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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

PROPOSAL RECEIPT DATE

NOVEMBER 3, 2008

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

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

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

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

U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

SOLICITATION OF THE 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-08-050.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, 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) and in the NIH Guide for Grants and Contracts as it becomes available. Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers."

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 Mental Health (NIMH)

Centers for Disease Control and Prevention (CDC)

- National Center on Birth Defects and Developmental Disabilities (NCBDDD)

- National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)
- Immunization Safety Office (ISO)

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 applicant 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. Denise Burton
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: 404-639-4641
Email: DBurton2@cdc.gov

Mr. Jerald O'Hara
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: 404-639-4796
Email: JOHara@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, *"How does the SBA determine 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) 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 trials, or (d) development of new technologies.

(2) Epidemiologic and Behavioral Studies.

(3) Outcomes Research and Health Services Research.

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

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

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

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

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

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

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial*. An NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or control intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

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 applicant'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.

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), 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 humans 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, 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.)

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 offeror organization to have the appropriate level of authority and responsibility to direct the project or program to be supported by the award.

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 that includes designs, protocols, questionnaires, software, devices, etc.

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.
- A systematic study directed specifically toward applying new knowledge to meet a recognized need.

- 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.

Typically, these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level may be considered 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 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 small business concern is one that, at the time of award of Phase I and Phase II, meets *all* of the following criteria:

1. Is independently owned and operated, is not dominant in the field of operation in which it is proposing, has its principal place of business located in the United States, and is organized for profit.
2. Is at least 51% owned and controlled by either: (a) one or more natural persons (individuals who are citizens of, or permanent resident aliens in, the United States); or (b) another for-profit business concern that is itself at least 51% owned and controlled by one or more natural persons (individuals who are citizens of, or permanent resident aliens in, the United States)(See 13 CFR 121.105 (defining "business concern")).
3. Has, including its affiliates, *a number of employees not exceeding 500*, and meets the other regulatory requirements found in 13 CFR Part 121. Business concerns, other than investment companies licensed, or state development companies qualifying under the Small Business Investment Act of 1958, 15 U.S.C. 661, et seq., are affiliates of one another when either directly or indirectly, (a) one concern controls or has the power to control the other; or (b) a third-party/parties controls or has the power to control both.

Control can be exercised through common ownership, common management, and contractual relationships. The term "affiliates" is defined in greater detail in 13 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 must not exceed 25 single-sided, single-spaced pages, including the cover sheet, abstract, cost breakdown, and all enclosures or attachments. Pages should be of standard size (8 l/2” X 11”), and you should use an Arial, Helvetica, Palatino Linotype or Georgia typeface and a font size of 11 points or larger. Excluded from the 25-pages are cover letters, Human Subjects Research and Vertebrate Animal information, letters of commitment from collaborators and consultants and letters to determine eligibility, and, if applicable, the list of prior SBIR Phase II awards (see Section 4.2). Unless specifically solicited by a Contracting Officer, no other appendices or attachments may be submitted, and if submitted, they will not be considered in the evaluation of scientific and technical merit. Proposals in excess of the page limitation shall not be considered for review or award.

4.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

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

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 | 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. A minimum of two-thirds of the research and/or analytical work in Phase I, as measured by direct and indirect costs, must be carried out by the proposing firm, unless otherwise approved in writing by the contracting officer.

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 1-10 set forth below.

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

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, but is excluded from the 25-page limitation.

4.2.6 Proposed Cost Breakdown

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

- Under "Government Solicitation No.," enter "PHS 2009-1."
- 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.
- *Normally, at least two-thirds or 67% of the entire research or analytical effort must be carried out by the offeror*, i.e., subcontracts for portions of the scientific/technical effort and consultant fees normally may not exceed 33% of the total cost breakdown.

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, but is excluded from the 25-page limitation.

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), (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, but is excluded from the 25-page limitation.

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

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

1. Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
2. Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
3. Provide information on the veterinary care of the animals involved.
4. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
5. Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

Guidance and Additional Instructions

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal (http://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 sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

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

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

4.3 LIMITATIONS ON USE OF APPROPRIATED FUNDS

The Department of Health and Human Services Appropriation Act for Fiscal Year 2008 (Public Law 110-161), limits the use of appropriated funds on NIH grant, cooperative agreement, and contract awards for Fiscal Year 2008, as specified below. It is anticipated that these statutory provisions will continue in subsequent fiscal years.

Salary Rate Limitation

Public Law 110-161 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. 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, 2008, the Executive Level I salary is $191,300 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 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 | 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 VII) 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 generally should not exceed a total of 150 single-spaced pages, including all enclosures and attachments. Pages should be of standard size (8 1/2" x 11") and you should use an Arial, Helvetica, Palatino Linotype or Georgia typeface and a font size of 11 points or larger. Excluded from the page limitation are cover letters and letters from collaborators and consultants.

6.2 TECHNICAL PROPOSAL FORMAT AND CONTENT REQUIREMENTS

1. **Phase II Technical Proposal Cover Sheet** - Use Appendix D (MS Word | PDF).
2. **Table of Contents**
3. **Abstract of the Research Plan** - Use Appendix B (MS Word | PDF). State the broad, long-term objectives and specific aims. Do not include any proprietary information. Briefly and concisely describe the research design and methods for achieving these goals.
4. **Anticipated Results of Phase I Effort** - Briefly discuss and summarize the objectives of your Phase I effort, the research activities to be carried out, and the anticipated results.
5. **Research Plan**
   a. *Detailed Approach and Methodology* - provide an explicit 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 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, and NIH Guide NOT-OD-04-042.

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, 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 | 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 | 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 | PDF).

2. **Proposed Cost Breakdown** – **For Phase I**, use Appendix C (MS Word | PDF). Explain the basis for all costs and submit documentation to support all proposed costs. Prepare a separate Appendix C for each year of the contract and a summary of the entire project. **For Phase II Fast-Track**, use Appendix C. Delete the fringe benefit costs, indirect costs and fee. Prepare a separate Appendix C for each year of the contract and a summary of the entire project.

3. **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: a. Whether the outcome of the proposed research activity will likely lead to a marketable product or process. b. 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	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)	52-70	Scientific and Technical Merit Review: May 2009 Anticipated Award Date: July 2009
	National Center for Research Resources (NCRR)	6	Scientific and Technical Merit Review: February 2009 Anticipated Award Date: June 2009
	National Heart, Lung, and Blood Institute (NHLBI)	26	Scientific and Technical Merit Review: February-April 2009 Anticipated Award Date: July-Sept 2009
	National Institute on Alcohol Abuse and Alcoholism (NIAAA)	4-9	Scientific and Technical Merit Review: March 2009 Anticipated Award Date: June-Sept 2009
	National Institute of Allergy and Infectious Diseases (NIAID)	1-6	Scientific and Technical Merit Review: March 2009 Anticipated Award Date: June 2009
	National Institute on Drug Abuse (NIDA)	14-19	Scientific and Technical Merit Review: March 2009 Anticipated Award Date: August 2009
	National Institute of Mental Health (NIMH)	3	Scientific and Technical Merit Review: January 2009 Anticipated Award Date: May 2009
Centers for Disease Control and Prevention (CDC)	National Center on Birth Defects and Developmental Disabilities (NCBDDD)	4	Scientific and Technical Merit Review: February 2009 Anticipated Award Date: May 2009
	National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	7	Scientific and Technical Merit Review: February 2009 Anticipated Award Date: May 2009
	Immunization Safety Office (ISO)	9	Scientific and Technical Merit Review: February 2009 Anticipated Award Date: May 2009
	National Center for Immunization and Respiratory Diseases (NCIRD)	1	Scientific and Technical Merit Review: February 2009 Anticipated Award Date: May 2009

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 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, and NIH Guide NOT-OD-04-042.

(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, 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

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

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

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

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

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

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

Clauses That Apply to Contracts Exceeding $100,000

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

10. ***Examination of Records.*** The Comptroller General (or a duly authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
11. ***Default.*** The Government may terminate the contract for default if the contractor fails to perform the work described in the contract and such failure is not the result of excusable delays.
12. ***Contract Work Hours.*** The contractor may not require an employee to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (i.e., overtime pay).
13. ***Covenant Against Contingent Fees.*** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.
14. ***Patent Infringement.*** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.

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 3, 2008

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) 480-3338
E-mail: taylorjc@nhlbi.nih.gov

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

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

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

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 Affairs
National Heart, Lung, and Blood Institute
6701 Rockledge Drive
Room 7091
Bethesda, MD 20892-7924 *

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

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
NIDDK Office of Acquisitions

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)

Ms. Barbara Shadrick
Phone: (301) 496-7288
Fax: (301) 402-0972
Email: bs92y@nh.gov

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

Ms. Barbara Shadrick
Contracting Officer, MIDRCB-B
OA, DEA, NIAID
6007B Rockledge Dr., Room 3214
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. Craig Sager
Phone: (301) 443-6677
Fax: (301) 443-7595
Email: cs591t@nih.gov

Proposals to the NIDA must be mailed or delivered to:

Mr. Craig Sager
Contracting Officer
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 Mental Health (NIMH)

Ms. Suzanne Stinson
Phone: (301) 443-2696
Fax: (301) 443-0501
Email: sstinson@mail.nih.gov

Proposals mailed to the NIMH must be addressed to:

Ms. Stephanie Powell
Contract Specialist
Contracts Management Branch
National Institute of Mental Health
6001 Executive Boulevard

Room 8154, MSC 9661
Bethesda, MD 20892-9661*

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

10.2 CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Dr. Denise Burton
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: (404) 639-4641
Email: DBurton2@cdc.gov

Mr. Jerald O'Hara
Office of Public Health Research (OPHR)
Office of the Chief Science Officer
Phone: (404) 639-4796
Email: JOHara@cdc.gov

National Center on Birth Defects and Developmental Disabilities (NCBDDD)
National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)

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

Proposals to the NCBDDD or NCCDPHP must be mailed or delivered to:

Mrs. Theresa Routh-Murphy
Contracting Officer
CDC Procurement and Grants Office
2920 Brandywine Road, MS-E09
Atlanta, GA 30341

Immunization Safety Office (ISO)

Mr. Alan Sims
Phone: (770) 488-2896
Fax: (770) 488-2670
Email: auy0@cdc.gov

Proposals to ISO must be mailed or delivered to:

Mr. Alan Sims
Contract & Grants Management Specialist
Centers for Disease Control and Prevention (CDC) Acquisition and Assistance,
Branch B, Team IV
2920 Brandywine Road
Atlanta, GA 30341

National Center for Immunization and Respiratory Diseases (NCIRD)

Mr. Paul Rota

Phone: (404) 639-4181
Fax: (404) 639-4187
Email: prota@cdc.gov

Proposals to NCIRD must be mailed or delivered to:

Mr. Paul Rota
Centers for Disease Control and Prevention
Mailstop C-22
Building 18, Rm 5-131
1600 Clifton Rd
Atlanta, GA, USA 30333

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 novel funding mechanism entitled the SBIR Phase II Bridge Award. This notice is for informational purposes only and is not a call for Phase IIB Bridge Award proposals. This informational notice does not commit the government to the development of a Phase IIB Bridge Award mechanism for, or making such awards to, contract awardees.

Successful transition of SBIR research and technology development into the commercial marketplace is not easy and SBIR Phase II awardees often encounter challenges, including significant ones in regulatory affairs, 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 and in order to help address these difficult issues, it has developed the SBIR Phase IIB Bridge Award under the grants mechanism. The specific requirements for the Phase IIB Bridge Award are described in the full RFA announcement (http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-021.html).

The Phase IIB Bridge Award is meant 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 NCI anticipates expanding this program in the future to also include awardees funded under the SBIR contract mechanism.

It is anticipated that the Phase IIB 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). NIH SBIR Phase II contractors who satisfy the above requirements may be able to apply for a Phase IIB Bridge Award under a future Phase IIB Bridge Award grant/cooperative agreement funding opportunity announcement (FOA), if they meet the eligibility requirements detailed therein. Selection decisions for a Phase IIB 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:

229 Development of Molecular Pharmacodynamic Assays for Targeted Therapies

Number of anticipated awards: 4-6

(Fast-Track proposals will be accepted.)

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

The NCI requests that qualified small businesses submit proposals to develop pharmacodynamic assays for measuring a number of high-priority molecular targets. (For a list of the targets of interest to NCI, please see: http://sbir.cancer.gov/). The short term goal of this contract is to develop new rigorous, validated assays to measure molecular-level response to treatment in conjunction with preclinical development of new candidate therapeutic agents. These assays should measure 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 clinic in conjunction with a clinical trial are highly desirable. Ideally, these assays should also have a known correspondence to tumor modulation in animal efficacy models for 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.

Project goals: The long term goal of this contract is to provide a mechanism to develop a series of molecular pharmacodynamic assays to allow clinical target validation for a wide array of cancer therapeutics to determine earlier in the drug development process if the intended target is modulated 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 qualified or validated with human tumor/tissue samples. In addition, the goal is for companies to extend this work into developing research kits or diagnostic agents to stratify patients for clinical trial selection or to evaluate response to new therapeutic agents.

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. 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. Grant mechanisms thus far have not been an effective method of developing these assays, as they have little publication value. 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.

Two different tracks will be considered:

Track 1 will focus on the development of pharmacodynamic assays for measuring a number of high priority molecular targets. (For a list of the molecular targets of high priority to NCI, please see http://sbir.cancer.gov/.) 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.

For Track 2 small businesses are invited to submit proposals for the development of assays that measure molecular targets relevant to oncology therapeutics development which have been identified by the small business.

All proposals will be reviewed by NCI, and overall priority will be given to proposals to develop pharmacodynamic assays of high priority to NCI. Both tracks will have the following deliverables.

Phase I Activities and expected deliverables:

- Develop a research pharmacodynamic assay for the molecular target described.
- Characterize assay reproducibility, variability and accuracy.
- Deliver to NCI the SOP of the research pharmacodynamic assay for the molecular target described.

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.

249 System to Analyze and Support Biomarker Research and Development Strategies

Number of anticipated awards: 3-4

(Fast-Track proposals will be accepted.)

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

Summary:

Because of the rapid expansion of the worldwide biomarker research data in volume and breadth, there is a critical need for integrating all of these data within a knowledge management system that supports automated review and evaluation of current research and development efforts, particularly within the context of all cancer research and therapeutic and diagnostic product development. Such a system permits rapid identification and decision-making to allocate resources where they can most efficiently be used to enhance product development. Thus, the objective of this project is to expand the present methodology of biomarker research data analysis and strategic planning using a system that allows review and analysis of biomarker research and development projects as they relate to available worldwide data.

Project Goals:

The system would permit rapid identification and correlations of parameters of interest to the users' senior scientific staff, while simultaneously providing high-efficiency development pathways for program areas of interest. The system should incorporate parameters allowing evaluation of methods/assays, tissue and disease specificities, clinical applications, and regulatory and clinical development status. The system when fully developed may be applied over a broad range of technologies such as genomics and proteomics, imaging modalities, immunohistochemistry, and histopathology. Also, when fully developed, the system should be usable by the private sector (e.g., pharma, biotech, diagnostics industries, etc.) and the public sector (e.g., NCI programs such as Developmental Therapeutics, SPOREs, EDRN, Cancer Imaging, OBQI, PACCT, NTROI, and intramural and extramural investigator-initiated research). Potential offerors can propose projects to comprehensively include all relevant cancer-related biomarkers or specific subsets (e.g., toxicity biomarkers) under a relational database system.

An example application would be selection of a biomarker of a molecular target (e.g., a mutated tyrosine kinase), all published drugs/chemicals that interact with the target, all cancer target organs that have the biomarker and in what incidence, stage(s) of cancer progression where the biomarker is found, existing assays to measure the biomarker and their states of development and use, toxicity associated with biomarker modulation, etc.

System Requirements:

The core of the system will be a database cataloging and classifying the biomarker research projects with links to the original data sources. The remainder of the system will be tools (reports and algorithms) for summarizing, analyzing, and integrating the data with other sources. Multiple parameters describing the biomarkers cited shall be extracted into the database—e.g., biomarker name, clinical use, cancer target organ (clinical and nonclinical), specimen source, technology/assay methodology and/or assay target, biological process related to neoplastic progression (e.g., angiogenesis, proliferation, apoptosis), signaling pathway, drug or other intervention used in study (as appropriate), biomarker category (e.g., prognostic, predictive, risk, drug effect), disease stage, study population demographics, and phase of clinical study. The database shall be fully searchable (for individual records and categories of data) on all these parameters. The database shall be capable of supporting a large base of concurrent users via a user friendly, web-based user interface.

The database and other components of the system shall be built with open source code compatible with current industry and NCICB standards (e.g., J2EE, ANSI compliant SQL and Eclipse). Since NCI has invested substantially in developing informatics for cancer-specific uses, where possible, applications previously developed by NCICB should be leveraged. For example, applications developed for the Cancer Bioinformatics Grid (caBIG) should be considered, and the system should be integrated with caBIG applications, if appropriate. The system should be fully integrated with the NCI Enterprise Vocabulary System (EVS) and should use EVS terminology (and should comply with NCI's Cancer Data Standards Repository (caDSR) metadata standards, using NCI approved Common Data Elements where appropriate). However, the system developed should be compatible with other users' specific requirements.

System and user documentation shall be provided, quality control procedures shall be developed and applied to maintenance of the system, and quality assurance audits shall be carried out periodically. The project shall also include organization and administration of technical and scientific advisory groups involved in the design and implementation of the system.

Phase I activities and expected deliverables:

- Review a large, representative sample of relevant biomarker data and literature to develop an overall biomarker research program analysis and support model. Determine what, if any, algorithms exist to convert present research portfolio databases (electronic, manual, and hybrid) into an integrated automated knowledge management system that fulfills strategic research and business planning requirements for multiple users.
- Determine what, if any commercial software products exist that may serve as a platform for the proposed research program analysis and support tool. For example, the proposed product might be best developed as an add-on to an existing portfolio management package.
- Convene a focus group of senior scientists to solicit input on the scientific content and functionality required for the proposed product.
- Evaluate the availability of research data in the world-wide scientific literature with respect to the desired selection and measurement parameters. Identify problems with comparability and availability of research and administrative data over time and as collected by different systems.
- Develop a statement of functional requirements and user interface requirements for the product.
- Develop a prototype of the system using a representative sample of biomarkers.
- Include funds to present Phase I findings and system design.

Phase II activities and expected deliverables:

- Conduct a formal use study of the software with representative users to evaluate the prototype system developed in Phase I. Enhance and modify the prototype's functionality and user interface based on this feedback.
- Complete two iterations of the tracking program software, including technical documentation of the system and a training manual. Documentation of the system design, business procedures (SOPs), data sources, data extraction guidelines and evaluation criteria shall be prepared. An indexed/searchable User Guide describing data sources, data parameters, evaluation criteria, and system functionality (e.g., searching, report generation and linking to data sources) shall be prepared. SOPs shall include quality control procedures for data entry (e.g., data edit checks).
- Develop and implement a project plan for populating, updating, and maintaining the biomarkers database.
- Develop evaluation measures.
- Demonstrate the flexibility of design that would permit updating the software as new biomarkers, research modalities, treatments, data formats, or other parameters of interest are added.
- Documentation of the database design, business procedures (SOPs), data sources, data extraction guidelines and evaluation criteria shall be prepared on implementation of the database and shall be updated annually. An indexed/searchable User Guide describing data sources, data parameters, evaluation criteria, and database functionality (e.g., searching, report generation and linking to data sources) shall be prepared and loaded on the database website. SOPs shall include quality control procedures for data entry (e.g., data edit checks).

- Identify Phase II barriers to evaluating the impact of the software and resolutions to these barriers.
- In the first six months of the first year of the contract, provide the program and contract officers with a letter of commercial interest to either purchase or subscribe to the system once it is created.
- In the first six months of the second year of the contract, provide the program and contract officers with a letter of commercial commitment based on the successful outcome of the Phase II. It is anticipated that potential customers would be the NCI, NIH, and others in the public sector; and pharma, biotech, diagnostics industry, clinical laboratory industry, and others in the private sector.

255 Development of Anticancer Agents

Number of anticipated awards: 7

(Fast-Track proposals will be accepted.)

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

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.

Project goals:

The goal of the NCI SBIR program is to fund small businesses to develop commercially viable products that advance the research and development that ultimately 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 is to enable a small business to bring a fully developed cancer therapeutic agent to the clinic and eventually to the market.

Recipient companies will benefit in several ways:

- If appropriate, NCI will provide assistance to the small business in its development of an IND-directed development plan. Assistance might include assistance in study design and identification of necessary studies that would be appropriate for filing of an IND.
- Potential for further collaboration with NCI inventors/investigators.
- Potential for an early-stage clinical development partnership with NCI upon project completion.

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.
- Mutually agreed-upon 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.
- A comprehensive IP and development plan, outlining how the small business will develop and commercialize the subject therapeutic agent. If relevant, finalize clinical co-development agreement with NCI.

256 Innovative Methods for Manufacturing Safe, Effective Cancer Therapeutics

Number of anticipated awards: 2

(Fast-Track proposals will not be accepted.)

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

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. At the same time, 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. Many product failures are attributed to inadequate product design, characterization, scale-up and manufacturing. The potential for recent advances in basic and translational research cannot be fully realized without technological research targeting improved methods for production of safe and effective drugs.

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 pharmaceutical-grade reagents. Production failures increase both the cost and time required to bring a drug to market and often result in missed opportunities to evaluate promising new approaches. 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. Production lot failures that occur during manufacturing or product testing significantly increase production costs and time-to-market. Innovative, state-of-the art technologies are critical to cost-effective, regulatory compliant pharmaceutical manufacturing at the commercial-scale.

The use of standardized approaches to product characterization, specifications, testing strategies, manufacturing processes, stability evaluation and reference standards leads to more rapid, cost-effective drug development and a higher level of regulatory success. Achieving this level of standardization for cancer therapeutics requires specific, pragmatic scientific research directed at modernizing the product production process.

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 the quality of the final product. The purpose of this initiative is to facilitate the development of innovative methods that improve and modernize the medical product manufacturing process for biologic drugs for cancer treatment. The focus of this research includes:

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

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

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

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

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

- Scientific data demonstrating the feasibility of the manufacturing improvement or assay.
- Scientific data demonstrating the proposed scalability of the manufacturing improvement.
- Beta-testing of the manufacturing improvement.
- Qualification of the assay including, but not limited to: identification of reference standards, system suitability criteria, reproducibility, matrix effects, robustness.

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

- Prototype with detailed specifications for hardware/software manufacturing improvements.
- Full validation of process improvements.
- Full validation of novel assays or assay improvements including, but not limited to: system suitability, reproducibility, matrix effects, robustness.
- Standard operating procedures for each assay.

257 Biopsy Instruments and Devices that Preserve Molecular Profiles in Tumors

Number of anticipated awards: 2-3

(Fast-Track proposals will be accepted.)

Budget: Phase I: $250,000; Phase II: $2,000,000

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. Expeditious 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 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 establish regulatory requirements for clearing the proposed instrument of device through the FDA prior to submitting the proposal. Research plan should contain quantifiable, testable feasibility milestones.

Phase I activities and expected deliverables:

- 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 Strategies to Protect Radiosensitive Organs and Structures During Radiation Therapy

Number of anticipated awards: 3-5

(Fast-Track proposals will be accepted.)

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

Summary:

Radiation therapy is an essential tool in the cancer treatment arsenal. More than one million patients undergo radiation therapy in the US each year, and recent improvements in instrumentation have increased the clinical utility of this treatment modality. Despite significant progress, there are still situations where patient/organ motion limits 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 enhancing the efficacy of therapy, if better knowledge of radiation dose distribution could be obtained and organ motion during the radiation delivery better controlled. This contract solicitation seeks to stimulate research, development, and commercialization of innovative devices and methodologies designed to protect radiosensitive organs and structures during radiation delivery.

Project goals:

The short-term goal of the project is to perform proof-of-principle technical feasibility demonstration of innovative strategies 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.

It is expected that the proposed innovation is driven by clinical need, therefore, in addition to standard proposal components; the contract proposal should 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 advantages of proposed system.
3. Quantitative estimate of number of patient cases where the strategy will help to deliver better result per typical clinical site. This evaluation should be supported by literature, letters from radiation oncologists, radiologists, medical physicists, or other qualified specialists. It is expected that the company will establish regulatory requirements for clearing the proposed system through the FDA prior to submitting the proposal.

Research should be proposed with quantifiable, testable feasibility milestones.

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 implementing the proposed method.
- Development or procurement of an appropriate phantom or model necessary to evaluate the performance of the proposed system
- Validation of the prototype system with the phantom or model

Documentation providing 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. 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 other 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.

259 Quantitative Tissue Imaging For Clinical Diagnosis and Treatment

Number of anticipated awards: 4-6

(Fast-Track proposals will be accepted.)

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

Summary:

This SBIR announcement solicits submissions of proposals from small businesses interested in developing automated assays to identify and quantify subsets of specific cells in tumor biopsy tissue. An automated cell-based assay could become an important alternative to approaches based on genetic, epigenetic or proteomic profiles that focus on molecular features of tumor tissue to predict response to therapy. These methods are often slow, complicated, and may fail to detect small populations of specific cells within tumors such as cancer stem cells, or host immune or stromal cells whose presence may determine the clinical outcome of a treatment.

Assays designed to measure quantitatively the presence of cell subpopulations may be easier to perform on tissue biopsies than those that measure profiles of all the molecules in extracts of tissues. In addition, monitoring the presence of specific cells within tumor biopsies may provide a more accurate assessment of treatment response than molecular profiles of extracts of small biopsies. This will enable the use of specifically identified cell subsets as therapeutic targets and potentially open new avenues to monitor therapeutic response. These objectives are consistent with several NCI strategic goals in molecular medicine, nanotechnology and development of novel therapeutics.

This initiative is intended to stimulate and fund development of rigorous, validated automated assays to measure cells in tumor tissues based on the application of current state of the art image acquisition and quantitative analysis. The cell types may be cancer stem cells, host immune, stromal, endothelial or other cells (please see : http://sbir.cancer.gov/ for examples). Initial development may involve use of preclinical models but the intent of this initiative is for the development of clinically useful assays. Deployment of the new assays may be via a central laboratory service or distribution of equipment and specific kits to clinical laboratories. Validation of analytical performance of the assay will be required by an alternative technology. Offerors may submit proposals that will measure cellular subsets of their own choosing that are alternatives to the foregoing suggestions, so long as they remain relevant to oncology therapeutics development.

Project goals:

The short term goal of this contract is to develop rigorous, validated assays to measure cell subsets present within neoplastic tissue that may be predictive or prognostic markers. The focus of this solicitation is development of automated image acquisition and quantitative analysis in real time of cell populations in tissues collected in accordance with guidelines provided by the Office of Biorepositories and Biospecimen Research (OBBR, please see http://biospecimens.cancer.gov/). The assay design can be aimed to provide either a service by a clinical laboratory or a kit with equipment, supplies and Standard Operating Procedure (SOP) for end users. For either choice, an SOP for the assay must be developed and provided to the NCI. Validation data from a second technology that confirms the quantitative measurements of the specified cell subsets (e.g., by flow cytometry or functional assay) must be provided to the NCI. Small business respondents may submit proposals to develop assays of their own invention or those they have identified in the literature as the company has appropriate rights to commercialize the technology.

The long term goal of contracts under this RFP is the development of a series of imaging assays for cell-based markers that provide prognostic, predictive or therapeutic response information on clinical tissue biopsies of potential value to clinical practice. Any successes would support the goal of the NCI SBIR program to fund small businesses developing commercially viable products that improve public health and well being. Specifically, 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, and their integration into clinical trials.

Market analysis indicates that developments of quantitative imaging assays are valuable first steps to eventual commercialization of cancer diagnostic and laboratory assays. It is expected that companies will apply their assay service or kit developments to the task of patient stratification for clinical trial selection and/or to predict or evaluate response to new therapeutic agents.

Phase I activities and expected deliverables:

1. Develop an automated quantitative imaging assay for a defined cellular subset in a preclinical model that is consistent with the current DICOM standard. The NCI is interested in a specific list of candidate cells (please

see http://sbir.cancer.gov/ for this list of candidates). The identification of each cell type is expected to require simultaneous measurement with two or more analyte-specific reagents. The imaging assay must demonstrate adequate accuracy in both fresh and formalin-fixed tissues. The SBIR contract recipient must deliver SOPs for specimen collection, processing and stability of the cell subset under the conditions of the imaging assay.

2. The SBIR contract recipient must deliver data that demonstrate research assay reproducibility, variability and accuracy in a preclinical model and that show consistency with the current DICOM standard and assay SOPs.
3. The SBIR recipient must confirm the quantitative analysis in the first deliverable with a second technology that assesses phenotype or function of the cell of interest. This validation should also involve both fresh and formalin-fixed tissues. The data for this validation must be presented to the NCI.
4. The SBIR recipient must demonstrate acceptable real-time assay performance in preclinical model tissue such that assay results will be generated within 3 – 5 days of initiating tissue analysis.
5. Research should be proposed with quantifiable, testable feasibility milestones.

Phase II activities and expected deliverables:

1. Provide data to NCI that validates the automated quantitative imaging assay from Phase I for the cell subset in clinical samples with a second technology that measures the subset phenotypically and/or functionally. 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. The assay must be applicable in the clinical laboratory setting as well as in its intended use and conform to current DICOM standards. The assay may be distributed as either a service by a central laboratory or as a kit with equipment, supplies and SOPs when fully developed and validated.
2. Provide data to NCI from studies performed to characterize the correlation between the resulting assay in tumor versus surrogate tissues (e.g. blood, serum), if applicable.
3. Provide the SOP for specimen collection and processing and of the imaging assay for the cell subset with the exception of proprietary information.

260 High Level Programming Language to Expedite Development of User Interfaces

Number of anticipated awards: 1-2

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: $200,000; Phase II: $750,000

Summary:

The development of new statistical methodology represents a key component of biomedical research as we face increasingly varied challenges such as optimizing the design of randomized controlled trials (RCT's), exploring high dimensional genetic data, and applying data mining techniques for pharmaco-surveillance of large administrative data bases. A recent workshop held by the NCI entitled, "Barriers to the Development of User-Friendly, Well-Tested Software for Cutting Edge Statistical Methodology", identified the cost of development of user interfaces as a major impediment to the speed with which new statistical methods become usable by the broader audience of biomedical researchers. The development of statistical methodology and associated software goes through phases. In the earliest phase, a statistical calculation engine is created (with no interface) to be used primarily by the developers of the methodology and other research level statisticians. In a second phase, the efficiency of the calculation engine is improved and a basic interface is developed so that end users may apply the method in various types of applications and test the practical usefulness of the methodology. In a third phase, the programming of the calculation engine is further enhanced by professional programmers, a full blown interface is developed, and/or the methodology is incorporated into well developed statistical packages (e.g. SAS, STATA, SPSS).

Project Goals:

The goal of this solicitation is to develop a high level programming language which could be used directly by statisticians to develop user interfaces in the 2nd phase of the development of statistical methodology. The user interface would have to be readily accessible to a broad audience (e.g. EXCEL), and the product should be able to connect the interface with the most commonly used languages for the development of statistical calculation engines (e.g. R, C++, Proc IML in SAS, Gauss). The product could be written in various languages (e.g. Visual Basic for Applications - VBA) but would have to be easy to learn and use for those not formally trained as programmers. Since biomedical researchers other than statisticians often face the same problem of linking a calculation engine to a user interface (e.g. risk communication tools, patient decision making tools, policy evaluation tools), an important aspect of phase I of development will be to assess the broader market for this tool.

Phase I Activities and Expected Deliverables:

- Develop a basic prototype user interface programming language with limited features (e.g. fixed length inputs and outputs).
- Test the usability of the system by demonstrating the development of a basic user interface for one statistical and one non-statistical application. The user interfaces should be programmed by the developers of the calculation engines.
- Convene focus groups or conduct interviews with potential end-users to determine the acceptability of the system contents, format, etc.
- Document the ease of use of the system based on these applications.
- Identify potential target audiences beyond statisticians.
- Develop suggested features of a full-blown system.
- Demonstrate the system at statistical and/or non-statistical conferences.
- Provide monthly reports.
- Develop a working prototype of the system.
- Include travel funds to present Phase I findings and demonstrate product prototype to an NCI Evaluation Panel.

Phase II Activities and Expected Deliverables:

- Develop a full featured high level programming language as proposed in Phase I.
- Develop a well written user manual for the product.
- Develop a working group of interested users of the product comprised of both statisticians and non-statisticians. Seek guidance from this working group on a regular basis about usability, flexibility and features of the product both from the developer and end-user points of view.
- Test out the programming language with groups of experienced and non-experienced users for feedback and modifications to the product.
- Produce quarterly reports summarizing how the development of the product is being guided by the user group.
- Identify Phase II barriers and resolutions.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.

- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.
- Include $30,000 in the budget for evaluation of the system at the NCI Evaluation Lab.
- Provide a final report summarizing the product, it features, and potential user groups.
- Include sufficient travel funds for the P.I. to participate in an NCI/DCCPS SBIR Showcase.
- Prepare at least one manuscript describing the development and evaluation of the product for publication in a peer-reviewed scientific journal.
- Submit final Phase II report in the template provided by the NCI program officer.

261 Mobile Computing for Consumer-centered Cancer Prevention and Control

Number of anticipated awards: 1-2

(Fast-Track proposals will not be accepted.)

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

Summary:

The evolution of the geo-spatial web (http://en.wikipedia.org/wiki/Geoweb) combined with the convergence of computers and mobile phones into “smart phone” technologies will allow for geo-positioning capabilities that can deliver real-time context specific health-related information to consumers. Devices such as these will have applications that capitalize on existing geo-spatial databases describing the environment, similar to current GPS navigation devices or web-based mapping services used for personal cartography. Other potential applications include range and orientation-sensing, and health monitoring capability with wearable sensors, as projected by the Centers for Disease Control and Prevention and the Institute for the Future (http://www.iftf.org/taxonomy/term/44).

With annual savings estimated to be over $77 billion dollars (RAND Health IT Report: http://rand.org/pubs/research_briefs/RB9136/index1.html) public-private collaboratives such as the American Health Information Community 2.0, are striving to develop shared standards, ontologies, and systems to integrate health and bio-medical information at a “cells to society” level that includes population data and personal health records. In this regard, one of the challenges in developing next generation mobile device applications for health promotion and communication lies in their ability to effectively integrate formal and informal geo-spatial, behavioral, psychosocial, and biomedical data and metadata for consumer-facing applications. For example, mobile devices providing real-time dietary/nutrition information triggered by geo-spatial location, such as walking into a restaurant, entails potential integration of geographic, dietary behavior, and biomedical information.

Through this integration of data from multiple sources, mobile ‘smart phones’ have the potential to transform cancer control and prevention through applications for cancer communication, health promotion, surveillance, treatment, clinical trials and health systems research. Such a device could serve both communication (multi-directional, between consumers, providers, and scientists) and real-time data capture (geo-spatial, environmental, biomedical sensor, and behavioral) purposes. Examples of applications include health coaching for smoking cessation, sun-safety reminders triggered by UV sensors, automated mapping of walking/running/bike paths based on location and tailored physical activity goals, portable assessment of patient/caregiver self-care, location-based health risks/hazards, and monitoring symptoms and behaviors of patients in treatment and follow-up.

Project Goals:

The National Cancer Institute (NCI) promotes the use of state-of-the-art mobile technology to support products and applications that 1) are needed by professionals or the public to reduce cancer risk or improve the quality of life of cancer survivors; 2) help fill gaps in research; 3) resolve barriers to use so that products can be used effectively in a variety of settings including medical and community-based contexts; and 4) improve

communication behaviors between health care professionals, researchers, and patients/care-givers in cancer-related matters.

Short-term goals include development of a prototype mobile device (i.e, smart phones or other appropriate electronic devices) or enhancement of existing mobile devices through software and/or hardware devices that are ideally interoperable with current widely used standards. This mobile device should be able to usefully integrate behavioral, psychosocial, and/or biomedical data with real-time geo-spatial information for cancer control and prevention-related health communication, health promotion, surveillance, and/or treatment. The development process should emphasize principles of user-centered design. Another goal could be to develop applications for groups at higher risk of cancer, namely racial-ethnic minorities, socio-economically disadvantaged groups, and low literate populations. Interdisciplinary collaborations (e.g., behavioral researchers, computer scientists, nutrition specialists, exercise physiologists, health disparities scientists, etc.) are highly recommended to move the field forward in an integrative manner.

Long-term goals include evaluation and refinement of the mobile device with robust data interoperability across geo-spatial, behavioral, psychosocial, and/or biomedical datasets, potentially including linkages to information stored in electronic/personal health record (EHR/PHR) systems.

Phase I Activities and Expected Deliverables:

- Develop a fully functional prototype of an electronic mobile “smart phone” device or software and/or hardware attachments for existing mobile devices that can integrate behavioral, psychosocial, and/or biomedical data with real-time geo-spatial information for cancer control and prevention-related health communication, health promotion, surveillance, and/or treatment.
- Convene focus groups or conduct interviews with potential end-users of the device to determine if the system contents, format, etc. are appropriate for ease of use.
- Develop real-time or information feedback options to the user in all developed mobile device applications/tools.
- Develop the ability for the device to operate in both online and offline environments (i.e., disconnected from network) when appropriate.
- Provide outlines for an operation manual and primer for consumer-level and scientific/research applications/tools when appropriate.
- Develop software designs and specifications, where applicable.
- Include in the proposals, letters of agreement from organizations participating in Phase I feasibility testing and evaluation.
- Provide monthly progress reports.
- Include funds in budget to present Phase I findings and demonstrate the final prototype to an NCI Evaluation Panel.

Phase II Activities and Expected Deliverables:

- Develop and beta-test a mobile “smart phone” device or software application and/or hardware attachment for existing mobile devices with individuals from different population groups, and with researchers.
- Evaluate and refine the device and related applications/tools based on user feedback.
- Develop the final mobile “smart phone” device, applications/tools, and documentation where applicable.

- Develop related operations manuals and primers, addressing both technical implementation and social/cultural change management.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.
- Provide quarterly progress reports.
- Include $30,000 in the budget for evaluation of the mobile "smart phone" device at NCI's Evaluation Lab.
- Present final research findings and demonstrate the final product at an NCI/DCCPS sponsored Product Showcase.
- Develop at least one article describing the development and evaluation of the mobile "smart phone" device and related applications/tools that is suitable for publication in scientific venues.
- Submit final report in the template provided by the NCI program officer.

262 Health Information Technology to Facilitate Patient-centered Communication in Cancer-related Care

Number of anticipated awards: 1-2

(Fast-Track proposals will not be accepted.)

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

Summary:

The 2001 Institute of Medicine (IOM) report titled "Crossing the Quality Chasm" cited a need to make care "patient-centered". To achieve that end physicians and organizations who are delivering care must begin to see medical care from the patient perspective. As outlined in a recent NCI report on Patient-Centered Communication (2007), "patient-centeredness" is a multi-dimensional concept that goes beyond the notion of satisfaction. Care for cancer patients can be described as a series of visits, an aggregated experience often called episodes of care. Those episodes might include a short series of visits to attend to an acute illness or multiple visits and hospitalizations to deal with chronic life-threatening conditions. Information technology (IT) that could begin to integrate cancer-related care during episodes of care in a patient-centered manner addresses DHHS and IOM priorities for electronic/personal health records and healthcare quality improvement. As suggested by the industry-standard Health Information and Management Systems Society (HIMSS; http://www.himss.org), developing electronic tools and applications that support patient-centeredness in clinician-patient communication is a fast growing market area.

Consequently, the goal of this topic is to encourage the development of novel technology-based solutions that will assist clinicians in accomplishing key functions of patient-centered communication in cancer care: fostering relationships, exchanging information, responding to emotions, enabling patient self-management, managing uncertainty, and making decisions. Potential applications could be targeted to any specific problem or domain of cancer treatment—e.g., specific treatments for particular malignancies—but would need to address all of the key functions of patient-centered communication in an integrative manner. For example, clinical decision support tools and applications to improve care coordination and follow-up; the emphasis is on solutions that successfully address the multiple domains of patient-centeredness in patient-clinician communication. Such technology could interact with the health system, primary care providers, and oncologists to remind patients when they were scheduled to see a physician, help them schedule when they needed to, provide access to information relevant to those visits, and even guide the patient to the office. A patient-centered development process to develop information technology that could provide these and other functions patients identify as critical to their care is the focus of this topic.

Project Goals:

The major goal of this project is to create patient-centered clinical applications in primary care and oncology designed to improve patient empowerment through improved access to crucial decision-making information.

Phase I Activities and Expected Deliverables:

- Develop a system prototype that registers referrals, appointments, and all patient-provider and provider-provider communication throughout the coordination of the diagnostic process. This system could include the software application for a handheld device and/or telephone, and the relevant software to link with existing electronic health records. The application should also solve the problem of how to link the electronic health records of two separate medical offices with each other and the patient.

- Develop a software prototype that includes a real time visual simulation of the coordination process with alerts, reminders and other signals that support the patient's progress and information needs, while clarifying the accountability of individual team members, and assuring the integrity of the entire coordination effort.

- Develop a program that is capable of integrating into a larger system of home based coordinated cancer care (ideally a ubiquitous system with minimal patient burden); avoid redundant documentation.

- Review the VA/NCI cancer care coordination model, other coordination protocols and relevant literature to develop an overall cancer coordination process model.

- Establish a team or set of teams that includes providers in FQHCs who will conduct cancer care coordination during the diagnostic process.

- Conduct interviews with team members and selected community participants to develop a set of use case scenarios (from first abnormality (abnormal screening test or symptomatic presentation in a physician's office through diagnosis for one cancer type) that will serve as the basis of the coordination simulation software program.

- Convene focus groups or conduct interviews with potential end-users of the system to determine if the system contents, format, etc. are appropriate for ease of use.

- Provide a report detailing the coordination tracking program design, including theoretical and methodological bases for the evaluation.

- Provide a set of use case scenarios that have been approved by members of the team for tracking.

- Develop a working prototype of the cancer care coordination tracking program.

- Include in the proposal, letters of agreement from organizations participating in Phase I feasibility testing and evaluation.

- Include funds in the budget to present Phase I findings and demonstrate the final prototype to an NCI Evaluation Panel.

Phase II Activities and Expected Deliverables:

- Complete 2 iterations of the tracking program software, including technical documentation of the system and a training manual.

- Develop evaluation and outcome measures.

- Evaluate and refine the program based upon user feedback.

- Integrate the tracking program into telehealth monitoring, electronic patient record, and viable personal health record systems.
- Test and evaluate the complete system serving cancer patients and their care coordination team using process and outcome measures as described above.

System Requirements include:

1) Embedding the tracking software into a home telehealth monitoring and reporting system based upon the VA/NCI model of home centered coordinated cancer care; this could involve partnering or licensing with other vendors or developers of these components.
2) Integrating the home centered coordinated cancer care system into a community's existing IT infrastructure using the IT interoperability standards offered by The U.S. Department of Health and Human Services (www.hhs.gov/healthit). Eligible communities are those that have been funded by The Foundation for eHealth Initiative which provides seed funding and support to multi-stakeholder collaboratives within communities (both geographic and non-geographic) who are using electronic health information exchanges (HIE) and other information technology tools to drive improvements in healthcare quality, safety, and efficiency (www.ehealthinitiative.org).
3) Evaluating the system in a real community setting, according to cost, quality of care, quality of life and access outcome measures in addition to the community's own health and IT standards. Community members should be included in the research and development team from the beginning of the research and development project.

In the first year of the contract, provide the program and contract officers with a letter (s) of commercial interest.

In the second year of the contract, provide the program and contract officers with a letter (s) of commercial commitment.

Include $30,000 in the budget for evaluation of the product at NCI's Evaluation Lab.

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 system for publication in a peer-reviewed scientific journal.

263 Antibody Array for Cancer Detection and Diagnosis

Number of anticipated awards: 3-5

(Fast-Track proposals will not be accepted.)

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

Summary:

The purpose of this initiative is to provide support for the development of high throughput antibody arrays for quantitative analysis of multiple biomarkers for cancer detection, diagnosis and prognosis. These arrays may include antibodies based on the applicant's own research and/or knowledge of the literature. The selected applicants will develop microarrays, the chemistry of which may be based on nanotechnology and/or microfluidics. Applicants should focus initial development on the diagnosis and detection of prostate, breast, lung, colon, and other major epithelial cancers. In Phase II, the antibody microarray developed in Phase I will be validated under a plan developed with the NCI project officer.

Project Goals:

The specific objectives are:

- Prepare and purify biomarker-specific antibodies in the form of recombinant antibodies or monoclonal antibodies (mAb) and construct arrays;
- Develop and/or improve methodologies for quantitative measurements of the bound antigens on Ab microarrays;
- Perform analytical validation, e.g., test the reproducibility, sensitivity, specificity and dynamic range of detection.

Currently, there is no single marker or a combination of biomarkers that has sufficient sensitivity and specificity to detect and diagnose early stage cancer. However, recent developments in gene and proteomic profiling of precancerous and cancerous lesions suggest that a combination or a patterns of markers may be used to distinguish between cancer and non-cancer with high sensitivity and specificity (95-100%). Innovative technologies, such as microfluidics and nanotechnology, combined with antibody arrays are likely to provide a reliable, sensitive and quantitative detection tool for measuring differentially expressed biomarkers from a limited amount of sample (20ul or less of serum). The involvement of small businesses through the SBIR contract mechanism will strengthen NCI's efforts in the development, validation and commercialization of biomarkers for cancer detection, diagnosis and prognosis.

Phase I Activities and Expected Deliverables:

Relevant biomarkers could be selected from published literature.

- Establish the proof of principle
- Develop an antibody microarray for detection of 3 biomarkers using innovative technologies
- Demonstrate that the tiled antibodies perform as well or better than a conventional ELISA in the detection of these biomarkers in serum from cancer patients

Phase II Activities and expected deliverables:

- Develop antibody microarrays with a capability to simultaneously detect and measure the concentration of 30-50 biomarkers.
- Develop SOPs for antibody microarray assays utilizing limited amounts of sample.
- Validate antibody microarrays for performance including sensitivity, specificity and dynamic range of the assay.
- Produce and test up to 1000 microarrays with samples from normal and case subjects

264 Novel and Improved Methods for Detecting Epigenetic Modifications

Number of anticipated awards: 2-3

(Fast-Track proposals will be accepted.)

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

Summary:

Epigenetic markers have shown promise for early detection and diagnosis of cancerous lesions. However, it is unlikely that any single epigenetic marker has sufficient sensitivity and specificity to accurately and reliably detect early cancers, or to predict cancer risk and progression. Also, methods used to measure epigenetic modifications need to be improved to increase specificity, sensitivity, reproducibility, and throughput. For example, most methods to measure CpG methylation at specific sites require bisulfite treatment, which is time consuming and can result in incomplete conversion of cytosines to uracils, leading to fluctuations in methylation measurements

and poor accuracy. Assays, methods and arrays or chips need to be developed to integrate and improve the ability to detect epigenetic modifications as a non-invasive approach for early cancer detection, risk assessment, diagnosis, prognosis, and clinical response. Responses to this solicitation may include assays for epigenetic modifications such as CpG methylation, histone modification, as well as others.

Project Goals:

The purpose of this initiative is to solicit small businesses to develop innovative and improved assays, methods, or chips for detecting epigenetic modifications applicable for clinical assessment of epigenetic markers of cancer. This SBIR contract solicitation encourages: (1) development of new methods for methylation detection that do not require bisulfite treatment or increase the conversion rate of cytosine to uracil by bisulfite; (2) development of chips for high throughput detection of epigenetic modifications; and (3) development of more sensitive techniques that allow for epigenetic modifications to be measured in small volumes of bodily fluids such as sera or sputum. Most current methods require large volumes, making them unsuitable for use with these bodily fluids and hence for use in early cancer detection and diagnosis.

Phase I activities and expected deliverables:

Develop innovative and improved epigenetic modification detection methods or increase analytical sensitivity to allow for measurement of modifications in low abundance;

- Demonstrate proof of principle for the development of the assay, method or chip;
- Establish a panel of epigenetic cancer markers of interest to be used in testing the assay, method or chip;
- Demonstrate feasibility by testing a panel of 5 to 10 target epigenetic markers;
- Test the usefulness of these methods using DNA extracted from cell lines or clinical samples;
- Obtain input from potential customers and the clinical community in preparation for developing a comprehensive commercialization plan for the assay, method or chip.

Phase II activities and expected deliverables:

Refine and analytically validate the assays, methods, or chips to test accuracy, sensitivity, precision, and dynamic range.

- Provide data comparing the assay, method or chip to previous widely used assays detailing improvements in accuracy, sensitivity, precision, dynamic range, throughput and sample size;
- Use these assays, methods, or chips to characterize more than 30 epigenetic markers;
- Clinically validate the sensitivities and specificities of assays and methods using appropriate clinical samples;
- Generate a scientific publication regarding assay or method performance targeted to the end user audience.

265 Development of shRNA Library Screening Technology for Cancer-Related Targets

Number of anticipated awards: 1

(Fast-Track proposals will not be accepted.)

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

Summary:

The goal of this SBIR contract topic is to develop improved shRNA screening technologies for identification of molecular components of pathways in cancer. An shRNA library will be used to inhibit expression of every gene in the genome which will determine whether a given gene product is required for a specific process in cells. To allow for high throughput, stable and transient transduction of the shRNAs using a wide variety of dividing and non-dividing cells, a lentiviral vector should be employed. Cellular readouts of protein expression and degradation such as fluorescently tagged fusion constructs should be used in the screening system. The selected offeror should then adapt the cellular readout to a rapid throughput system that can be screened against the shRNA library. Phase I will involve development of a rapid throughput system for transduction of shRNAs into a dividing and non-dividing cells and validation for a limited number of target transcripts. Phase II will adapt this transduction system to both human and mouse shRNA libraries that include sequences targeting multiple regions of all annotated genes. The output of this screening system will be information on candidate gene products that participate in the pathway being examined.

Project Goals:

To determine whether a given gene product is involved in a molecular pathway shRNAs can be designed that specifically degrade the given message. The shRNA approach can also be used to identify new components of a pathway by individually blocking each product of the genome. For example, to identify factors that are involved in the pathway to Mcl-1 protein expression in cancer cells, an shRNA library could be screened for factors that interfere with Mcl-1 expression. When Mcl-1 is fused with GFP, the proteosomal degradation of Mcl-1 also extinguishes GFP fluorescence. Thus, a cancer cell transfected with Mcl-1-GFP would fluoresce unless it harbors shRNA that destabilizes the message or enhances degradation of the protein in the cancer cell. Conversely, a growth factor dependent cell line transfected with Mcl-1-GFP would, in the absence of growth factor, lose fluorescence unless it harbors an shRNA that protects Mcl-1. The latter could, for example identify an E3 ubiquitin ligase that specifically targets Mcl-1 degradation, or it could identify any component upstream of the E3. Like Mcl-1, levels of $p27^{kip1}$ are regulated by ubiquitination and proteasomal degradation. The mechanisms of the specific targeting of $p27^{kip1}$ in cancer cells are unclear, and these pathways could be explored using $p27^{kip1}$-GFP and the shRNA library. Both such screenings require development of an shRNA screening mechanism amenable to individually testing a large number of clones (60,000 or more). Some shRNA libraries are commercially available and are being improved, the goal being to knock down all known genes by about 75% on average, to assure a detectable biological effect. Application of these libraries in a suitably large scale arrayed screening mechanism is currently unavailable. The NCI aims to stimulate development of this technology to advance cancer research. It is hoped that the selected offeror would move to provide this valuable technology as a fee for service to investigators in academic as well as pharmaceutical and biotechnology industries.

NCI encourages offerors to consider including appropriate shRNA clones to study the MCL-1 and $P27^{kip1}$ protein and their role in both human chronic lymphocytic leukemia (CLL) line and an untransformed murine T lymphocyte line that is dependent on interleukin 7 for survival and proliferation. Offerors may also assume in their proposals that NCI investigators will make fluorescent cellular readout systems and these cell types available for the development of the shRNA screening system. **Please Note:** Ultimately the choice of gene targets, cellular readout proteins and cell types will be at the discretion of the offeror. However, in all cases selected targets, cellular readouts and cell types must be relevant to cancer biology. Technical merit of each proposal will be determined based on the offeror's ability to execute on the deliverables listed below.

In summary the selected offeror must:

- Develop a high throughput infection and screening system.
- Acquire or develop lentiviral shRNA libraries that cover all expressed human and mouse genes.
- Apply screening to a cell readout system, such as a fluorescent signal.
- Identify candidate gene products.

All inventions conceived or first actually reduced to practice by the selected offerors under this contract will be the property of the selected offeror in accordance with the Bayh-Dole Act (35 USC Section 200, et.). It is intended that data and information related to the development of the high throughput shRNA screening platform developed by

the contractor be the core of the SBIR endeavor and subject to the FAR Clause 52.227-20 Rights in Data-SBIR Program. Output screening data including gene targets are explicitly excluded as SBIR Data pursuant to FAR Clause 52.227-20, and such data will be subject to FAR Clause 52.227-14 Rights in Data-General. It is intended that these screening data and gene target clones delivered to NCI by the contractor be shared with the research community as appropriate and consistent with the Principles of Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources. Intellectual property discovered jointly by the selected biotech company and any NCI investigators will be jointly owned by the biotech company and NCI consistent with the contract terms.

Phase I activities and expected deliverables:

1. Array and apply shRNAs in lentiviral vectors to knocking down cellular targets. This delivery system must be amenable to scaleup to about 60,000 clones in Phase II.
2. Determine the efficacy of gene silencing for ~100 gene targets, with a depth of coverage of at least 3 shRNAs per transcript, following lentivirus transduction of standard epithelial cell line(s) plus at least one cell line of lymphocyte origin. Efficacy for all shRNAs will be determined at the RNA or protein level.

Phase II activities and expected deliverables: (For projects that continue into phase II additional materials may be made available through negotiations with the Contracting Officer and the Contracting Officers Technical Representative.)

1. Scale up all deliverable from Phase I to whole genome levels (human and mouse).
2. Complete high throughput screens of whole genome shRNAs (human and mouse) against cellular targets with fluorescent readouts.
3. Construct, acquire or purchase human and mouse specific shRNA libraries corresponding to 4,000 to 7,000 gene targets (all RefSeqs including transcript variants) in lentiviral-based vectors screening purposes. The depth of coverage will be 3 to 8 shRNAs per transcript.
4. Generate lentiviral stocks for the 4,000 to 7,000 gene target shRNA library in a fully arrayed format.
5. Conduct two pilot, fully arrayed, shRNA mediated RNAi screens using the whole genome libraries.

266 Nanotechnology Imaging and Sensing Platforms for Improved Diagnosis of Cancer

Number of anticipated awards: 3-5

(Fast-Track proposals will be accepted.)

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

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, sensing, and detecting purposes. Further functionalization 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.

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, 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 diagnostic solutions comprising of imaging and/or monitoring of prognostic biomarkers.

To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable nanotechnology-based imaging agents and/or sensing 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 platforms 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 platforms can be used for early detection/imaging of initial onset of disease, or be used as post-treatment monitoring to detect/image recurrence of disease. Strategies can also include screening assays that provide a better mechanistic understanding 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 work on metastatic disease. Novel imaging and sensing diagnostic nanoplatforms could also be used, in a preclinical setting, both for high throughput screening assays to locate new metastasis-directed compound and for validating the new compounds either in vitro, in situ, or ultimately, in vivo.

Potential relevant imaging and sensing nanoplatforms could include, but are not limited to:

1) Imaging and Sensing 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.).
2) Nano-enabled Sensing Platforms; Examples: Use of functionalized nanomaterials (nanowires, nanotubes, nano-cantilevers, etc.) to build sensing 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.
3) High throughput Screening Nanoplatforms; Examples: Single or combinations of nanotechnologies (nanopatterning, imaging agent, sensing platform, microfluidics) for assay development. Applications: Locating 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. Research should be proposed with quantifiable, testable feasibility milestones.

Phase I Activities and Expected Deliverables

Platform design:

- Development of sensing/imaging methodology
- Demonstration of unique spatial/temporal capabilities enabled by nanotechnology
- Proof of concept experiments
- Benchmarking experiments against conventional methodologies

First-stage validation of design in relevant preclinical samples as listed below,

- Medical imaging agents: In vivo small animal efficacy studies
- Sensing platforms: Candidate biomarkers in serum-free samples
- High throughput imaging and 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
- Medical imaging agents: In vivo small animal toxicology studies that can be used for regulatory filing purposes
- Sensing platforms: Candidate biomarkers in patient samples
- High throughput imaging and screening assays: primary cells and/or tissues obtained from patients
- Submitted regulatory application (for example IDE, IND, etc.) to obtain necessary approval for clinical validation.

267 Multifunctional Therapeutics Based on Nanotechnology

Number of anticipated awards: 3-5

(Fast-Track proposals will be accepted.)

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

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 or imaging 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 emerging. This process can utilize epitopes expressed on specific signatures of tumor cells or other cellular markers of biological processes such as angiogenic and apoptotic pathways. In molecular oncology, this is 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 therapeutics, designed to deliver chemotherapeutics 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 develop an in vivo nanodevice-based delivery platform with improved efficacy as compared to currently used treatments. For example, such devices can take 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 can be administered orally, intravenously, or can be implanted. They may include, but are not limited to the following:

- Novel therapeutic nanodevices;
- Novel tumor targeting and concentrations schemes;
- Novel drug loading and releasing schemes;
- Novel nanodevices which are able to cross the blood-brain barrier.

Phase I activities and expected deliverables:

- Fabrication techniques resulting in the manufacturing of nanodevices with good reproducibility should be developed. The novel use of existing particles acquired from commercial manufacturers 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.

Phase II activities and expected deliverables:

- Demonstration of targeting (multiple biomarkers) and concentration techniques 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.

Fast-Track justification:

While not necessary for all grantees, there are specific situations where fast-track funding would be appropriate. Fast-track combines Phase I and Phase II projects into one submission and allows for a faster transition between the phases. If there is a significant amount of preliminary data, or proof of concept demonstration already exists, this approach may result in a faster rate of technology development. A fast-track proposal requires inclusion of quantitative and specific deliverables in the Phase I portion of the application.

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.

268 Novel Antibody Epitope Mapping Technologies

Number of anticipated awards: 4

(Fast-Track proposals will be accepted.)

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

Summary:

The purpose of this initiative is to provide support for the development of novel epitope mapping technologies. Epitope Mapping encompasses all the major methods for the identification and definition of epitopes. The ability to characterize the epitope of an antibody on its target protein is now being extensively employed to develop new therapeutics and biomarkers. This epitope information can help researchers to understand the "mechanism of action" of an antibody, to predict the potential cross-reactivity and connecting a SNP polymorphism to a specific protein structure. In addition, epitope mapping has been used as a powerful tool for rational drug design. Studies have revealed that while off-rate is an important factor in determining antibody potency, it is not the critical factor. Antibodies can recognize a linear string of amino acids, but they frequently bind to discontinuous/conformational epitopes (i.e. amino acids in a protein sequence that are brought together in the three-dimensional protein fold but are disparate in its linear sequence). Therefore the quality of antibodies results from the fine specificity of the molecular interactions, rather than simple binding parameters. A number of computational algorithms are now available for mapping conformational discontinuous epitopes. Additionally, various methods namely use of synthetic peptides, expression cloning, site directed mutagenesis and protein footprinting have also been used for epitope mapping.

Specifically, the NCI is interested in proposals that focus on the development of novel, fast, reliable and economical epitope mapping techniques. Proposals should explicitly describe how the proposed technology/system will develop and characterize monoclonal antibody epitope mapping.

Project Goals:

Information about the epitopes of proteins recognized by antibodies is important for their use as biological or diagnostic tools as well as for understanding molecular recognition events. The information about Ab-antigen interactions gained from epitope mapping can be utilized in two important ways: either by using engineered Abs as bait for the detection of antigens in biologic samples; or by using recombinant proteins as diagnostic tools for the presence of Abs produced in an immune response. The purpose of this project is to stimulate the development of novel, fast, reliable and economical monoclonal antibody epitope mapping technologies including mass spectrometry (MS) based methods.

Offerors are encouraged to coordinate and pursue selected monoclonal Abs developed by the Clinical Cancer Proteomics community. These Abs are being generated from biomarkers listed 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

- Demonstrate the feasibility of the innovative monoclonal Ab epitope mapping method (including MS-based techniques).
- Produce an initial product prototype in working with the Clinical Proteomic Technologies Initiative community.
- Demonstrate that epitope mapping method can be made reproducibly and economically.
- Epitope map at least 10 monoclonal Abs (offerors are encouraged to select targets in coordination with the Clinical Cancer Proteomics community).
- Functionally characterize the mapped epitopes e.g. demonstrate which amino acids are critical for binding.
- Present findings to NCI program staff.
- 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 epitope mapping technology. Achievement of such criteria could be derived by comparison with existing technologies.
- Epitope map at least 100 monoclonal Abs (targets to be selected in coordination with the Clinical Cancer Proteomics community).
- Functionally characterize the mapped epitopes e.g. demonstrate which amino acids are critical for binding.
- Work with the Clinical Proteomics community to integrate platform into the technology assessment programs and greater scientific community.
- Research should be proposed with quantitative feasibility milestones.

269 Development of Novel Protein Expression Technologies for Glycosylated Cancer Related Proteins

Number of anticipated awards: 4

(Fast-Track proposals will be accepted.)

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

Summary:

The purpose of this initiative is to provide support for the development of novel technologies for the expression of cancer-related glycosylated proteins. Many proteins become post-translationally modified (PTM) during the "secretory process" which involves of a journey from their site of synthesis in the rough endoplasmic reticulum (ER), through the Golgi apparatus and then to various cellular and extracellular destinations. Various covalent modifications often occur, either during or after assembly of the polypeptide chain, that are indispensable for the activity of these proteins. Knowledge of these modifications is extremely important because they may alter the proteins' physical and chemical properties, folding, conformation distribution, stability, activity, and consequently, function. Moreover, the modification itself can act as an added functional group. Examples of the biological effects of protein modifications include glycosylation, phosphorylation, acetylation, and amidation. Of these, the most complex procedure, involving several enzymes, is glycosylation. Hence, glycoproteins are the most diverse group of biological compounds that are ubiquitous constituents of almost all living organisms. A given glycoprotein may contain N-linked (asparagine-linked) oligosaccharide chains only, O-linked (threonine- or serine-linked) oligosaccharide chains only, or both. The carbohydrate units of glycoproteins exhibit considerable variation in size and structure ranging from mono- or disaccharide- to a branched oligosaccharide composed of as many as 20 monosaccharide residues. Consequently, the analysis of proteins and their post-translational modifications is particularly important for the study of cancer, neurodegenerative diseases, heart disease and diabetes.

Specifically, the NCI is interested in proposals that focus on the development of glycosylated human proteins. Proposals should explicitly describe how the proposed technology/system will develop/express, isolate and characterize the glycosylated proteins.

Project Goals:

Increasing demand for recombinant glycosylated proteins has focused research on techniques for improving protein expression and controlling post-translational processing. The purpose of this project is to stimulate the development on all aspects of glycosylated protein expression including novel cell systems, expression vectors, and culture conditions. Glycosylated proteins selected for production are to entail low abundance cancer-related proteins from bodily fluids preferably developed in coordination with the Clinical Proteomics community. Furthermore, these glycosylated proteins must be made available as a resource to the greater scientific community.

Offerors are encouraged to coordinate selection of analytes with the Clinical Proteomics Technologies for Cancer community during Phase I. Targets for Phase II are to be selected in coordination with this community from

glycosylated biomarker candidates listed 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 glycosylated protein development approach.
- Produce an initial glycosylated protein production prototype.
- Produce evidence that the glycosylated proteins are well characterized (preferably using MS-based techniques).
- Demonstrate that glycosylated proteins can be made reproducibly and economically.
- Generate at least 10 glycosylated targets (offerors are encouraged to select targets in coordination with the Clinical Proteomic Technologies for Cancer community).
- Research should be proposed with quantitative feasibility milestones.

Phase II Activities and Expected Deliverables

- Generate at least 100 glycosylated targets (to be selected in coordination with the Clinical Proteomic Technologies for Cancer community)
- Glycosylated proteins are to be well characterized (preferably using MS-based techniques).
- Work with the Clinical Proteomic Technologies for Cancer community to integrate glycosylated proteins into the technology assessment programs and greater scientific community.
- Research should be proposed with quantitative feasibility milestones.

270 Peptide Aptamers: New Tools to Capture and Study Protein Interactions in Lieu of Immunological Reagents

Number of anticipated awards: 4

(Fast-Track proposals will be accepted.)

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

Summary:

The purpose of this initiative is to provide support for the development of peptide aptamers that can be used instead of antibodies for immunological uses. The Production of polyclonal and monoclonal antibodies is now well established and many of the antibodies are commercially available. Yet, man antibodies remain poorly characterized and suboptimal across multiple applications. In addition, polyclonal antibodies are typically not a renewable resource. Moreover, the specificity of a monoclonal antibody against a target of interest there is not guaranteed, nor is there any certainty as to whether or not a monoclonal will work in the needed assay, or can be used in combination with other antibodies due to an antibody's large size and subsequent competition for overlapping binding domains. Furthermore, 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 peptide aptamers as alternative protein capture reagents for the cancer research community. Peptide aptamers are most commonly used as disrupters of protein–protein interactions in vivo, but the flexibility of protein engineering means that peptide aptamers can be turned into tools for virtually any type of biological study. For example, peptide aptamers can provide a basis for the development of novel diagnostic and therapeutic strategies, with implications for a broad variety of different disease entities including cancer. The development of these affinity capture reagents will be done in coordination with NCI's Clinical Proteomic

Technologies for Cancer and be targeted to a list of purified recombinant proteins being constructed and characterized through this initiative.

Project Goals:

NCI is interested in proposals that focus on developing peptide aptamers as alternative affinity capture reagents that can effectively compete against antibody technologies in terms of protein recognition, binding affinity, and detection and can be reproducibly produced in a cost-effective and efficient manner. Furthermore, these capture reagents must pass performance characterization criteria and be made available as a resource to the scientific community.

The peptide aptamers are required to demonstrate equivalent or improved performance to other affinity-based platforms. It is expected that peptide aptamers have dissociation constants that are comparable to or better than antibodies and can be used in the same way as antibodies. Suggested choices of performance applications that could be validated include immunoblot, and immunoprecipitation. In addition, other considerations include the actual binding epitope, 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.

Offerors are encouraged to coordinate selection of analytes with the Clinical Proteomics Technologies for Cancer community during Phase I. Targets for Phase II are to be selected in coordination with this community included 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

Demonstrate feasibility of the innovative method for peptide aptamer production

- Work with the clinical proteomics community and private and public sectors to identify appropriate minimum characterization criteria/validation assays
- Generate peptide aptamers to at least 10 protein targets and demonstrate equivalent or improved performance to other affinity-based platforms
- Demonstrate that peptide aptamers have improved cost effectiveness and throughput capabilities in production compared to antibodies
- Present findings to NCI program staff
- Research should be proposed with quantitative feasibility milestones

Phase II Activities and Expected Deliverables

- Implement strategy and project plan for a fully functional peptide aptamer reagent development platform for at least 100 protein targets. 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 other affinity platforms
- Work with the cancer clinical proteomics community to integrate the platform into the technology assessment programs and greater scientific community.
- Research should be proposed with quantitative feasibility milestones.

NATIONAL CENTER FOR RESEARCH RESOURCES (NCRR)

The National Center for Research Resources (NCRR) provides clinical and translational researchers with the training and tools they need to understand, detect, treat, and prevent a wide range of diseases. This support

enables discoveries that begin at a molecular and cellular level, move to animal-based studies, and then are translated to patient-oriented clinical research, resulting in cures and treatments for both common and rare diseases. NCRR connects researchers with one another, as well as with patients and communities across the Nation, to harness the power of shared resources and research.

This solicitation invites proposals in the following areas.

012 Visualizing Biomedical Research Characteristics

(Fast-Track proposals will be accepted.)

Biomedical research can be characterized in a multitude of ways. Publications, grant applications, progress reports, funding, experimental approach, specific aims, collaborations, scientific networks, organizations and people with specific expertise, 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. For example, 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. There is a variety of visualization techniques based on well-developed scientific principles. They 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 the management of a research portfolio.

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 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 identify and work with complex dimensions, i.e., not necessarily linear combinations of a number of data elements. The applicants are encouraged to apply the elements of principal component analysis (PCA) for identifying meaningful combinations of data elements and research characteristics
- have transparent, validated, and well-documented protocols for all steps of data processing (cleansing, filtering, analysis, visualization, etc.)
- have source code available
- be accompanied by documentation of data processing algorithms, data accuracy, precision, and other features necessary for the most accurate basis to interpret the produced visualization
- have Application Programming Interface (API) that does not require programming skills
- take advantage of high-resolution display screens

Deliverables

- Phase 1 should produce meaningful visualizations of a test dataset(s), e.g., a subset of publications in a particular domain from PubMed, that address some sample areas below and demonstrate "proof of concept" for the Phase 2 deliverable
- Phase 2 deliverable is web-enabled software that can be used for multidimensional data exploration and portfolio analysis

Sample areas of interest to NCRR

- Distribution of funding among various scientific domains, institutions, types of grantees
- Evolution of scientific domains, collaborations, and concepts
- Landscape of science where a location and interconnectivity of an entity (scientist, organization, paper, or concept) can be identified
- Scientific forecasts
- Pathways for translating Discovery into Innovation
- Success factors for translational research, e.g., infrastructure, people, funding
- Visualization of cross-discipline evolution pathways for people, concepts, etc
- Clinical and Translational Science Awards (CTSA) domain, subjects, and networks
- Productive career pathways, e.g., those leading to significant awards
- Visual thesaurus of scientific domain fingerprints or other complex 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
- Visualization that enables meaningful exploration of high-dimensional data
- Map of NCRR-related entities, activities, funding, networks, etc. that represent online knowledge resource for the researchers

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
- innovative ways to display complex concepts
- collaborations and other networks

Data sources

The analysis should be done using a number of various data sources, e.g., journal publications, conference proceedings, 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/.

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.

035 Ultrasonic Wave Transmitter, Transmission Line and Receiver for Interventional MR

(Fast-Track proposals will be accepted.)

At the present time, signals from electronically active devices used within an MR scanner are transmitted out of the scanner on coaxial cables. This includes signals from "marker" coils on interventional devices such as catheters and guidewires. These long transmission lines couple with the transmitted RF which can potentially cause heating in the patient. If the conductor length can be made lower than a quarter of the transmitting wavelength, the heating problem can be eliminated; but, this length is approximately 30 cm within the body and the average length of intravascular catheters is about 1 meter. A non-conductive transmission line was designed to carry RF signals to eliminate this heating problem. In this design, a conductive coil at the distal tip of the catheter receives RF signals emitted by the tissue. The received signal reaches the micro piezoelectric transducer (MPT) and the MPT converts the RF signal into an ultrasonic wave. A custom designed acoustic wave guide transmits the signal until it reaches the proximal end of the catheter. At this point another MPT receives the ultrasonic wave and converts it back to an electronic RF wave, and after amplification of the signal it reaches the scanner receiver for MR image reconstruction. This will be the first application of ultrasonic waves to visualize interventional MRI catheters. The most challenging part of this project is miniaturizing the technology to fit inside a 0.035” outer-diameter catheter. To manufacture the first prototype, we need acoustic transducers, transducer electrodes and custom designed acoustic wave guide defined by using photolithographic techniques.

The Phase I application should provide proof of concept for conversion of the RF signal to acoustical domain, and transmission of the acoustical signal in a wave-guide. In this phase, available materials will also be evaluated in terms of performance and efficiency. Iterative designs will consider available materials and fabrication methods that may be suitable for later phases. The electrodes on the transducer will be patterned using microelectromechanics techniques such as photolithography. Tools will be developed to align and attach the transducers and the wave-guide. Phase I will yield a functional prototype.

The Phase II application will translate the Phase I findings into a clinical grade device. The wave-guide will be similar to the final product in terms of acoustical properties. The whole device will be composed of two transducers, an acoustic wave-guide and a low noise amplifier. The project includes in vitro and in vivo testing.

040 Nanoprobes for Non-Invasive Detection of Atherosclerotic Plaques

(Fast-Track proposals will be accepted.)

Coronary heart disease is a major cause of death and disability in the U.S. and other industrialized societies. The underlying cause, in most cases, is the development of atherosclerotic lesions in the coronary arteries. The atherosclerotic lesion progresses largely in a clinically silent and asymptomatic manner to form plaques that severely block the coronary arteries. Many of these plaques are prone to rupture resulting in acute coronary thrombosis and myocardial infarction.

Many of the factors involved in the atherosclerotic process have been identified and a complex interaction exists between the cellular entities involved in the atherosclerotic process. Endothelial cells, smooth muscle cells, platelets, leukocytes are all involved in the formation of an atherosclerotic lesion. Plaque erosion, stenosis, and hemorrhage are thought to be important in plaque rupture as are force imbalances within the plaque and acute changes in intraluminal coronary pressure. Currently, a significant limitation to early detection is the unavailability of non-invasive imaging modalities for the detection of a developing plaque, a plaque prone to rupture, or a plaque that is stable.

The goal of this proposal is to develop nanoprobes for non-invasive or minimally invasive visualization/detection of a developing atherosclerotic plaque and its characteristics. Early detection of atherosclerotic plaques would be

extremely useful in risk assessment and appropriate targeting of preventive measures. Further, early detection and characterization of atherosclerotic plaques susceptible to rupture may decrease morbidity and mortality.

Phase I applications should address initial development and feasibility testing of novel technologies for plaque detection and Phase II applications should be focused on completing the development of the technology for incorporation into the clinic. The work is expected to include in vitro and in vivo studies to demonstrate effectiveness.

043 Development of Pathogen Inactivation Technologies for Blood Components

(Fast-Track proposals will be accepted.)

Great strides have been made over the past 25 years greatly improving the safety of the nation's blood supply. Current blood donor screening and laboratory testing has drastically reduced the risks of acquiring infectious disease through blood transfusion. However, the potential for new, emerging infectious agents entering the blood supply continues to be a serious concern of the blood banking community. Pathogen inactivation of blood and blood components provides an additional layer of protection from such agents. The effectiveness of pathogen inactivation technology is best exemplified with the virtual elimination of certain infectious agents from manufactured plasma derivatives. Since 1985, there have been no transmissions of human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) by U.S. licensed plasma derivatives. However, because of the labile nature of red blood cells and platelets, these technologies are far too harsh for use with cellular blood components. During the past several years, new technologies have been developed and evaluated in clinical studies offering hope that blood components can also be treated to destroy the infectivity of a wide array of microbial agents without significantly reducing the component's therapeutic effectiveness. These technologies include leukoreduction of blood, photochemical treatment of platelets or plasma with ultraviolet light and psoralen compounds, and various chemical treatments of red blood cells which may or may not involve irradiation with ultraviolet or visible light. Some of these technologies have been shown to reduce infectivity in a wide array of infectious agents. While much progress has occurred in the development of these technologies in recent years, there is still no U.S. licensed pathogen inactivation process for cellular blood components. There is a need to evaluate other new, promising compounds and procedures. It does not appear that any one inactivation technology will be effective in treating all classes of agents (e.g., viruses, bacteria, protozoa, prions). It is likely that a combination of techniques that remove and/or inactivate agents will be needed. These technologies are generally sophisticated and costly. They probably will be utilized by the developed world if found to be safe and effective. However, because of costs they will be out of reach for resource-poor countries where blood-borne agents are highly prevalent and laboratory screening irregular or nonexistent. In such settings, the availability of simple, cost-effective inactivation procedures could save millions of lives. This solicitation encourages research leading to the development of pathogen inactivation procedures for blood components, particularly red blood cells and platelets, although work on plasma components would also be responsive to this solicitation. Research on the development of simple, low cost procedures for use by less practiced laboratory personnel in the developing world would also be responsive and is highly encouraged.

The Phase I application shall focus on studies that provide proof of concept that the pathogen inactivation procedure is capable of reducing the infectivity of infectious agents in the blood component(s) while maintaining the function of the component at an acceptable therapeutic level. The inactivation kinetics of the infectious agents being studied shall be determined. The effect of the procedure on the viability of the blood component shall be determined using a variety of different approaches depending on the component such as flow cytometry studies to determine the extent of platelet activation, platelet aggregation studies or assays for the red cell storage lesion (e.g., extracellular potassium leakage).

Phase II studies will extend the efforts of the Phase I studies and shall focus on in vitro and in vivo studies and scale-up of the process and prototype device including ancillary equipment such as blood bags. Studies shall include the use of human blood in quantities comparable to those amounts to be treated in the blood bank. In vivo studies shall be designed to demonstrate acceptable product performance as predetermined by FDA regulations (RBC) or by agreement with FDA staff (platelets). The array of infectious agents to be tested can be expanded in this phase. The therapeutic effectiveness of the component shall be investigated. Safety studies of the treated

component shall be conducted and shall include toxicity, reproductive toxicity, and mutagenic and carcinogenic potential.

044 Development of Cell-based Bioassays Using Induced Pluripotent Stem (iPS) Cell Lines

(Fast-Track proposals will be accepted.)

Recent new technology enabling the production of induced Pluripotent Stem (iPS) cell lines has created significant opportunities for the development of new cell lines for use as cell-based bioassays such as in screening assays. The technology provides the means to expand the iPS cell lines to the numbers needed for bioassay applications and will enable the derivation of cell lines with specific phenotypic or genetic characteristics uniquely suited to specific assay requirements. Thus, iPS cell lines represent an excellent substitute for improving upon cell-based assays currently carried out with existing lines or limited supplies of primary cells. Basic research studies are needed to obtain sufficient quantities of the iPS cell line to test their suitability and for comparison to existing assay methods. And fundamental research to improve upon the methods used for iPS cell derivation will accelerate all commercial opportunities. The availability of the initial iPS cell-based assays will benefit those investigators utilizing these assay tools in their research as well as serve as prototypes for investigators who may wish to develop new bioassays using iPS cell lines.

The goal of this solicitation is the development and production of new bioassays based on iPS cell technology to be used for research purposes and to be made available to the scientific community. The assays may be designed for basic research applications and potentially with future clinical assays. The derivation and expansion of the cell lines must be well defined and produced under appropriate manufacturing practices and quality control. The cell-based bioassay must be developed and validated including the use of existing assays as comparators. The successful applicant must develop a production plan to commercialize the assay.

Phase I proposals should focus on the development of a well-characterized iPS cell line and bioassay for research applications. Investigations in this phase will involve laboratory research and early scale-up studies.

Phase II proposals shall focus on scale-up and production of a bioassay for distribution. Assay validation will be required.

045 Development of Novel Formulations for Iron Chelators to Treat Iron Overload in Patients on Transfusion Therapy

(Fast-Track proposals will be accepted.)

Inherited disease of anemia, such as sickle cell disease, the thalassemias and aplastic anemia often require chronic transfusion therapy in order to sustain life or prevent devastating events such as stroke. The administration of repetitive transfusions, however, increases the levels of iron in the body, which, if not removed, causes toxicity to the organs where it is deposited. Traditionally, excess iron is removed from the body through the use of iron chelating molecules. For many years the primary iron chelator used to treat iron overload has been deferoxamine. Although an excellent chelator, it must be delivered intravenously through a slow infusion pump over many hours. This procedure is both time consuming and uncomfortable for the patient often leading to a lack of compliance. More recently, other iron chelators, that can be taken orally, have been developed. While these chelators are more convenient to take, they have their own side effects which may not make them beneficial to all patients**.**

The goal of this solicitation is to develop novel formulations or modifications of existing iron chelators that will provide effective chelation, while at the same time offer a more convenient therapy regimen with minimal side effects. Novel formulations may include liposomal or other encapsulation methods, attachment to target molecules that facilitate homing to organs, or coating with inert molecules. Changes in formulation to reduce rapid metabolism or reduce adverse side effects should be considered.

Phase I proposals should focus on the use of these formulations in animal models to demonstrate proof of principle.

Phase II proposal should involve the development of a well-defined formulation produced under good manufacturing practices (GMP), be uniform from lot to lot and be certified under quality control. The proposal should focus also on scale up and production for future Phase I clinical study.

046 Multiplexed Assay Platforms for Protein Biomarkers of Cardiovascular Disease

(Fast-Track proposals will be accepted.)

Proteomic technologies have the potential to identify and quantify novel proteins in the plasma that can function as biomarkers of the presence or severity of clinical disease states and hold great promise for clinical use. Multiplex arrays that simultaneously measure multiple protein markers are useful in disease screening, assessing disease severity, and prognosis. They economize on time, cost, sample consumption, and reagent volumes while increasing sample throughput relative to single protein measurement. The information provided by a single protein marker is limited and a multimarker approach is more useful in deriving information about the diverse physiologic pathways that contribute to diseases activity.

Antibody based enzyme-linked immunoassays have been adapted for multiplex biomarker assessment and different multiplex platforms relevant to the cardiovascular disease spectrum are being developed for research purposes. However, they are plagued with lack of sensitivity and reproducibility, high variability and correlation of variances, and non-specific binding. The goal of this proposal is to develop multiplex assay platforms specific for cardiovascular diseases that overcome the above limitations. These platforms can be antibody or other protein capture method based but must be scalable and amenable to high throughput formats.

Phase I applications should address initial development and feasibility testing of the multiplex platforms and Phase II applications should be focused on completing the development of the technology for incorporation into the clinic.

047 Transcatheter Ablation Devices for Arrhythmia Treatment

(Fast-Track proposals will be accepted.)

Cardiac arrhythmias represent a major public health burden associated with a high degree of morbidity and mortality. Among the arrhythmias, atrial fibrillation is the most common form of sustained cardiac arrhythmia, and its occurrence which increases with age leads to increased risks for heart disease and stroke. In the United States, there are over 2 million adults diagnosed with atrial fibrillation, affecting about 4% of the population over 60 years of age and contributing to approximately 75,000 strokes per year.

Cardiac transcatheter ablation is an important component of the available therapies for atrial fibrillation, particularly in patients who are intolerant or insensitive to antiarrhythmic pharmacotherpies. A variety of transcatheter ablation devices are in use today which employ heating energy (e.g., radiofrequency, microwave, laser, and high-frequency ultrasound) or freezing energy (e.g., rapid cooling using liquefied refrigerants like nitrous oxide and argon) to destroy the atrial tissue and block electrical conduction or source of the triggers of atrial fibrillation. Currently, the technologies and devices for thermal ablation are relatively mature and are in extensive use. By contrast, cryoablation technologies, which may offer some key advantages over thermal ablation in terms of better tissue preservation, are still evolving and need further development.

The purpose of this SBIR contract solicitation is to foster novel cryoablation technologies and devices in order to significantly improve the efficacy and safety of cardiac ablation treatments over currently available methods. Applications are invited from research teams to develop innovative transcatheter cryoablation technologies and devices to improve treatment of atrial fibrillation.

The Phase I research is expected to focus on demonstrations of proof-of-concept of the new technologies and devices proposed (e.g., development and initial testing of the prototype) and how it can significantly improve the safety and efficacy of treatment of atrial fibrillation over currently available methods.

Phase II studies should extend the efforts of the Phase I studies and focus on further refinement of the technologies and devices, their testing in appropriate animal models, and fulfilling FDA regulatory requirements in order to initiate human safety trials.

048 Developing Novel Anticoagulants and Synthetic Heparins

(Fast-Track proposals will be accepted.)

Anticoagulants are essential in treating stroke patients, deep vein thrombosis, pulmonary embolism, cardiac arrhythmias, or during open heart surgery, and kidney dialysis. Until very recently, pharmacologic prophylaxis of thrombosis was based on three types of anticoagulants: vitamin K antagonists (e.g., warfarin), unfractionated heparin (UFH), and low-molecular-weight heparins (LMWH). The vitamin K antagonists, the only oral anticoagulants currently approved for use, have a number of limitations. There is a need for safer oral anticoagulants that do not require routine coagulation monitoring. Despite advances with low-molecular-weight heparin and unfractionated heparin, more potent parenteral anticoagulants are still required. LMWHs, which are derived from UFH using a variety of chemical and biosynthetic processes, have different fine chemical structures that significantly impact their activity and pharmacological profile. Recently oversulfated chondroitin sulfate was identified as the contaminant in UFH that led to adverse clinical events. Synthetic heparins that are pharmacologically effective, safe and cheap could eliminate the concerns associated with the animal derived products. Bleeding is the major complication associated with all the anticoagulant drugs. Agents that target specific steps in clot formation may be able to reduce this serious complication. Given these considerations, development of new anticoagulants is likely to take into account properties such as non-hemorrhagic side-effects, drug-bioavailabilty, more favorable pharmocokinetics and a predictable dose response that will not require hospitalization and coagulation monitoring.

In keeping with our continuing quest for better anticoagulants, the goal of this solicitation is to develop more effective, safer and cheaper antithrombotic drugs. Phase I applications should focus on the development of a well characterized compound, proof-of principle, in-vitro testing and pharmacokinetic evaluations. Phase II will translate the Phase I findings into large animal models, scale-up and production. Programs that may be further advanced in development may submit applications with appropriate Phase I milestones and Phase I and II specific aims.

049 Development of Gene Transfer Approaches for Correction of Genetic Blood Diseases

(Fast-Track proposals will be accepted.)

Gene therapy has the potential to provide specific and effective treatment for hereditary blood diseases such as the hemophilias and sickle cell anemia. The development of safe delivery systems that are targeted and efficient is critical to realizing effective therapy. There has been major progress in the research of several viral vector approaches, but additional work is needed to realize the full potential of these systems. Toxicity, chromosomal integrations and immune response are safety issues for viral vectors that need to be addressed as new approaches are developed. Recent studies have increased the understanding of the mechanisms involved in the development of undesired side effects in gene therapy. Furthermore, animal models and methods have been developed to evaluate the gene transfer approaches. Non-viral gene delivery systems offer alternatives that may avoid some of the safety issues of the viral vectors. However, these systems have challenges of targeting select tissues and long term expression. All systems must carefully consider all the safety issues, especially for genetic blood diseases which require lifetime treatment. Each genetic blood disease has its own unique requirements and challenges and careful consideration should be given to achieve a safe and effective system that addresses the needs of the specific disease.

Phase I applications should at a minimum evaluate the feasibility of the gene transfer approach for delivery of the gene to correct a hereditary blood disease. Phase II applications should at a minimum further develop the gene transfer approach, evaluate safety and demonstrate efficacy in an appropriate animal model of the specific blood disease.

050 Wireless Communications Systems for Magnetic Resonance Imaging (MRI) Guided Surgery

(Fast-Track proposals will be accepted.)

Magnetic resonance imaging has potential to revolutionize minimally invasive surgery and interventional procedures, by affording surgery-like visualization without conventional surgical incisions for exposure. Unfortunately, magnetic resonance imaging creates acoustic noise that makes it difficult or impossible for surgical or interventional teams to communicate. The loud noise also makes it difficult to communicate with and monitor awake patients undergoing procedures inside the MRI bore. A few commercial systems are available that suppress acoustic noise and permit “open microphone” communications among staff and patients on two or more parallel audio channels. However, these systems require tethered transmission lines that dramatically impair staff mobility in a way that detracts from surgery or procedure conduct. “Circulator” nurses and technologists are unable to gather and assemble devices, implants, and drugs that may be stored within or without the suite. Monitoring technologist and anesthesiologists have insufficient mobility to move around the suite to tend to instantaneous patient needs and administer medications. Operators are unable to change position or move to different surgical tables and fields.

Wireless communications systems are necessary to conduct advanced image guided interventional and surgical procedures under real-time magnetic resonance imaging. To date there are no suitable commercial solutions.

Wireless communication systems are technically feasible to support MRI guided clinical interventional procedures. A development system should be able to suppress at least 35-40 dB of acoustic noise to the operator at the dominant frequencies generated during rapid magnetic resonance imaging. The system should permit clear “open microphone” communications between all staff and patients even during scanning. The system should have at least two audio channels permitting all combinations of monitoring and/or speaking to staff on either or both channels. The system should be self-powered or battery powered to last at least 8 hours. The headset systems should be comfortable for prolonged wear, and should have controls that can be mounted for operation by sterile operators. The signal transmission should be robust to headset position and orientation and should not require line-of-site alignment with a single receiver. The system should afford headsets to least 6 operators and one patient, as well as headset or hands-free communication with technologist staff outside the scanner. The system should include additional slave audio outputs. The system should include an interruptible audio input for patient entertainment or distraction. The system should operate at field strengths ranging between 1.0T and 3.0T. 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 radiofrequency patient physiologic telemetry systems used during MRI.

The Phase I application should provide a working prototype for a wireless communications system to support MRI guided clinical interventional procedures.

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

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

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

This solicitation invites proposals in the following area:

034 Simple, Low-Cost, Onsite Biomarker Test Kits for Alcohol-Associated Disorders

(Fast-Track proposals will be accepted.)

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. Several biomarkers have been in limited clinical use for many years. The traditional biomarkers for alcohol consumption include the enzymes gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and carbohydrate-deficient transferrin (CDT). Other biomarkers include mean corpuscular volume (MCV), 5-hydroxytryptophol (5-HTOL), a serotonin metabolite, and ethyl glucuronide (EtG), a metabolite of alcohol. Biomarkers of alcohol-induced tissue injury, such as alcoholic liver disease (ALD), include alpha-smooth muscle actin (SMA), fibronectin, collagen type I, serum hyaluronate, matrix metalloproteinase alpha and chemokine ligand 2. Tumor necrosis factor increases with the degree of heart dysfunction, while, biomarkers of fetal alcohol exposure and pancreatitis include fatty acid ethyl esters (FAEE), ethyl oleate and ethyl linoleate.

The use of many of these biomarkers in research and clinical practice has been limited by the cost of the assays, the difficulty of the assay technique, the accessibility of the biological source material, and the need to process, store, and ship samples. Clinical trials of therapeutics for alcohol-associated disorders could be significantly advanced with low-cost onsite, field serviceable biomarker assays. Sample collection and the assay must be relatively simple and acceptable to practitioners and patients.

- Phase I of the requested SBIR contract should be aimed at demonstrating the feasibility of the low-cost, onsite assay technology with potential alcohol-associated biomarkers. Emphasis should be placed on those biomarkers that show acceptable sensitivity and specificity for alcohol exposure or tissue damage over a reasonable time delay and utilize easily accessible tissues or employ non-invasive methods. Animal models and/or humans should be used for these studies. Fast Track (combined Phase I and Phase II) applications could be proposed. Two to three contracts are anticipated to be awarded for this topic.

035 Biological Sample Repository for Alcohol Research

(Fast-Track proposals will be accepted.)

The development of alcohol-related laboratory methodology and other technology-driven translational research efforts, including alcohol biomarker and alcohol biosensor development frequently require well-characterized biological samples for method discovery and assay validation. However, currently investigators must rely upon informal relationships with colleagues to acquire, characterize, annotate, store and ship such samples to them for use in their research. No standardized sample set exists employing either alcohol-exposed human or animal biological materials of interest to alcohol researchers. Such materials of interest include blood products (e.g. whole blood, plasma, white cells, and platelets), cerebrospinal fluid and urine from alcoholic and non-alcoholic individuals of each sex obtained from genetically representative ethnic groups wherein such individuals are or are not exposed to known and standardized blood alcohol concentrations at the time of collection. Tissue pathology samples (e.g. liver, brain, and lung) from known alcohol and non-alcoholic individuals would also be useful. In addition, a parallel sample set could be obtained for strains of laboratory research animals commonly employed in basic alcohol research (e.g. rat, mouse, hamster, rhesus monkey) with and without standardized alcohol exposure. One to three contracts are anticipated to be awarded for this topic.

The purpose of this SBIR Contract is to develop an Alcohol Research Sample Repository that:

- Acquires both human and animal model biological samples (with/without known alcohol exposure) in a standardized fashion,
- Characterizes them in an information system,
- Appropriately indexes and stores the samples to maintain their research utility,
- Implements a distribution system to get samples to qualified investigators needing this resource to advance their alcohol research.

036 Identification of miRNAs as Biomarkers for Alcohol-Induced Disorders

(Fast-Track proposals will be accepted.)

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 predictive, 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 or alcohol-induced disorders would be a valuable biomarker. Therefore, the detection of changes in the full complement of miRNAs associated with alcohol exposure or alcohol-induced disorders in biological specimens can provide new avenues for alcohol biomarkers. 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 or alcohol-induced disorders in humans. 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. Fast Track (combined Phase I and Phase II) applications could be proposed. One to three contracts are anticipated to be awarded for this topic.

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 exposure, 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.

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).

017 Clinical Sample Collection and Processing Technologies for Infectious Disease Diagnostics

(Fast-Track proposals will be accepted.)

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

There is an urgent need for rapid, highly sensitive and specific clinical diagnostics that are easy to use, cost-effective and can diagnose individuals infected with pathogens or individuals that have been exposed to toxins. The clinical sample collection and processing steps represent barriers to the development of rapid medical diagnostics for infectious diseases and toxins.

Improved clinical sample collection and processing technologies must be developed for all classes of samples used to diagnose infectious diseases and detect exposure to toxins, including nasopharyngeal fluids, blood, plasma, serum, sputum, cerebrospinal fluid, urine, feces, etc. The final purification product(s) may include nucleic acids, proteins, lipids, metabolites, and/or other analytes of interest.

Project goal: The goal of this project is to develop rapid, modular, clinical sample collection and processing technologies that can be incorporated into integrated, closed sample infectious disease diagnostic platforms. The final product should require minimal operator effort and expertise, and should address one or more of the infectious diseases listed on the NIAID Division of Microbiology "Small Business High Priority Areas of Interest" website at http://www.niaid.nih.gov/ncn/sbir/sbirareas.htm#dmid.

Areas of research will include:

- Development of improved methodologies and technologies for rapid clinical sample collection, processing, and if appropriate, concentration
- Development, incorporation, and validation of process controls.

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:

099 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.

100 Instrument Development

(Fast-Track proposals will not be accepted.)

Easy-to-use assessment instruments are needed to enhance epidemiology research. Areas of interest include but are not limited to:

a. *Community Assessment.* The development of community diagnostic instruments for psychometrically sound assessment of community characteristics is essential to improve our understanding of how community factors affect drug abuse and ensuing behavioral and social consequences. Standardized assessments of community characteristics are needed to better understand the full impact of drug use and to develop targeted interventions to specific community needs.

b. *Assessment of Psychiatric Comorbidity in Community Settings.* Easy to use, reliable, and valid instruments are needed to assess psychiatric comorbidity in different populations of drug abusers, including adolescents and those in community drug abuse treatment settings.

c. *Assessment Instruments to Measure CNS Function Related to Drug Abuse.* The development of age-appropriate assessment instruments to measure behavioral and cognitive function over the course of development will contribute to our understanding of vulnerability to drug abuse and functional impairment due to drug use.

101 Rapid Assessment Tools of Sexual and Drug Use Risk Behaviors

(Fast-Track proposals will not be accepted.)

This SBIR concept seeks the development of rapid assessment tools for sexual and drug use risk behaviors that provide feedback to client populations about those risks and link that feedback to behavior change messages. Clients can be provided with these messages directly or they can be used as a basis for tailored, brief counseling by service providers. Rapid assessment tools like these would have application in a wide variety of health care and public health environments. They provide a simple way of addressing sensitive behaviors and enabling the kind of counseling that is otherwise very time-consuming for providers to formulate and deliver. These tools also provide a way to bridge sexual and drug use risks, which has often been difficult to accomplish in practice. In settings such as STI clinics, providers have protocols and benchmarks for addressing sexual behaviors, but do not have the same means to deal with substance use, including non-injection drug use. Conversely, substance use settings often have difficulty approaching sexual behaviors and their risk reduction protocols often neglect or provide limited coverage of sexual risks, even in the context of substance use. There are AIDS research centers, AIDS service organizations, community-based organizations and other high volume settings that are seeking to build systems that can accept risk assessments as well as modular behavior change tools in electronic formats. These tools could be incorporated into routine services such as primary care, STI screening, with prevention messages tailored to different providers' needs (e.g., providers in an AIDS service organization may have more familiarity with sexual and drug use risk than end users in a general internal medicine clinic). In addition to their value in integrating assessment and behavior change, the risk assessment portions of these tools may provide process or outcome data for the evaluation of interventions in a variety of settings, particularly if they provide evidence of reliability and validity. These tools also may provide a way of easily collecting routine client data in agency settings that are required by CDC, HRSA, and other funders.

102 Electronic Drug Abuse Treatment Referral Systems for Physicians

(Fast-Track proposals will not be accepted.)

Research shows that primary care physicians often do not screen for drug abuse disorders or HIV/AIDS. While this may be related to stigma attached to illicit drug use and HIV/AIDS or to a lack of adequate health insurance, it may also be due in large part to the lack of an adequate referral system that primary care physicians can use for the patients they identify as having a potential drug problem or are HIV positive. The lack of a referral system places a greater burden on the physician to secure treatment resources for the patient, and also places the physician at greater risk if no appropriate treatment can be found. The purpose of this initiative is to develop and test a practical and usable electronic drug abuse treatment and HIV/AIDS referral system for use by physicians in primary care settings, including doctor's offices, emergency rooms, etc. The system should be targeted at local needs, for example by taking into account local private insurance coverage and the types of insurance accepted by local treatment providers. The referral system should include an actively-maintained database of local providers, and which should include information such as insurance carrier, geographic "catchment" area of treatment providers, types of substance disorders treated, types of co-occurring disorders (mental disorders, etc.) treated, HIV status, gender, age, other pertinent treatment factors needed by primary care physicians to make appropriate referrals. The system should be designed to be reliable and efficient. For example, it should allow the primary care physician to schedule an appointment for the patient at the time of the visit or make other needed arrangements to ensure a successful referral. The proposal should address requirements both for primary care physicians and for drug abuse treatment providers who enroll with the referral system. For example, treatment providers should be able to "rapidly" assess referrals and enroll those in need of treatment services. The applicant should demonstrate a thorough understanding of the incentives and disincentives that exist in primary care to

screen, assess, and refer patients to substance abuse treatment and HIV testing, as well as the incentives by treatment providers to accept referrals for treatment services. The applicant should design a Phase I study that demonstrates the feasibility of creating an information and referral system that meets the needs of the primary care physician who currently has no efficient or reliable means of referring patients having a suspected substance use disorder to treatment. Phase II will entail a demonstration of the financial viability of the electronic referral system. The applicant should be able to identify customers and should demonstrate the ability to adapt the electronic referral system to the needs of specific customers, such as physician groups, insurance payers, and treatment providers.

103 Virtual Reality Simulations to Train Caregivers/Providers

(Fast-Track proposals will not be accepted.)

There is a growing movement and body of research on the power and utility of virtual healing, virtual data collection, and virtual training or service delivery. For instance, experiments have shown that the experience of pain can be softened through virtual interventions that redirect patients senses toward pleasurable memories and sensations. In addition, many tools have been or are currently in development to facilitate collection of data, and to promote use of evidence-based prevention interventions. Virtual technology can also be used as a tool to train service providers or caregivers in the administration of best practices to participants in an intervention. As an example, virtual technology could provide a “practice family” or a set of example families to guide practitioners through conflict resolution and mediation for use in family-based interventions. The technology could also be used to assist service providers in addressing the needs of vulnerable and difficult-to-reach populations. Web-based and virtual reality platforms allow for multiple approaches to training and service delivery, and could include game-based models of trainer-participant/provider-client interactions. These platforms could walk users through scenarios to promote skills-development, to test response patterns in a wide variety of situations, and to gauge the effectiveness of different techniques. The purpose of this SBIR contract is to stimulate the development of virtual reality simulations to enhance the quality of intervention training and/or service delivery.

104 Improvement of Reliability and Validity of Reporting of Sensitive Data

(Fast-Track proposals will not be accepted.)

The reliability and validity of self-report of drug use and related behaviors (e.g., HIV risk behavior) is a matter of great concern. Use of new technologies for real time data collection in ecological settings is of great interest because these technologies enable collection of drug consumption data in context. Studies to improve methodologies based on variations of standard survey protocols or computer-assisted self-interview (CASI) and personal interview (CAPI) are also encouraged.

105 Development of Therapeutic Agents for Substance Use Disorders

(Fast-Track proposals will be accepted.)

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

Project goals: The neurophysiological underpinnings of substance abuse appear to involve numerous neurotransmitter systems including opioid, dopamine, serotonin, GABA and glutamate across multiple brain regions. Small businesses have used government grant programs to conduct basic research and early preclinical testing; however, many of these projects are still in an early drug development stage and are not yet candidates for capital funding. Thus, the short-term goal of this SBIR contract is to create a mechanism of ‘bridge funding’ whereby novel therapeutic agents or immunotherapies that have demonstrated promising pre-clinical findings can be further evaluated in clinical trials. It is anticipated that these funds, long term, will help shepherd promising products from ‘bench to bedside’.

Proposed work: The goal of this NIDA SBIR program is to assist small businesses in developing a commercially-viable therapeutic agent that is indicated for substance abuse (e.g., cocaine, opioids, cannabis and methamphetamines) and nicotine dependence. Companies are asked to submit proposals for the development of their own new chemical entities (NCEs) or immunotherapies (e.g., vaccines, monoclonal antibodies). Novel NCEs

or immunotherapies should be in the late-stage preclinical development, where the expected time to initial clinical testing is <1 year.

Proposed work should prioritize initiating clinical trials as quickly as is safely possible to expedite the identification of the most promising treatment opportunities in an FDA-compliant manner. Studies can be in the form of a pilot study, Phase I safety trial, or Phase II randomized, double-blind, placebo-controlled clinical trial. Special emphasis will be given to NCEs or immunotherapies designed to treat and/or prevent the development of substance abuse and co-morbid psychological disorders. Preliminary preclinical safety data should also be included. All preliminary data submitted will remain confidential and the intellectual property of the firm.

NIDA will provide assistance to the small business for the development of its investigational new drug (IND)-directed developmental plan. Regulatory guidance will be provided to help with filing of an experimental IND with the US Food & Drug Administration (FDA). Subsequently, the firm is encouraged to use these data to continue to develop this therapeutic agent independently, in collaboration with academia, or in partner with industry.

Phase I activities and expected deliverables:

- Mutually agreed-upon developmental/statistical plan that describes in detail the experiment(s) necessary to file an (exploratory) IND, depending on the agent selected.
- Demonstrated ability to deliver results for the initial set of experiments (project-specific, according to the development/statistical plan above).
- Begin enrollment of clinical subjects.

Phase II activities and expected deliverables:

- Completion of experiment(s) outlined in the development/statistical plan (can be re-evaluated, if needed).
- If warranted, provide sufficient data to file an (exploratory) IND for the candidate therapeutic agent with indications for substance abuse and dependence.
- As per the FDA's Exploratory IND Guidance, the firm should demonstrate the ability to produce a sufficient amount of clinical-grade materials suitable for an early clinical trial (http://www.fda.gov/cder/guidance/7086fnl.htm).
- A comprehensive intellectual property (IP) and development plan, outlining how the company will commercialize the potential therapeutic agent.

Potential applicants should submit a letter of intent.

106 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. The Specific areas of interest include, but are not limited to the following:

1) Approaches to improve bioavailability of compounds with poor oral bioavailability. The pharmaceutical agents of interest include, but are not limited to, delta-9-tetrahydrocannabinol (THC) and lobeline. 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. The oral bioavailability of both THC and lobeline is very low and frequent dosing is required. Formulations to improve bioavailability and/or to reduce dosing frequency would be expected to improve the therapeutic effectiveness.

In Phase I, the contractor is expected to demonstrate the feasibility of the dosage form by formulating a prototype dosage form based on biopharmaceutical and pharmaceutical rationale. In Phase II, the contractor will carry out pharmacological, toxicological and pharmacokinetic evaluations. 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.

2) Development of controlled release dosage forms for addiction treatment medications in order to maintain therapeutic drug levels for extended periods of time to alleviate compliance problems associated with addiction treatment or to significantly reduce the abuse potential of prescription drugs/drug products.

   In Phase I, the contractor is expected to demonstrate the feasibility of the dosage form by formulating a prototype dosage form based on biopharmaceutical and pharmaceutical rationale. In Phase II, the contractor will carry out pharmacological, toxicological and pharmacokinetic evaluations. 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.

3) 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 through in vitro tests and/or preliminary in vivo evaluations of the batches. In Phase II, the contractor is expected to select the most promising technology/approach, establish the procedures for a GMP scale-up production, and manufacture the GMP batch of the macromolecule. 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.

107 Design and Synthesis of Treatment Agents for Drug Abuse

(Fast-Track proposals will be accepted.)

Budget (total costs): Phase I: $100,000 (1 year); Phase II: $750,000 (2 years)

The purpose of this contract is to design and synthesize novel compounds intended specifically for the treatment of substance abuse including cocaine, methamphetamine or cannabinoid abuse. The classes of pharmacotherapeutic agents include, but are not limited to, compounds interacting with corticotrophins, cannabinoid, biogenic amines, GABA, and glutamate systems. The design and development of antibodies or vaccines as immunopharmacotherapy for methamphetamine or opiate abuse will also be of interest.

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 pharmacological and toxicological evaluations and select lead compounds as potential clinical candidates.

108 Repository for Substance Abuse Brain Imaging Data (SBIR/STTR)

(Fast-Track proposals will not be accepted.)

All classes of brain imaging studies, anatomical, functional and neurochemical, are well suited for secondary analysis and meta-analysis. A substantial barrier to conducting such secondary analysis is access to primary data collected across multiple laboratories and multiple file formats. However, there have been demonstration projects (e.g., fMRI Data Center) that have successfully shown that brain imaging data can be stored, retrieved and used for secondary analysis (c.f.,Van Horn JD, Ishai A Mapping the human brain: new insights from FMRI data sharing Neuroinformatics. 2007). However, existing repositories often are limited to one imaging modality (e.g., anatomical or functional MRI)

This solicitation would seek proposals to establish a comprehensive brain imaging repository that would be appropriate for substance abuse researchers which could eventually be sustainable as a commercial enterprise.

109 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.

110 Development of Science Education Materials or Programs

(Fast-Track proposals will be accepted.)

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

Therefore to address these issues this contract solicitation seeks innovative projects or programs that will substantially improve scientific literacy among one or more of the following groups: 1) students and teachers at the kindergarten through 12th grade levels; 2) the general public; 3) health care practitioners; 4) members of the judicial system; 5) other groups that have a need to be scientifically literate. Programs or projects must seek to improve general scientific literacy with a specific focus on drug abuse related research. For example, a project could teach basic neuroscience first and then subsequently teach how abused drugs act in the brain and body. Programs and projects aimed at school children should convey the scientific process in a way which makes

learning science fun and interesting for the students and which captures their enthusiasm for science. Student programs and projects must also adhere to the National Science Education Standards. Programs or projects aimed at other groups should be directed to increasing their knowledge of scientific terms, concepts, reasoning, and their ability to understand scientific public policy issues. Regardless of the intended audience, all programs and projects must include an evaluation component that can provide useful and accurate information on the efficacy of the program or project.

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

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

111 Screening, Characterization and Validation Assays for Protein Capture Reagents

(Fast-Track proposals will not be accepted.)

NIDA seeks proposals to develop and validate methods to characterize protein affinity reagents and to establish standard operating procedures for those methods.

The utility of protein affinity reagents is greatly enhanced by information regarding in situ or in vitro binding conditions, effects of post-translational modifications of the protein target on reagent binding, reagent selectivity and stability.

Phase I of this SBIR will be development and validation of methods for such characterization. Part of Phase I will also be development of standard operating procedures. It is important that methods developed can be implemented for high throughput screening of affinity reagents.

Phase II will use methods and SOPs developed in Phase I to characterize commercially available affinity reagents. The characterization data and appropriate metadata will be made publicly available.

Contract submitted under this concept can be up to $200,000 for phase 1 and $1,500,000 for phase II. Contracts can also extend to up to 4 years for the phase II award.

112 Tool Development for New or Improved Capture Reagents

(Fast-Track proposals will not be accepted.)

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.

Contract submitted under this concept can be up to $200,000 for phase 1 and $1,500,000 for phase II. Contracts can also extend to up to 4 years for the phase II award.

NATIONAL INSTITUTE OF MENTAL HEALTH (NIMH)

The mission of the National Institute of Mental Health (NIMH) is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. Mental disorders constitute an immense burden on the U.S. population, with major depression now the leading cause of disability in the U.S., and schizophrenia, bipolar disorder, and obsessive-compulsive disorder ranked among the ten leading causes of disability. NIMH also takes a leading role in understanding the impact of behavior on HIV transmission and pathogenesis, and in developing effective behavioral preventive interventions. The NIMH conducts a wide range of research, research training, research capacity development, as well as public information outreach and dissemination to fulfill its mission.

This solicitation invites proposals in the following areas:

061 Home-Based Lithium Level Testing for Bipolar Patients

(Fast-Track proposals will not be accepted.)

The purpose of this contract is to assess the feasibility of a home-based lithium level test. Lithium is both an effective and commonly used treatment for bipolar disorder (BD). Management of patients on lithium, however, is complicated by a narrow therapeutic range (0.6 to 1.2 mmol/L) with inappropriate levels resulting in poor symptom control or lithium toxicity. Improved lithium level monitoring could result in better clinical management and increased treatment adherence.

Recently, a reliable office-based method for obtaining lithium levels was developed and received FDA approval, indicating that lithium levels can be obtained routinely and relatively inexpensively. As chronic disease self-management models evolve, there is an increasing need to provide patients with the tools to monitor and manage their care. A home-based lithium level test would provide BD patients and their families with the tools to monitor their lithium levels on a regular basis and adjust treatment accordingly as directed by their health professional.

Phase I should include development of a prototype home-based lithium test, assess usability of the prototype with bipolar patients, and compare the results of the prototype to standard lab-based lithium levels. Since the degree of complexity of this project may require more than six months to complete, the offeror should clearly identify the amount of time and support needed to complete their proposed scope of work. Up to one year of work would be allowed for a Phase I contract and up to $200,000 total costs. Phase II contracts would allow up to two years and up to $750,000 total costs.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

National Center on Birth Defects and Developmental Disabilities (NCBDDD) provides national leadership for preventing birth defects and developmental disabilities and for improving the health and wellness of people with disabilities. Our work includes research for helping children to develop and reach their full potential and promoting health and well-being among people of all ages with disabilities. Critical evidence from this research advances knowledge of major risk and protective factors and modifiable environmental exposures related to birth defects, disabilities, and blood disorders. Research findings flow to information consumers through a variety of channels including peer-reviewed articles, reports, conference presentations and other channels of communication such as web-based publication databases. The knowledge gained from these studies provides an important basis for informing others and for developing new prevention and intervention strategies.

This solicitation invites proposals for the following topic area:

008 Development of Website with Modules for Study Participants and Fellow Researchers

Birth defects affect 1 in 33 babies and are a leading cause of infant mortality in the United States. More than 5,500 infants die each year because of birth defects. While we know how to prevent some birth defects like spina bifida and fetal alcohol syndrome, the causes of about two-thirds of birth defects are not known.

CDC is working with partners in Arkansas, California, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah on the Birth Defects Prevention Study (BDPS), the largest case control study of children with birth defects in the United States. This ongoing study enrolls mothers of children with birth defects, and mothers of children without birth defects and asks them to participate in an interview and to provide buccal swabs that will be used to study genetic determinants.

Impact: Increasing the knowledge about risk factors for birth defects will enable prospective parents to make choices to ensure a healthier pregnancy. An interactive overview of the literature on risk factors for birth defects for fellow researchers will improve the quality of birth defects research worldwide.

Objective: There is a need to inform potential and past participants in the BDPS as well as fellow researchers, the general public and policy makers about the importance of the BDPS by showcasing its products, the importance to participate from a parent's perspective and to be a resource on risk factors for birth defects. We are seeking to identify a vendor to develop an interactive website which will capture our audience and provide them with the information they are looking for. It is important that the website be 508 compliant and that it use creative technologies to display the information. The system could possibly be hosted on the CDC network and would then have to undergo a Federal Information Security Management Act (FISMA) certification and accreditation as well as adhere to CDC and Coordinating Center for Health Promotion (CoCHP) standards for web development (i.e., secure coding practices). We will need a module that will show our participants what is involved in participating in the study, a module for scientists and researchers that will let them search interactively through the existing birth defects literature and a module for the general public on what are birth defects and what is known about risk factors for major birth defects. Once developed, different aspects of the website such as the information research module can be adapted for other research or commercial uses for information dissemination.

009 Development of a Publication Database and Information Retrieval System with Announcement Feature

Improving our ability to address a number of areas that contribute to critical health outcomes is an important public health priority and requires informing a variety of audiences with timely information. Some examples demonstrating the significance of the research which supports and addresses issues related to birth defects and developmental disabilities, blood disorders, disabilities and human development are as follows:

- Birth defects affect 1 in 33 babies and are a leading cause of infant mortality in the United States. More than 5,500 infants die each year because of birth defects.
- Bleeding and clotting disorders pose important problems for women because of the relationship of these disorders to reproductive issues.
- In 2005, disability prevalence across all 50 states ranged from 11.4% to 25.8%, with an average or median estimate of 20%.

Objective: There is a need to identify a feasible, innovative technology that improves upon how information in the existing database is archived, up-dated and retrieved. The National Center on Birth Defects and Developmental Disabilities proposes the following project for an SBIR contract. We seek to develop an electronic tool to manage and inventory our publications and presentations to support our research and public health practice portfolio. This information should be available to people within CDC as well as our external partners. We need an easily maintained and up-datable, bibliographic database and informational retrieval system capable of capturing the outputs generated by research activities, grantees, collaboratives and conferences. It is important that this system provide the public with an easy to access tool and search mechanism to locate publication information to replace the current system (http://www2.cdc.gov/ ncbddd/pubs/). This retrieval system publication database will also be used internally for program evaluation purposes.

Briefly, the system developed should: (a) be sufficiently robust as to track publications and conference presentations into a searchable bibliographic database and map these artifacts to the Center, Division, HHS and CDC health protection goals and (b) make this information easily accessible to a variety of information consumers (such as other researchers, local, state and national organizations that deliver birth defects prevention services and the general public). The system would be hosted on the CDC network and must undergo a Federal

Information Security Management Act (FISMA) certification and accreditation as well as adhere to CDC and Coordinating Center for Health Promotion (CoCHP) standards for web development (i.e., secure coding practices).

For an excellent example of a searchable bibliographic database that captures the agency specific publications, reports, symposium proceedings and/book chapters that appear in the scientific literature, please follow the links to the CDC National Institute for Occupational Safety and Health (NIOSH) publication database (NIOSHTIC-2):

http://www2a.cdc.gov/nioshtic-2/n2info.asp

http://infoserve.sandia.gov/electronic/nioshtic2.html

010 Development of Standardized Evaluation Software for Blood Disorder Public Health Surveillance Systems

The Division of Blood Disorders (DBD) has established a public health surveillance system called the Universal Data Collection (UDC) system in the federally supported hemophilia treatment center (HTC) system comprised of about 135 HTCs located primarily in educational institutions throughout the United States and its territories.

The stakeholders have worked with a software development company to create a specialized electronic medical record database for use in the HTCs to monitor the care of their patients. DBD has worked with this company to make it possible for the UDC surveillance data to be captured by this software and transmitted to CDC. Most of the country's HTCs have adopted this software which facilitates the collection of these data. In addition, the stakeholders are working with the vendor to convert this database to a web application.

Impact: It is important that the surveillance system be evaluated as this transition is occurring to ensure that the resulting system is useful, efficient, accurate, reliable and effective in the performance of its purpose. The surveillance system is central to the Division's ability to carry out our mission which is to reduce or prevent the complications of bleeding and clotting disorders. The surveillance system enables us to identify and measure the occurrence of complications, identify risk factors and high risk groups, develop interventions, and assess the effectiveness of the interventions in decreasing the rate of the complications.

Objective: The objective of this announcement is to develop evaluation software compatible for use with the specialized surveillance systems. The software will be sold to treatment centers, other providers and industry professionals as a means to validate individual and collective health related events, gather credible information regarding performance of the system and help DBD state and justify conclusions regarding the validity of the data collected by this surveillance system.

011 Animated Software depicting Iron Out of Balance

Iron out of balance affects millions of Americans. It refers to a number of disorders that occur when there is too little or too much iron in the body. The cause of these disorders may be either inherited or acquired.

Hemachromatosis is an inherited disorder that leads to iron out of balance. Persons with this disorder absorb too much iron from their diet. It is estimated that one million U.S. Caucasians have the genetic predisposition for hemochromatosis (HHC).

Iron out of balance may also be acquired as a result of repeated transfusions. The management of blood disorders such as Thalassemia and Sickle Cell Disease requires repeated transfusions which may result in iron overload.

The body has no means of excreting iron, except in minute amounts; therefore, over time, the excess iron accumulates in vital organs resulting in disease such as cirrhosis, heart failure, arthritis, diabetes, hormone imbalances or complete organ failure and death. Early detection and treatment to remove iron excesses can save lives and prevent disease.

Impact: Through early detection and treatment morbidity and mortality associated with iron overload may be prevented. Research conducted by the CDC and others indicates that primary care physicians may lack the

knowledge they need to be able to identify at risk patients. These studies have also identified widespread misunderstanding among health care professionals about the appropriate diagnostic tests and treatments. Until the last decade, diagnosis of iron overloading conditions most commonly relied on diagnosing the triad of cirrhosis, diabetes mellitus, and skin bronzing, and was only confirmed through a liver biopsy. These methods could only confirm disorders which had progressed to their later stage, the impact of which resulted in high excessive morbidity and mortality.

Objective: There is a need to enhance public health translation of interventions developed and implemented to reduce complications of blood disorders to medical personnel, patients and their family members and communities. Improved translation activities will facilitate diagnosis, management and screening for blood disorders. We are seeking to identify a vendor to develop animated learning modules which enhance the understanding of complicated blood disorders. Once developed the modules would be validated and sold for profit to providers, patients, medical schools, and industry professionals.

012 Development and Evaluation of Web-based Applications Using Emerging Technologies and New Media

NCBDDD's work includes identifying the causes of and preventing birth defects and developmental disabilities, helping children to develop and reach their full potential, and promoting health and well-being among people of all ages with disabilities. One way in which NCBDDD communicates our science related to birth defects, developmental disabilities, disabilities, and blood disorders is through our Website. Our goal for our Website is that our audiences are able to find information easily, understand the information and use the information appropriately. Our audiences include the public, partners, public health and health professionals, educators, and policy-makers. To accomplish our goal we have undertaken an initiative to improve the usefulness, usability, and effectiveness of our existing website through a user-centered, data-driven, research-based process.

Impact: Our website must be science-based, audience-focused, standardized and streamlined, compliant with CDC and HHS standards. The website will have an accessible reading level, and will be evaluated on an ongoing basis. By creating a science-based, audience-focused website that incorporates emerging technologies and new media we will increase the impact of NCBDDD's science.

Objective: The objective of this announcement is to develop applications using emerging technologies and new media that can be incorporated on the NCBDDD Website. The applications should be interactive so that our audiences may connect with our information effectively and efficiently. Examples of possible applications are videos, eGames, or simulations. These applications must be 508 compliant. The applications should be based on principles and evidence-based research related to human computer interaction, communication and education. Once developed and evaluated, the technology or applications can be sold for profit.

013 Application of Gaming Technology to Communicate Health Messages and Promote Healthy Living among Persons with Disabilities

About 50 million Americans, or one in five people, are living with at least one disability, and most Americans will experience a disability some time during the course of their lives. The Surgeon General's Call to Action to Improve the Health and Wellness of Persons with Disabilities encourages Americans to help increase the quality of life for people with disabilities through better health care and understanding. Being healthy means the same thing for all people-getting and staying well to lead full, active lives. That means having the tools and information to make healthy choices and knowing the risk factors for illness. For people with disabilities, it also means that problems such as pain, depression, and a greater risk for certain illnesses can be treated or prevented.

Impact: People with disabilities, birth defects, developmental disabilities, and blood disorders require health care, information, and education to help them learn about and live healthy lifestyles. Electronic games or eGames are an innovative tool to provide targeted health messages about healthy living. These electronic applications have been shown to improve health in a variety of target audiences and for a number of health issues such as increasing physical activity, combating dementia, or improving medical compliance in cancer patients.

Objective: The objective of this announcement is to develop an application for cutting edge games and/or game technologies designed to promote healthy living among persons (children, teens, and adults) with disabilities, birth

defects, developmental disabilities, and blood disorders. For example, these could be applications/games designed to improve self-care, to increase physical activity, or enhance other health behaviors. These might be a series of interactive health games that could be played through an electronic application such as the Internet, a video game console, a mobile phone, or a portable media player. Once developed, the technology or games could be sold for profit to educators, health professionals, or the public.

014 Use of Cutting-edge Technology to Communicate with and Educate Health Care Professionals about Birth Defects, Developmental Disabilities and Ways to Improve the Health and Wellness of Persons with Disabilities

NCBDDD's work includes identifying the causes of and preventing birth defects and developmental disabilities, helping children to develop and reach their full potential, and promoting health and well-being among people of all ages with disabilities. NCBDDD seeks to provide health care professionals with current scientific information related to the persons with birth defects, developmental disabilities, disabilities, and blood disorders. To accomplish this NCBDD has developed practice guidelines, continuing education courses, and a variety of materials.

Impact: It is important that NCBDDD reaches health care professionals, including first responders, with timely, scientific information related to those populations whom NCBDDD serves. For example, NCBDDD has developed *Guidelines for Fetal Alcohol Syndrome Referral and Diagnosis* and *Recommendations to Improve Preconception Health and Health Care* designed to provide guidance to health care professionals. Additionally, our information about vulnerable populations such as those who are pregnant or have disabilities may be used to educate first responders about how to best protect these persons during a disaster.

NCBDDD would like to translate our scientific information into electronic and/or digital formats that would enhance the effectiveness and efficiency in how we communicate our practice guidelines and professional development materials with health care professionals. Sharing this information with health care professionals who work directly with the populations we serve will ultimately impact the heath of those persons with birth defects, developmental disabilities, disabilities and blood disorders.

Objective: The objective of this announcement is to develop an application(s) using cutting edge technology to communicate with and educate health care professionals about NCBDDD science and guidelines related to birth defects, developmental disabilities, disabilities, and blood disorders. The application should increase health care professionals' knowledge, attitudes, and/or skills. The application(s) could incorporate interactive game technologies, role-based electronic simulations or interactive fiction. These could be communication and educational activities designed for electronic applications such as the Internet, a video game console, a mobile phone, or a portable media player. Once developed, the technology or applications could be sold for profit to health care professionals or health professions educators.

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.

This solicitation invites proposals for the following topic areas:

The Division for Heart Disease and Stroke Prevention, National Center for Chronic Disease Prevention and Health Promotion, in collaboration with the National Centers (DHDSP/NCCDPHP/CDC) for Health Statistics (NCHS/CDC) are working to collect, analyze, and disseminate data relating to the screening, diagnosis, and management of hypertension and to develop methods to improve the accuracy and reliability of electronic blood pressure monitors.

028 Inexpensive, Portable, User-friendly Calibration of Aneroid and Electronic Blood Pressure Devices

Proposals are invited for the development of an inexpensive, portable, user-friendly method (i.e., instrument or device with corresponding technique) to calibrate electronic blood pressure monitoring devices for accurate and reliable readings of systolic and diastolic blood pressure, pulse rate and pulse pressure. This method and device should include documentation of its capacity, accuracy and reliability of the calibration of the various equipment currently in use in the United States (i.e., Omron, Hyundai, Lifesource). The methods should be sufficiently portable to be able to be carried by any ambulatory adult and require minimal amount of training for accurate and reproducible calibration results of most all of the currently available commercial brands of electronic blood pressure devices used in clinics, pharmacies, hospitals, and homes. Evaluation of the method should address, at a minimum: accuracy, reproducibility, ruggedness, costs of operation, user friendliness, and portability.

Background: Since 2001 Mercury Reductive and Disposal, the use of the mercury spyghmanometer blood pressure devices are being phased out due to environmental concerns of mercury exposure (Sustainable Hospitals Guidelines 2002). Professional aneroid blood pressure devices used in hospitals and clinics that have lifetime calibration warranties and are recommended to be maintained regularly for accuracy and reliability. The seventh report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood (JNC7) recommends that all non-mercury blood pressure devices are appropriately validated and checked routinely for accuracy (in other words) calibrated (Chobanian et al., 2003; Franklin et al. 2001). The use of electronic blood pressure devices have become increasingly more popular in hospitals, clinics and even in pharmacies for self monitoring or screening; new inexpensive and portable methods of calibration are required. Additionally, when the sixth report of Joint National Committee on Blood Pressure Education and Control was released with recommendations for use of electronic home blood pressure devices for hypertension control management, there is an increased need for user-friendly, portable calibration devices. The electronic home blood pressure devices are inexpensive and widely available for the general population to buy at pharmacies, Walmart, Target and other retail stores in the United States. Unfortunately, the calibration of these electronic devices have not been developed.

Understanding the design and construction of the electronic blood pressure device is integral to knowing the accuracy of the blood pressure measurement taken for hypertension screening, diagnosis, and management. Changes in the types of devices used during the past thirty years can influence the outcome of the blood pressure measurement readings that influence screening, diagnostic and management outcomes. However, the accuracy and reproducibility of aneroid devices compared to mercury device (considered the gold standard) are inherently questionable due to the bellow/spring mechanism of the device as well as the type of training required systolic and diastolic assessment inter and intra-reader accuracy and reliability (personal communication Yechaim Ostchega, 2008). Unfortunately, the calibration of these electronic devices have not been developed. A recent study a NCHS was conducted and found that the Omron could be Digimat calibrated and proved to be more accurate and reliable than the aneroid device. Thus, it is imperative that routine calibration of these electronic blood pressure devices can be incorporated which required the development of inexpensive, portable, user-friendly method (i.e., instrument or device with corresponding technique).

The proposal should include 1) a plan to develop an inexpensive, portable, user-friendly method (i.e., instrument or device with corresponding technique) to calibrate aneroid blood pressure spyghmanometer and electronic blood pressure monitoring devices for accurate and reliable readings of systolic and diastolic blood pressure, pulse rate and pulse pressure, 2) documentation of the capacity and accuracy of the method, 3) verification of the reliability of the calibration equipment for the various equipment, and 4) evidence that the instrument or device with corresponding technique (method) is applicable to all current varieties of commercial brands of aneroid and electronic blood pressure devices used in clinics, pharmacies, hospitals, and homes. Evaluation of the method should address, at a minimum: accuracy, reproducibility, ruggedness, costs of operation, user friendliness, and portability.

029 Dynamic Health Promotion Decision Making for Preconception Health and Healthcare

Develop a marketable software product to aide individuals to assess their health risks and guide health care decisions.

Proposals are invited for development of a web-based dynamic education and decision making software product that will assist individuals decisions about risk reduction and health promotion interventions based on the most current evidence tailored to their individual situation. This education and decision making software must include a database of the scientific literature that will support the dynamic decision making based on the information provided by consumers. The tool developed under this award must be focused on the content of preconception health and healthcare and include both clinical lifestyle components. This software has broad applications in other domains of health promotion for consumers as well as for healthcare providers.

Background: In the last 100 years there has been substantial improvements made in reducing both maternal and infant morbidity and mortality. Unfortunately for the past 20 years we have seen a leveling off and in some cases increasing rates of morbidity and mortality. The reasons for the slowing of the improvement are not well understood. It appears that we have maximized the improvements made through the provision of prenatal care. Much of the morbidity and mortality observed today is the result of health risks and chronic conditions that are present long before pregnancy. There are efforts in the fields of public health, clinical medicine, consumer education and policy and finance to address this issue. One important component of these efforts is to facilitate the education and support decision making of consumers on the health risks associated with preconception health and healthcare.

Individual decision making around risk reduction and health promotion information is highly complex. Individuals must consider multiple behaviors and risks simultaneously and consider the best health promoting behaviors that they can implement in their daily lives. For these decisions to have impact on health and well being the information provided needs to be based on scientific evidence, interpretable by the individual and relevant to their specific situation. Currently there is an endless amount of health related information available to individuals, some of it science based some of it not and none of it is organized in a manner that individuals can use in their daily lives. Being able to provide individuals with decision making tools that can provide evidence based information about their health conditions will improve health literacy and support decisions about health behavior change that is relevant to them.

The proposal plan should include:

1. Collection and synthesis of the most current science on domains of health and health behaviors related to preconception care including (but not limited to) use of medications, management of chronic disease, health promotion interventions to reduce risks, family planning methods, environmental exposures and family history of genetic conditions.
2. A dynamic database that can identify relevant information to individuals based on responses to questions on general health and condition specific questions.
3. A software product that is consumer friendly and does not require high computer and health literacy skills. This interactive software should include general questions as well as specific questions about risks identified in the initial screening/general health portion.
4. An output mechanism that can provide the user information that is understandable, relevant and useful in their day to day lives as well as for guiding discussions with healthcare and social service providers.

CDC staff will be available for relevant discussions with the successful vendor. The applicant will retain all rights for the commercial marketing and application of this tool for other content areas and audiences such as the medical community or the general public.

The Prevention Research Centers Program

The Prevention Research Centers (PRC) Program (www.cdc.gov/prc) enables CDC to fund extramural research centers that add to knowledge and practice of chronic disease prevention and control. The program aims to build partnerships that draw on the perspectives and resources of diverse communities and actively partner with them; build long-term relationships for engaging communities as partners in research; work with populations having the greatest burden of disease and disability, especially people affected by adverse socioeconomic conditions; implement and evaluate interventions that help improve health outcomes; strive to develop communities' long-term capacity; disseminate successful results to comparable communities throughout the nation; promote the

quality and availability of public health services through proven interventions; train and offer technical assistance to community and public health practitioners; strengthen the public health infrastructure by sharing information, offering training and technical assistance, and testing interventions for implementation; and facilitate communication among public health professionals and community members through conferences, training, publications, and other means.

030 Development and Evaluation of a Quality and Affordable Electric-Assist Bicycle for Commuting

Studies have shown that integrating moderate cardiovascular exercise into daily routines is highly beneficial to health. Cycling can help with weight management; improve psychological well-being; maintain strength and coordination; allow cyclist to absorb lower pollutant levels from traffic fumes than from car driving; reduce carbon emissions; reduce commuting expenses; reduce the stress of driving in traffic; and create a sense of accomplishment.

Reports and studies show that people do not commute to work via a bicycle for many reasons: 1) they are not physically fit; 2) roads are not safe; 3) bicycle lanes are lacking; 4) it takes too much time to commute; 5) distance between point A and B is too far; 6) terrain is challenging (e.g., steep hills, potholes); 7) bicycle is uncomfortable; 8) do not own a reliable bicycle; 9) convenient and secure bicycle parking is not available; 10) have to commute while at work; 11) the nature of work does not allow for bicycle commuting; 12) no storage for personal items; 13) have to shower to refresh; 14) have to have a change of clothes; 15) vulnerable to weather conditions; and 16) possible physical injuries resulting from falls or accidents.

The PRC Program is soliciting proposals from small businesses in partnership with University of North Carolina at Chapel Hill Center for Health Promotion and Disease Prevention (UNC PRC), http://www.hpdp.unc.edu, to design and produce a quality and affordable electric-assist bicycle for commuting. The PRC Program would like to know if a combination of electricity and human power can increase people's use of a bicycle for commuting to the work place. A qualified small business with assistance from UNC PRC will be funded to design and produce an electric-assist bicycle that creatively addresses the 16 barriers to bicycle commuting mentioned above. At a minimum, the following criteria should be included in the design and production of this bicycle: 1) Quality powerful hi-torque electric-motor; 2) Long-life powerful re-chargeable battery; 3) Adjustable electric assist; 5) Affordable; 6) High performance quality parts and accessories; 7) Warranty comparable to that given by quality bicycle manufacturers; 8) Attractive and light weight; 9) Base model includes needed accessories (i.e., lock, mirror, storage rack, etc.)

In addition, UNC PRC together with the small business will pilot test the new electric-assist bicycle. The pilot study should involve appropriate stakeholders, quality community-based participatory research methods, and a built-in social marketing component. The evaluation should help determine whether an electric-assist bicycle can increase bicycle commuting to, during, and from work, and measure intermediate health outcomes or behaviors. Preparation of the application for this solicitation must be done in collaboration with the small business and UNC PRC.

IMMUNIZATION SAFETY OFFICE

The Vaccination Technology (VAXTECH) Unit of the Immunization Safety Office, CDC, promotes applied research and development to enhance the effectiveness, efficiency, safety, and acceptability of immunization through crosscutting initiatives, projects, and consultations. A major focus is alternative delivery systems and related technologies for safer, swifter, and simpler vaccination that avoid the dangers and drawbacks of conventional needle and syringe. 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.

VAXTECH invites phase I SBIR contract proposals in response to the following solicitation:

006 Novel or Enhanced Technology for Vaccination Delivery and Immunization Programs

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 IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

The Measles, Mumps, Rubella and Herpesvirus Laboratory Branch (MMRHLB), Division of Viral Diseases, is responsible for providing laboratory support for surveillance for measles, mumps, rubella and varicella zoster in the United States. MMRHLB conducts a wide range of serologic and molecular assays to detect infections and provide genetic characterization of the agents responsible for these diseases. MMRHLB also supports the Global Measles/Rubella Laboratory Network of the World Heath Organization by serving as a Global Specialized Laboratory.

001 Novel Methods for Detecting Viruses in Clinical Samples

The MMRHLB has already developed a wide variety of standard PCR and real time PCR techniques for detection of measles, mumps, rubella and herpes viruses 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 potentially deployed in resource limited areas would also be considered a high priority.

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.*

Those considering submission of proposals in response to this solicitation are encouraged to contact the following scientific/technical officer for questions and feedback on proposed topics: Paul Rota, (prota@cdc.gov). Otherwise, general SBIR administrative program questions should be posed to the appropriate contact person, and formal letters of intent should be directed to the relevant contracting officer, as instructed and both designated elsewhere in this announcement.

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 ClinicalTrilas.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

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

4.1.1Risks 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.

4.1.2Adequacy 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.

4.1.3Potential 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.

4.1.4Importance 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.

4.1.5Data 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.

4.1.6ClinicalTrials.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)).

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/aprqtr/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.

4.2.1Additional 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) 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, 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://www4.od.nih.gov/oba/rac/guidelines/guidelines.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, 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 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 do **not** apply to research involving prisoners or subjects who become prisoners (see Subpart C). Although Exemptions 1 and 3-6 apply to research involving children (see Subpart D), 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. 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 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 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.