for stability and availability of all reagents and calibrators.
3. Demonstrate acceptable real-time assay performance in clinical tissues appropriate for the intended use of the assay.
4. If the product will be a research kit, the kits must be provided to NCI for evaluation. Kits should include:
 - a. package insert
 - b. critical reagents
 - c. calibrator slides

Cell Types and Haptens:

Candidate Cell Types to be Measured by a Minimum of 3 Markers

Cancer Stem Cells (ALDH1A1, CD133, CD44v6)

Macrophages

Endothelial Cells

Endothelial Cells with specific receptors (VEGFRs, EGFR, PDGFRs, ALK, etc.)

T cells

B Cells

Memory B Cells

Dendritic Cells

Tregs

TRECs

Other T cell subsets

Other B cell subsets

MDSC

Specific cancer cell subsets (e.g., HER2+ER-, HER2-ER-PR-, Pathway specific Smo, PTCH1, Gli1 etc.)

Candidate Haptens As Examples To Which Secondary Reagents Might Be Directed

Biotin

Avidin

Dioxygenin

DNP

Fluorescein

Oregon Green

275 Development of Generic Antibodies for the Treatment of Cancer

Number of anticipated awards: 3

(Fast-track proposals will NOT be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget (total costs): Phase I: \$300,000; Phase II: \$2,500,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

New biological agents for the treatment of cancer are steadily entering the market. These targeted biologics carry the hope of ushering in the next generation of cancer therapy. Yet, there are often toxicities associated with them and they are very expensive, costing more than \$100,000 per year to administer. The overall goal of this SBIR contract topic is to support small businesses to develop generic and lower priced versions of therapeutic biologics for the treatment of cancer.

Project Goals:

The goal of the NCI SBIR program is to accelerate the development of products that benefit cancer patients. As such, the short-term goal of this project is to stimulate the development of biosimilars for cancer therapy, whereas its long term objective is the enhancement of competition in the biologics arena in order to reduce the cost of therapy for this class of molecules. The long-term goal would be the commercialization of generic versions of therapeutic antibodies for the treatment of various cancers.

Phase I activities and expected deliverables:

- Molecule selection (e.g. FAb)
- Molecule optimization (e.g. binding studies using SPR, Biacore, Binding Assays, FACS)
- Construction of the biologic (e.g. IgG) and its purification (CHO/other system)

Phase II activities and expected deliverables:

- Functional studies in cells
 - o Identification of signal transduction pathways (e.g. AKT inhibition)
 - o Determination of mode of action (e.g. apoptosis, proliferation, angiogenesis, migration)
- Functional studies in animals- non-GLP
 - o PK studies, including PK assay development
 - o PD studies, including PD assay development
 - o Efficacy studies in mice or other appropriate species
 - o Determination of cross-reactivity of the biologic with its target from various species in order to identify relevant species for non GLP studies
- ADCC/CDC (for antibodies) assessment
- Non-GMP Manufacturing
 - o Clone Selection for Highest Expresser (e.g. using FPLC/ FACS/ELISA)
 - o Potency assay development for manufacturing
 - o Stability studies
- Non-GLP studies

- o Non-GLP Dose determination study in 2 relevant species (rodent and primate)
- o Immunogenicity assay development
- Toxicology
 - o GLP studies (tox/PK) in primates including GLP PK assay development and immunogenicity assessment
 - o GLP studies (tox/Pk) in rodents or non-primate
 - o GLP tissue cross reactivity in human and two relevant species

276 Development of Novel Medicinal Food Products for the Mitigation of the Side-Effects of Cancer Chemotherapy

Number of anticipated awards: 2

(Fast-track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget (total costs): Phase I: \$150,000; Phase II: \$1,500,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

About 1,479,350 new cancer cases are expected to be diagnosed in 2009. Many of these patients will be treated with one form or another of chemotherapy; however, side effects are common, as chemotherapeutic agents also affect healthy cells, including those of the digestive tract, hair and bone marrow leading to nausea, vomiting, hair loss and fatigue. Indeed, it is the cumulative damage to multiple systems caused by chemotherapy that can limit the dose, frequency, and in many cases the efficacy of the therapy. Although serotonin receptor antagonists are currently being used as antiemetics, the more severe side-effects of chemotherapy such as neutropenia, thrombocytopenia and neurotoxicity remain problematic. Thus, there remains a need to develop new modalities for the mitigation of chemotherapy side-effects. Recent studies have demonstrated that short term caloric restriction and down regulation of insulin-like growth factor signaling can differentially protect normal cells, but not cancer cells, against oxidative stress and high doses of chemotherapeutic agents. These observations suggest that novel modalities that mimic short term caloric restriction, including substitution of glucose with other carbon sources, can be used to protect cancer patients against the side-effects of chemotherapy. As such, the overall goal of this SBIR contract topic is to support small businesses to develop novel modalities for the treatment of the side effects of cancer chemotherapy.

Project Goals:

The aim of this project is to stimulate the development of novel modalities, including medical foods containing specific combinations of carbon sources, vitamins and minerals as well as sugar and amino acid substitutes that mimic the short term caloric restriction, and thus differentially protect normal cells against chemotherapeutic agents while providing the necessary nourishment to patients.

Phase I activities and expected deliverables:

- Develop of one or more medical food products with the potential to protect patients against multiple side effects caused by widely used chemotherapeutic drugs.
- Offerors should provide compelling clinical or pre-clinical data supporting the development of the proposed products, as well as proof that the products do not enhance the survival of cancer cells.

- Phase I efforts should include animal studies aimed at demonstrating a statistically significant increase in the therapeutic index of a commonly used chemotherapeutic drug (e.g. 5-fluorouracil, cisplatin, etc) as a result of the administration of the medical food product.
- The plan for the development of the product should be formulated in consultation with NCI.

Phase II activities and expected deliverables:

- Complete the development of the medical food product for the differential protection of normal cells in cancer patients receiving chemotherapy.
- Perform animal studies demonstrating utility of the medical food product for protection against the toxicity of several other commonly used chemotherapeutic regimens.
- Appropriate preclinical data should be accumulated that support a Phase I clinical trial.
- Perform human studies to determine safety.
- Provide NCI with updates on a comprehensive IP and development plan, outlining how the small business will develop and commercialize the product.

277 Companion Diagnostics: Predictive and Prognostic Tests Enabling Personalized Medicine in Cancer Therapy

Number of anticipated awards: 4

(Fast-Track proposals will be accepted.)

Budget: \$200,000 for Phase I; \$1,500,000 for Phase II

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Recently the demand for companion diagnostics has greatly increased with the recognition that personalized medicine can improve patient care and may decrease health care costs by bringing specific therapies to individuals more likely to benefit from such treatments. More than a dozen companion diagnostic tests have been approved by the FDA to guide the prescription of products in oncology, cardiovascular diseases, and infectious disease. Among them, tests of the Philadelphia chromosome, tumor-associated EGFR overexpression, and HER2 protein overexpression have been identified by the FDA as “required” for the identification of candidate cancer patients for receiving Gleevec, Erbitux (cetuximab) and Herceptin (trastuzumab), respectively, in certain indications.

Despite initial success, many therapies in the cancer area are still lacking prediction and guidance from companion diagnostics. In particular, many patients die from recurrence and metastasis as a result of unpredicted drug resistance developed during therapy. Guidance to facilitate effective and safe therapy is therefore much in need. Companion diagnostics include tests that are developed after a drug has come to market and tests that are being developed in conjunction with the development of a drug. This contract topic seeks to stimulate research, development, and commercialization of innovative tests and technology platforms for both types of companion diagnostics. Companies with advanced biomarkers are particularly encouraged to apply.

Project Goals:

The goal of this contract topic is to develop companion diagnostics for selecting patients in whom a particular therapeutic regimen, including existing drugs and those in late clinical development, will be safe and effective. Although the example companion diagnostic tests mentioned above are for targeted therapy, tests can be for

therapeutics outside of this class as well. Tests may include, but are not limited to, tumor RNA/protein expression or overexpression, gene mutation or deletion/insertion, allelic variation, and enzymatic deficiency. Noninvasive sampling methods are preferred, but minimally invasive technologies are also acceptable if they provide improved predictive value and accuracy. This topic is not intended to support the development of assays unless they provide predictive/prognostic information for a therapy. For example, development of an assay for the sole purpose of pharmacodynamic analysis would not be considered responsive.

Phase I activities and expected deliverables:

- Develop a working test
- Characterize the variation, reproducibility and accuracy of the test
- Demonstrate suitability of the test for use in the clinic, conduct benchmarking studies against current tests (if available). Algorithms must be tested with datasets other than those used for their development.
- In cases where the drug for which the companion diagnostics being developed is not yet commercially available on the market, the applicant must provide proof of collaboration or partnership with the entity that is developing the therapeutic agent.
- Deliver the SOP of the working test to NCI

Phase II activities and expected deliverables:

- Demonstrate clinical utility and value by testing sufficient numbers of patients to unequivocally prove statistical significance with regarding to patient selection for the therapy
- If phase I conclusion is mainly based on animal experiment or ex vivo modeling, then a correlation study between these models and treatment in human subjects may be expected.
- Establish marketing partner or alliance, as appropriate, with pharmaceutical companies that are developing the therapy unless the therapy is on the open market
- Deliver the final SOP to NCI

278 Data Harmonization and Advanced Computation of Population Health Data

Number of anticipated awards: 2

(Fast-tracks are not accepted. Information about Phase II is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget (total costs): \$100,000 for Phase I; \$750,000 for Phase II

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

The National Institutes of Health (NIH) face a key inflection point in confronting the 'cells to society' deluge of health-related electronic data spanning the genomics/proteomics, biomedical, behavioral, and population health disciplines (HHS, 2008). The challenge of understanding and, more importantly, making effective use of this fragmented information environment underscores what the Institute of Medicine (IOM) describes as the "structural inability" of conventional medicine to exploit the unprecedented amount of electronic information available at our fingertips (IOM, 2007). Partially in response to this challenge, the Federal government's national HIT strategic plan has been predicated on the notion of appropriate access to and sharing of electronic health information through a national health information infrastructure (HHS, 2008). This is elaborated on in the National Research

Council's recent recommendations on Federal investment in cyberinfrastructure and computational techniques for cancer prevention and control (National Research Council, 2009).

NCI is responding to these challenges by connecting the cancer community through the cancer Biomedical Informatics Grid (caBIG®), an Internet-scale distributed network for sharing health related information, promoting scientific collaboration, and applying advanced computational techniques for large volumes of electronic data. To date, caBIG has been utilized most effectively by the biomedical and genomic/proteomics communities. Consequently, there is a clear need for development of computational applications, services, and tools for behavioral and population health sciences that can 1. Mount and harmonize population health data including behavioral, psychosocial, environmental, and clinical data onto caBIG; and 2. Extract useful information from the harmonized datasets using innovative computational techniques (both linear and non-linear methods including signal detection, data-driven modeling approaches such as neural networks, clustering, functional modeling, and many other data/signal processing techniques) and data visualization methods for decision support tools that help improve cancer prevention and control in patients, providers, and/or the research enterprise.

Health and Human Services (2008). Coordinated Federal Health Information Technology Strategic Plan: 2008-2012. The Office of the National Coordinator for Health IT. Washington, DC: Department of Health and Human Services.

Institute of Medicine (2007). The Learning Healthcare System: Workshop Summary. Edited by L.A. Olsen, D. Aisner, and J. M. McGinnis. Washington, DC: National Academies Press.

National Research Council (2009). Computational Technology for Effective Healthcare: Immediate steps and strategic directions. Edited by W. Stead and H. Lin. Washington, DC: National Academies Press.

Project Goals:

The goal of this topic is to encourage development of innovative computational applications, services, and tools for caBIG that can accommodate the electronic population health data described in the topic summary to accelerate knowledge discovery. Potential applications could target any specific problem or domain in cancer prevention and control including decision support tools in health communication and informatics, screening, survivorship, diet and physical activity, tobacco use, health disparities, biological mechanisms of psychosocial effects on disease, and clinical and public health systems (see <http://cancercontrol.cancer.gov/>). Proposals must be capable of harmonizing disparate population health datasets (e.g., data from behavioral surveys, the built environment, geographic information systems, large public health surveillance datasets, clinical EHR systems, PHR systems,...) onto caBIG, with at least one of these data sources being behavioral medicine and social science-related data. The caBIG-based application should also be able to extract useful information from the harmonized data using innovative computational techniques (both linear and non-linear methods including signal detection, data-driven modeling approaches such as neural networks, clustering, functional modeling, and many other data/signal processing techniques) and data visualization methods for scientists, patients, and/or providers for cancer prevention and control.

Phase I activities and expected deliverables:

- Develop a fully functional prototype application that can integrate and harmonize disparate datasets as described in topic summary and goals.
- The software prototype should be targeting a specific problem or domain in cancer prevention and control, including health communication and informatics, screening, survivorship, diet and physical activity, tobacco use, health disparities, biological mechanisms of psychosocial effects on disease, and clinical and public health systems.
- The application must be fully integrated with caBIG, meeting requisite vocabulary, metadata, and related protocols for mounting and harmonizing data into the caBIG Enterprise-wide Vocabulary System (EVS).
- Develop a functioning analytic service that can extract useful information from the datasets mounted on caBIG using innovative computational techniques (e.g., linear and non-linear regression, signal

detection, data-driven modeling approaches including neural networks, clustering, functional modeling, and many other data/signal processing techniques).

- Establish a project team that includes expertise in cancer prevention and control, behavioral sciences and population health, computational thinking, and health informatics that will effectively address all aspects of the current topic.
- Convene focus groups or conduct interviews with potential end-users of the system if needed to determine if the application data, analytics, visualization, user interface, etc... are appropriate.
- Provide a report detailing the application's planned data (constructs, measures, data sources, metadata...) and analytic capabilities (theories, methods, strengths and weaknesses of related analyses), with relevant caBIG protocol documentation.
- Provide outlines for an operation manual and primer for consumer-level and scientific/research applications when appropriate.
- Develop software application design and specification documentation, where applicable.
- Include in the proposals, letters of agreement from organizations participating in Phase I feasibility testing and evaluation.
- Obtain letters from interested participants for Phase II testing and evaluation.
- Present Phase I findings and demonstrate the final prototype to an NCI Evaluation Panel.

NOTE: Offerors are required to fully develop their individual product in Phase II to meet the goals of this SBIR contract topic. Where feasible and appropriate, Phase II contractors are encouraged to collaborate, coordinate, or communicate with other NCI funded contractors or programs. Offerors are also required to develop a dissemination package that enhances marketability.

Phase II activities and expected deliverables: *(Same format as for Phase I)*

- Develop and beta-test the application with individuals from the target market segment(s)
- Include sufficient funding in the budget for evaluation of the application's user interface and functionality at NCI's Usability Evaluation Lab or similar facilities.
- Develop evaluation measures and evaluation plan that will refine the application/tools based on user feedback and commercial considerations. The evaluation should also focus on verification of the validity of the computational methods and results of the analyses.
- Develop the final application and documentation where applicable.
- Develop and refine application integration with caBIG and relevant datasets as defined in Phase I.
- System Requirements could include: (refer to CBITT caBIG guidelines)
- In the first year of the contract, provide the program and contract officers with a letter of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter of commercial commitment.
- Present final research findings and demonstrate the final product at an NCI/DCCPS sponsored Product Showcase.

- Prepare at least one manuscript describing the development and evaluation of the application/tool for publication in a peer-reviewed scientific journal.
- Submit final report in the template provided by the NCI program officer.

279 Facilitating the Transfer of Statistical Methodology into Practice

Number of anticipated awards: 2

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget: Phase I: \$100,000; Phase II: \$750,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

The development of new statistical methodology represents a key component of biomedical research. For cutting-edge statistical methodology to be used by people other than the developer, accompanying user-friendly, robust software is necessary. Often the developer of the statistical methodology does not have the time, knowledge, or skills to convert research-quality code for calculation engines into professional-quality software to be used by the general medical research community. In addition, the incentive mechanisms that drive a research statistician to put final touches on a paper submitted to a journal are not present to encourage a researcher to create user-friendly, robust software.

This SBIR announcement solicits submissions from small businesses interested in facilitating the transfer of newly developed cutting-edge statistical methodology with medical applications from the methodology developer to the user. The small business will consider the demand for the methodology, create user-friendly, robust software based on the calculation engine of the methodology developer, and make that software widely publicized and available. The small business will focus on creating software that is user-friendly, robust, and potentially interoperable with other common software packages that are part of the caBIG initiative.

Project Goals:

The goal of this contract topic is to accelerate the time from the initial development of statistical methodology to when it can be readily used by a wide audience.

The short term goal of this contract topic is to transfer the software of one important, highly-sought biostatistical technique from a research stage to a professional stage, developing the foundations in Phase I for a full-blown product to be completed in Phase II. In particular, the following steps should be accomplished.

1. Consider the demand of the end-users to help in the choice of cutting-edge statistical methodologies. Confirm the lack of availability of existing professional-quality tools for those methodologies.
2. Partner with the statisticians who developed the cutting-edge statistical methodology to create a professional software product based on the statistician's research code for one method or a suite of related methods.
3. Test and refine the usability, robustness, and interoperability of the software and documentation. Solicit feedback from principle consumers and modify the product based on the feedback.
4. Commercialize a professional final product, possibly by incorporating it into a widely-used statistical package or creating a new package.

In preparing an application, the applicant should choose one cutting-edge biostatistical methodology (or a suite of related methodologies) that has excellent commercial potential and meets the following criteria:

1. There is a demonstrated demand for the methodology and a lack of available professional software to implement the methodology.
2. The developer of the statistical methodology has agreed to act as a consultant to verify the accuracy of the newly developed software. Research should be proposed that includes quantifiable, testable milestones for developing the software using the statistical methodology. Letters of support from potential user groups verifying the demand for the particular methodology chosen will strengthen an application. The long term goal of this contract topic is to encourage small businesses to gain expertise in facilitating the quick transfer of cutting-edge statistical methodology from the academic or other developers to the medical researcher end-user, potentially via an existing software company. It is expected that once this process is developed, the small business could operate profitably, independent of government funding.

Phase I activities and expected deliverables:

- Create a prototype of user-friendly, robust software for one methodology with appropriate documentation.
- Test the robustness and usability of the software prototype by consulting a working group comprised of likely end-users.
- Demonstrate comprehension of caBIG methods, philosophy, and principles.
- Provide program and contract officers with
 - o letter(s) of commercial interest to transfer the product, or
 - o a detailed plan to commercialize the software (possibly as part of a new package) or to incorporate the software into a popular existing package.
- Provide monthly reports.

Phase II activities and expected deliverables:

- Based on the Phase I findings and feedback from the working group, create user-friendly, well-tested, robust software with full user interfaces for the methodologies with appropriate, full documentation and instructional materials.
- Demonstrate capability to obtain caBIG bronze/silver compatibility.
- Obtain an affidavit from the developer of the original methodology, stating his/her belief that the software is accurate. The developing statistician must be consulted until he/she is comfortable signing the affidavit.
- Present the products at a statistical and/or non-statistical conference and to an NCI evaluation panel.
- Provide program and contract officers with letters of commercial commitment to transfer the product (if applicable)
- Provide program and contract officers with quarterly reports. The final report should evaluate the strengths and weaknesses of the process by which the technology was transferred from the academic researcher to the end user.

Research should be proposed with a refined commercialization plan based on Phase I findings and quantifiable, testable milestones.

280 Direct Sequencing of Nucleic Acids without Clonal Amplification or Synthesis for the Molecular Characterization of Cancer

Number of anticipated awards: 2

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: \$150,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Nucleotides in DNA and RNA are frequently modified by exogenous and endogenous insults, leading to a broad spectrum of chemical modifications (e.g., oxidation, alkylation, formation of cyclobutane pyrimidine dimers, etc). These chemical modifications can significantly alter the functional expression of genes *in vivo*, resulting in genome instability and variations in the sequence of a transcript and/or polypeptide. Moreover, knowledge of these sequence variations in normal, premalignant and malignant cells in a human biospecimen may provide critical information in understanding the molecular basis of cancer. Unfortunately, interrogating such sequence variations is presently intractable because the currently available high-throughput methods for nucleic acid sequencing depend on enzymatic clonal amplification using high-fidelity polymerases. In particular, these methods conceal many DNA lesions inherent to the original nucleic acid sequence by incorporating a non-damaged nucleotide opposite the adduct (mismatch, etc), followed by amplification of this undamaged sequence. In effect, this amplification step masks the underlying information contained in the original sequence. Therefore, to understand the true functional nature of the individual genome and/or transcriptome, new high-throughput sequencing techniques are required that are highly sensitive and specific at the single molecule level. Such methods must also be capable of detecting nucleic acid adducts to obtain an accurate read of the non-amplified genome or transcriptome.

Project Goals:

The primary goal of this topic is to encourage small businesses to develop novel high-throughput technologies that will enable researchers to directly capture nucleic acid sequence information without the need for amplification. Such technologies are expected to aid researchers in identifying specific and predominant variants involved in the development of disease phenotype(s). In particular, sequence information of DNA, messenger RNA (mRNA) and/or microRNA (miRNA), which is obtained from human cancer biospecimens, is expected to provide new insights into cancer onset and progression. Future benefits of these technologies (which are beyond the scope of the current topic) may include new approaches for risk assessment in cancer epidemiology, and potentially new cancer prevention and/or therapeutic strategies.

Examples of novel technologies and approaches that might be developed under this topic include the following: near-field optical techniques in combination with nanotip-enhanced vibrational spectroscopy, high throughput molecular imaging techniques, novel hybridization techniques that increase the sensitivity of detection to the single molecule level, and novel nucleic acid stabilization methods. These approaches are not meant to be exhaustive. Offerors are encouraged to develop any appropriate innovative technology to meet the goals of this contract topic. Technologies and approaches aimed at sequencing all of the sequence and splice variants in a cell are of particular interest to NCI.

Phase I activities and expected deliverables:

- Develop a novel technique to directly capture nucleic acid sequence information without the need for amplification (i.e., develop an approach to obtain sequence information at the single molecule level)
- Show proof-of-concept by applying the technology to obtain sequence information for one or more of the following: DNA, mRNA and/or miRNA
- Demonstrate the ability to successfully detect both unaltered (i.e., non-damaged) nucleotides, as well as cancer-relevant, chemically-altered (i.e., adducted) nucleotides

Phase II activities and expected deliverables:

- Apply the technique(s) to biospecimens, such as cancer cell lines
- Adapt the techniques for the high-resolution, high-throughput screening of cancer biospecimens
- Characterize and demonstrate the accuracy and specificity of the technique/assay
- Develop a commercially viable assay that is capable of directly obtaining sequence information for one or more of the following in a cancer biospecimen: DNA, mRNA, and/or miRNA

281 Biosensors for Early Cancer Detection and Risk Assessment

Number of anticipated awards: 3

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: \$150,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

A primary cause of poor survival rates from cancer is that many cancers are detected late, after they have spread or metastasized to distant sites. For most types of cancer, the earlier the detection the greater the chances of survival. For example, when colorectal cancer is detected in its earliest stages, the 5-year survival rate is as high as 95%, but if detected after it has spread, the survival rate is less than 10%. Five year survival rates for cancers where screening tools are available are 4-6 times greater than for cancers for which there are no viable screening tools. However, even for cancers where screening tools currently exist, there is room for improvement in the accuracy of the tests or in making them more acceptable to patients. Consequently, there is a need to develop methods to noninvasively and accurately detect cancers at early stages of development and to determine those individuals at increased risk of developing cancer. Given the heterogeneity of transformed cells found in many tumors, it is unlikely that a single biomarker will be able to provide sufficient sensitivity and specificity to be useful as an early detection screening assay. Thus, there is a need for devices that can accurately and reproducibly measure multiple cancer biomarkers or circulating tumor cells in bodily fluids or other specimens obtained by minimally invasive methods. As these biomarkers or tumor cells are likely to be present in low abundance, the device must be very sensitive. Biosensors have the potential to fulfill this need. In cancer research and detection, a biomarker refers to a substance or process that is indicative of the presence of cancer in the body. It might be a molecule secreted by a malignancy itself, or it can be a specific response of the body to the presence of cancer. Biomarkers include genes, genetic and epigenetic variations, mRNA, microRNA, protein, post-translational modifications of proteins, and metabolites.

Project Goals:

The purpose of this solicitation is to develop biosensors for early cancer detection and risk assessment. Biosensors are bioanalytical devices that combine biochemical recognition or binding elements, physicochemical transducers, and readout modalities. Biochemical recognition elements include antibodies, proteins and peptides, nucleic acids, aptamers, cell receptors, enzymes, and tissues. The transducer may be optical, electrochemical, thermometric, piezoelectric or magnetic. Biosensors for early cancer detection and risk assessment have potential advantages over other analytical methods including the capability for multi-target analyses, automation, speed, flexibility and reduced costs. Given the complexity of biological specimens, it may be necessary to incorporate front end sample preparation. The incorporation of nanotechnology into biosensor design and fabrication will aid in detecting novel biomarkers, such as epigenetic changes and microRNAs for early detection and risk assessment of cancer.

Phase I activities and expected deliverables:

- Design novel biosensors or improve existing biosensor technologies that can be used either to measure physiological concentrations of multiple known biomarkers for early cancer detection or risk assessment or to capture and measure circulating tumor cells and tumor stem cells.
- Perform analytical validation (e.g. accuracy, reproducibility, sensitivity, specificity and dynamic range) using purified samples in an artificial matrix that mimics the clinical specimens.

Phase II activities and expected deliverables:

- Complete the development and automation of the biosensor and demonstrate its speed, flexibility, and ability to reduce costs.
- Perform analytical validation (e.g. accuracy, reproducibility, sensitivity, specificity and dynamic range) using appropriate patient specimens (e.g. urine, sera, plasma, or sputum).
- Determine clinical sensitivity and specificity.

282 Imaging of Cancer Stem Cells

Number of anticipated awards: 2

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget: Phase I: \$150,000; Phase II: \$1,500,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Numerous studies have indicated that several human cancer types, including those of breast, brain, colon, head & neck, leukemia, liver, ovarian, pancreas and prostate, may arise from the malignant transformation of stem cells and their progenitors. With evidence in support of a cancer stem cell (CSC)/tumor initiating cell (TIC) model for carcinogenesis, it becomes critically important to identify and image these cells in vivo or in human tissues. The purpose of this initiative is to provide support for the development of imaging technology for identification of CSCs/TICs. The selected offerors will develop technologies for imaging of CSCs/TICs, so that CSCs/TICs can be identified in a cancer or a subtype of a cancer. Offerors should focus initial development on the imaging of CSCs/TICs in one of the cancer types/subtypes such as prostate, breast, lung, colon, or other major epithelial cancers, where CSCs/TICs have been detected. In Phase II, the technology of imaging developed in Phase I will be validated under a plan developed with the NCI project officer.

Project Goals:

The goal of the project is to develop imaging technology of CSCs/TICs with a resolution that is able to distinguish CSCs/TICs from non-CSCs/TICs. The technology development can include methodology that can help better mechanistic understanding of CSC generation, migration, frequency and potency. The imaging technology that will be developed can also be used to monitor efficacy of drugs in CSCs/TICs. The imaging technology could further be used, in a preclinical setting, both for high throughput screening assays to locate CSCs/TICs. The technology development should be platform driven. For example, the procedure for the imaging of breast cancer or its subtype should be easily applied for developing imaging technology of other cancer types/subtypes, such as colon cancer or prostate cancer. The modality could be one of the following, but is not limited to: optical imaging, PET, or MRI. The imaging agent could include, but is not limited to: antibodies, peptides, DNA/DNA analogs, small molecules, or nano particles.

Phase I activities and expected deliverables:

- Identification and validation of a set of markers for the CSCs/TICs in the cancer of choice.
- Demonstration of simultaneous detection of multiple of markers, the presence of which indicates CSCs/TICS.
- Quantification of the imaging signals to determine the number of CSCs/TICs present.
- Demonstration of capabilities enabled by the imaging to distinguish CSCs/TICs from non-CSC/TIC in both cells and tissues.
- Validation of molecular imaging agents with in vivo small animal efficacy studies.

Phase II activities and expected deliverables:

- Determine biosafety of the imaging agents with in vivo small animal toxicology studies.
- Demonstration of high reproducibility and accuracy of the imaging technology in an animal model.
- Demonstration of high specificity and sensitivity of the technology when compared to other non CSC/TIC.
- Validation of high throughput imaging and screening assays with primary cells and/or human tissues
- Demonstration of capabilities to monitor efficacy of drugs in CSC in cell lines and/or animals.

283 Development of a Molecular Diagnostic Assay to Detect Basal-like Breast Cancer

Number of anticipated awards: 2

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget: Phase I: \$150,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Breast cancer is a heterogeneous disease with a number of distinct biological entities that are associated with specific morphological/immune-histochemical features and clinical behavior. Basal-like breast cancer is one of the five intrinsic subtypes, which was classified by gene expression profiling in breast cancer. The four other subtypes include luminal A, luminal B, human epidermal growth factor receptor-2 (HER2) over expressing, and normal-like. 15-20% of breast cancer patients have basal-like subtype, which is the most aggressive subtype in breast cancer. It is associated with high grade, poor prognosis, and younger patient age. Population-based study has shown that this subtype is more prevalent in premenopausal African American women, which may contribute to the poor outcomes seen among these patients. Currently there is no effective assay product with low cost to detect basal-like subtype in the market. The purpose of this initiative is to provide support for the development of a molecular diagnostic assay to detect basal-like breast cancer. The selected offerors will develop an assay for detection of basal-like subtype at cell, protein or DNA level, so that basal-like breast cancer can be identified specifically. The final assay should enable test to be completed within one day at a low cost. In Phase I, the development of molecular diagnostic assay should focus on proof of concept. In Phase II, the assay developed in Phase I will be validated under a plan developed with the NCI project officer.

Project Goals:

The goal of the project is to develop a molecular diagnostic assay to detect basal-like breast cancer with sensitivity and specificity that is able to distinguish basal-like breast cancer from other subtypes in both human cells and tissues. The assay can be used for early detection of basal-like breast cancer, or be used as post-treatment monitoring to detect recurrence of the cancer. The assay may also be used to provide a better mechanistic understanding of basal-like tumor development, so the knowledge can help develop preventive, diagnostic, or therapeutic agents that target specifically against basal-like subtype and further improve patient outcome. The assay development should be platform driven, meaning that the procedure for the assay development should be easily applied for a new assay development for the detection of other cancer subtypes in breast cancer or other cancer types such as prostate or colon cancers.

Phase I activities and expected deliverables:

- Identification and validation of a set of markers for detection of basal like breast cancer.
- Develop an assay to identify these markers effectively to distinguish basal-like subtype from other subtypes in breast cancer with cell lines and/or tissues.
- Demonstration of high reproducibility and accuracy with blinded samples from cell lines and/or tissues
- Demonstration of high specificity and sensitivity of the assay when compared to other subtypes.
- Deliver to NCI the SOPs of the molecular diagnostic assay for basal-like breast cancer.

Phase II activities and expected deliverables:

- Demonstration of the assay that enables a test to be finished within one day.
- Perform studies to characterize the assay in animal models with different subtypes of breast cancer.
- Validation of high throughput screening assays with primary cells and/or tissues obtained from patients.
- Demonstration of platform capability that enables the procedure of the assay development be easily applied to a new assay development for the detection of other subtypes of breast cancer or other cancer types/subtypes.
- Validation of the assay in the clinical setting.
- Submission of regulatory application to obtain necessary approval for clinical validation.

284 Alternative Biospecimen Stabilization and Storage Solutions

Number of Anticipated Awards: 2

(Fast-Track proposals will not be accepted. Phase II information is provided only for informational purposes to assist Phase I proposers with their long-term strategic planning.)

Budget (total costs): \$150,000 for Phase I, \$1,000,000 for Phase II

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Current methods for stabilizing tissue specimens for downstream molecular analyses, including freezing and embedding in paraffin, have not undergone significant improvements for many years, are not energy efficient, and require long-term investments in complex and expensive infrastructure. Biorepositories, especially those that store frozen specimens, require significant investments in personnel, space, and sophisticated monitoring and alarm systems to assure that optimal temperatures are maintained. Various dry storage techniques have been

developed to provide an alternative to freezing and paraffin embedding, including blood and saliva spot cards. Such techniques have been widely used, for example in the CDC's neonatal screening program. However such methods have not been routinely developed for solid tissue specimens. New approaches are needed that are more universally suited to a variety of tissue types, and maintain the stability of all macromolecules. Such methods should not require hazardous chemicals or expensive equipment and should provide an alternative to the high energy costs required to maintain ultralow temperatures. A method suitable for room temperature storage is preferable. The stabilization process should be easily reversible in order for samples to be used quickly as needed. Finally, given the rapid turnover of RNA and other macromolecules, stabilization must occur almost immediately after removal from the patient.

Project Goals:

The focus of this solicitation is on the development of novel, innovative or improved methodologies or reagents for the stabilization and/or storage of cancer tissue biospecimens and their resulting molecular analytes. As discussed in the above section, the NCI is interested in proposals that demonstrate how the product will overcome one or more of the limitations and disadvantages of current methods for stabilization and storage of biospecimens intended for use in molecular research, namely formalin-fixed paraffin embedded (FFPE) and frozen tissues. The project scope could include reagents and/or novel methodologies for biospecimen fixation, biospecimen storage, and short term post operative biospecimen stabilization for tissue evaluation and/or transport.

The short term goal of this project is the identification and development of a technical strategy with the potential to serve as a useful alternative storage and/or stabilization reagent or method for use by the cancer research community.

The long term goal of this project is to thoroughly test such a method or reagent for effectiveness as a storage and/or stabilization method for cancer biospecimens and/or analytes. Such testing will include evaluating the performance of alternatively fixed/stored biospecimens and analytes against case-matched biospecimens stabilized and stored in liquid nitrogen or FFPE. Performance evaluation of the product should focus on biospecimen molecular integrity and utility for molecular research platforms.

Phase I activities and expected deliverables: Develop innovative and improved methods or reagents for the stabilization and/or storage of biospecimens and/ or their resulting molecular analytes.

- Demonstrate proof of principle for the development of the reagent or method;
- Provide a description of the technical strategy for the stabilization or storage reagent highlighting the critical operating principles and the experimental design for testing if feasibility has been achieved
- Demonstrate feasibility of use by providing a summary report of results from feasibility testing;
- Test the usefulness of the methods and/or reagent by comparing the outcome of appropriate molecular analysis (dependent on disease and specimen type) with that from matched frozen or FFPE biospecimens;
- Obtain input from potential customers in the research community in preparation for developing a comprehensive commercialization plan for the method or reagent.

Phase II activities and expected deliverables: Refine and analytically validate the reagent or method.

- Provide data comparing the fixation and/or stabilization method and/or reagent to previous widely used methods or reagents detailing performance and any improvements in 1) stabilization of proteins and nucleic acids, 2) quality of biospecimen or resulting analytes for molecular research, 3) general accessibility and ease of use, 4) cost effectiveness compared to FFPE or frozen storage, and 5) hazard level of the involved reagents.

- Demonstrate the use of the method or reagent by stabilizing or storing more than 20 disease matched biospecimens accompanied by matched samples stabilized by FFPE and by freezing, or more than 100 molecular analytes in comparison to all other currently available applicable stabilization and storage methods.
- Provide all comparison data to the NCI
- Generate a scientific publication regarding assay or method performance targeted to the end user audience.

285 Multifunctional Therapeutics and Theranostics Based on Nanotechnology

Number of Anticipated Awards: 5

(Fast-track proposals will be accepted.)

Budget: Phase I: \$200,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Nanoscale devices carrying therapeutic payloads and delivered within close proximity of the tumor in vivo can play a significant role in increasing the effectiveness of the treatment while decreasing severity of side effects. Such techniques would be highly relevant, particularly, for organs that are difficult to access because of a variety of biological barriers, including those developed by tumors. For example, nanoparticles are capable of crossing the blood-brain barrier due to their small size and thus are an excellent candidate for non-invasive treatment of brain tumors.

Multifunctional nanoscale devices, which are currently emerging, allow for a combination of diagnostic agent with a therapeutic and even a reporter of therapeutic efficacy in the same nanodevice package. In conjunction with the development of these devices, local targeting techniques are also emerging. This process can utilize epitopes expressed on the surface of tumor cells or other cellular markers of biological processes such as angiogenic and apoptotic pathways. In molecular oncology, this is more intriguing and potentially useful as a general approach since it allows for targeting of multiple cancers or even more broadly for targeting of multiple diseases. For instance, there are already examples of multi-functional nanoparticles that target vascular peptides, growth factor receptors, transmembrane proteins such as ion channels, and are utilized for both cancer and cardiovascular disease recognition.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based multifunctional therapeutic and theranostic (combining diagnostic and therapeutic capabilities) structures designed to deliver treatment to cancerous cells while sparing normal, healthy tissue- leading to increased therapeutic index and improved patient outcomes.

Project Goals:

The goal of this project is to demonstrate in vivo nanodevice-based delivery platform with improved efficacy as compared to currently used treatments. These devices can take, for example, the form of multi-functional targeted nanoparticles or multi-chamber chips carrying encapsulated drugs. Further, the devices may also utilize imaging agents for a combination of therapeutic and diagnostic modalities that aim to provide real-time feedback and monitoring of therapy. The devices operating in vivo can be administered orally, intravenously, or can be implanted. They may include, but are not limited to the following:

- novel therapeutic nanodevices
- novel theranostic nanodevices capable of diagnosing and subsequently treating cancer

- devices involving novel tumor targeting and concentrations schemes
- novel theranostic nanodevices which contain both a therapeutic agent and a reporter of tumor environment (e.g., pH, hypoxia, necrosis, vascular collapse)
- novel drug loading and releasing schemes
- novel nanodevices which are able to cross the blood-brain barrier
- novel nanodevices which predict the tumor response to a particular therapeutic agent prior to the administration of the therapeutic agent (i.e., a predictor of efficacy)

Phase I activities and expected deliverables:

- manufacturing techniques resulting in the manufacturing of nanodevices with good reproducibility should be developed. The novel use of existing particles acquired from the commercial manufacturer will also be considered under this program.
- in vitro (cell culture) demonstration of drug efficacy
- proof-of-concept small animal studies showing improved therapeutic efficacy as compared to the use of free drug
- demonstration of simultaneous diagnosis and treatment in both cell culture and small animal models for theranostic devices

Phase II activities and expected deliverables:

- demonstration of targeting (multiple biomarkers) and nanoparticle aggregation at the tumor site for a specific organ/disease
- in vivo small animal drug efficacy demonstration (at least 60 day study with statistically relevant number of animals) utilizing an appropriate animal model
- long term toxicity studies (biodistribution and bioelimination for IV administered nanodevices and biocompatibility for implanted devices)
- nanodevice manufacturing and scale-up activities
- IND-enabling studies carried out in a suitable pre-clinical environment
- initiation of large animal studies

286 Nanotechnology Imaging Agents or Devices for Improved Detection of Cancer

Number of Anticipated Awards: 3

(Fast-track proposals will be accepted.)

Budget: Phase I: \$200,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Nanotechnology involves the design, synthesis, and manipulation of materials at the nanoscale to take advantage of novel material properties (e.g. large surface to volume ratio, increased conductivity, enhanced imaging

contrast, etc.) that are not normally present in conventional bulk length scales. These properties render nanomaterials as ideal candidates for imaging and sensing purposes. Further functionalization of these materials can be achieved by conjugating biological ligands (e.g. oligonucleotides, short peptide sequences, antibodies, etc.) that can serve to achieve specific targeting of cells/tissues/organs or specific capturing of genomic/proteomic candidate biomarkers.

Early detection of cancer is a vital key in the fight against cancer. By the time patients are diagnosed with breast, lung, colon or ovarian cancer, more than 60% already have hidden or known metastases. For example, more than two thirds of ovarian cancer cases are detected at an advanced stage, and the 5-year survival rate is 40%. However, if this disease is detected and treated at Stage I (when it is still confined to the ovary) the survival rate increases to 90%. Consequently, efforts are currently being made to develop new diagnostic solutions comprising of imaging agents providing for higher spatial resolution.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based imaging agents that will ultimately assist and improve current clinical protocols of cancer detection and diagnosis.

Project Goals:

The goal of the project is to develop nano-enabled imaging agents or devices that can provide increased resolution both spatially, and more importantly, temporally, in detecting cancer that would ultimately offer clinicians a way to maximize the chance of positive clinical prognosis. The agents and devices can be used for early imaging/detection of initial onset of disease, or be used as post-treatment monitoring to image/detect recurrence of disease.

Potential relevant imaging agents could include, but are not limited to:

Imaging nanoparticles

Examples: Fluorescent agents (quantum dots, quantum rods, etc.); medical imaging agents (MR, CT, SPECT, PET, etc.); *in vivo* sensors (FRET sensors, biologically-activated systems, etc)

Potential Applications: Use of agents as secondary-tags to improve existing *in vitro/ex vivo* assays; Detecting smaller lesions and/or better delineation of tumor margins with traditional clinical imaging modalities (MR, CT, PET, etc.) before, during, and after interventions (resection, chemotherapy, etc.); Novel *in vivo* sensors to monitor cancer biology-related activities (enzymes, cleaved peptides, etc.).

Imaging agents for intra-operative applications

Examples: Fluorescent, bioactivated imaging agents (quantum dots, quantum rods, etc.) which are applied directly to the tumor site during resection or via systemic routes to delineate tumor cells from normal, healthy tissue and allowing the surgeon to successfully assess the tumor tissue margins.

Potential Applications: Use of novel imaging agents to assure complete tumor resection during the surgery and thus eliminating the need for follow-up surgery due to imperfect identification of tumor margins.

Imaging apparatus or equipment

Examples: Apparatus or equipment incorporating nanotechnology into the final instrument capable of delineating normal tissue from tumor tissue using X-ray, MR, CT, PET modalities.

Potential Applications: Imaging instrumentation with higher performance and lower cost than existing technologies

Proposals may include, but are not limited to, any of the above examples. Given the diversity of potential applications discussed above, submitted proposals *should place emphasis on the specific nanotechnology-enabling component of the proposed imaging agent or device.*

Phase I activities and expected deliverables:

- Design describing:
 - o imaging methodology
 - o unique spatial/temporal capabilities enabled by nanotechnology
 - o proof of concept experiments
 - o benchmarking experiments against conventional methodologies
- First-stage validation of design in relevant preclinical samples,
 - o Imaging agents and nanoparticles: *In vivo* small animal efficacy studies
 - o Apparatus and equipment: Small animal imaging studies
- Successful completion of benchmarking experiments demonstrating a minimum of 2x improvement against conventional methodologies

Phase II activities and expected deliverables:

- Second-stage validation of design for potential clinical adaptation
 - o Imaging agents and nanoparticles: *In vivo* animal toxicology studies that can be used for regulatory filing purposes
 - o Apparatus and equipment: Animal imaging studies that can be used for regulatory filing purposes
- Submitted IND or IDE application to obtain necessary regulatory approval for clinical validation.

287 Nanotechnology Sensing Platforms for Improved Cancer Detection

Number of Anticipated Awards: 3

(Fast-track proposals will be accepted.)

Budget: Phase I: \$200,000; Phase II: \$1,000,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Nanotechnology allows for the design and manufacture of complex multi-functional devices which could lead to the miniaturization of biological assays. Current diagnostic assays require a patient visit a physician or travel to a laboratory. Nanotechnology-based instruments hold the potential for point-of-care applications where assays could be conducted by the primary care physician in their office or by the patient in their home as well as by health care workers in remote geographical locations or in hospitals for bed-ridden patients. Additionally, these systems require much smaller volumes of sample for analysis than conventional assays thus reducing the cost associated with reagents and the time required for conducting of some of these assays (e.g., heating and cooling in PCR-based assays).

For several types of cancer, the primary cause of poor survival is late detection, almost often after the disease has spread to distant sites. For example, most melanomas that are found without evidence of metastasis can be cured with surgical resection. In contrast, for the patients with advanced or metastatic melanoma, the prognosis is poor (a 5-year survival of 5-10%). Consequently, efforts are currently being made to develop new early-stage diagnostic solutions relying on highly sensitive and specific devices and the use of prognostic biomarkers.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based diagnostic platforms that will ultimately assist and improve current clinical protocols of cancer detection and diagnosis.

Project Goals:

The goal of the project is to develop nano-enabled diagnostic platforms that can provide increased sensitivity and specificity in recognizing cancer that would ultimately offer clinicians a way to maximize the chance of positive clinical prognosis. The platforms can be used for early detection of initial onset of disease, or be used as post-treatment monitoring to detect recurrence of disease. Strategies can also include screening assays that provide a better understanding and prediction of metastasis which can help develop better therapies and further improve patient outcome. As current drug development continues to rely mainly on reductions in overall size of tumors, many validated compounds may not be effective for eradication of metastatic disease.

Potential relevant sensing nanoplateforms could include, but are not limited to:

Nano-enabled Sensing Platforms for in vitro Applications

Examples: Use of functionalized nanomaterials (nanowires, nanotubes, nano-cantilevers, etc.) to develop diagnostic platforms with optical or electrical output.

Potential Applications: Novel platforms that would enhance sensitivity/specificity of existing candidate biomarker detection and validation; Sensing of tumor metastasis and/or recurrence post-treatment; detection, isolation and/or evaluation of circulating tumor cells (CTCs).

Nano-enabled Sensing Platforms for ex vivo Applications

Examples: Use of functionalized nanomaterials introduced into patient organism and subsequently collected for ex-vivo ascertaining of biochemical, metabolic and/or pharmacological data regarding tumor status or therapeutic efficacy.

Potential Applications: Long-term monitoring of treatment effectiveness, determination of therapeutic efficacy, monitoring tumor metastasis.

High throughput Screening Nanoplateforms

Examples: Nanotechnologies (using nanopatterning, imaging agent, sensing platform, microfluidics) for highly parallel, high throughput assay development.

Applications: Identifying and detecting novel cancer biomarkers that may be undetectable using traditional assays; detecting cellular changes using nano-sensors to screen for novel therapeutic agents.

Given the diversity of potential applications discussed above, submitted proposals *should place emphasis on the specific nanotechnology-enabling component of the proposed platform.*

Phase I activities and expected deliverables:

- Design describing:
 - o unique temporal capabilities enabled by nanotechnology
 - o proof of concept experiments
 - o benchmarking experiments against conventional methodologies
- First-stage validation of design in relevant preclinical samples,
 - o In vitro sensing platforms: Candidate biomarkers in serum-free samples
 - o In vivo sensing platforms: Candidate biomarkers in cell culture
 - o High throughput screening assays: Non-primary cell lines and/or tissue samples
- Successful completion of benchmarking experiments demonstrating a minimum of 2x improvement against conventional methodologies

Phase II activities and expected deliverables:

- Second-stage validation of design for potential clinical adaptation
 - o In vitro sensing platforms: Candidate biomarkers in patient samples
 - o In vivo sensing platforms: Candidate biomarkers in animal models
 - o High throughput screening assays: primary cells and/or tissues obtained from patients
- Submitted IDE application to obtain necessary regulatory approval for clinical validation.

288 Development of Alternative Affinity Capture Reagents for Cancer Proteomics Research

Number of Anticipated Awards: 3

(Fast-track proposals will be accepted.)

Budget: Phase I: \$150,000; Phase II: \$750,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Thousands of antibodies are produced every year by commercial companies. However, many of these antibodies are known to be poorly characterized and suboptimal across multiple applications. Polyclonal antibodies lack the reproducibility of monoclonal antibodies. Likewise, the production of monoclonal antibodies is expensive and may months to produce. Even after production, a monoclonal antibody may not be specific for the target of interest, may not work in the needed assay, or could not be used in combination with other antibodies due to an antibody's large size and subsequent competition for overlapping binding domains. As such, the high costs associated with producing even small quantities of monoclonal antibodies represent a large barrier towards cost-effective reagents and resources for proteomic technology research and clinical adaptation. The goal of this project is to develop reproducible, highly qualified/characterized alternative protein capture reagents for the cancer research community. The development of these affinity capture reagents will be done in coordination with NCI's Clinical Proteomic Technologies for Cancer (CPTC) and be targeted to a list of over 100 purified recombinant proteins being constructed and characterized through this initiative. There is a strong support for the development of renewable, alternative capture reagents that could be produced more efficiently and cost-effectively than monoclonal antibodies and hence, provide an inexpensive, well-characterized resource for the scientific community. Several technologies such as yeast single chain antibodies, or synthetically produced capture reagents such as aptamers, peptide aptamers, synbodies and nanotechnology reagents demonstrate a potential for alternative, reproducible, cost-effective reagents in proteomics research.

Project Goals:

The goal of this project is to develop alternative affinity capture reagents that can effectively compete against ELISA-based antibody technologies in terms of protein recognition, binding affinity, and detection and can be reproducibly produced in a cost-effective and efficient manner. These affinity reagents will ultimately be designed to target proteins developed in coordination with the Clinical Proteomic Technologies for Cancer that is producing purified cancer-related proteins for research programs. Furthermore, these capture reagents must pass performance characterization criteria and be made available as a resource to the scientific community. The suggested choices of performance platforms the affinity reagents must be required to surpass include ELISA-based assays, Mass spectrometry-based quantitative assays, Western blot, immunohistochemistry, and immunoprecipitation. In addition, other considerations include quantitative information for affinity reagents (K_d, on-rate, off-rate), the actual binding epitope in order to interpret the quantitative characterization, and application in multiplex platforms such as microarrays. While it is expected that initial development and quality assurance/quality control costs may be comparable to that of monoclonal antibodies, it is intended that production costs of these renewable reagents will be significantly lower.

During the phases I and II, offerors are encouraged to coordinate and pursue selected antigen targets in the following reference: Malu Polanski and N. Leigh Anderson. (2006) "A List of Candidate Cancer Biomarkers for Targeted Proteomics." Biomarker Insights 2:1-48.

Phase I activities and expected deliverables:

- Work with the Clinical Proteomic Technologies for Cancer community (<http://proteomics.cancer.gov>), private and public sectors to identify appropriate minimum characterization criteria/validation assays (Commercially available ELISA kits can serve as appropriate tests for performance criteria).
- In coordination with Clinical Proteomic Technologies for Cancer program staff, select and generate affinity reagents to at least ten protein targets and demonstrate equivalent or improved performance to ELISA and other affinity-based platforms.
- Present findings to an NCI CPTC Evaluation Panel and demonstrate how the capture reagents compare in binding affinity to antibody-based platforms such as ELISA and have improved cost effectiveness and throughput capabilities in production compared to antibodies.
- Research should be proposed with quantitative feasibility milestones.

Phase II activities and expected deliverables:

- Implement strategy and project plan for a fully functional affinity reagent development platform for at least 75 protein targets developed through CPTC. The reagents should be able to capture the target of interest from complex biological mixtures such as blood, plasma, or tissue.
- Test performance criteria against ELISA and other affinity platforms.
- Work with CPTC to integrate capture reagents into the proteomic research platforms.

289 Physical Property-Based High-Throughput Protein Sequencing

(Fast-track proposals will be accepted)

Number of Anticipated Awards: 2

Budget (direct costs): Phase I: \$150,000; Phase II: \$750,000

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

The availability, in recent years, of the nucleotide sequences of entire genomes, has radically reshaped approaches to protein sequencing. Protein sequencing by tandem mass spectrometry (LC/MS/MS & MALDI-TOF/MS) involves taking a protein and digesting it into peptides, with subsequent spectra obtained for the major peptide ions. The sample spectra are then matched to theoretical spectral sequences of proteins derived from the human genome (or genome of an organism). While this method has become popular over the recent years due to its relatively high-throughput, the process heavily relies on algorithms that tend to produce false protein identifications. Furthermore, proteomics experiments identify proteins on the basis of several sequenced peptides, which might or might not distinguish between all the possible isoforms of the protein. As a result, the theoretical sequence approaches that are used to identify proteins are not optimal for proteomics experiments. Some estimates indicate that up to 90% of tandem mass spectra in a typical liquid chromatography tandem mass spectrometry analysis cannot be identified using database search algorithms due to the poor quality of the spectra.

Therefore, the NCI is interested in proposals that focus on the development of novel, fast, reliable and economical protein sequencing alternative technologies that rely on approaches other than tandem mass spectrometry involving theoretical spectral sequences. The purpose is to stimulate the community to develop new HT-protein sequencing technologies based solely on physical, chemical, or biological properties. Proposals should explicitly describe how the proposed technology/system will rely on sequencing solely-based on physical, chemical, or biological properties where the full protein is sequenced in a manner equivalent of N-terminal Edman sequencing and amino acid analysis, and does not use theoretical sequencing methods or algorithm involvement, as is the case with mass spectrometry-based sequencing methods.

Project Goals:

The purpose of this project is to stimulate the development of novel, fast, reliable and economical alternative protein sequencing & identification technologies that rely solely on physical properties, equivalent of N-terminal Edman sequencing. Thus, classical tandem mass spectrometry coupled to theoretical spectra or mass spectrometry coupled to spectral libraries will not be explored. Furthermore, the spirit of this proposal is not to support the development of autosamplers that increases the number of samples to a classic Edman cyler protein sequencer.

During the phases I and II, offerors are encouraged (but not required) to coordinate and pursue selected antigen targets in the following reference: Malu Polanski and N. Leigh Anderson. (2006) "A List of Candidate Cancer Biomarkers for Targeted Proteomics." Biomarker Insights 2:1-48.

Phase I activities and expected deliverables:

- Demonstration of feasibility of the innovative alternative protein sequencing & identification technology based solely on physical chemical, or biological properties.
 - o Must give exact amino acid sequence.
- Produce an initial product prototype in working with the Clinical Proteomic Technologies for Cancer community (<http://proteomics.cancer.gov>).
- Demonstrate that alternative protein sequencing & identification technology can be made reproducibly and economically (compared to cost per run on a tandem mass spectrometer or Amino Acid Analyzer).
- Sequence at least 10 antigen targets (full-length proteins) (targets to be selected in coordination with the Clinical Proteomic Technologies for Cancer community).
 - o Antigen requirement (femtomole to picomole)
 - o Speed requirement: 10 unique proteins per hour.
- Present findings to an NCI Evaluation Panel.
- Research should be proposed with quantitative feasibility milestones.

Phase II activities and expected deliverables:

- Implement strategy and project plan for a fully functional novel, fast, reliable and economical alternative protein sequencing & identification technology based solely on physical properties.
- Sequence at least 200 full-length proteins with the speed, sensitivity, and cost parameters stated in Phase I (targets to be selected in coordination with the Clinical Proteomic Technologies for Cancer community).
- Project to be done in coordination with the Clinical Proteomic Technologies for Cancer community to integrate platform into the technology assessment programs and greater scientific community.
- Research should be proposed with quantitative feasibility milestones.

290 siRNA Resource for Synthetic Lethal Screening of DNA Repair and Damage Signaling Networks

Number of Anticipated Awards: 2

Fast-track proposals will be accepted.

Budget (total costs): \$200,000 for Phase I, \$1,000,000 for Phase II

(Note: Proposals with budgets exceeding the above amounts will be returned without review. Phase I project periods may last a maximum of 9 months. Proposals with durations exceeding 9 months will be returned without review.)

Summary:

Human cancers appear to be highly and differentially vulnerable to targeted attack on individual gene expression within their DNA repair networks, especially those pathways that are closely associated with DNA replication. However such lethal combinations (i.e., synthetic lethals) are generally not obvious or easily predicted a priori. What is needed to establish the generality of synthetic lethality for DNA- repair- related genes in human cancers is a systematic screen of the major DNA repair and DNA damage pathways, ablating gene pairs (or larger combinations).

Cancer researchers use a variety of methods to detect these lethal combinations including pair-wise siRNA knockdown protocols, or a genotoxic insult (e.g., cis-Platinum, ionizing radiation) plus siRNA knockdown of individual genes, or other approaches that would yield the same information (e.g. binning combinations of genes followed by secondary screens of subsets of DNA-repair-related genes). Currently they must develop these siRNA resources themselves or piece them together from existing collections, often in different vectors with differing quality control methods.

To expedite the capability to detect synthetic lethal combinations in human, cancer biologists and clinical researchers need high-quality, validated reagent sets targeting DNA-repair genes with minimal off-target effects and antibody reagents for detecting and typing DNA-repair and DNA-signaling defects within primary samples from individual patients. In this project an extensive set of such siRNA constructs would be validated in at least two different human cancer cell lines plus a normal reference (non-cancerous) control, representing different organ sites and demonstrate synthetic lethality in at least one of the tested reference cell lines.

Project Goals:

- Demonstrate siRNA knock down 400 chosen human DNA damage and damage signaling (DDR) genes with minimal off-target effects,
- Establish which pairs (or combinations) confer synthetic lethality in one or more of the reference the cell lines, 3 siRNA targets per gene, using an unbiased screening approach.
- Development of an extensible computer searching capability/database for potentially lethal siRNA combinations of human DDR genes using accepted eukaryotic ontologies conserved within the human DDR response network.

Phase I activities and expected deliverables:

- 40 genes knocked down, genes may be from homologous recombination pathways, replication signaling complex, end joining, and/or mismatch repair networks (established genes from the literature). At least two different pathways or networks must be targeted.
- Show at least two examples of known synthetic lethal combination using the above mentioned constructs in the synthetic lethal screen to be employed in phase II.
- Prototype database/data collection: genes mentioned above fully annotated as to their siRNA targets, pathways, and other available functional annotation as well as information on synthetic lethal partners.

Phase II activities and expected deliverables:

- 400 genes knocked down and annotated as in phase I.
- Extension of synthetic lethal screens, pair wise, or higher combinations of DDR genes, to an array of human established human cancer cell lines representing major malignancies (e.g., breast, prostate, pancreatic, brain, leukemias); targets should be tested in at least two different cell lines.
- Validation of synthetic lethal relationships in two reference human cancers which are known to demonstrate synthetic lethality, plus effects that maybe lethal or non-lethal and that are produced in reference control (non-malignant) human cell lines.

NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR)

The National Center for Research Resources (NCRR) provides laboratory scientists and clinical researchers with the tools and training they need to understand, detect, treat, and prevent a wide range of diseases. NCRR supports all aspects of clinical and translational research, connecting researchers, patients, and communities across the nation. This support enables discoveries made at a molecular and cellular level and through animal-based studies. These discoveries are translated to patient-oriented clinical research, with the ultimate aim of improved patient care. Through its programs, NCRR stimulates basic research to develop and provide access to state-of-the art technologies and instruments for biomedical and clinical research; improves the public understanding of medical research; and provides information about healthy living. NCRR supports all aspects of clinical and translational research, connecting researchers, patients, and communities across the nation..

This solicitation invites proposals in the following areas.

012 Visualizing Biomedical Research Characteristics

(Fast-Track proposals will be accepted.)

The complexity of NCRR programs require an innovative approach to both understanding scientific developments at large and managing its scientific portfolio. Biomedical research can be characterized in a multitude of ways. Publications, grant applications, progress reports, funding, specific aims, experimental designs, hypothesis, outcomes, scientific evidence, experts, collaborations, organizations, and networks, as well as many other factors reflect the complex activity of biomedical research. These elements are interlinked and often are represented by large volumes of data, e.g. thousands of papers are produced weekly. To make sense of these data and to aid in seeing the big picture, new methods are needed. Visualization has proven to be useful for extracting information from abundant data. A variety of scientific visualization techniques enable us to identify patterns and relationships and provide other useful information, especially for the process of making decisions. NCRR invites SBIR proposals that will facilitate the introduction of visualization technology into understanding the big picture of science, management of a research portfolio, and communication of complex scientific information.

Main requirements:

The outcome of this contract is expected to be software that assists in exploring multidimensional textual data, understanding complex concepts, and portfolio analysis. The software must

- meaningfully visualize massive amounts of high-dimensional data from potentially diverse data sources
- enable data exploration, change of displayed dimensions, and viewing at different levels of details (zooming in and out)
- be able to work with complex data dimensions, utilizing the elements of principal component analysis (PCA) or other appropriate techniques
- have transparent, validated, and well-documented protocols for all steps of data processing (cleansing, filtering, analysis, visualization, etc.)

- be accompanied by documentation of data processing algorithms, data accuracy, precision, and other features necessary for the most accurate interpretation of the produced visualization
- have Application Programming Interface (API) that does not require programming skills

Deliverables

- Phase 1 should produce meaningful visualizations of a test dataset(s) that address some sample areas below and demonstrate "proof of concept" for the Phase 2 deliverable. Examples may include visualizations of topics, networks, or evolutionary pathways based on any public source such as PubMed, patent database, NIH RePORT, or online community resources.
- Phase 2 deliverable is web-enabled software that can be used for multidimensional data exploration and portfolio analysis and can work with multiple data sources.

Sample areas of interest to NCRR

- Evolution of scientific domains, experts, collaborations, and concepts
- Landscape of knowledge that enables exploration of underlying evidence
- Landscape of knowledge about human health
- Visualizing differences in understanding of health in various cultures and communities
- Map of science where locations and interconnectivity of entities (e.g. scientists, organizations, papers, or concepts) can be explored
- Scientific forecasts
- Pathways for translating discovery into innovation
- Productive career pathways, e.g., those leading to significant achievements
- Visual thesaurus of complex scientific concepts
- Map of existing standards and their applicability and usefulness for specific tasks and environments, which may assist in choosing one or a combination for a project
- Visualizations that assist in navigation of complex and distributed on-going research activities
- Map of NCRR-related entities, expertise, activities, collaborative projects, funding, networks; e.g. Clinical and Translational Science Awards (CTSA) displaying multiple layers of communities and collaborative research activities
- Success factors for translational research, e.g., infrastructure, people, funding
- Distribution of funding among various scientific domains, institutions, types of grantees, and mechanisms

Visualization implementation

Various visualization techniques can be used. Examples of visualizations can be found at <http://www.scimaps.org> and include knowledge/domain/concept maps, networks, and innovative ways to display complex concepts.

Data sources

The analysis should be done using a number of various data sources, e.g., publications, World Wide Web, and NIH databases. The identification of appropriate sources is determined by the offeror. The choices must be justified, analyzed, and well documented with advantages and limitations of every source.

Other project clarifications

The offerors are encouraged to utilize the multiple principal investigator option to bring in experts from academia http://grants.nih.gov/grants/multi_pi/.

013 Collecting, Integrating, Accessing and Using Disease Models-Related Data

(Fast-Track proposals will be accepted.)

The biomedical research enterprise is facing a period of transition which offers vast potential yet equally apparent challenges. Recent technological advances have led to larger numbers and more complex research modalities with generation of massive amounts of data. Unfortunately, efficient use of information derived from animal models, computer models, in vitro studies, and other means of scientific investigation is becoming an increasingly intractable process.

A great urgency exists for development of efficient capabilities for integration and computation of disease models data. The problem is not specifically a lack of resources but rather a lack of ability to effectively utilize data across experimental groups, institutions, and domains. This solicitation seeks responses that will provide the initial steps to help build a framework for effective computation on existing and newly generated animal models data with the goal of facilitating translational science. The proposed projects should result in a distinct product: a lead compound or a newly validated animal model. Just as importantly, the data used and generated in conducting the project should be made available to benefit other translational efforts. Parameters defining the deposition or repositioning of data/information used and generated during the proposed efforts will be determined by a joint effort between the offeror and the appropriate representative of NCRR's LAMHDI (Linking Animal Models to Human Disease Initiative) contract, http://www.ncrr.nih.gov/comparative_medicine/linking_animal_models_to_human_disease.asp. This collaborative effort between the offeror and NCRR is not intended to influence ownership of the data or information resulting from the proposed projects but is rather an attempt to maximize use of project-specific data/information by others to enhance translational progress in related areas. This joint effort will be sensitive to intellectual property issues.

Requirements

The offeror will work with NCRR's LAMHDI representative to define the best means for data collection and deposition.

Two categories of translational science projects will be considered:

1. Drug Discovery Efforts Using Preclinical Models for Lead Identification and Optimization
 - This can entail small molecule efforts or protein/antibody efforts.
 - Methods will be used to provide easy access to data used and generated as well as the data processing tools.
2. Models validation
 - Statement of need for validation a particular model
 - o Clinical disease in the model is similar to human but the mechanisms leading from gene perturbation to phenotype expression are unknown.
 - o The model may not express clinical disease but is known (or suspected) to express a "disease-related" target that is comparable to the human target.
 - Comparison of the model to human condition

- o Comparison of clinical disease between human and model.
- o Comparison of gene/gene product pathways or networks in human and model.
- As with category 1, every effort will be made to provide easy access to data used and generated and the data processing tools.

Deliverables

Phase I should result in a comprehensive report that defines:

- Detailed plan generated by offeror and NCRR for data/information as described above.
- Documented need in terms of moving a distinct therapeutic into clinical trials or in terms of validating a model to allow moving a class of therapeutics (e.g. immunomodulators) into clinical trials.
- What is the known target in the model to be used for testing a specific therapeutic and how was this target determined to be analogous to the human target.
- What is the disease-related pathway/network that needs to be defined and compared in human and model to validate a model before testing and how will this be done
- Initial results from testing specific therapeutics or initial results that show comparable disease-related pathways/networks between human and model: i.e. proof of concept.

Phase II should result in the identification and optimization of a lead with expected marketing potential or validation of a model that would provide for a “testing service” for high potential, innovative therapeutic approaches such as immunomodulation.

Other project clarifications

The offerors are encouraged to utilize the multiple principal investigator option to bring in experts from academia http://grants.nih.gov/grants/multi_pi/.

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.

051 Technologies for *In Vivo* Electrophysiology Studies in Transgenic and Knock Out Mice and Other Small Animals

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2

Cardiac arrhythmias are a major public health burden. There are 250,000 - 400,000 sudden cardiac deaths (SCD) in the US every year, accounting for up to 20% of all deaths in adults; the majority of these are due to ventricular fibrillation. In addition, approximately 2.5 million Americans now suffer atrial fibrillation (AF), a number that is expected to surpass 5 million by 2050. Strong evidence indicates that risk for both SCD and AF includes a prominent genetic component.

Hundreds of transgenic and knock-out mouse models expressing gene defects associated with human cardiac arrhythmias have been made and are being used to define mechanisms and potential treatments for arrhythmias. Recently, genetic models of heart failure and arrhythmias have been developed in rat, rabbit, and guinea pig. Miniature, implantable telemetric devices for monitoring ECG in non-restrained mice or other small animals in vivo have been developed and are commercially available. However, miniature implantable pacemaker devices are not available. Thus, it is not possible to routinely administer precise electrophysiological tests or do extensive electrophysiological studies in small animal models of arrhythmias in vivo. Investigators who desire to test various types of programmed stimulation in transgenic small animal models of arrhythmias and heart failure must now fabricate their own versions of implantable stimulators or pacemakers.

The purpose of this SBIR contract solicitation is to foster development of novel technologies and devices that would significantly improve the quality and quantity of cardiac electrophysiology data obtained from transgenic and knock-out models of heart failure and arrhythmias. Although this contract is aimed at basic science studies, it is anticipated that technologies developed might also be translatable to pediatric cardiology. Applications are invited from research teams to develop implantable, wirelessly programmable devices that could be used in transgenic mice and other small animals to monitor cardiac electrical activity and to deliver programmed electrical stimulation in vivo.

Phase I research is expected to focus on demonstrations of proof-of-concept of the proposed new technologies and devices (e.g., development and initial testing of a prototype) and how they will surmount the combined obstacles of miniaturization, lead placement, and electrical stability of the implanted unit, as well as battery power, size and longevity.

Phase II studies should extend the efforts of the Phase I studies and focus on further refinement of the technologies and devices, and their testing in appropriate small animal models of arrhythmias.

052 Protein Capture Agents for Cardiovascular Research

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2

One of the biggest roadblocks to the translation of basic proteomic discoveries to potential clinical applications is the lack of robust and sensitive reagents that can capture a given protein reproducibly from different type of matrixes. While antibodies have been the major players of protein capture, alternate reagents are urgently needed to overcome the lack of sensitivity, specificity, and reproducibility associated with many of the current antibodies to help translate cardiovascular protein biomarker discoveries into clinical utility.

The goal of this proposal is to develop sensitive, well characterized and reproducible protein capture reagents for the cardiovascular research community. The focus is on developing alternative affinity capture reagents that have robust protein binding affinities and can be produced reproducibly in a cost-effective manner. The reagents being developed should be targeted to proteins involved in cardiovascular physiology or pathology.

Phase I applications should address initial development and feasibility testing of the multiplex platforms.

Phase II applications should be focused on completing the development of the technology for incorporation into the clinic.

053 Innovative Tools, Techniques, and Software for the Screening, Recruitment, and Follow-up of Participants in Pediatric Research

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-3

Screening and recruitment of children into multi-center clinical trials poses unique challenges not seen in the adult population. Screening tools, recruitment strategies, registries to provide baseline data on which to base future clinical trials and ways to document follow-up are needed. Validated materials and tools applicable to diverse

populations and for use in community practices, which often do not have the resources of larger hospitals or academic institutions, are particularly relevant. These tools should apply to a wide range of pediatric heart, lung, blood, and sleep disorders studies and would be developed to improve clinical trial performance. **The ultimate goal is to make trial recruitment and management more efficient and effective via tools or strategies offered to the public as an open-source product.**

Tools are not limited to, but can include:

- Interactive gaming strategies for older children and adolescents that have the potential to stimulate interest in scientific research areas related to heart, lung, blood and sleep disorders. This is an innovative and proven way to engage users (particularly youth) and deliver essential health messages, such as the importance of clinical research in improving health, what is involved when one joins a study, and to highlight the role of NHLBI in biomedical research.
- Infrastructure development for a registry in congenital heart disease such as case report forms, development of a web-based portal, and needs assessment for sustainable operation (manpower, maintenance, IT support, etc.). Activities for back end operations could include assessment of existing information systems, development of software to facilitate interoperability of current systems, development of software that can extract data from current electronic medical records and/or electronic monitoring systems, and development of a flexible database platform that can draw data from varied sources.
- Reminder tools for clinical trial participants, educational resources (pamphlets, public websites), novel and improved consent tools (forms, videos, web-based), and clinical trial costs assessment tools that can be easily used by investigators or sponsors.
- Approaches to facilitating adoption of evidence-based guidelines.

Phase I research is expected to focus on development of a new technology or strategy, to provide initial testing of the prototype and demonstrate how it will improve pediatric trial recruitment or trial management.

Phase II studies should further refine the technology or strategy and test its effectiveness for incorporation into the clinical research setting.

054 Interventional MRI and X-ray Invasive Hemodynamics Telemetry

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Magnetic resonance imaging has potential to revolutionize minimally invasive surgery and interventional procedures, by affording surgery-like visualization without conventional surgical incisions for exposure. Many such procedures can be expected to be conducted in parts under X-ray guidance and nearby under MRI guidance.

Invasive and interventional cardiovascular procedures require high fidelity hemodynamic recording for diagnostic measurement as well as procedural monitoring of physiological signals such as electrocardiography and invasive blood pressure.

There are no commercially available invasive hemodynamic recording systems available for MRI, nor for dual MRI and X-ray use. MRI creates problems imposed by transmission of physiological signals during MRI. The MR environment generates noise both from magnetic field gradients and from magnetohydrodynamic effects. Transmission lines for physiological transducers are susceptible to heating during radiofrequency excitation. Connections between the patient transducers or electrocardiography leads must be interrupted for intermodality transfer between the X-ray and MRI interventional systems, and this interruption may be required during periods of clinical instability. Leads, transmission lines, and transducers may not have features required both for X-ray (for example, radiolucency) and for MRI (for example, avoiding loop formation, attenuating heating, etc). Physiological

signals acquired in the MR environment will require preprocessing before transmission into conventional hemodynamic recording systems.

A high fidelity hemodynamic recording system is necessary to conduct interventional cardiovascular and other high risk procedures under MRI guidance and with seamless bidirectional transfer to and from X-ray. To date there are no suitable commercial solutions.

A wireless telemetry and preprocessing system is technically feasible that supports high fidelity hemodynamic recordings in a multimodality interventional environment using either MRI or interventional X-ray. Such a system would allow acquisition of hemodynamic signals (multichannel electrocardiography, invasive blood pressure, hemoglobin saturation, temperature, etc) safely in either an MR environment or an X-ray fluoroscopy environment, preprocessing to remove identifiable noise, wireless transmission to base stations in both environments, and automated transmission of signal that conform automatically to inputs of a commercial hemodynamic recording system.

The system must operate safely at MRI field strengths of 1.0 to 3.0T. The system should accommodate inputs for popular commercial hemodynamic recording systems. The system should provide up to 10 electrodes for diagnostic electrograms (six standard ECG chest and 3-4 limb leads) under an X-ray environment and at least four electrodes for filtered surface electrograms (one chest, three limbs) under an MRI environment or for non-cardiac X-ray applications. Specific attention should be paid to robust and safe disposable electrode attachment to patient skin to address hair, perspiration, conductivity, and current flux density distribution for signal fidelity and risk of burns. The electrode and lead system should be safe for operation under MRI, resistant to inadvertent loop formation, and should be radiolucent for operation under X-ray even with extreme double-oblique projection angles. The system should allow transduction of 3 simultaneous channels of invasive blood pressure from fluid-filled catheters, ideally with commonly used clinical invasive blood pressure transducers. The system should control and acquire non-invasive blood pressure, continuous hemoglobin oxygen saturation, and MRI-safe and X-ray compatible respiratory bellows. Options to transmit additional physiological information, such as temperature and respiratory gas concentrations, are desirable. It is recommended that all physiological signals be aggregated in a single connector box (patient interface unit) for wireless telemetry. Telemetered physiological signals must not interfere with MRI and must be received in at least one base station in each modality, for example one in the X-ray lab and another in the MRI lab, with automatic or semi-automatic handoff from one to the other. The base stations should connect to widely available commercial hemodynamic recording systems (specifically Siemens *Sensis* and General Electric *MacLab*). The patient interface unit must have a safe source of power that allows uninterrupted operation for at least 8 hours, and can connect to the multimodality patient transfer shell. The system should have a signal preprocessing unit to filter MRI-specific noise. The system must handle noise caused by MRI gradient switching events and be robust to a range of rapid pulse sequences with continuous duty cycle, including single and multi-slice real-time and 3-dimensional gradient echo, balanced steady state free precession, and (non-real-time) turbo spin echo techniques, especially during "opening and closing" gradient switching used widely for "magnetization preparation" and "multi-slice imaging. The system may access the MRI gradient waveforms to filter or exclude noise related to low-frequency MRI gradient switching events. The sponsoring NIH laboratory is willing to provide access to acquire physiological signals without preprocessing; alternatively the offerer should have access to such a laboratory independently for development and for testing. The system should not generate radiofrequency noise that interferes with MRI of hydrogen, carbon, fluorine, and phosphorus species used for MRI in these fields. The system should be safe for operators and patients inside and near the magnet bores. The system should not interfere with common commercial Bluetooth and other common radiofrequency patient physiologic telemetry systems used during MRI.

The Phase I application should provide a proof-of-concept working prototype to support MRI guided clinical interventional procedures.

The Phase II application will translate the Phase I findings into a clinical grade system.

055 Catheter for Delivering High Intensity Focused Ultrasound for Transluminal and Endocavitary Interventional MRI

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Magnetic resonance imaging is attractive to guide therapeutic ablation of tissue because it can identify pathology in target tissue, guide positioning of therapeutic devices, and guide thermal alterations during delivery of energy. Targets for therapeutic ablation include endocavitary and endobronchial tumors and endomyocardial tissue for cardiac rhythm disorders.

While technically feasible, there are no commercially available flexible catheter devices to deliver high intensity focused ultrasound energy under real-time MRI guidance to endoluminal or endocavitary targets. Such technology would enable novel approaches to therapy for malignancy, for cardiac rhythm disorders, and perhaps for other unanticipated applications.

The offering should deliver energy sufficient to ablate accessible endocavitary and endovascular tumors of variable volumes and geometry as small as 1mm x 10mm (for individual lines of ablation) and at least as large as 10mm x 10mm (for tumor ablation) during each application of energy. The system should be able to deliver ablative energy at a distance of as little as adjacent and as much as 30mm or further away from the distal end of the ablation system. The different ablation strategies (adjoining, linear, at-a-distance) can be accomplished using different catheter designs. The catheter should have a maximum outer diameter of 3mm but preferably less than 2mm. The catheter should be up to 1 meter in usable length. The catheter should be widely deflectable and torquable with several degrees of freedom to allow navigation of distal and tortuous endocavitary targets within the tracheobroncheal, gastrointestinal, hepatobiliary, urogenital, endovenous, transarterial, transseptal atrial, and transaortic endoventricular treatment zones. A minimal solution would allow deflection between 0 and 135 degrees from longitudinal with a variable radius of tip curvature from 2 to 8cm. The catheter should be able to maintain stable position against moving tissues. Solutions should assure adequate transmission of ultrasound energy in both vascular and non-vascular cavities. The catheter solutions should accommodate ports or options for local flushing and for obtaining for local electrograms at the catheter tip. The offering should be designed with specific tumor ablation applications in mind, including a realistic volume of overall ablation during a realistic treatment interval (typically less than one hour). Ablation modes should consider both thermal and cavitation effects, both therapeutic and deleterious. Applications are encouraged that offer tailored, image-guided, non-spherical ablation geometries to target individual pathology and spare healthy bystander tissue. In intravascular modes, offerings should consider strategies to minimize bystander intravascular thrombosis.

The catheter solutions should be "MRI safe" and "MRI compatible" without heating or local magnetic field disruption according to accepted industry standards and should be designed for safety in a clinical environment. The system must operate safely at MRI field strengths of 1.0 to 3.0T. Control of the system should be possible from a bedside operator and from a console-based operator outside the radiofrequency MRI system shield.

The sponsoring NHLBI laboratory is willing to provide technology for catheter shaft and tip "active" visualization and tracking during MRI. Offerers should incorporate one or more 0.020" lumens into their catheter designs for this MRI visualization technology. The sponsoring NIH laboratory is willing to provide access to a 1.5T MRI system for phantom and in vivo testing of prototypes; alternatively the offerer should have access to such a laboratory independently for development and for testing.

The system should not generate radiofrequency noise that interferes with hydrogen proton MRI in these fields. The system should be safe for operators and patients inside and near the magnet bores. The system should not interfere with common commercial Bluetooth and other common radiofrequency patient physiologic telemetry systems used during MRI.

The Phase I application should provide a proof-of-concept working prototype to support MRI guided preclinical interventional procedures.

The Phase II application will translate the Phase I findings into a clinical grade system.

056 Development of Blood Donor Screening Tests for the Presence of Human Babesia Microorganisms

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2

Human babesiosis is a malaria-like illness due to infection of red blood cells by various species of protozoan parasites belonging to the genus *Babesia*. Most human infections reported in the United States are caused by *B. microti* which is endemic in parts of the northeast and north central United States. *B. microti* infections are often asymptomatic but can also progress to severe illness and even death particularly in individuals who are immunosuppressed, asplenic or elderly. The parasite is transmitted primarily by the bite of the deer tick however it can also be transmitted by blood transfusion. More than 60 cases of transfusion-transmitted babesiosis have been identified over the last 40 years. During the past four years, there has been an alarming increase in the number of deaths due to transfusion-transmitted babesiosis. For a number of years, there were no babesiosis deaths associated with blood transfusion. However, in 2006 two deaths were reported to the FDA due to blood transfusion, three deaths in 2007 and five deaths in 2008. These Babesiosis cases accounted for 71% (5/7) of all types of microbial infections associated with transfusion fatalities in FY 2008 as compared to 50% (3/6) in FY 2007 and 29% (2/7) in FY 2006. Hence, the incidence of transfusion-transmitted cases of babesiosis resulting in death is increasing and there is an urgent need to minimize the risk. One approach is to develop and implement laboratory screening assays to detect babesia or antibodies to babesia in blood donors. There are currently no FDA-approved tests for blood donor screening for the presence of babesia. There are a number of tests that can be used to aid in the diagnosis of babesiosis including blood-film microscopy, serologic assays such as the indirect immunofluorescent assay (IFA), enzyme immunoassay (EIA), western blot, and immunoblot, and assays which detect the organism directly such as PCR. Some are too cumbersome to use as screening tests and those that could be used such as EIA or PCR have not been shown to be sensitive and/or specific enough for use as blood donor screening assays. Clearly, screening tests are needed to interdict infectious units however the tests must be sensitive and specific enough to be used in a blood center setting. The prevalence of antibody to *B. microti* may be as high as 5% in endemic areas, and it is unclear what proportion of those individuals would harbor infectious *Babesia* microorganisms in their blood. Testing algorithms may need to include the use of both antibody-based and NAT screening assays to determine the safety of a donated unit for transfusion. While *B. microti* is the most prevalent species of *Babesia* in the United States, other species such as *B. divergens* have also been identified. Thus, the presence of the different *Babesia* species in the U.S. will also need to be addressed by test developers. The purpose of this solicitation is to encourage development of a blood donor screening test for the presence of *Babesia* microorganisms and submission of an application to the FDA for licensure of the assay. The tests must be highly sensitive and specific and may include the development of antibody-, antigen-, or NAT-based assays.

The Phase I application shall focus on studies that provide proof of concept that the screening assay being developed is capable of identifying *Babesia* microorganisms with a sensitivity and specificity required for use in a blood collection center screening laboratory. During this phase, preclinical test refinement shall be initiated. The contractor shall verify specificity, sensitivity, and reproducibility of the test using serological reference panels, clinical specimens from human cases of Babesiosis and other diseases including other parasitic disorders such as Lyme disease.

Phase II will be devoted to conducting the clinical trial to evaluate the assay along with test validation studies. The clinical trial will be conducted using blood donor specimens obtained from areas in which *Babesia* species are prevalent. This study may be conducted in house or at blood centers. In the event that it is determined that the number of specimens needed cannot be obtained in a blood bank setting, alternative sources of specimens may be considered. The contractor will be responsible for designing, conducting, coordinating, and managing all steps necessary to perform the clinical trial and validation studies. The data obtained from the study shall be used by the contractor in applying to FDA for licensure of the assay.

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 disorders. 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 areas:

036 Identification of miRNAs as Biomarkers for Alcohol-Induced Disorders

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4

Applicants must submit both hard copies and electronic files in CD of the contract proposals.

Alcohol use and abuse have wide ranging effects on the public health. Even moderate alcohol consumption can have deleterious effects on multiple organ systems in the body. As with all disease, early detection and early intervention improve prognosis and reduce complications. Thus, there is a need for biomarkers that signal 1) alcohol consumption or relapse in recovering alcoholics or 2) early alcohol-induced damage of liver, pancreas, breast, immune function, heart and other tissues. Therefore, NIAAA is committed to the development of highly predictable, sensitive and reliable biomarkers for alcohol-induced disorders, including alcohol-induced organ damage and alcohol dependence. For the biomarkers to be of clinical significance, it is essential that the tissues or samples used are easily obtainable. Sample collection and the assay must be relatively simple and acceptable to practitioners and patients.

MicroRNA (miRNA) analysis holds great promise as a measure of metabolic changes that occur after alcohol consumption and for detection of tissue injury. Changes in the miRNA panel resulting from alcohol exposure would be a valuable biomarker. Therefore, the development of methods for the detection and quantification of the full complement of miRNAs in biological specimens is encouraged. Assay optimization and validation should focus on easily obtainable biological tissues or fluids, although validation of the method could use samples from blood, brain, and liver. Phase I of the requested SBIR contract should be aimed at the feasibility of the study and initial identification of miRNA species that are altered by alcohol exposure or associated with alcohol-related phenotypes in animal models. If a sensitive, reproducible, high-capacity method is demonstrated to be useful and cost-effective for small volume samples, the purpose of a Phase II contract may be a service contract with NIAAA to provide analysis of specimens from the greater alcohol community. Such a service would allow extramural scientists to investigate specific questions without redundancy of effort and would provide consistency between laboratories. Animal models and/or humans should be used for these studies.

Areas to be addressed under this topic include, but are not limited to:

- Identification of miRNAs, either single entities or combinations (biomarker signatures), for alcohol-induced organ damage (for liver, pancreas, lung, brain, etc) or alcohol dependence in blood or plasma and/or in other easily accessible tissues or by employing non-invasive methods.

037 Real-time Detection of Neurochemical Changes in Response to Alcohol Drinking

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4

Applicants must submit both hard copies and electronic files in CD of the contract proposals.

Many pharmacological mechanisms of ethanol action in the brain are mediated by time-dependent neurochemical events in multiple brain regions. Despite great progress in identifying ethanol's neurochemical actions, we do not fully know how neurochemicals change in real time following ethanol administration and drinking (acute and chronic). Multidimensional measurement of neurochemical change (i.e., concentration, time, region) are needed to reveal kinetics underlying alcohol effects to guide future medication development and promote mechanistic understanding of alcohol drinking.

With this contract solicitation topic, we seek development and testing of biosensors enabling monitoring of regional neurochemical changes in the brains of rats and/or mice in real time as they drink alcohol. Recent studies report the plausibility of using microsensors coupled with wireless detection methods to instantaneously monitor multiple neurochemical changes in animals. We seek development of microsensors with sufficient

resolution to provide neuroanatomical regional specificity. In addition to brain ethanol concentration, neurochemicals of interest include, but are not limited to, glutamate, dopamine, GABA, acetylcholine, and BDNF. Work under this contract should be directed toward integrating microsensors with wireless reporting devices to provide real-time reports of extracellular neurochemical and brain ethanol concentrations in behaving animals.

References:

- Agnesi F, et al. Wireless Instantaneous Neurotransmitter Concentration System-based amperometric detection of dopamine, adenosine, and glutamate for intraoperative neurochemical monitoring. J Neurosurg. 2009 May 8. [Epub ahead of print]
- Bledsoe JM, et al. Development of the Wireless Instantaneous Neurotransmitter Concentration System for intraoperative neurochemical monitoring using fast-scan cyclic voltammetry. J Neurosurg. 2009 May 8. [Epub ahead of print]
- Oldenziel WH, Dijkstra G, Cremers TI, Westerink BH (2006). In vivo monitoring of extracellular glutamate in the brain with a microsensor. Brain Res 1118, 34-42.

038 Biomarkers for Alcohol-Induced Disorders

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4

Applicants must submit both hard copies and electronic files in CD of the contract proposals.

Alcohol use and abuse have wide ranging effects on the public health. Even moderate alcohol consumption can have deleterious effects on multiple organ systems in the body. As with all disease, early detection and early intervention improve prognosis and reduce complications. Thus, there is a need for biomarkers that signal 1) alcohol consumption or relapse in recovering alcoholics or 2) early alcohol-induced damage of liver, pancreas, breast, immune function, heart and other tissues. Therefore, NIAAA is committed to the development of highly predictable, sensitive and reliable biomarkers for alcohol-induced disorders, including alcohol-induced organ damage and alcohol dependence. It is anticipated that new and novel biomarkers will be discovered and validated by using integrative global approaches in which unique molecular entities could be ascertained. For the biomarkers to be of clinical significance, it is essential that the tissues or samples used are easily obtainable. Sample collection and the assay must be relatively simple and acceptable to practitioners and patients. In addition, NIAAA is also interested in determining alcohol metabolites and adduct concentrations in tissues and organs after a single physiological dose, a large dose (e.g., binge drinking), and chronic consumption of alcohol. Determining the concentrations of fatty acid ethyl esters (FAEEs) in brain, pancreas, heart, and other tissues after a single dose or chronic consumption is also encouraged. To accomplish these objectives, investigators are expected to employ state-of-the-art tools and technologies, including genomics, proteomics, metabolomics, micro RNA analysis, other applicable biochemical procedures, or newly developed non-invasive imaging techniques. Methods for the detection and quantification of the full complement of micro RNAs in biological specimens are encouraged.

Development and validation should focus on easily obtainable biological tissues or fluids, although validation of the method could include blood, brain, and liver. If a sensitive, reproducible, high-capacity method is demonstrated to be useful and cost-effective for small volume samples, a service contract with NIAAA to provide analysis on specimens from the greater alcohol community may be considered.

This solicitation is intended to promote the utilization of bioinformatics tools in an effort to integrate biological, clinical, and behavioral data for the identification of biomarkers that could be useful in the prognosis, diagnosis, and treatment of alcohol-induced tissue injury during the lifespan of individuals, including fetal development. New research studies focusing on the identification of early biomarkers of alcohol-induced tissue injury in well-defined patient populations are encouraged.

Phase I of the requested SBIR contract should be aimed at the feasibility of the study and initial identification of the potential biomarkers that are either direct products of ethanol oxidation or adducts of ethanol metabolites and/or cell constituents that are altered by alcohol exposure. Animal models and/or humans should be used for these studies. Fast Track (combined Phase I and Phase II) applications could be proposed. The Phase I component can be carried out using animal or human samples, but the Phase II component should concentrate on the validation of the identified biomarker(s) in human samples.

Some of the areas to be addressed under this topic include, but are not limited to:

- Identification of biomarkers, either single molecules or combinations of them (biomarker signatures), for alcohol-induced organ damage (for liver, pancreas, lung, brain, etc) or alcohol consumption in blood or plasma and/or in other easily accessible tissues or employing non-invasive methods. Types of biomarkers of interest include, but are not limited to, genomic, proteomic, metabolomic, or micro RNA biomarkers.
- Development and/or application of bioinformatic tools to mine the genomic, proteomic, metabolomic, and clinical and biological/behavioral data that will enable their integration at the systems level.

039 Human Stem Cells as a Model for Understanding and Treatment of Alcohol Induced Tissue Damage

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4

Applicants must submit both hard copies and electronic files in CD of the contract proposals.

Recent progress in stem cell research is opening up unprecedented opportunities for the development of new strategies to repair and replace alcohol-damaged organs. Another equally important and interesting way to apply stem cells is to use them in disease modeling and toxicity screening in drug discovery and development. The development of stem cell culture systems that mimic alcohol-induced diseases will provide ideal models to dissect the molecular and cellular events driving pathological changes during disease conditions. Such models may be created using human adult or embryonic stem cells carrying or induced to carry defective genes relevant to the disease. This is especially useful in alcohol research where animal models do not faithfully simulate the symptoms and conditions that occur in humans. These in vitro disease models may then be employed for drug screening and developing novel pharmacological therapies. Both cell-based disease modeling and drug discovery technologies are realistic prospects that can be carried out by small business companies.

The following examples illustrate areas that are of high interest; other innovative projects are also encouraged.

- Develop genetically engineered disease-specific human stem cell lines useful for alcohol research (for example, by introducing mutations into alcohol-metabolizing enzymes or inflammatory cytokines)
- Establish human stem cell lines derived from biopsies of alcohol-related diseases through reprogramming somatic cells
- Develop human stem cell-based models that can be used in alcohol toxicity screening and in drug discovery process
- Evaluate the ability of human stem cells to proliferate and differentiate into tissue-specific cell types in the presence of alcohol
- Study epigenetic instability of human pluripotent cells due to alcohol
- Study the effects of endocannabinoids on pathways that control cell fate for reprogramming and differentiation.

040 Alcohol Biosensors and Data Analysis Systems

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1-3

Applicants must submit both hard copies and electronic files in CD of the contract proposals.

It is anticipated that innovative and improved alcohol sensors would be useful in a variety of situations including, but not limited to: clinical monitoring, forensics and human or animal research. Specific sensor characteristics should complement their intended use. This applies to characteristics such as: sampling frequency, degree of accuracy, data storage capacity and data transmission frequency. Depending on their intended purpose and use, alcohol sensors may be augmented with additional information such as other physiological measurements or geospatial determinations. Devices need to be compatible with human comfort, and devices to be worn for weeks or months may present particular challenges. Since alcohol readings are likely to be baseline most of the times, sensing devices generally require ways to monitor contact and readiness to record. Moreover, where necessary, measurement fidelity should be robust to subject's activities including active efforts at tampering. The mode of data storage will need to conform to power limitations and strategies for data transmission which may require telemetry.

In addition to alcohol monitoring and data transmission, this topic also includes the opportunity to develop appropriate data analysis systems. Examples include: estimating blood alcohol concentrations, reconstructing patterns of alcohol consumption, and monitoring large numbers of devices to identify significant, but infrequent, events while minimizing false positives.

Of particular interest would be the incorporation of existing alcohol sampling systems into large-scale data analysis with the purpose of relating biosensor readings with various biological and behavioral outcomes. The system would need to collect sufficient information to estimate blood alcohol concentrations (BACs) and to permit the determination of patterns of drinking over sustained periods of time while also permitting appropriate checks on validity and accuracy.

It is expected that projects of this type would require collaborations between biosensor users and manufacturers, and alcohol researchers skilled in interpreting alcohol-related data and relating the results to significant scientific issues related to alcohol consumption.

041 Generation of Rat Knockout Strains for Alcohol Research

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Applicants must submit both hard copies and electronic files in CD of the contract proposals.

The Rat has been historically an important animal model for alcohol research. For example, Alcohol Preference (P) and non-alcohol-preference rats have been widely used to study the behavior and mechanisms underlying alcohol preference. Compared to the mouse model, the rat offers many advantages in modeling human diseases. The bigger size of rats makes many surgical manipulations possible and physiological monitoring easier (for example, for the study of cardiovascular disease). The sizes of substructures of various organs are more proportional, which is important for many studies. The metabolism of alcohol in mice and rats are quite different. In many cases, the physiological changes induced by alcohol administration in rats more resemble the corresponding human condition.

Since the mouse knockout and transgenic technologies were developed, more researchers have chosen to use mouse models because of the tools available for their genetic manipulation. The research using rat models has been limited or prohibited by the lack of tools in directed genetic manipulations in rats. However, in the past several years, some technologies of genetic manipulation have been developed in rats. These genetic tools for the rat have the potential to accelerate discovery and to increase our knowledge about alcohol-related biology and disease. Some of the alcohol-related biology already observed in rats could be better studied with genetic manipulations.

The goal of this SBIR contract topic is to solicit small businesses to develop and produce rat strains that carry the knockout genes important for alcohol research. This SBIR contract solicitation encourages applicants to consult with alcohol researchers to develop a high priority list of genes important for alcohol research and include them in the proposal. The solicitation also encourages applicants to consult with alcohol researchers for the selection of background strains used for these knockouts. In addition to the generation of rat knockout strains, the applicants should also provide detailed plan on how these strains will be grown and maintained, and how they will be distributed to alcohol and non-alcohol researchers.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. For more than 50 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world.

The NIAID Small Business Programs (SBIR and STTR) judiciously fund research and development of products or services that prevent, diagnose, and treat infectious, immunologic, and allergic diseases. For information on the NIAID Small Business Grants Program and links to small business resources, see the NIAID Small Business Grants website at <http://www.niaid.nih.gov/ncn/sbir/>.

This solicitation is for the NIAID SBIR Contracts Program. SBIR Phase I and Phase II contract awards may not exceed the limits for total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under the topic area. Phase II proposals may only be submitted upon the request of the NIAID Contracting Officer, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure (described in Section 5).

018 Aminoglycosides: Formulation for Oral Delivery

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1-5

Budget (total costs): Phase I: \$250,000; Phase II: \$750,000

Aminoglycosides are an important class of antibiotics for the treatment of aerobic, gram-negative bacteria (*Pseudomonas*, *Acinetobacter*, *Enterobacter*) and mycobacteria (*Mycobacterium tuberculosis*, *M. avium*). Widespread use of aminoglycosides has been limited due to their toxicity (nephrotoxicity and ototoxicity) and inconvenient route of administration (intravenous or intramuscular). Adverse effects are related to plasma drug levels. For example, use of amikacin for first-line therapy is limited due to poor oral absorption, a short half-life, and serious renal and auditory toxicities which necessitate frequent intravenous administration, with concomitant monitoring of drug levels to ensure that the levels in plasma remain within a narrow therapeutic window.

Project goal: The goal of this solicitation is to develop novel formulations or modifications for at least one existing aminoglycoside (e.g., amikacin, streptomycin, gentamycin, capreomycin, kanamycin) that can be orally administered, will increase the therapeutic index, and decrease adverse events (nephrotoxicity and ototoxicity). Also, the formulated aminoglycoside should be directed against at least one bacterial or at least one mycobacterial pathogen.

Phase I proposals should demonstrate proof of principle and must contain:

- A medicinal chemistry component focusing on the methodologies to be used to formulate aminoglycosides for oral administration.
- A biological testing component to quantitatively assess the product(s) for:

- o in vitro activity in an existing standardized, reproducible, and validated in vitro culture and intracellular test systems, and provide quantitative assessment of cytotoxicity of the formulated products(s); and/or
- o in vivo efficacy in an existing standardized, reproducible, and validated small animal model of infection which detects statistically valid differences between formulated and nonformulated products.

Phase II proposal should involve:

- Extended preclinical studies;
- Development of a well-defined formulation under good manufacturing practices (GMP);
- Uniformity from lot to lot and be certified under quality control;
- Scale-up and production for future Phase I clinical study.

019 High Throughput in Vitro Immunization System For Evaluating Human B Cell Immune Responses to HIV-1 Vaccine Antigens

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1-5

Budget (total costs): Phase I: \$250,000; Phase II: \$750,000

There is a critical need to develop high throughput in vitro systems that mimic in vivo human immune responses in order to more rapidly and cost effectively evaluate HIV vaccine antigens for the induction of neutralizing antibodies. New technologies developed over the last decade suggest the feasibility of developing advanced in vitro systems to evaluate human B cell immunological responses. These advanced systems would use high-throughput immune-monitoring assays to perform systematic analyses. This effort will require developing a bioinformatics infrastructure to handle large amounts of complex information, and to integrate different types of data in the search for markers and patterns of markers that correlate with particular immune functions.

Phase I activities and expected deliverables

Proposals should demonstrate proof of principle and must include:

- Development of a standardized, reproducible in vitro B cell culture test system for the primary induction of antibody responses to HIV envelope antigens from fresh or frozen human PBMC
- Assay components to quantitatively assess in vitro responses for the frequency of antigen specific B cells, and the specificity, cross reactivity, and neutralizing activity of secreted antibodies
- Development and standardization of an in vitro B cell model test system suitable for prime boost strategies and the study of affinity maturation
- Conduct 2 pilot studies to standardize the human B cell culture model system to mimic primary and memory human B cell responses

Research should be proposed with quantifiable, testable feasibility milestones.

Documentation providing description of the prototype system design, protocols, testing results and a plan for validation should be provided to NIAID as part of Phase I progress report.

Phase II activities and expected deliverable

Proposals should involve:

- Scale up throughput capacity of B cell model system for testing multiple human samples and HIV envelope antigens
- Validation of the in vitro B cell model system in a large sample study (40-60 samples) using multi parameter B cell profiling analyses
- Support the “in vitro” components of a comparison study with “in vivo” Phase I HIV-1- clinical vaccine studies in collaboration with other DAIDS grantees
- Optimization of in vitro B cell model system to evaluate additional platforms for the induction and augmentation of and antigen specific memory B cells including molecular adjuvants and immune modulatory molecules

Phase I applications should address initial development and feasibility testing of the in vitro B cell platform. Phase II applications should be focused on completing the development and validation of the technology for testing in parallel with DAIDS sponsored Phase I clinical trial.

Before Phase II funding is awarded, a progress report towards meeting of the Phase I milestones must be received. Only upon successful evaluation of this report by the contracting officer will Phase II funding be approved.

020 In Vitro Immunization System For Evaluating Human T Cell Immune Responses to HIV-1 Vaccine Antigens

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1-5

Budget (total costs): Phase I: \$250,000; Phase II: \$750,000

There is a critical need to develop high throughput in vitro systems that mimic in vivo human immune responses in order to more rapidly and cost effectively evaluate vaccine antigens for HIV. Human T cell responses elicited in vitro from virus-naïve individuals can identify target epitopes in the HIV-1 proteome. The epitopes defined by T-cell responses will provide target antigens for use in defining the nature of protective or harmful T-cell responses and will inform the rational design of epitope-based vaccines and immune-monitoring strategies. Furthermore, a high throughput test system should enable the systematic evaluation of molecular adjuvants, cytokines, and immunostimulatory molecules for induction of primary HIV T cell responses to vaccine antigens. This effort will require developing a bioinformatics infrastructure to handle large amounts of complex information and to integrate different types of data in the search for markers, and patterns of markers, that correlate with specific immune functions.

Phase I proposals should develop an optimized in vitro priming system and must include:

- Cell culture methodologies to optimize in vitro culture systems for the induction of primary T cell responses.
- A multi level testing component to assess the in vitro priming system to:
 - o characterize the magnitude and functional properties of T cell responses.
 - o identify gene expression, phenotype and functional properties of dendritic cells.
- Development of algorithms for the identification and evaluation of T cell responses and HLA restriction.
- A plan to standardize in vitro monitoring assays to allow statistical comparisons between in vitro primed T cell responses and T cell responses elicited in vivo during acute HIV-1 infection or T cell responses observed in prophylactic vaccine trials (samples to be provided by DAIDS).

Research should be proposed with quantifiable, testable feasibility milestones.

Documentation providing description of the prototype system design the corresponding protocols and plans for validation should be provided to NIAID as part of Phase I progress report.

Phase II proposal should involve:

- Establishing the reproducibility and validation of the in vitro priming system, including a certified quality control program
- Further enhancements in bioinformatic analyses
- Scale up and automation of the in vitro priming system
- Development of platform for analyzing molecular adjuvants, cytokines, and immunostimulatory molecules for induction of primary HIV T cell responses to vaccine antigens
- Support future human volunteer testing using the technically validated in vitro priming system in parallel with a Phase I vaccine study. The clinical study itself will be conducted by other DAIDS grantees or contractors.

Phase I applications should address initial development and feasibility testing of the in vitro T cell platform and Phase II applications should be focused on completing the development and validation of the technology for testing in parallel with DAIDS sponsored Phase I clinical trial.

Before Phase II funding is awarded, a progress report towards meeting of the Phase I milestones must be received. Only upon successful evaluation of this report by the contracting officer will Phase II funding be approved.

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:

113 New Technologies: Integrating data from Prescription Monitoring Program(s) to Current Clinical Practice

(Fast-Track proposals will be accepted.)

In some states the prescription monitoring program collects prescription data for controlled substances into a central database which can then be used by limited authorized users to assist in deterring the illegitimate use of prescription drugs. Only those persons authorized by law can be provided information from the database. Prescribers and dispensers in some states may query the database to assist in determining treatment history and to rule out the possibility that a patient is "doctor shopping" or "scamming" in order to obtain controlled substances. In that case, a prescriber must obtain written consent from the patient before submitting an inquiry. However, limited time/resources of busy medical offices might be a barrier to obtaining and utilizing this information to improve quality of treatment for each individual patient. This initiative will support development and testing of the effectiveness of new technologies that facilitate utilization of data collected by Prescription Monitoring Program(s) in clinical practice. Applications may include, but are not limited to, the development and testing of new and innovative Internet-based systems that provide a) practitioners with current information of their patients' treatment/medication compliance; b) transfers data automatically to patients chart, etc. The goal is to minimize barriers of clinical staff to obtain, record and utilize the data while maintaining strict security requirements (i.e., confidentiality, integrity, and availability). These new technologies should provide a more cost effective way of identifying treatment non-compliance and help adjust the treatment plan according to the needs of individual patients as well as decrease potential diversion of controlled substances.

114 Development of Innovative Techniques/Tools for the Screening, Recruitment, and Follow-up of Clinical Trial Participants

(Fast track proposals will be accepted.)

Screening and recruitment of participants for multi-center clinical trials pose a number of problems. Tracking devices/programs are needed to document and manage a patient's interaction throughout a clinical trial. This would include screening tools, recruitment strategies that could be followed, and steps to increase and document follow-up practices. Validated materials/tools applicable to diverse populations for use in education and counseling of potential participants are needed. These tools would be applicable across trials and would provide a strategy for management to improve clinical trial performance. Both the participants and the research clinicians administering the trial would benefit from this product. Goal: This SBIR project is to develop innovative techniques and/or tools for the screening, recruitment and follow-up of clinical trial participants in multi-center trials. These tools or techniques can be from the standpoint of clinicians who are running the clinical trials to patients who are participants in the drug abuse trials. Tools can include software for following up on participants, reminder tools for clinical trial participants, technological devices for clinician or patient use. The ultimate goal is to make the trial management more efficient and effective.

115 Innovative Diagnostic Drug Screening Tests for Drug of Abuse

(Fast track proposals will be accepted.)

Drug screening and the detection of drug use/abuse prior to and during treatment episodes are an important factor in defining treatment progress and outcome. Rapid results from the tests are important in addressing a patient's behavior in a clinically effective manner. The time and personnel resources required to perform this function are costly and cumbersome. Current urine tests often require visual corroboration from a staff member of the same gender as the participant in order to ensure that the urine samples are legitimate. This takes staff time away from other duties and requires a separate facility for patients to give urine samples. Clinics have to schedule enough male and female employees to observe these tests. Effective and cost-efficient approaches to testing using oral swabs, patches, and/or other methods would be welcomed by the treatment clinics. To date the newer technologies are not cost effective for most programs. Additionally, immediate or less than 24-hour results are not available as is true with most urine screens. Goal: This SBIR project seeks innovative technologies and/or products that provide for on site and rapid drug screening that are minimally invasive for the patient and gender neutral for the program staff.

116 Marketing Evidence-Based Prevention Interventions for Substance Abuse Prevention

(Fast track proposals will be accepted.)

The purpose of this SBIR contract is to stimulate the development and testing of technologies to enhance the large scale dissemination of evidence-based drug abuse preventive interventions through communication and technological marketing strategies. Over the past 30 years a large number of drug abuse prevention programs and practices have been rigorously tested using randomized control trials. Many of these interventions have been demonstrated to be both efficacious and effective. Despite the success of the research, few evidence-based interventions have been adopted and sustained on a wide scale basis. There are many explanations for this situation; one of the most powerful is the lack of adequate communication and marketing infrastructures for the dissemination of evidence-based substance abuse interventions to schools, communities, health centers, community based organizations and others.

To promote greater identification and implementation of evidence-based drug abuse prevention programs and practices, enhanced communication and marketing strategies need to be developed and tested. In response to this solicitation, these strategies should focus as much as possible on innovative and technologically feasible ways to enhance access to and use of effective programs and practices. Critical features that need to be considered in the development and testing of dissemination strategies to enhance access and widespread use of evidence-based prevention approaches might include the processes associated with decision making, as well as issues related to adoption, financing, management and utilization of scientifically validated interventions by service systems. Maximizing use of the existing and limited resources of the institutions likely to implement the

interventions, such as schools and community-based organizations, is another key consideration in the development of these marketing and dissemination strategies. The extent to which the setting allows for the strategies to be implemented under controlled, uncontrolled or uncontrollable conditions, while maintaining the quality and integrity of the original practice, should also be considered.

117 Using Handheld Devices to Support Recovery

(Fast track proposals will be accepted.)

Disease management requires that patients have access to information, support, and decision-making tools at critical moments. Smartphones, web-linked personal data assistants (PDAs) and similar devices provide web-based and other multimedia options that can be used to support addiction recovery and to promote healthy lifestyles, but to date these have not been leveraged to their full capacity. For example, some currently available smartphone applications include logs for tracking individuals' caloric consumption, exercise routines, smoking behavior, medication schedules, blood glucose levels, and other health-related activities that can benefit from regular monitoring. New advances in smartphone technologies and third-party software development platforms expand opportunities for designing programs that could leverage the internet to provide real-time feedback, including graphical representation of the user's data; web or phone access to nurse-staffed call centers or recovery sponsors; periodic alerts or prompts for users to report current levels of craving; or support groups drawing on social networking platforms. Software could support self-monitoring, or be incorporated into the delivery of formal treatment services (e.g., to maintain connections between weekly on-site counseling sessions, or to promote continued recovery activities following participation in residential services). Such programs can readily incorporate secure data transmission and required confidentiality protections, while providing clients with unprecedented access to needed information and support. Phase I would support testing of the feasibility of technological solutions for connecting clients with information and support services while outside the clinic walls. Phase II would involve further development of those approaches deemed feasible in Phase I and the testing of those technologies with recovering clients both in coordination with, and independent of, formal treatment settings.

118 Tools to Promote Security and Appropriate Prescribing of Scheduled Prescription Drugs

(Fast track proposals will be accepted.)

According to SAMHSA, drug treatment admissions for prescription pain killer misuse have risen dramatically over the past decade, representing 5% of all admissions in 2007. This trend mirrors a trend toward an increase in prescribing of these medications as well as non-medical use of these medications by youth. The misuse of prescription pain killers as well as other scheduled prescription drugs presents new challenges for drug abuse prevention efforts because of their wide availability and perceived safety. This SBIR contract seeks to stimulate the development and testing of tools that will facilitate the appropriate prescribing and safe use of prescription medications with abuse potential. Technologies can be developed to assist medical professionals in the assessment of pain or the potential for pain when making prescribing decisions. Tools may also be developed to help providers to educate patients and their caretakers regarding the importance of following directions explicitly, avoiding self-treatment outside of the prescribed intent for the medication, and avoiding diversion to other users. Special training materials, tools and techniques can target parents of adolescents with regard to access to and monitoring of medicines. Technologies can be developed for schools or other child service institutions that have a need to dispense medicines to ensure accurate dispensing of these medicines while providing both security and privacy to the youth. This contract will support efforts to develop products for the diverse groups identified above, and patients of all ages, to enable the appropriate treatment of medical conditions while reducing the opportunities for misuse and diversion of scheduled prescription medications.

119 Innovative Technologies to Support Economic Research in the Drug Abuse Treatment System

(Fast track proposals will not be accepted.)

This initiative will support research to design and develop data systems for financial management and economic analysis of treatment programs and larger systems in new healthcare settings and managed care networks. Managerial decision-making requires the implementation of sophisticated data systems to facilitate routine

budgeting processes, allocation of resources, performance measurement, and pricing decisions. The focus is on the needs of managers within the organization and managers outside of the organization. Data system development must be based on standard cost behavior and profit analysis. Data systems must be designed with correct cost concepts (accounting and economic) in order to permit cost and pricing decisions to be developed for new treatment technologies and management of ongoing systems. In research settings, such an initiative is vital for the assessment of new technologies developed for transfer to practice.

120 Development of State-of-the-Art Mechanisms for Epidemiological Research

(Fast track proposals will be accepted.)

The purpose of this proposed SBIR project is to encourage the development of state-of-the-art mechanisms to facilitate the use of Geographical Information Systems (GIS) in community epidemiology studies (for example Community Epidemiology Work Groups) and other drug abuse research.

The questions NIDA seeks to answer in epidemiological investigations are often inherently spatial in nature, for example, 'How do neighborhood contextual factors influence the prevalence of cocaine users?', 'How are overdose mortalities related to potential sources of environmental exposure and the location of treatment resources?', and 'Are rates of methamphetamine use elevated around production outlets?' Such investigations require that spatially referenced data concerning demographic characteristics of the population, their health, and the environment in which they live, be combined in a common geographical framework for analysis. Geographical Information Systems provide one way of doing this.

The role of GIS in public health management and practice continues to evolve. Application of this technology is an important step towards better understanding drug abuse issues and their inherent complexities. The ability to evaluate geospatial information provides a unique perspective of public health issues such as emerging and shifting epidemics, the utilization of treatment services, and rapid assessment of the impact of incidents ranging from natural disasters to bioterrorism. When used alongside more traditional epidemiological techniques, GIS provides epidemiologists the ability to address new questions, refine, or enhance existing analyses. This initiative encourages the development of both software and hardware to facilitate the development of GIS interfaces, database management, visualization, and innovative spatial analysis capabilities.

Phase I would involve the development and pilot testing of the new technology. Phase II would involve widespread testing and the development of manuals and other support materials.

121 Rapid and Sensitive Method for Nicotine and Its Metabolites in Biological Fluids

(Fast track proposals will be accepted.)

Budget (total costs): Phase I: \$150,000 (6 months); Phase II: \$1,000,000 (2 years)

NIDA seeks to develop a rapid, economical, easy to use, sensitive and specific test for nicotine and its major metabolites, cotinine (COT) and 3'-hydroxycotinine (3HC), which would allow for obligatory determination of the 3HC/COT ratio in biological specimens such as saliva, urine and/or plasma. The test should be user-friendly enough for use in physician's offices to optimize and personalize smoking cessation for nicotine replacement and bupropion pharmacotherapies.

In phase I, the contractor should demonstrate the feasibility of a new test and, in phase II, the contractor should develop and evaluate the test for its use in physicians' offices. The contractor should also demonstrate the commercial potential of this newly developed test.

122 Tool Development for New or Improved Capture Reagents

(Fast track proposals will not be accepted.)

Budget: Phase I: \$200,000; Phase II: \$1,500,000

Contracts can also extend to up to 4 years for the phase II award.

NIDA seeks proposals to begin to establish a library of protein capture reagents for addiction-relevant proteins and their variants. Relevant proteins would include membrane proteins such as receptors, transporters and ion channels as well as signaling proteins, transcription factors and other nuclear proteins.

Phase I (6 months) will be to develop new and improved in vitro technologies to generate renewable protein capture reagents that have the potential to specifically or selectively recognize, bind and “capture” proteins and distinguish their natural variants [splice variants, post- translationally modified variants (e.g., glycosylation, phosphorylation, acetylation, oxidation, etc.)]. Initial feasibility will be demonstrated by development of selective reagents for 10 addiction-relevant proteins including variants of those proteins.

Phase II (24 months) will cover development of selective reagents for 100-200 addiction- or neuroscience-relevant proteins including variants of those proteins.

123 Development of Alternate Drug Delivery Dosage Forms for Drugs Abuse Studies

(Fast track proposals will be accepted.)

Budget: Phase I: \$100,000 (6 months); Phase II: \$750,000 (2 years)

NIDA seeks to design and develop alternate dosage forms of drugs that are not orally administered (such as nicotine and marijuana) for conducting addiction-related research.

Proposed work: The small business companies are invited to submit proposals to develop and test alternate to smoking dosage forms of nicotine and/or marijuana such as deliverable through oral, nasal and/or mucosal routes. Such drug delivery dosage forms, once developed, should be tested and evaluated for efficacy.

In phase I, the contractor should demonstrate the feasibility of the developing such dosage forms and in phase II the contractor should develop and test the innovative dosage forms.

124 Design and Synthesis of Treatment Agents for Drug Abuse

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year); Phase II: \$1,000,000 (2 years)

The purpose of this contract solicitation is to design, synthesize and evaluate small molecules and protein-based therapies intended specifically for the treatment of and relapse prevention for substance abuse including cocaine, methamphetamine or cannabinoid. Specific areas of interest include, but are not limited to the following:

- Molecular library syntheses and specific assays for novel targets. The purpose of this contract solicitation is to promote the development of targeted small molecular libraries and/or specific assays for new drug discovery in the treatment for and relapse prevention of substance abuse. Some of the receptors and proteins involved in addiction have already been targeted and have led to the production of efficacious medications for other major diseases; whereas, some are less explored or have no known ligands. Examples of this latter type are neurotensin receptor agonists, selective muscarinic-M5 receptor antagonists, and selective antagonists of NPY or neuropeptide S. These as well as other less studied targets will be the interest of this solicitation.

In Phase I, the Contractor will either develop efficient synthesis approaches, e.g. target guided synthesis, computational modeling, etc. for the generation of the compound libraries and identification of lead compounds with existing screening assays. Or, the Contractor will develop high performance screening assays, specific and sensitive to the targeted receptors or proteins and validated with existing ligands. Phase I can also be used as a pilot study with already developed synthetic approaches and screening assays. In Phase II, the Contractor will continue to generate, refine, and screen the targeted small molecular libraries and identify lead compounds.

- The synthesis and development of small molecules as new pharmacotherapies. The classes of pharmacotherapeutic agents include, but are not limited to, compounds interacting with corticotrophins, cannabinoid, biogenic amines, GABA, and glutamate systems.

In Phase I, the Contractor will design and synthesize new entities as potential treatment agents and carry out in vitro and/or in vivo pharmacological screens. In Phase II, the Contractor will perform pharmacokinetic, pharmacological and toxicological evaluations and select lead compounds as potential clinical candidates.

- The development of protein-based therapies, such as drug metabolizing enzymes, vaccines or monoclonal antibodies. Unlike small molecules targeting the neural pathways and receptors involved in drug addiction, these protein therapies target the abused drugs, providing alternative strategies for medications development.

In Phase I, the Contractor will design and synthesize protein-based therapies and carry out in vitro and/or in vivo characterization and screens. In Phase II, the Contractor will perform optimization, characterization, and preclinical evaluations of the efficacy and toxicity leading to the selection of promising clinical candidates. The preclinical evaluations include but are not limited to pharmacokinetic, pharmacological and toxicological studies.

Potential applicants should submit a letter of intent.

125 Pharmaceutical Approaches for Development of Pharmacotherapies for Drug Addiction

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year); Phase II: \$1,000,000 (2 years)

NIDA is seeking SBIR contract proposals on innovative pharmaceutical approaches to improve the effectiveness, lower toxicity, and/or minimize the abuse potential of therapeutic agents for drug abuse/dependence. Specific areas of interest include, but are not limited to the following:

- Approaches to improve bioavailability of drugs with poor oral bioavailability. The pharmaceutical agents of interest include, but are not limited to, delta-9-tetrahydrocannabinol (THC), lobeline, and buprenorphine. THC has been shown to alleviate marijuana withdrawal symptoms and thus has potential for treating cannabinoid dependence. Lobeline is currently under clinical evaluation as a potential pharmacotherapy for methamphetamine abuse. Buprenorphine is on the market as sublingual dosage form for the treatment of opioid dependence.

In Phase I, the contractor is expected to demonstrate the feasibility of a prototype dosage form based on biopharmaceutical and pharmaceutical rationale. In Phase II, the contractor will carry out pharmacological, toxicological and pharmacokinetic evaluations. In addition, the contractor is expected to provide a GMP scale-up of a stable dosage form with acceptable in vitro and in vivo bioavailability in animal models and/or in humans.

- Development of controlled release dosage forms for addiction treatment medications to maintain therapeutic drug levels for extended periods of time, to alleviate compliance problems and/or to significantly reduce abuse potential.

In Phase I, the contractor is expected to demonstrate the feasibility of a prototype dosage form based on biopharmaceutical and pharmaceutical rationale. In Phase II, the contractor will carry out pharmacological, toxicological and pharmacokinetic evaluations. In addition, the contractor is expected to provide a GMP scale-up of a stable dosage form with acceptable in vitro and in vivo bioavailability in animal models and/or in humans.

- Approaches to improve the efficiency of large scale production of currently available macromolecules (i.e. monoclonal antibodies and vaccines) with potential for treating cocaine, methamphetamine or opiate addiction.

In Phase I, the contractor is expected to explore various technologies and approaches to improve the efficiency of large scale production of the macromolecules with potential for treating cocaine, methamphetamine or opiate addiction. The contractor shall produce pilot batches and demonstrate the feasibility of the scale-up approaches through in vitro tests and/or preliminary in vivo evaluations of the batches. In Phase II, the contractor is expected to select the most efficient technology/approach, establish the procedures for a GMP scale-up production, and manufacture the GMP batch of the macromolecules. The

contractor shall also perform in vitro and in vivo characterizations including quality control and stability testing, and preliminary pharmacological, toxicological or immunological evaluations.

Potential applicants should submit a letter of intent.

126 Web Based Cognitive/Neuropsychological Testing for Substance Abuse

(Fast-Track proposals will be accepted.)

This solicitation would emphasize the porting of one or more of either existing or novel tasks that are relevant to substance abuse related cognitive/neuropsychological dysfunctions to a web-based environment so that testing may be conducted from any remote location with internet access.

There is increasing evidence that cognitive and neuropsychological dysfunctions are associated with substance abuse disorders. Such dysfunctions can also include not only domains that are part of classical cognitive/neuropsychological testing (e.g. memory, executive function, and sensory/motor processes), but also domains that have recently become amenable to objective testing, such as (but not limited to) emotional and cue reactivity, inhibitory control, planning, risk and decision-making, and even social perception and interactions. Cognitive and neuropsychological dysfunctions appear to be not only a consequence of drug use, but may also represent risk factors for initiation of drug use as well as impediments to treatment and abstinence. Furthermore, these cognitive/neuropsychological dysfunctions may be relatively subtle or may not be accessible to awareness (i.e., is implicit) or overt behavior. As a result, neither the patient nor a treatment provider may be aware of these dysfunctions in the absence of specific testing.

Cognitive/Neuropsychological testing has traditionally been time consuming to administer and score, but some tests can or have already been adapted to computerized administration. Advances in computer technology and the widespread availability of internet access opens the possibility that subjects in research projects and patients in treatment can be tested using interactive on-line versions of existing or novel tasks. This solicitation proposes to take computerized administration of these tasks to the next level so as to permit a person to take one or more tests from any location with access to the internet. The development of such on-line capabilities would greatly increase the ability to collect test data from larger cohorts of subjects in a more efficient manner than previously possible.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES (NIEHS)

Human health and human disease result from three interactive elements: environmental exposures, individual susceptibility and time. The mission of NIEHS is to reduce the burden of human illness and dysfunction from environmental exposures by understanding each of these elements and how they interrelate. NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. This Small Business Innovation Research Program (SBIR) uses a combination of research and technology transfer in order to develop new products that will aid the mission of NIEHS.

This solicitation invites SBIR proposals in the following areas:

105 Computer Assisted Sperm Analysis System

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year)

There is a need for an integrated sperm motility analysis system to allow quantitative evaluation sperm in humans and laboratory animals that 1) have been exposed to environmental or pharmacological agents known or suspected of having detrimental effects on male fertility, 2) or have unknown causes of male infertility that may include abnormal sperm function, 3) or have known or unknown spontaneous or chemically-induced germ cell mutations effecting male fertility, 4) or have been modified genetically by insertion of transgenes, targeted gene deletions (gene knockouts) or targeted gene mutations (gene knockins).

The goal of this project is therefore to develop an integrated sperm motility analysis system for quantitative evaluation of sperm from animal species and humans. The characteristics of the integrated sperm motility analysis system should be 1) a microscope to visualize sperm at selected magnifications (e.g., 10X, 16X, 25X), 2) a high speed digital camera and image capture system (60 Hz or higher), 3) MS Windows compatible modular software packages for analyzing sperm motility parameters in captured images of sperm in a field of view in the microscope (i.e., total and percent motile and immotile, total and percent with and without forward progressive motility, rate of forward progressive motility, lateral head displacement, lateral flagellar displacement, and other parameters as required), 4) modular software packages for analysis of motility parameters of sperm from different species with different morphological and motility characteristics (e.g., human, mouse, rat, rabbit), 5) MS Windows computer system that can be upgraded with advances in computer operating systems and allows software operation, image capture storage, and output data storage for the computer assisted sperm analysis system.

106 Development of Quantitative High Throughput Screens For Environmental Toxicants that Induce DNA Damage

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year)

The National Toxicology Program (NTP) Vision for the 21st Century is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. Thus, NTP is placing an increased emphasis on the use of alternative assays for targeting key pathways, molecular events, or processes linked to disease or injury, and has established a High Throughput Screening (HTS) program, representing a new paradigm in toxicological testing. NTP is using this HTS approach to screen for mechanistic targets active within cellular pathways critical to carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity. NTP is partnering with the National Human Genome Research Institute's NIH Chemical Genomics Center (NCGC) and the U.S. Environmental Protection Agency's National Center for Computational Toxicology (Tox21 Partnership) to test ~ 10,000 compounds that broadly characterize and define the chemical-biological space occupied by chemicals of toxicological concern. Data generated, along with full chemical characterization and assay protocol details, are deposited into PubChem (<http://pubchem.ncbi.nlm.nih.gov/>), a publicly accessible, relational database. The goals of this HTS program are to:

- prioritize substances for further in-depth toxicological evaluation
- identify specific mechanisms of action for further investigation
- develop predictive models for in vivo biological response

In regard to this HTS program, the ability of chemicals to interact with and induce damage in DNA is one area of special interest to the NTP. DNA damage is associated with a number of disease processes, notably cancer, and other adverse health effects. Compounds can induce DNA damage directly or through indirect mechanisms such as interference with DNA metabolism enzymes (e.g., polymerases). DNA damage can be monitored and assessed in a variety of cell types through a number of different methods (e.g., reporter gene assays, mutation induction, DNA adduct formation). **The goal of this SBIR project is to support the development of quantitative high throughput screens for the detection of chemicals that induce DNA damage.** These assays will be conducted at the NCGC using a robotic platform that imposes specific requirements on the experimental design that can be employed in the quantitative high throughput screens conducted there. The experimental design requirements are described in detail at http://www.ncgc.nih.gov/guidance/HTS_Assay_Guidance_Criteria.html. Screens developed must meet these requirements so they can be used at the NCGC.

107 Development of Mid to High-Throughput Toxicological Tests Using Model Organisms

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year)

In support of the High-Throughput Toxicological Testing Program for toxicology investigations, National Toxicology Program (NTP) is currently evaluating the utility of *Caenorhabditis elegans* as a model organism for toxicity testing to supplement the quantitative high throughput screening activities conducted at the NCGC. **NTP is looking to expand this approach by supporting the development of mid- to high-throughput alternative models that utilize other model organisms (e.g., *Drosophila melanogaster*, *Brachydanio rerio*, *Oryzias latipes*) for evaluating the ability of substances of concern to the NTP to induce toxicological effects (e.g., developmental toxicity, reproductive toxicity, cardiotoxicity, neurotoxicity).** This SBIR should focus on experimental procedures in model organisms that would accommodate screening a minimum of 1,000 compounds annually (2,000 is preferred) per toxicological endpoint, using a broad dose range to fully characterize the dose-response curve.

108 Integrated Prediction Systems to Support Environmental Toxicological Assessments

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year)

The last two decades have produced dramatic technological advances in molecular biology and computer science. The NTP is evaluating how best to incorporate these advances into its research and testing strategies in order to broaden scientific knowledge of exposure-related disease mechanisms. **To support these efforts, the goal of this contract is to develop a PC and/or Mac-based integrated prediction system to support environment toxicological assessments.** The developer will need to provide a user-friendly interface that will integrate tools commonly available for in silico predictions to provide data and predictions relating to the potential toxicological effects of a chemical of interest. The user must be able to enter a query via a Chemical Abstracts Service Registry Number, the chemical name, a structure data file, a molfile, a IUPAC International Chemical Identifier (InChI), or a Simplified Molecular Input Line Entry Systems (SMILES) code. Users must be able to limit their search criteria at least by toxicological endpoint (e.g., carcinogenicity, genotoxicity, immunotoxicity, reproductive toxicity).

109 Incorporation of Metabolism into Quantitative High Throughput Screening (HTS) Assays

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year)

One of the current limitations of the majority of *in vitro* HTS assays is the lack of hepatic or target organ metabolism in the testing strategy. Reporter gene assays have generally been constructed using easy-to-culture cell lines derived from cancer cells or from primary cells that have been immortalized. These cells generally lack the ability to metabolize compounds to the chemical entities to which laboratory animals and humans would be exposed and which may have biological activities that differ from the parent chemical. Many compounds require biotransformation to become active toxicants. Without an ability to integrate robust human and rodent hepatic or other target organ metabolism into the Tox21 HTS program, efforts to correlate *in vitro* test results with *in vivo* toxicities will continue to present challenges. **To support these efforts, the goal of this SBIR is to develop high throughput assays (e.g., 384 or 1536-well) that incorporate human or rodent hepatic metabolic capability.** Useful approaches might be based on (but are not limited to) (1) directly measuring gene expression or protein changes for critical pathways in primary hepatocytes, in stem cells that have been differentiated into hepatocyte-like cells, or in cell lines that retain appropriate kinds and levels of drug metabolizing activity; (2) transfecting such cells with reporter genes; or (3) co-cultivation of cells containing reporter genes with functional hepatocytes. Information on criteria for high throughput screens that can be conducted at the NCGC can be found at http://www.ncgc.nih.gov/guidance/HTS_Assay_Guidance_Criteria.html. The screen developed must meet these requirements so they can be used at the NCGC

110 Development of Quantitative High Throughput Screens for the Detection of Chemicals That Modulate Gap Junctional Intercellular Communication

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year)

The National Toxicology Program (NTP) is placing an increased emphasis on the use of alternative assays for targeting key pathways, molecular events, or processes linked to disease or injury, and has established a High Throughput Screening (HTS) program, representing a new paradigm in toxicological testing. NTP is using this HTS approach to screen for mechanistic targets active within cellular pathways critical to carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity. NTP is partnering with the National Human Genome Research Institute's NIH Chemical Genomics Center (NCGC) and the U.S. Environmental Protection Agency's National Center for Computational Toxicology (Tox21 Partnership) to test ~ 10,000 compounds that broadly characterize and define the chemical-biological space occupied by chemicals of toxicological concern. All compounds tested at the NCGC are screened over a broad concentration range (0.59 nM – 92 uM in DMSO). Data generated, along with full chemical characterization and assay protocol details, are deposited into PubChem (<http://pubchem.ncbi.nlm.nih.gov/>), a publicly accessible, relational database. The goals of this HTS program are to:

- prioritize substances for further in-depth toxicological evaluation
- identify specific mechanisms of action for further investigation
- develop predictive models for in vivo biological response

In regard to this HTS program, the ability of chemicals to modulate gap junctional intercellular communication is one area of special interest to the NTP. Gap junctions are clusters of intercellular channels connecting adjacent cells, which permit the direct exchange of ions and small molecules between cells. A large number of connexin genes, many of which are tissue-specific, are involved in regulating gap junctional intercellular communication. Gap junctional intercellular coupling is required both for rapid signaling between electrically excitable cells and for the slower spread of intercellular second messenger signals between other cell types. Compound-induced changes in cell-to-cell communication via alteration in gap junctions may result from inappropriate alteration of connexin gene expression, a form of epigenetic toxicity. For example, cancer cells, which lack normal controls on cell division and which do not terminally differentiate, do not have functional gap junction intercellular communication. A number of nonmutagenic compounds have been shown to inhibit gap junction communication, including, for example, certain estrogens, growth factors (EDG PDGR, TGF, TNF), pesticides (2,4-D; 2,4,5-T), and cytokines (prostaglandins). In contrast, many compounds have been shown to up-regulate gap junction communication, such as carotenoids, retinoids, green tea extracts, and vitamin D. **The goal of this SBIR is to support the development of quantitative high throughput screens for the detection of chemicals that adversely alter gap junction activities.** These assays will be conducted at the NCGC using a robotic platform that imposes specific requirements on the experimental design that can be employed in the quantitative high throughput screens conducted there. The experimental design requirements are described in detail at http://www.ncgc.nih.gov/guidance/HTS_Assay_Guidance_Criteria.html.

111 Monitoring in vivo Gene Expression Changes After Exposure to Toxicants in *Caenorhabditis elegans*

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year)

Exposure to environmental agents is associated with the development and progression of many human diseases, including cancer, learning and psychological disabilities, and congenital abnormalities. Many of the biological processes that contribute to the etiology of these diseases are controlled by genes and cognate regulatory pathways that are sensitive to environmental contaminants. Quantification of time- and tissue-specific changes in gene expression after contaminant exposure will allow for the elucidation of the molecular mechanisms for the pathology. The report by the National Academies, *Scientific Frontiers in Developmental Toxicology and Risk*

Assessment, identified many evolutionarily conserved developmental signal transduction pathways that are associated with human diseases. Thus, alternative model organisms, including the nematode *Caenorhabditis elegans*, can be used to connect disruption of signaling pathways with *in vivo* health effects. The *in vivo* expression of fluorescent reporter proteins, such as GFP and mCherry, under the control of endogenous promoters is frequently used to study spatial and temporal gene expression patterns in transgenic *C. elegans*. The fluorescent expression patterns of individual nematodes can be observed via microscopy and rapidly quantified using flow cytometry. **The goal of this contract would be to generate a collection of stable, integrated strains of transgenic *C. elegans* to monitor the effects of toxicants on gene expression *in vivo*. The collection would include a representative set of target genes from the signaling pathways known to be affected by exposure to environmental agents (e.g. DNA damage response, unfolded protein response, apoptosis, receptor mediated signaling, etc.). Ideally, several independent lines of low copy number transgenic strains would be generated and out-crossed for several generations.** The transgenic *C. elegans* can be used for rapid gene expression profiling to identify signaling pathways and molecular events that are perturbed following contaminant exposure. These strains could be used by multiple investigators to help reduce the numbers of animals used in research and provide potentially important diagnostic information.

112 Development of Biomarkers for Assessment of Exposure to Molds

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 (1 year)

A significant association exists between damp housing, accompanied by growth of molds, and respiratory disease. There are research gaps in reliable methods for detection and identification of molds and/or mold products in homes, schools and other public and commercial buildings. While it is possible to see mold if there is gross infestation it is not currently possible to quantitate the amount of mold exposures. **The purpose of this initiative is to develop quantitative tests for measuring environmental exposure to molds in damp housing and water-damaged buildings.** The test must accurately quantify mold exposure as well as the type of mold. Examples include tests for specific mold antigens/allergens or DNA based methods for mold identification and detection. Tests that measure multiple allergens using microarray technology are a high priority, as are tests directed towards molds of clinical significance, associated with allergic reactions, asthma, or other respiratory diseases.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)

The National Center for Chronic Disease Prevention and Health Promotion is leading efforts to promote health and well-being through prevention and control of chronic diseases that all people might live healthy lives free from the devastation of chronic diseases. Priorities focus on well-being, health equity, research translation, policy promotion and workforce development.

The Division of Reproductive Health is interested in the development of sensitive assays for the detection of markers of natural rubber and silicone that are released by latex condoms or diaphragms in genital secretions during intercourse, and in characterizing the residence time of such markers after intercourse.

This solicitation invites proposals for the following topic areas:

031 Development of a Method to Detect Traces of Natural Rubber and Silicone in Biological Specimens

Proposals are invited for the development of a method (i.e., method, technique, instrument, or device) to detect traces (e.g., specific proteins or other chemical markers) of natural rubber and silicone in biological specimens. The method should be of sufficiently high sensitivity to detect traces of rubber in vaginal fluid after intercourse protected using a condom or a diaphragm made of natural latex or silicone, should have high specificity (i.e., detection of a marker of latex or silicone should yield a low rate of false-positive results), should be scalable for use with large numbers of samples from field studies, and should have a reasonable projected cost in large-scale studies (<\$30/test).

The design of studies to evaluate the effectiveness of condoms or other barrier methods faces serious methodologic challenges. A key limitation of most studies is that they rely exclusively on self report to measure sexual activity (number and type of partners, number of acts, condom use). Self-reported sexual behaviors are prone to reporting bias. This bias is exacerbated in settings such as reproductive health care clinics, where safer sex messages are extensively promoted. The use of biomarkers of semen exposure (such as prostate specific antigen (PSA) or Y-chromosome DNA) has recently gained attention as a tool for corroborating self-report. Biomarkers of semen exposure may be most useful to determine the occurrence of semen exposure following unprotected intercourse, or intercourse with ineffective protection. However, such biomarkers provide only indirect evidence of barrier use. A direct approach would employ assays to detect chemicals released by barrier products during intercourse. A number of proteins of *Hevea Brasiliensis* (the rubber tree) have been characterized in an effort to identify the causes of human allergy to latex. Several proteins have been purified, genetically engineered systems have been developed to produce them in large amounts, and specific monoclonal antibodies are now available. Thus, it should be possible to develop assays to detect latex in vaginal fluid after use of a latex product such as a condom or a diaphragm. Analogous techniques could be developed to detect chemicals released by silicone-based products.

The proposal should include (1) a plan to develop a method (i.e., method, technique, instrument, or device) to detect markers of natural rubber and silicone; (2) documentation of the capacity and the accuracy of the method; (3) verification of the specificity of the markers in discriminating use of products made of natural latex or silicone, (4) evidence that the method is applicable to testing relatively small samples (100ul-1ml) collected by swabs. Evaluation of the method should address, at a minimum: ruggedness, sensitivity and limit of detection, specificity, cost of operation and scalability, and reproducibility.

NATIONAL CENTER FOR HIV/AIDS, VIRAL HEPATITIS, STD, AND TB PREVENTION (NCHHSTP)

The mission of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) is to maximize public health and safety nationally and internationally through the elimination, prevention, and control of disease, disability, and death caused by HIV/AIDS, Viral Hepatitis, other Sexually Transmitted Diseases, and Tuberculosis.

Website: <http://www.cdc.gov/nchhstp>.

Division of Viral Hepatitis

027 Manufacture of a Novel Technology to Identify Early HCV Infection by anti-HCV Detection

Hepatitis C is the most common chronic blood borne infection in the United States, affecting 3.2 million of Americans. Since 2000, an estimated 85,000 new HCV infections occur every year and approximately 19,000 new infections occurred in 2006. However, 50% of HCV infected persons are unaware of their infection. Additionally, several studies have estimated that 30% of HIV-infected individuals are also infected by HCV and 60-90% of individuals infected with HIV by intra-venous drug use (IVDU) have HCV. The total estimate for co-infected individuals in the USA is 300,000.

Infection by hepatitis C virus (HCV) is a leading cause of both end-stage liver disease and liver cancer. Identification of early infection is important because therapy initiated during the acute stage can significantly reduce the risk of developing chronic infection. The diagnostic of HCV infection is based on the detection of its molecular marker (HCV RNA), the serological marker (anti-HCV) and its biochemical marker (ALT). However, none of these markers can be used to distinguish acute from chronic HCV infection because these markers are also detected during late phase of infection. Moreover, distinguishing acute from chronic HCV infection on the basis of history and symptoms is difficult because many persons with acute infection are asymptomatic.

Surveillance for acute HCV infection is constrained owing to the lack of a commercial antibody-based diagnostic assay that can discriminate between acute and chronic HCV infection. Data generated from a high-throughput HCV recombinant protein microsphere immunoassay, developed in CDC's viral hepatitis laboratory, shows that it is possible to accomplish this task by simultaneously detecting IgG or IgM anti-HCV antibody binding activity to specific HCV recombinant antigens. It may be feasible for a small business to be interested in further optimizing, validating and marketing the assay for clinical use.

Research Priorities: This SBIR is aligned with several major NCHHSTP priorities including:

1. NCHHSTP's priority to decrease incidence and consequences of HIV/AIDS, Viral Hepatitis, STD, and TB, especially among racial and ethnic minorities, in the United States and in resource-constrained countries.
2. DVH Strategic Imperatives to reduce incidence of viral hepatitis and improve chronic disease prevention and control.
3. DVH Work Plan for Hepatitis C, as stated on Goal # 1: To conduct research to improve prevention of HCV infection and improve laboratory methods to detect HCV infection.

CDC's Healthiest Nation Goals: Prospective studies have shown that an average of 70% of infected persons develop chronic hepatitis, and population based-studies indicate that 40% to 60% of chronic liver disease in the United States is HCV related and may cause 8,000 to 10,000 deaths per year. This SBIR proposal is directly aligned with the People Prepared for Emerging Health Threats Objective # 1: to detect, monitor, report and evaluate public health threats; Healthy People in Every Stage of Life Objective # 5: to prevent chronic diseases and their consequences among adults; and Healthy People in a Healthy World Objective # 6: to prevent, detect, respond to, and contain health threats globally.

Suggested Projects: Develop, validate and market a high-throughput immunoassay for detecting early HCV infection for clinical use using specific HCV recombinant antigens in a high-throughput microsphere immunoassay.

Related projects which could take advantage of the same technology:

- Develop a high-throughput immunoassay to detect hepatitis B virus (HBV) infection caused by HBV vaccine escape and/or drug resistant mutants.
- Develop a high-throughput immunoassay to simultaneously screen for infections due to hepatitis viruses A, B, C and E).

Collaboration: This SBIR proposal offers an opportunity to collaborate with the DVH Epidemiology and Surveillance Branch, focusing on the development of novel alternatives for rapid diagnosis and surveillance of incident hepatitis C virus infections in the USA. Collaborations with other Divisions include, but are not limited to, the Division of HIV/AIDS Prevention (DHAP) and Global AIDS Program (GAP) since they could use similar technology to improve the diagnosis of HIV.

The proposed research and development work will be evaluated by a technical review panel applying the following criteria, which should be addressed in substantial detail within the space limitations specified elsewhere in this announcement: **1) Soundness and Technical Merit** (40 points) - The scientific basis and preliminary track record of the approach and the identification of clear measurable goals and milestones to be achieved during Phase I. **2) Personnel** (20 points) - The qualifications and experience of the proposed Principal Investigator, supporting staff, and consultants. **3) Technological Innovation** (10 points) - The potential for advancing the state of the art of the relevant field. **4) Commercial Application** (10 points) - The potential for profitable viability in the marketplace. **5) Facilities** (10 points) - The adequacy and suitability of the available equipment and research environment for the proposed work. **6) Public Health Impact** (10 points) - The potential for dramatic or revolutionary impact on hepatitis programs and population well-being.

028 An Integrated Relational Database Storage and Data Mining Software for Large-Scale Analyses of Infections Caused by Hepatitis Viruses

Hepatitis viruses are a diverse group of viruses with different major modes of transmission. Hepatitis A and hepatitis E viruses (HAV and HEV) may cause food-borne outbreaks. Hepatitis B and hepatitis C viruses (HBV and HCV) are blood-borne viruses. Although, infection with any of the hepatitis viruses has a similar clinical presentation, the degree of sequence heterogeneity of these viruses varies. Recent advances in laboratory technologies and computational biology have facilitated a comprehensive sequence analysis of the genomes of hepatitis viruses. This information allows for further refinement of molecular epidemiological approaches and provides opportunities to link molecular epidemiological data to demographic, clinical, laboratory and

epidemiological data. In the course of engagement in clinical and surveillance studies and outbreak investigations, CDC generates, collects and analyzes such data. Because of the diversity in the type and sources of these data the CDC's Division of Viral Hepatitis seeks a software application that will be able to integrate these disparate datasets and that will permit data mining and investigator-initiated analysis.

Research Priorities:

NCHHSTP: This SBIR is directly aligned with NCHHSTP priorities:

- Accelerate elimination of TB, hepatitis B, and syphilis in the United States
- Enhance the prevention and control of vaccine preventable STDs (HPV disease, hepatitis) in the United States
- Decrease incidence and consequences of HIV/AIDS, Viral Hepatitis, STD and TB especially among racial and ethnic minorities, in the United States and in resource-constrained countries.

CDC's Healthiest Nation Goals: The incidence of hepatitis A is falling rapidly, but outbreaks of food-borne hepatitis A outbreaks occasionally occur, and can involve large numbers of people. An estimated 50,000 Americans acquire new HBV infection annually. The health burden of persistent or chronic hepatitis B infection is also heavy, with high mortalities due to cirrhosis or cancer. Adding to the burden of 1.2 million people in the USA estimated to be chronically infected with HBV is an estimated 40,000 foreign-born, chronically infected persons per year resulting from immigration. Chronic hepatitis B causes liver cancer, and this cancer is a leading cause of death for certain population groups in the USA such as Asian-Americans. Hepatitis C is the most common chronic blood borne infection in the United States, affecting 3.2 million of Americans. Since 2000, an estimated 85,000 new HCV infections occur every year and approximately 19,000 new infections occurred in 2006. However, 50% of HCV infected persons are unaware of their infection. Additionally, several studies have estimated that 30% of HIV-infected individuals are also infected by HCV and 60-90% of individuals infected with HIV by intra-venous drug use (IVDU) have HCV. The total estimate for co-infected individuals in the USA is 300,000. About a fifth of the American population is estimated to be exposed to HEV, but the health impact of this exposure is unknown. This SBIR proposal is directly aligned with People Prepared for Emerging Health Threats Objective # 1: to detect, monitor, report and evaluate public health threats; Healthy People in Every Stage of Life Objective # 5: to prevent chronic diseases and their consequences among adults; and Healthy People in a Healthy World Objective # 6: to prevent, detect, respond to, and contain health threats globally.

Suggested Project: To develop data mining software that extracts, transforms, and loads structured data relating to infection with hepatitis viruses from diverse sources into a warehouse appropriate for mainframe, client/server, and PC platforms. This data will include but may not be limited to demographic, clinical, epidemiological, laboratory and phylogenetic information. The software will store and manage the data in a relational database system with a web-based interface to provide data access to the scientific community and analyze relationships in the stored data using end-user defined queries to discover disease patterns and trends. The software will have hook interfaces which allow data to be exported to external programs for additional analysis and retrieve those results into the database. The software will also export the outcomes of such analyses in publication ready formats.

Collaboration: This SBIR proposal offers an opportunity to collaborate with other divisions in the CDC that are involved in generating integrated databases and applying data mining tools for analyzing trends in the transmission of disease-causing bacteria, viruses and parasites.

The proposed research and development work will be evaluated by a technical review panel applying the following criteria, which should be addressed in substantial detail within the space limitations specified elsewhere in this announcement: **1) Soundness and Technical Merit** (40 points) - The scientific basis and preliminary track record of the approach and the identification of clear measurable goals and milestones to be achieved during Phase I. **2) Personnel** (20 points) - The qualifications and experience of the proposed Principal Investigator, supporting staff, and consultants. **3) Technological Innovation** (10 points) - The potential for advancing the state of the art of the relevant field. **4) Commercial Application** (10 points) - The potential for profitable viability in the marketplace. **5) Facilities** (10 points) - The adequacy and suitability of the available

equipment and research environment for the proposed work. **6) Public Health Impact** (10 points) - The potential for dramatic or revolutionary impact on hepatitis programs and population well-being.

Division of STD Prevention

029 Decision Support Tools and the Electronic Health Record (EHR)

Proposals are invited for development of decision support tools that could be embedded in an electronic health record for use in outpatient settings, and that would prompt providers to screen for Chlamydia trachomatis (CT) and offer human papilloma virus (HPV) vaccine in appropriate populations. This tool would ultimately be made available to public health partners at no cost, i.e. as “freeware”. In addition, the proposal should include a review of existing decision support tools specific to these clinical services, that are currently on the market and consistent with industry standards. This review should include operational parameters of each tool, evidence of effectiveness, cost and the nature and extent of current usage. This information would provide input to the development phase of the new software, and would also be made available to partners, to inform future purchases.

Impact: Increase the delivery of CT screening and HPV vaccine by 1) assessing the nature and effectiveness of existing decision support tools that prompt CT screening for sexually active young women and HPV vaccine for young female adolescents before they become sexually active; 2) building decision support tools that prompt CT screening and HPV vaccine for use in electronic health records and 3) supporting enhanced diffusion of these tools in clinical settings, including public health clinics and community health centers.

Objectives:

- 1) Identify existing EHR systems that incorporate decision support prompts, targeting delivery of CT screening and HPV vaccine
- 2) Assess/evaluate the effectiveness of existing prompts, at improving the delivery of targeted services
- 3) Assess/evaluate the state of industry-wide standards for decision support tools for integration into outpatient/ambulatory EHRs; evaluate the consistency of existing decision support tools targeting CT/HPV systems of demonstrated effectiveness with those standards
- 4) Build decision support prompts specific to CT screening for sexually active young women and HPV vaccine for young female adolescents before they become sexually active
- 5) Ensure that the new tool(s) are of demonstrated effectiveness and consistent with industry standards
- 6) Develop mechanisms for dissemination of EHR-compatible decision support prompts, that are consistent with industry standards and of demonstrated effectiveness at impacting CT screening and HPV delivery, into both private and public sector (e.g. community health centers) health care delivery settings.

The proposed research and development work will be evaluated by a technical review panel applying the following criteria, which should be addressed in substantial detail within the space limitations specified elsewhere in this announcement: **1) Soundness and Technical Merit** (40 points) - The scientific basis and preliminary track record of the approach and the identification of clear measurable goals and milestones to be achieved during Phase I. **2) Personnel** (20 points) - The qualifications and experience of the proposed Principal Investigator, supporting staff, and consultants. **3) Technological Innovation** (10 points) - The potential for advancing the state of the art of the relevant field. **4) Commercial Application** (10 points) - The potential for profitable viability in the marketplace. **5) Facilities** (10 points) - The adequacy and suitability of the available equipment and research environment for the proposed work. **6) Public Health Impact** (10 points) - The potential for dramatic or revolutionary impact on STD programs and population well-being.

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

The National Center for Immunization and Respiratory Diseases (NCIRD) promotes applied research and development to enhance the effectiveness, efficiency, safety, and acceptability of immunization through crosscutting initiatives, projects, and consultations.

Website: <http://www.cdc.gov/ncird>

Division of Viral Diseases

The Division of Viral Diseases (DVD) is responsible for providing laboratory support for surveillance for respiratory and enteric viruses in the United States and worldwide. Viral agents include vaccine preventable viral agents such as measles, mumps, rubella, varicella zoster virus, rotavirus, and poliovirus. In addition, DVD provides laboratory support for a number of other viral agents that are important causes of human disease such as enteroviruses, respiratory syncytial virus, caliciviruses, rotaviruses, human parainfluenza viruses, and coronaviruses. DVD currently conducts a wide range of serologic and molecular assays to detect infections and provides genetic characterization of the agents responsible for these diseases. DVD provides technical support to the global laboratory networks of the World Health Organization and surveillance networks for food-borne disease and respiratory disease in the US.

023 Novel Methods for Detecting Viruses in Clinical Samples

DVD has already developed a wide variety of standard PCR, real time PCR, and semi-nested or nested consensus degenerated pan viral PCR techniques for detection of various both known and novel viral agents and is interested in new or improved methods to detect viral proteins or nucleic acids in clinical samples. These novel techniques should have high levels of sensitivity and specificity. Techniques which require a minimum amount of specimen processing and handling, do not require nucleic acid extraction or amplification, and are amenable to high throughput screening are especially desirable. Tests that could be deployed in resource limited areas would also be considered a high priority.

The scope of diagnostic activities within DVD is very broad. While Phase 1 proposals should attempt to develop techniques with broad applicability, it is anticipated that proposals will initially need to focus on a virus or limited group of viruses to provide a proof of concept. Proposals that address the following active program areas are particularly encouraged:

1. Detection of the viral agents prevented by measles, mumps and rubella (MMR) vaccine.
2. Detection of cytomegalovirus and varicella zoster virus.
3. Detection of novel viruses by broadly reactive consensus degenerate pan viral PCR, such as novel coronaviruses by pan *Coronaviridae*, PCR, as an example.
4. Detection of group A rotavirus.
5. Direct detection of human respiratory viruses and noroviruses.

The proposed research and development work will be evaluated by a technical review panel applying the following criteria, which should be addressed in substantial detail within the space limitations specified elsewhere in this announcement: **1) Soundness and Technical Merit** (40 points) - The scientific basis and preliminary track record of the approach and the identification of clear measurable goals and milestones to be achieved during Phase I. **2) Personnel** (20 points) - The qualifications and experience of the proposed Principal Investigator, supporting staff, and consultants. **3) Technological Innovation** (10 points) - The potential for advancing the state of the art of the relevant field. **4) Commercial Application** (10 points) - The potential for profitable viability in the marketplace. **5) Facilities** (10 points) - The adequacy and suitability of the available equipment and research environment for the proposed work. **6) Public Health Impact** (10 points) - The potential for dramatic or revolutionary impact on immunization programs and population well-being.

024 Novel or Enhanced Technology for Vaccination Delivery and Immunization Programs

A major focus shared by the Division of Viral Disease and the Division of Bacterial Disease in NCIRD is development and testing of alternative delivery systems and related technologies for vaccination. The goal is to develop vaccination systems that avoid the dangers and drawbacks of conventional needle and syringe and are more effective, more affordable, simpler and safer. Such improvements in vaccination support many of the Health Protection Goals of CDC and the nation (<http://www.cdc.gov/osi/goals/goals.html>) by preventing disease at

various stages of life and work environments, and in response to natural, inadvertent, and intentional threats to health.

New or improved methods, systems, or accessories are encouraged in the following areas, listed alphabetically:

- A) Cutaneous Vaccination.** For example, delivery systems, carrier constructs, or adjuvants for depositing antigen into or onto the skin to reach immunoactive tissues of the epidermis or dermis, such as patches, minineedles, microneedles, microtines, or powders, using mechanical, kinetic, electromagnetic, chemical, sonic, ballistic, or other means to traverse the stratum corneum barrier.
- B) Jet Injection Vaccination.** For example, disposable-cartridge injectors or accessories for pressurizing liquid vaccines to propel them without needle into intramuscular (IM), subcutaneous (SC), and/or intradermal (ID) target tissues.
- C) Logistics for Immunization Programs.** For example, antigen carriers, formulation vehicles, or packaging systems for increased thermostability to reduce the costs and constraints of the cold-chain, for detecting freeze damage to avoid use of impotent product, for simplified reconstitution of lyophilized vaccines, or for reduced wastage from economical unit-dose primary containers.
- D) Oral Vaccination without Ingestion.** For example, constructs, carriers, adjuvants, or other techniques to target antigen for delivery to mucosal cells of the mouth or oropharynx (as distinct from ingestion for uptake in the distal gastrointestinal tract), such as oral sprays, sublingual tablets, or melting strips.
- E) Respiratory Tract Vaccination.** For example, 1) devices, formulations, or constructs for delivery of wet liquid or dry powder aerosols and nasal sprays to the upper or lower airways, 2) adjuvants or other methods for improved uptake, efficiency, and immune response of respiratory vaccines, or 3) *in vivo* animal, *in vitro* bench, or *in silico* software models to facilitate study of this route.

Encouraged and prioritized for award are proposals with high potential for dramatic improvements to overcome barriers and constraints for immunization programs, and for early affordability in developing countries. Credibility is enhanced by proposals which feature a specific vaccine in combination with a novel technology as “proof of principle”, and include evidence of collaboration or support of the antigen manufacturer.

The proposed research and development work will be evaluated by a technical review panel applying the following criteria, which should be addressed in substantial detail within the space limitations specified elsewhere in this announcement: **1) Soundness and Technical Merit** (40 points) - The scientific basis and preliminary track record of the approach and the identification of clear measurable goals and milestones to be achieved during Phase I. **2) Personnel** (20 points) - The qualifications and experience of the proposed Principal Investigator, supporting staff, and consultants. **3) Technological Innovation** (10 points) - The potential for advancing the state of the art of the relevant field. **4) Commercial Application** (10 points) - The potential for profitable viability in the marketplace. **5) Facilities** (10 points) - The adequacy and suitability of the available equipment and research environment for the proposed work. **6) Public Health Impact** (10 points) - The potential for dramatic or revolutionary impact on immunization programs and population well-being.

NATIONAL CENTER FOR ZOONOTIC, VECTOR-BORNE & ENTERIC DISEASES (NCZVED)

The National Center for Zoonotic, Vector-Borne, and Enteric Diseases (NCZVED) maximizes public health and safety nationally and internationally through the prevention and control of disease, disability, and death caused by zoonotic, vector-borne, foodborne, waterborne, mycotic, and related infections.

Website: <http://www.cdc.gov/nczved>

Division of Vector-Borne Infectious Diseases

001 Development of Soaps or Lotions Containing Natural Product Repellents or Toxicants for Tick and Mosquito Disease Vectors

Ticks and mosquitoes are important vectors of disease causing agents, including the Lyme disease spirochete and West Nile virus. The first line of defense against vector-borne diseases is personal protection, including the use of repellents or topical toxicants. Although commercial repellents containing DEET and toxicants such as permethrin in impregnated clothing are effective against mosquitoes and ticks, a significant portion of the general public are reluctant to use these chemicals due to concerns about their safety. Therefore, the development of safe and effective repellents and toxicants that contain natural products perceived by the public as environmentally friendly and safe are of significant public health importance in the fight against vector-borne diseases.

Scientists at CDC/DVBID have patented a class of compounds extracted from Alaska yellow cedar (AYC) and common to citrus products. Our research has revealed that these compounds, in particular nootkatone, are excellent candidates as acaricides, insecticides, and repellents against important public health vectors including ticks and mosquitoes. The goal is to formulate these compounds to be evaluated in both laboratory and field trials against disease vectoring arthropods. This includes formulating nootkatone in personal care product formulations to serve as both insecticides and repellents to control ticks that transmit Lyme disease mosquitoes that transmit West Nile virus. Desired formulations may include, but are not limited to, pump and/or aerosol spray formulations; "leave on" type applications including but not limited to moisturizers, lotions, sunscreens; and finally insecticidal/repellent soaps, preferably liquid based.

The proposed research and development work will be evaluated by a technical review panel applying the following criteria, which should be addressed in substantial detail within the space limitations specified elsewhere in this announcement: **1) Soundness and Technical Merit** (40 points) - The scientific basis and preliminary track record of the approach and the identification of clear measurable goals and milestones to be achieved during Phase I. **2) Personnel** (20 points) - The qualifications and experience of the proposed Principal Investigator, supporting staff, and consultants. **3) Technological Innovation** (10 points) - The potential for advancing the state of the art of the relevant field. **4) Commercial Application** (10 points) - The potential for profitable viability in the marketplace. **5) Facilities** (10 points) - The adequacy and suitability of the available equipment and research environment for the proposed work. **6) Public Health Impact** (10 points) - The potential for significant impact on reduction of Lyme disease transmission risks.

Division of Parasitic Diseases

002 Novel Methods for Detecting Parasites in Clinical Samples

DPD has already developed a wide variety of tools for the diagnosis of parasitic agents in clinical samples. This includes serological methods, standard PCR, real time PCR, and semi-nested PCR techniques for detection of various parasitic agents and is interested in new or improved methods to detect parasite products or nucleic acids in clinical samples. These novel techniques should have high levels of sensitivity and specificity. Methods which require limited amount of specimen processing and handling, simultaneously capable of detecting different species including drug resistant parasites, and are amenable to high throughput screening are especially desirable. Tests that could be deployed in resource limited areas with the capability to automatic transmission of data to remote locations would also be considered a high priority.

The scope of diagnostic activities within DPD is very broad. The Phase 1 proposals should attempt to develop techniques with wider scope of utility but, it is anticipated that proposals will initially need to focus on individual parasites or a group of parasites to provide a proof of concept. Proposals that address the following active program areas are particularly encouraged:

1. Detection of different species of malaria parasites using simple and reliable methods applicable in resource limited settings.
2. Detection of different drug resistant molecular markers of parasites using a simple platform such as a microchip.

3. Detection of parasites such as Plasmodium, Toxoplasma, Cryptosporidium, Cyclospora, and Babesia.
4. Detection of water borne organisms of U.S. national interest.

The proposed research and development work will be evaluated by a technical review panel applying the following criteria, which should be addressed in substantial detail within the space limitations specified elsewhere in this announcement: **1) Soundness and Technical Merit** (40 points) - The scientific basis and preliminary track record of the approach and the identification of clear measurable goals and milestones to be achieved during Phase I. **2) Personnel** (20 points) - The qualifications and experience of the proposed Principal Investigator, supporting staff, and consultants. **3) Technological Innovation** (10 points) - The potential for advancing the state of the art of the relevant field. **4) Commercial Application** (10 points) - The potential for profitable viability in the marketplace. **5) Facilities** (10 points) - The adequacy and suitability of the available equipment and research environment for the proposed work. **6) Public Health Impact** (10 points) - The potential for significant impact on the detection of parasitic agents in clinical samples.

COORDINATING OFFICE FOR TERRORISM PREPAREDNESS AND EMERGENCY RESPONSE (COTPER)

The Coordinating Office for Terrorism Preparedness and Emergency Response (COTPER) <http://emergency.cdc.gov/cotper/> has primary oversight and responsibility for programs that comprise the Centers for Disease Control and Prevention's (CDC) terrorism preparedness and emergency response portfolio. Through an all-hazards approach to preparedness that focuses on threats from natural, biological, chemical, nuclear, and radiological events, COTPER helps the nation prepare for and respond to urgent threats to the public's health. COTPER's mission is to "safeguard health and save lives by providing a flexible and robust platform for public health emergency response (proposed). To carry out its mission, COTPER (1) fosters collaborations, partnerships, integration, and resource leveraging to increase CDC's health impact and achieve population health goals; (2) provides strategic direction to support CDC's terrorism preparedness and emergency response efforts; (3) manages CDC-wide preparedness and emergency response programs; (4) maintains concerted emergency response operations—including the Strategic National Stockpile and the Director's Emergency Operations Center; and (5) communicates terrorism preparedness and emergency response activities to internal and external stakeholders.

COTPER interest in SBIR research is focused on the following research topic(s). Other research topics that are within the mission of COTPER are of interest:

002 Computer-Based Models For Evaluating Strategies and Outcomes in Pandemic Preparedness

As part of the National Strategy for Pandemic Influenza Implementation Plan, the Federal Government was tasked to "review and approve state pandemic influenza plans to supplement and support DHS State Homeland Security Strategies to ensure that Federal homeland security grants and other forms of assistance are applied to a common set of priorities in conformance with the National Preparedness Goal within 12 months". A priority area of this review was the topic of community containment and mitigation, which is the use of measures other than vaccination and drug treatment that might be useful during an influenza pandemic to reduce its harm. In February 2007, the Centers for Disease Control and Prevention released interim planning guidance on the use of non-pharmaceutical interventions to mitigate an influenza pandemic (Community Strategy for Community Mitigation, www.pandemicflu.gov); however, reviews of state pandemic influenza operational plans and feedback from state planners indicate that community mitigation is still an area where additional guidance and concrete methodology is needed. There is a need for state and local planners to better identify potential impacts and implications in each of the CDC defined pandemic severity index levels for mitigating disease spread, sustaining government and community infrastructure, and lessening the pandemic's impact on the economy and the functioning of society (schools, business, transportation, health, and other community sectors) if the federal government's pandemic interventions are implemented at the state and community level. A computerized modeling product using decision-tree algorithms is desired to help state and local planners examine possible outcomes related to the application of community containment interventions against state and local pandemic influenza plans. The model should be readily usable by staff in Federal, Tribal, State, Territorial, and Local health departments or by disaster planners and should be developed so that it can be made available at a low cost.

003 Development of an Improved Reusable Insulated [Cold-Chain] Shipping Container (ISC)

There is a need for cost-effective methodologies to ship vaccines and other drugs or biologicals while keeping the cold-chain intact. Research is needed to develop the technology for a reusable insulated cold-chain shipping container with specifications that would allow for various deployment conditions of assets in the Strategic National Stockpile.

Designs are needed for small, medium, and large Insulated Shipping Containers (ISC) to meet multi-performance ranges preferably within one ISC configuration for refrigerated and frozen specifications (not more than two separate configurations are desired). The temperature ranges for the new ISC design are: 1) Refrigerated specifications: 2° to 8° C; 2) Frozen specifications: -30° to -15° C and -30° to 8° C. Designs must meet or exceed all ISTA 7D temperature and drop tests on all 6 sides of ISC; ISC's must be ISTA certified and stamped. Designers must be capable of providing Qualification, Validation Performance testing in a licensed ISTA Lab with an ISO 9000/9001 certification for the design. In addition, the ISC must have state-of-the-art mold resistant and water/moisture retardant coating on all sides (inner/outer surface); Must contain disposable moisture absorbent padding material for the inner bottom of the ISC; Must utilize the same ISC machine tooling for the corresponding sizes between the 2°C to 8°C ISC and the -30°C to -15°C / -30°C to 8°C. All ISC's must have a Universal Pack-out Configuration with a desirable payload capacity for small: 10.2"x 5.1"x 4.5" (LxWxH); medium: 15" x 9.9" x 6.4"; large: 14.8" x 14.8" x 11". The ISC's should be deliverable as constructed and ready for long term storage and or immediate use. Complete packout of ISC's must take no longer than 30 seconds PCM (phase change materials) must enact at temperatures -22°C or warmer; No liquid nitrogen or dry ice PCM; No special considerations for safe disposal; ISC components and materials must be innocuous, non-toxic, and remain safe for use for minimum of 15 to 20 years; ISC's are to be 100% passive; No battery AC/DC powered components, No electronic circuitry permitted; the design should be such that it is functional for a minimum of 15 years under performance specifications and conditions/stipulations. The technology should be readily usable by staff in Federal, State and Local health departments or by disaster planners that require management or re-distribution of stockpile materials. Optimally, the systems developed should have low maintenance costs; estimated costs for development should be documented. In addition, evaluation and validation of the shipping systems are required. Validation specifications and maximum tare weight requirements will be provided upon request.

004 Training in Public Health Ethics for Public Health Responders

There is a need for specific training for public health responders about the complex ethical and social values that are involved in the planning, response, and follow-up phases of public health emergencies. Research is needed to develop training modules for public health professionals and practitioners on ethical principles and to explore key ethical issues related to public health emergency preparedness and response. Where appropriate, the training should provide guidance to reconcile potential ethics issues. When developing the training, the grantee should consider all available public health ethics frameworks. The specific frameworks utilized should be articulated in the proposed project. The training should be readily usable by staff in Federal, Tribal, State, Territorial, and Local health departments or by disaster planners and should be developed so that it can be made available at a low cost. In addition, evaluation of the effectiveness of the training should be incorporated into the training modules produced (e.g., exam questions). A computer or web-based training platform is desired but not essential.

005 State, Local, Community and Faith Based Tools and Resources for Protecting Vulnerable Populations from Excess Health Burden During All-Hazards Events

The unanticipated consequences of Hurricane Katrina uncovered a host of realities that need to be addressed to systematically prevent similar circumstances in the event of future hurricanes or other disasters of catastrophic magnitude. Although substantial progress has been made to design communication materials to reach vulnerable populations, the specific preparedness, response and recovery needs of vulnerable populations and the factors that contribute to vulnerability are still inadequately understood among first responders. Concerned public health professionals and first responders have engaged in efforts to develop guidelines and resources for protecting vulnerable populations during disasters. However, there continues to be a need for a useful, validated tool that can be used across the broad spectrum of preparedness stakeholders. Input from consumers and stakeholders indicate that research is needed to develop broad-spectrum, field-tested tools and resources to address

population specific and functional needs of vulnerable populations in response to all-types of public health hazards. This technology should be readily accessible to and usable by responders and staff from Federal agencies, State and Local health departments, National Volunteer Organizations Active in Disasters (VOAD), local community and faith-based organizations, and other disaster planners. Optimally, the tools and resources developed should have low maintenance costs and that can be documented. In addition, evaluation and validation of the tools and resources is required. The following is of particular interest:

- Development of tools and resources to systematically identify and plan for the All-hazards Emergency and Response needs of vulnerable populations. Tools should have the ability to target specific vulnerable population groups and functional needs such as the need for sheltering, food and water, medication, or transport and should go beyond currently available resources for vulnerable populations, be easily implemented, and adaptable to varying community and vulnerable population needs.

006 Pre-Hospital Transport Vehicle for the Acutely Injured

The management of injuries and trauma related morbidity during a public health emergency is a significant aspect in preparedness planning. In many cases those at greatest risk from injuries are the young or those with limited economic and social support systems. In addition to the scarcity of resources, such as may occur in rural settings, several factors may contribute to the difficulty in managing injuries during an event including:

- Remote locations with poor communication
- Traffic congestion
- Poor road infrastructure and access
- Lack of trained personnel
- Lack of appropriate equipment and supplies
- Deficiencies in ability to deliver timely definitive care

In these settings, effective public health interventions that are both economically and technically feasible will become increasingly important in mitigating the severe public health impacts of injuries, especially during an emergency event.

There is a need to develop pre-hospital transport capability (ambulances) specifically designed for application in such settings. The WHO, with support from CDC, led the development of trauma and emergency care systems that are applicable for conditions in an emergency event. WHO published Pre-hospital Trauma Care Systems and Guidelines for Essential Trauma Care to support the development and use of these systems internationally. A critical component in the care of the acutely ill or injured patient is timely transport to definitive care facilities under the challenging circumstances often encountered during various emergency events.

For use in these situations, the vehicle design process needs to take into account the following desired characteristics:

- Low manufacturing cost
- Low maintenance and fuel costs
- Capable of moving on paved and non-paved surfaces
- Capable of navigating narrow passages
- Warning devices and capability for poor weather use
- Seats with seatbelts for a driver, care provider

- Capable of securing a stretcher or having a padded bench with seatbelts for a patient to be able to lie flat
- Capable of securely carrying necessary equipment and supplies for the proposed level of care to be provided (e.g. as outlined in Pre-hospital Trauma Care Systems).

007 Technologies for Rapid and Efficient Communication in Emergency Response

Effective communication is crucial for emergency response before, during, and after a public health emergency event. Factors in emergency response communication include effective strategies to facilitate rapid information exchange, clear communication messaging to reach target audiences, established channels of communication, and others. Research is needed to develop or enhance existing communication technologies for use in emergency response. Design factors should improve upon existing technologies, such as improved ease of use under all hazard conditions, longer signal range, extended period of operability, lower cost to operate and/or to maintain, etc. Technology should be usable by responders and staff from Federal agencies, State and Local health departments, National Volunteer Organizations Active in Disasters (VOAD), local community and faith-based organizations, and other disaster planners.

PART II HUMAN SUBJECTS RESEARCH GUIDANCE AND INFORMATION SUPPLEMENT

1. INTRODUCTION

A Protection of Human Subjects section of the Research Plan is required for all proposals. The information provided in the section on Protection of Human Subjects should be consistent with the information provided on the face page of the application.

For all research involving human subjects, the Scientific Review Group (SRG) will assess the adequacy of protections for research participants against research risks, and the appropriate inclusion of women, minorities, and children, based on the information provided in the application.

To assist in preparing the section on Protection of Human Subjects, six possible scenarios are provided in Section 2 below. All research projects will fall into one of these six scenarios. Determine which scenario the proposed research falls into, then go to the specific instructions applicable to that scenario in [Section 3](#) of the Supplement. Where appropriate, Section 3 provides instructions on addressing the Inclusion of Women and Minorities, the Targeted/Planned Enrollment Table, and the Inclusion of Children. All definitions related to human subjects research are linked to text found in Part I, Section 3, [Definitions](#). [Section 5](#) of this Part includes descriptions of and links to the DHHS Human Subjects Protections regulations and NIH policies that apply to clinical research.

2. SCENARIOS

Scenario A. No Human Subjects Research

If no human subjects research is proposed in the proposal, check the box marked “No” on the Proposal Cover Sheet (Appendix A) and indicate “No” on the Proposal Summary and Data Record (Appendix G). If your proposed research involves human specimens and/or data from subjects, you must provide a justification for your claim that no human subjects are involved in the Protection of Human Subjects section of the Research Plan.

See the [instructions for Scenario A](#).

Scenario B. Non-Exempt Human Subjects Research

If research involving human subjects is anticipated to take place under the award, check the box marked “Yes” on the Proposal Cover Sheet (Appendix A) and indicate “Yes” on the Proposal Summary and Data Record (Appendix G). Enter your Human Subjects Assurance Number.

In the Protection of Human Subjects section of the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets (1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR Part 46), and (2) the requirements of NIH policies on inclusion of women, minorities, and children. Research involving a clinical trial will fall under either Scenario E or F below.

See the [instructions for Scenario B](#).

Scenario C. Exempt Human Subjects Research

If **all** of the proposed research meets the criteria for one or more of the exemptions from the requirements in the DHHS regulations (46.101(b)), check the box marked “Yes” on the Proposal Cover Sheet (Appendix A). Indicate “Yes” on the Proposal Summary and Data Record and insert E-1, E-2, E-3, E-4, E-5, or E-6 as appropriate, in the field for Exemption Number (Appendix G). Leave IRB Approval Date field blank since a Human Subjects Assurance Number is not needed for exempt research. Check “N/A” in field for “example of informed consent” and “Clinical Protocol” as these are not required for exempt research.

In the section on Protection of Human Subjects in the Research Plan, provide a justification for the exemption(s) containing sufficient information about the involvement of the human subjects to allow a determination by peer reviewers and NIH staff that claimed exemption(s) is/are appropriate.

The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. When in doubt, consult with the Office for Human Research Protections (OHRP), Department of Health and Human Services by accessing their website <http://www.hhs.gov/ohrp/> for guidance and further information.

The [exemptions](#) appear in Part I, Section 3, Definitions.

See the [instructions for Scenario C](#).

Scenario D. Delayed-Onset Human Subjects Research

If human subjects research is anticipated within the period of the award but plans for involvement of human subjects cannot be described in the application as allowed by the DHHS regulations (45 CFR Part 46.118), check “Yes” to “This proposed project involves human subjects” on the Proposal Cover Sheet (Appendix A) and indicate “Yes” on the Proposal Summary and Data Record (Appendix G). In the section on Protection of Human Subjects in the Research Plan, you should either include an explanation of anticipated protections for human subjects or an explanation of why protections cannot be described.

Examples of delayed-onset of human subjects research include:

- Human subjects research is dependent upon the completion of animal or other studies; or
- Human subjects research protocols to be included will undergo an independent decision-making process (often defined by a FOA).

See [instructions for Scenario D](#).

Scenario E. Human Subjects Research Involving a Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct a [clinical trial](#) during the project period, check the boxes marked “Yes” on the Proposal Cover Sheet (Appendix A) to “This proposed project involves human subjects,” and “Clinical Trial?” Indicate “Yes” on the Proposal Summary and Data Record (Appendix G). In addition, complete the items regarding the Institution’s General Assurance, Institution’s Review Board, informed consent and clinical protocol.

In the section on Protection of Human Subjects in the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets:

- 1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR Part 46);
- 2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
- 3) the ClinicalTrials.gov requirements if applicable;
- 4) the requirements of NIH policies on inclusion of women, minorities, and children; and
- 5) the requirements of NIH policy on reporting race and ethnicity data for subjects in clinical research.

See [instructions for Scenario E](#).

Scenario F. Human Subjects Research Involving an NIH-Defined Phase III Clinical Trial

If research involving human subjects is anticipated to take place under the award, and you intend to conduct an [NIH-defined Phase III clinical trial](#) during the project period, check the boxes marked “Yes” to the following statement/questions on the Proposal Cover Sheet (Appendix A):

- This proposed project involves human subjects.
- Clinical Trial?
- Agency-Defined Phase III Clinical Trial?

Also indicate “Yes” on the Proposal Summary and Data Record (Appendix G) to the following question: Does this proposal involve human subjects research? In addition, complete the items regarding the Human Subjects Assurance Number, Institution’s Review Board, informed consent and Clinical Protocol.

In the section on Protection of Human Subjects in the Research Plan, you must provide sufficient information for reviewers to determine that the proposed research meets:

- 1) the requirements of the DHHS regulations to protect human subjects from research risks (45 CFR Part 46);
- 2) NIH policy requirements for Data and Safety Monitoring for Clinical Trials;
- 3) the ClinicalTrials.gov requirements if applicable;
- 4) the requirements of NIH policies on inclusion of women, minorities, and children;
- 5) additional Requirements for NIH-defined Phase III clinical trials; and
- 6) the requirements of NIH policy on reporting race and ethnicity data for subjects in clinical research.

See [instructions for Scenario F](#).

3. INSTRUCTIONS FOR PREPARING THE SECTION ON PROTECTION OF HUMAN SUBJECTS

Scenario A. No Human Subjects Research Proposed

Criteria

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

Instructions and Required Information

In the proposal narrative, create a heading labeled “Protection of Human Subjects” and include the following statement below the heading: “No Human Subjects Research is proposed in this proposal.”

If proposed studies using coded human data or biospecimens do not involve human subjects as described in the OHRP Guidance on Research Involving Coded Private Information or Biological Specimens (<http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm>), provide an explanation of why the proposed studies do not constitute research involving human subjects.

The explanation could include: a description of the source of the data/biospecimens; the role(s) of providers of the data/biospecimens in the proposed research; and the manner by which the privacy of research participants and confidentiality of data will be ensured.

Research that does not involve intervention or interaction with living individuals, or identifiable private information, is not human subjects research (see Part I, Section 3, [Definitions](#)).

Research that only proposes the use of cadaver specimens is not human subjects research because human subjects are defined as “living individuals.” The use of cadaver specimens is not regulated by 45 CFR Part 46, but may be governed by other Federal, State or local laws.

Scenario B. Non-Exempt Human Subjects Research

Criteria

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

Instructions and Required Information

Although no specific page limitation applies to this section of the proposal, be succinct.

In the proposal narrative, create a section entitled "Protection of Human Subjects" and create a subheading for each of the following items.

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

Protections for Human Subjects - [Section 4.1 - 4.1.4](#)

[HumanSubjects.doc - Human Subjects Research RisksToSub](#)Inclusion of Women and Minorities - [Section 4.2](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

If the research involves collaborating sites, provide the information identified above for each participating site.

Scenario C: Human Subjects Research Claiming Exemption 1, 2, 3, 4, 5, or 6

Criteria

Human Subjects Research	Yes
Exemption Claimed	1, 2, 3, 4, 5, or 6
Clinical Trial	Yes or No
NIH-Defined Phase III Clinical Trial	No

Instructions and Required Information

Although no specific page limitation applies to this section of the proposal, be succinct. The [exemptions](#) appear in Part I, Section 3, [Definitions](#).

Although the research may be exempt from the DHHS regulatory requirements, it is still research involving human subjects and the application must follow the instructions that are identified for each of the following topics and provide the information that is requested.

In the proposal narrative, create a heading entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research falls under Exemption(s)”

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

Justification for Claimed Exemption(s):

In this section, identify which exemption(s) (1, 2, 3, 4*, 5, or 6) you are claiming. Justify why the research meets the criteria for the exemption(s) that you have claimed.

If the research will include a clinical trial, even if exempt, include a Data and Safety Monitoring Plan – [Section 4.1.5](#), and address the ClinicalTrials.gov requirements if applicable – [Section 4.1.6](#).

Inclusion of Women and Minorities - [Section 4.2](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

*NOTE: If all the proposed research meets the criteria for Exemption 4, then the requirements for inclusion of women and minorities, targeted/planned enrollment table, and inclusion of children, do not need to be addressed.

Scenario D: Delayed-Onset Human Subjects Research

Criteria

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

Instructions and Required Information

In rare situations, proposals are submitted with the knowledge that human subjects will be involved during the period of support, but plans are so indefinite that it is not possible to describe the involvement of human subjects in the proposal. The kinds of activities that lack definite plans are often institutional awards where the selection of specific projects is the institution's responsibility, research training grants, and projects in which the involvement of human subjects depends upon completion of instruments, animal studies, or purification of compounds.

If the involvement of human subjects is indefinite, create a heading entitled “Protection of Human Subjects” and provide a detailed explanation why it is not possible to develop definite plans at this time. The explanation should be specific and directly related to the Specific Aims in the proposal. If the involvement of human subjects depends upon information that is not presently available (e.g., completion of instruments, animal studies, purification of compounds), be explicit about the information and the factors affecting the availability of the information. Describe the information that will be necessary in order to develop definite plans for the involvement of human subjects, why that information is not currently available, and when the information is expected to become available during the course of the project.

If an award is made, prior to the involvement of human subjects the grantee must submit to the NIH awarding office for prior approval either (1) detailed information as required in the Research Plan, Protection of Human

Subjects (addressing risks to the subjects, adequacy of protection against risks, potential benefits of the proposed research, importance of the knowledge to be gained, and data and safety monitoring plan if applicable) and certification of IRB approval, OR (2) if all of the research meets the criteria for one or more exemptions, identification of which exemption(s) is/are applicable to the research, and a justification for the exemption with sufficient information about the involvement of human subjects to allow a determination that the claimed exemption is appropriate. If the research is not exempt, the request for prior approval must also address the inclusion of women and minorities, the inclusion of children, and provide completed targeted/planned enrollment tables as required in the Research Plan.

Under no circumstance may human subjects be involved in non-exempt research until approval is granted by the awarding entity, and certification of IRB approval has been accepted by the agency.

In the proposal narrative, create a section entitled Protection of Human Subjects and a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and EITHER provide as much of the information that is requested as possible; OR describe why it is not possible to provide the information due to delayed-onset of human subjects research:

Protection of Human Subjects - [Section 4.1 - 4.1.4](#)

If the research will include a clinical trial, include a Data and Safety Monitoring Plan - [Section 4.1.5](#), and address the ClinicalTrials.gov requirements if applicable – [Section 4.1.6](#).

Inclusion of Women and Minorities - [Section 4.2](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

Scenario E: Clinical Trial

Criteria

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

Instructions and Required Information

In the proposal narrative, create a section entitled “Protection of Human Subjects” and include the following statement below the heading: “This Human Subjects Research meets the definition of a clinical trial.” (See definition of “[clinical trial](#)” in Part I.) Create a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protection of Human Subjects - [Section 4.1 - 4.1.6](#)

Inclusion of Women and Minorities - [Section 4.2](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

If the research involves collaborating sites, provide the information identified above for each participating site.

Scenario F: NIH Defined Phase III Clinical Trial

Criteria

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

Instructions and Required Information

In the proposal narrative, create a section entitled "Protection of Human Subjects" and include the following statement below the heading: "This Human Subjects Research involves an NIH-Defined Phase III Clinical Trial." (See "[NIH defined Phase III Clinical Trial](#)" in [Definitions](#).)

Create a subheading for each of the following items. Follow the instructions that are identified for each of the following topics and provide the information that is requested:

Protection of Human Subjects - [Section 4.1 - 4.1.6](#)

Inclusion of Women and Minorities - [Section 4.2](#)

Additional Instructions and Requirements when NIH-Defined Phase III Clinical Trials are Proposed - [Section 4.2.1](#)

Targeted/Planned Enrollment Table - [Section 4.3](#)

Inclusion of Children - [Section 4.4](#)

If the research involves collaborating sites, provide the information identified above for each participating site.

4. INSTRUCTIONS PERTAINING TO NON-EXEMPT HUMAN SUBJECTS RESEARCH

In your proposal narrative, **create a section entitled "Human Subjects."** Although no specific page limitation applies to this section of the proposal, be succinct. Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the protection of human subjects. DHHS regulations and policies governing human subjects research are described and referenced in Section 5 below. **Use subheadings** to address the issues listed under items 4.1-4.4 below. If your research includes a clinical trial, include a subheading "Data and Safety Monitoring Plan" and follow the instructions in 4.2 below. If your research includes an NIH-Defined Phase III Clinical Trial, follow the additional instructions in 4.2.1 below.

4.1 PROTECTION OF HUMAN SUBJECTS

4.1.1 Risks to Human Subjects

a. *Human Subjects Involvement and Characteristics*

- Describe the proposed involvement of human subjects in the work outlined in the Human Subjects Research 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 and collaborating investigators in performing the proposed research.

b. Sources of Materials

- Describe the research material obtained from living individuals in the form of specimens, records, or data.
- Describe any data that will be collected from human subjects for the project(s) described in the application.
- Indicate who will have access to individually identifiable private information about human subjects.
- Provide information about how the specimens, records, or data are collected and whether material or data will be collected specifically for the proposed research project.

c. Potential Risks

- Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the subjects.
- Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

4.1.2 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. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.

b. Protections Against Risk

- Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
- Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:
 - Additional Protections for Pregnant Women, Human Fetuses and Neonates:
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartb>
 - Additional Protections for Prisoners:
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc>
OHRP Subpart C Guidance: <http://www.hhs.gov/ohrp/policy/index.html#prisoners>
 - Additional Protections for Children:
<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd>
OHRP Subpart D Guidance: <http://www.hhs.gov/ohrp/children/>

- 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 general description of the plan for data and safety monitoring of the research and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

4.1.3 Potential Benefits of the Proposed Research to Human Subjects and Others

- Discuss the potential benefits of the research to research participants and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

4.1.4 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 biologics) 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 FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

4.1.5 Data and Safety Monitoring Plan

The NIH Data and Safety Monitoring Plan Policy is described and referenced in [Section 5.3](#).

- If the research includes a clinical trial, create a heading entitled "Data and Safety Monitoring Plan."
- 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:
 - a. PD/PI (required)
 - b. Institutional Review Board (IRB) (required)
 - c. Independent individual/safety officer
 - d. Designated medical monitor
 - e. Internal Committee or Board with explicit guidelines
 - f. Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site 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.

- 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>). For additional guidance on creating this Plan, see the above reference.

4.1.6 ClinicalTrials.gov Requirements

Public Law 110-85 mandates registration and results reporting of "applicable clinical trials" in ClinicalTrials.gov. Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Review the statutory definition of applicable clinical trial to identify if registration is required to comply with the law (See [PL 110-85](#), Section 801(a), adding new 42 U.S.C. 282(j)(1)(A) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf)).

NIH encourages registration of ALL trials whether required under the law or not.

Registration is accomplished at the ClinicalTrials.gov Protocol Registration System Information Website (<http://prsinfo.clinicaltrials.gov/>). A unique identifier called an NCT number will be generated during the registration process.

For new and renewal (competing) applications that include ongoing clinical trials which require registration and results reporting, provide the NCT number/s, Brief Title/s (as defined by ClinicalTrials.gov, see <http://prsinfo.clinicaltrials.gov/>), and the identity of the responsible party (or parties) in the human subjects section of the Research Plan under a section heading entitled ClinicalTrials.gov. The entity responsible for registering is the "responsible party." The statute defines the responsible party as:

(1) the sponsor of the clinical trial (as defined in 21 C.F.R. 50.3) (http://a257.g.akamaitech.net/7/257/2422/14mar20010800/edocket.access.gpo.gov/cfr_2003/aprqrtr/pdf/21cfr50.3.pdf), or

(2) the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (provided that "the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements" for submitting information under the law) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).

If a new applicable trial is proposed, under the heading ClinicalTrials.gov include a statement that the application includes a trial which requires registration in ClinicalTrials.gov. The signature on the application of the Authorized Organizational Representative assures compliance for the registration of any such trial.

4.2 INCLUSION OF WOMEN AND MINORITIES

Create a section heading entitled "Inclusion of Women and Minorities" and place it immediately following the "Protection of Human Subjects" section. Although no specific page limitation applies to this section of the proposal, be succinct. The NIH Policy on the Inclusion of Women and Minorities in Clinical Research is described and referenced in [Section 5.6](#).

Scientific Review Groups will assess each proposal as being acceptable or unacceptable with regard to the protection of human subjects.

In this section of the Research Plan, 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 in 4.3.) If using existing specimens and/or data without 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, describe the women and minority composition of the population base from whom the specimens and/or data will be obtained. Include the Targeted/Planned Enrollment Table in this section.

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; or
 - 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; or
 - 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; or
 - 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 research.

4.2.1 Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If the proposed research includes an [NIH-Defined Phase III Clinical Trial](#), the section on Inclusion of Women and Minorities also must address whether clinically important sex/gender and/or race/ethnicity differences are expected from the intervention effect. The discussion may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies. The 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:

- 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.

4.3 INSTRUCTIONS FOR COMPLETING THE TARGETED/PLANNED ENROLLMENT TABLES FOR REPORTING RACE AND ETHNICITY DATA FOR SUBJECTS IN CLINICAL RESEARCH

The NIH Policy on Reporting Race and Ethnicity Data for Subjects in Clinical Research is described and referenced in [Section 5.8](#).

A. New Proposals

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 Inclusion Enrollment Report (http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc) for reporting summary data on participants to NIH includes two categories of ethnicity and five categories of race and is based on the Office of Management and Budget (OMB) reporting standards for data on race and ethnicity. Investigators should review the instructions and Frequently Asked Questions about using the Enrollment Table format at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>.

When reporting these data in the aggregate, investigators should report: (a) the number of research participants in each ethnic category; (b) the number of research participants who selected only one category for each of the five racial categories; (c) the total number of research participants who selected multiple racial categories reported as the "number selecting more than one race," and (d) the number of research participants in each racial category who are Hispanic or Latino. Investigators may provide the detailed distributions, including all possible combinations, of multiple responses to the racial designations as additional information. However, more detailed data should be compiled in a way that they can be reported using the required categories.

Instructions for Completing Targeted/Planned Enrollment Table

(http://grants.nih.gov/grants/funding/424/SF424R-R_enrollment.doc)

Provide the study title.

The “Total Planned Enrollment” means the number of subjects that are expected to be enrolled in the study, consistent with the definition in ClinicalTrials.gov.

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 an ethnic, 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.

Submitting Applications or Proposals Using Existing Data in Clinical Research with No Plans for Collecting New/Additional Data:

Investigators are instructed to provide plans for the total number of subjects proposed for the study and to provide the distribution by ethnic/racial categories and sex/gender using the Targeted/Planned Enrollment Table. Under these circumstances, investigators are not required to re-contact subjects solely to comply with the newly revised categories.

If Data Collection is Ongoing, Such that New Human Subjects Will be Enrolled and/or Additional Data Will be Collected from Human Subjects:

Investigators should report ethnicity/race and sex/gender sample composition using the Inclusion Enrollment Report.

If Data Collection is Complete, Such that No New/Additional Subject Contact is Planned:

Investigators should use the Inclusion Enrollment Report.

Research Conducted at Foreign Sites:

If proposed studies involve a foreign site, investigators are encouraged to design culturally sensitive and appropriate data collection instruments that allow research participants to self-identify their racial and ethnic affiliation. However, these items should be designed in a way that they can be aggregated into the OMB-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 that describe research in foreign sites, investigators should asterisk and footnote the table indicating that data includes research participants in foreign sites. If the aggregated data only includes participants in foreign research sites, the investigator should provide information in one table with an asterisk and footnote. However, if the study includes both domestic and foreign sites, the investigator should complete two separate tables – one for domestic and another for foreign participants.

B. Progress Reports

The Inclusion Enrollment Report (http://grants.nih.gov/grants/funding/424/SF424R-R_enrollmentreport.doc) must be used for reporting accrual data to the NIH. In annual progress reports, investigators conducting clinical research are required to provide the cumulative total enrollment of subjects to-date, showing the distribution by ethnic/racial categories and sex/gender on the Inclusion Enrollment Report, and update the Targeted/Planned Enrollment Table as needed.

4.4 INCLUSION OF CHILDREN

The NIH Policy on Inclusion of Children is referenced and described in [Section 5.7](#). Instructions for this item under the “Human Subjects” heading of the Research Plan are as follows:

- Create a section entitled “Inclusion of Children” and place it immediately following the Targeted/Planned Enrollment Table.
- 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, present an acceptable justification for the exclusion (see below).
- 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 as being acceptable or unacceptable 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](#) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd>)) apply and must be addressed under the Protections Against Risk subheading (4.1.2.b).

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 clinical research 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 needlessly 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 condition is relatively rare 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 planned, to allow inclusion of children 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 are 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 can be justified by the investigator and found acceptable to the review group and the Institute Director.

5. HUMAN SUBJECTS RESEARCH POLICY

Human Subjects Research Policy includes DHHS regulations for the protection of human subjects and the following NIH policies related to human subjects research.

5.1 PROTECTION OF HUMAN SUBJECTS

The Department of Health and Human Services (DHHS) regulations for the protection of human subjects provide a systematic means, based on established, internationally recognized ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the DHHS. The regulations stipulate that the awardee organization, whether domestic or foreign, bears responsibility for safeguarding the rights and welfare of human subjects in DHHS-supported research activities. The regulations require that offeror organizations proposing to involve human subjects in nonexempt research hold a Federal-wide Assurance (FWA) with the Office for Human Research Protections (OHRP), and establish appropriate policies and procedures for the protection of human subjects. These regulations, [45 CFR Part 46](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>), Protection of Human Subjects, are available from OHRP, Department of Health and Human Services, The Tower Building, 1101 Wootton Parkway, Suite 200, Rockville, MD; telephone: 1-866-447-4777 (toll-free) or (240) 453-6900; email: ohrp@osophs.dhhs.gov.

Nonexempt research involving human subjects may only be conducted under a DHHS award if the organization is operating in accord with an approved FWA and provides verification that an Institutional Review Board (IRB) that is registered under the specific FWA has reviewed and approved the proposed activity in accordance with the DHHS regulations. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the DHHS regulations. Foreign offeror organizations must also comply with the provisions of the regulations unless a determination of equivalent protections is made in accord with 45 CFR 46.101(h).

Under DHHS regulations to protect human subjects, certain research areas are [exempt](#). However, if an offeror makes inappropriate designations of the noninvolvement of human subjects or of exempt categories of research, this may result in delays in the review of an application or the return of the application without review. The PHS will make a final determination as to whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the Research Plan. With the exception of research projects that meet the criteria for Exemption 4, studies that are exempt from the human subjects regulatory requirements must still address the inclusion of women, minorities and children in the study design.

Regulations of the Food and Drug Administration (21 CFR 50, 21 CFR 56) generally apply to biomedical research involving an unapproved drug, device or biologic and may apply to certain studies of approved products. Additional information on FDA regulations is available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>. If work falls under FDA's regulatory requirements, the grantee must follow both DHHS and FDA human subject protection regulations.

The *National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* apply to all projects (NIH-funded and non NIH-funded) involving recombinant DNA molecules that are conducted at or sponsored by an institution that receives NIH support for recombinant DNA research. As defined by the *NIH Guidelines*, recombinant DNA molecules are either: (1) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell; or (2) DNA molecules that result from the replication of those described in (1). The *NIH Guidelines* set forth principles and standards for safe and ethical conduct of recombinant DNA research and apply to both basic and clinical research studies. The *NIH Guidelines* should be carefully reviewed and implemented to ensure that proper biosafety and containment practices are employed for all projects involving recombinant DNA research, including review by an Institutional Biosafety Committee that meets the requirements of the *NIH Guidelines*. Further, the *NIH Guidelines* include special review and reporting requirements for the conduct of human gene transfer studies (under Appendix M). Failure to comply with the *NIH Guidelines* may result in suspension, limitation, or termination of NIH funds for recombinant DNA research at the organization or a requirement for NIH prior approval of any or all recombinant DNA projects at the organization. A copy of the *NIH Guidelines* is posted at the following URL: http://oba.od.nih.gov/rdna/nih_guidelines_oba.html and may be obtained from the NIH Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 750, Bethesda, MD 20892, 301-496-9838.

Federal requirements to protect human subjects apply to most research on human specimens (such as cells, blood, and urine), residual diagnostic specimens, and medical information. Research involving the collection or study of existing data, documents, records, pathological specimens, diagnostic specimens, or tissues that are individually identifiable is considered "research involving human subjects." The NIH Office of Extramural Research Human Subjects website contains additional information and Frequently Asked Questions to help investigators understand how these federal requirements apply to their research. See <http://grants.nih.gov/grants/policy/hs/index.htm>.

The DHHS regulations require the NIH to evaluate all proposals involving human subjects (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.120>). This independent evaluation is conducted at the NIH through the peer review system and NIH staff review, and, as required, will take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. On the basis of this evaluation, the NIH may approve or disapprove the proposal, or enter into negotiations to develop an approvable one.

5.2 VULNERABLE POPULATIONS

Investigators who conduct research involving pregnant women, human fetuses and neonates, prisoners, or children, must follow the provisions of the regulations in Subparts B, C, and D of [45 CFR Part 46](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>), respectively. The subparts describe the additional protections required for conducting research involving these populations. Relevant information may be obtained at the OHRP website (<http://www.hhs.gov/ohrp/policy/index.html>).

REMINDER: DHHS regulations at [45 CFR Part 46, Subpart C](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc>) describe requirements for additional protections for research involving prisoners as subjects or individuals who become prisoners after the research has started. Refer to: <http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.htm> for complete instructions.

[Exemptions 1-6](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc) do **not** apply to research involving prisoners or subjects who become prisoners (see [Subpart C](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartc>)). Although Exemptions 1 and 3-6 apply to research involving children (see [Subpart D](http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartd>)).

subpartd)), [Exemption 2](#) can only be used for research involving educational testing or observations of public behavior when the investigator(s) do not participate in the activities being observed.

5.3 DATA AND SAFETY MONITORING PLANS FOR CLINICAL TRIALS

For each proposed clinical trial, NIH requires a data and safety monitoring plan that describes oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. Prior to the accrual of human subjects, a detailed data and safety monitoring plan must be submitted to the offeror's IRB and to the funding entity for approval. Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other appropriate offices or agencies. This policy requirement is in addition to any monitoring requirements imposed by [45 CFR Part 46](#) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>). NIH policy specifically requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials.

5.4 IRB APPROVAL

NIH does not require certification of IRB approval of the proposed research prior to NIH peer review of a proposal. See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html>.

Following NIH peer review, the offeror organization will be notified of the need for review and approval of the proposed research by an IRB that is registered with OHRP. See <http://www.hhs.gov/ohrp/> to register an IRB. Certification of IRB approval must be sent to the Grants Management Office identified in the notice requesting documentation. Certification of IRB review and approval must include: the PHS SBIR proposal number, title of the project, name of the program director /principal investigator, date of IRB approval, and appropriate signatures. Grantees may also use the optional form "Protection of Human Subjects - Assurance Identification/IRB Certification/Declaration of Exemption (Common Rule)" (OMB Form No. 0990-0263 <http://www.hhs.gov/ohrp/humansubjects/assurance/OF310.rtf>) to meet this requirement.

The OHRP has determined that an institution is automatically considered to be engaged in human subjects research when it receives an NIH award to support nonexempt human subjects research. See <http://www.hhs.gov/ohrp/humansubjects/assurance/engage.htm>. All institutions engaged in human subjects research must obtain a Federal Wide Assurance (FWA) from OHRP. Instructions for applying for a Federal Wide Assurance (FWA) are available from the OHRP website at http://www.hhs.gov/ohrp/assurances/assurances_index.html.

Any modifications to the Research Plan in the proposal, required by either NIH or by the IRB, must be submitted with follow-up certification of IRB approval to the NIH before the competing award is made. It is the responsibility of the PD/PI and the offeror organization to submit the follow-up documentation.

If more than a year will have elapsed between the initial IRB review date and the anticipated award date, the awarding unit staff shall require re-review by the IRB prior to award.

5.5 REQUIRED EDUCATION IN THE PROTECTION OF HUMAN RESEARCH PARTICIPANTS

NIH requires education on the protection of human research participants for all individuals identified in PHS applications as Senior/key Personnel who will be involved in the design or conduct of human subjects research, before funds are awarded for applications or contract proposals involving human subjects. For information relating to this requirement, see the following notices <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html> and <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html>, and Frequently Asked Questions at: http://grants.nih.gov/grants/policy/hs_educ_faq.htm. Prior to award, offerors will be required to provide a description of education completed in the protection of human subjects for all Senior/key Personnel involved in the design or conduct of human subjects research. Although NIH does not endorse specific programs, there are curricula available that can provide guidance or that can be modified to provide training in this area. See <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp> 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>.

5.6 NIH POLICY ON THE INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

NIH policy requires that women and members of minority groups and their subpopulations must be included in all NIH-supported biomedical and behavioral research projects involving [clinical research](#) unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant IC Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances may be made by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. All NIH-supported biomedical and behavioral research involving human subjects is defined as clinical research. This policy applies to research subjects of all ages.

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. The Research Plan should 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.

5.7 NIH POLICY ON INCLUSION OF CHILDREN

Research involving children (see definition of “[child](#)”) must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. Investigators should obtain full copies of the Policy and Guidelines from NIH staff, or from <http://grants.nih.gov/grants/funding/children/children.htm>.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH unless there are clear and compelling reasons not to include them. Therefore, proposals for clinical research must include a description of plans for including children. If children will be excluded from the research, the proposal must present an acceptable justification for the exclusion.

The involvement of children as subjects in research must be in compliance with all applicable subparts of [45 CFR Part 46](#) (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm>) as well as with other pertinent Federal laws and regulations.

IRBs have special review requirements to protect the well-being of children who participate in research. These requirements relate to risk, benefit, parental/guardian consent, and assent by children, and to research involving children who are wards of the state or of another institution. The local IRB approves research that satisfies the conditions set forth in the regulations.

5.8 NIH POLICY ON REPORTING RACE AND ETHNICITY DATA: SUBJECTS IN CLINICAL RESEARCH

The Office of Management and Budget (OMB) (<http://www.whitehouse.gov/omb/fedreg/ombdir15.html>) defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies (including NIH). The standards were revised in 1997 and include two ethnic categories (Hispanic or Latino and Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White). Reports of data on race and ethnicity shall use these categories. The categories in this classification are social-political constructs and should not be interpreted as being anthropological in nature. NIH is required to use these definitions to allow comparisons to other federal databases, especially the census and national health databases. The following definitions apply to the minimum standards for the ethnic and racial categories.

Ethnic Categories:

Hispanic or Latino: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, “Spanish origin,” can be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories:

American Indian or Alaska Native: A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

Asian: A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American: A person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or Other Pacific Islander: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

Ethnic/Racial Subpopulations: In addition to OMB ethnic and racial categories, NIH uses the following definition for ethnic/racial subpopulations:

Subpopulations: Each ethnic/racial group contains subpopulations that are delimited by geographic origins, national origins, and/or cultural differences. It is recognized that there are different ways of defining and reporting racial and ethnic subpopulation data. The subpopulation to which an individual is assigned depends on self-reporting of specific origins and/or cultural heritage. Attention to subpopulations also applies to individuals who self identify with more than one race. These ethnic/racial combinations may have biomedical, behavioral, and/or social-cultural implications related to the scientific question under study.

Guidance on Collecting Race and Ethnicity Data from Human Subjects

When an investigator is planning to collect data on ethnicity and race, the categories identified above should be used. The collection of greater detail is encouraged, for example on ethnic/racial subpopulations. However, any collection that uses more detail must be designed in a way that data can be aggregated into these minimally required categories. Use self-report or self-identification to collect this information by asking two separate questions – one on ethnicity and one on race. Collect ethnicity information first followed by the question on race and provide subjects with the option to select more than one racial category. An example of a format for collecting information from study subjects in the US that meets the OMB requirements can be found in the Ethnic Origin and Race section of the Personal Data Form Page <http://grants.nih.gov/grants/funding/phs398/phs398.html> in the PHS 398.

See NIH Policy on [Inclusion of Women and Minorities](http://grants.nih.gov/grants/funding/women_min/women_min.htm) and http://grants.nih.gov/grants/funding/women_min/women_min.htm.

5.9 RESEARCH ON TRANSPLANTATION OF HUMAN FETAL TISSUE

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if research on the transplantation of human fetal tissue is conducted, the offeror organization will make available, for audit by the Secretary, DHHS, the physician statements and informed consents required by section 498A (b)(2) and (c) of the Public Health Service Act, 42 U.S.C. 289g (b)(2) and (c), or ensure DHHS access to those records, if maintained by an entity other than the offeror organization.

5.10 RESEARCH USING HUMAN EMBRYONIC STEM CELLS

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if research using human embryonic stem cells is proposed, the offeror organization 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>). See <http://stemcells.nih.gov/index.asp> for additional information on stem cells, and <http://stemcells.nih.gov/policy/guidelines.asp> for Federal policy statements and guidelines on federally funded stem cell research.

5.11 CLINICALTRIALS.GOV REQUIREMENTS

In signing the proposal Cover Page, the Authorized Organizational Representative/Corporate Official of the offeror organization certifies that if the research is an applicable clinical trial under Public Law 110-85, the offeror organization will be in compliance with the registration and reporting requirements of Public Law 110-85, if applicable (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). The law, enacted 09/27/2007, amends the Public Health Service Act to expand the scope of clinical trials that must be registered in ClinicalTrials.gov. It also increases the number of registration fields that must be submitted, requires certain results information to be included, and sets penalties for noncompliance.

The trials that must be registered are called "applicable clinical trials." Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. NIH encourages registration of ALL trials whether required under the law or not.

For additional information see NIH Guide Notices at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html> and <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-023.html>.