

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS), THE
NATIONAL INSTITUTES OF HEALTH (NIH) AND THE CENTERS FOR
DISEASE CONTROL AND PREVENTION (CDC) SMALL BUSINESS
INNOVATIVE RESEARCH (SBIR) PROGRAM**

PROGRAM SOLICITATION PHS 2014-1

Closing Date: November 13, 2013, 4:30PM Eastern Time

Participating HHS Components:

- The National Institutes of Health (NIH)
- The Centers for Disease Control and Prevention (CDC)

IMPORTANT

Deadline for Receipt: Proposals must be submitted by November 13, 2013, 4:30PM Eastern Time

Solicitation Changes:

As a result of program reauthorization, the solicitation has been EXTENSIVELY rewritten and follows the changes of the SBIR/STTR reauthorization. Please read the entire solicitation carefully prior to submitting your proposal.

Please go to <http://www.sbir.gov/about/sbir-policy-directive> to read the SBIR/STTR Policy Directive issued by the Small Business Administration.

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1 INTRODUCTION

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 12.0](#), and to commercialize the results of that R&D, are encouraged to participate.

While the Phase II proposal process is covered in this announcement, **this solicitation is for Phase I, and in some cases, FAST TRACK proposals only. Some NIH Components utilize a contract mechanism called FAST TRACK which allows for the simultaneous submission of Phase I and Phase II proposals for review and possible award of Phase I with an option for Phase II work. FAST TRACK PROPOSALS WILL ONLY BE SUBMITTED UNDER THE FOLLOWING TOPICS AND ALL OTHER PHASE II PROPOSALS WILL NOT BE CONSIDERED.**

TOPIC NUMBER	TOPIC TITLE FOR FAST TRACK PROPOSALS
NCI 327	Reformulation of Failed Chemotherapeutic Drugs
NCI 328	Validation of 3D Human Tissue Culture Systems that Mimic the Tumor Microenvironment
NCI 329	Proteomic Analysis of Single Cells Isolated from Solid Tumors
NCI 330	Generation of Site-Specific Phospho-Threonine Protein Standards for use in Cancer Assays
NCI 331	Development of a Biosensor-Based Core Needle Tumor Biopsy Device
NCI 332	Development of Radiation Modulators for Use During Radiotherapy
NCI 333	Software Tools for the Development of Environmental Measures Related to Cancer Health Behaviors and Resources
NHLBI 081	Passive MRI Cardiovascular Guidewire
NHLBI 082	MRI Myocardial Needle Injection Catheter
NHLBI 083	Transcatheter Pulmonary Artery Resistor
NHLBI 084	Value of Information Models for Clinical Trial Assessment
NHLBI 085	Development of Molecular Imaging Agents and Methods to Detect High Risk Atherosclerotic Plaque
NHLBI 086	Tools for Educating Children about Clinical Research
NIA 087	Development of Calorie-restricted and Nutrient-balanced Medicinal Food Products for Mitigation of Age-related Diseases or Conditions
NIAAA 045	Development of a Database of Non-English Measures and Instruments for Use in Alcohol Research
NIDA 152	Technological Tools to Facilitate Implementation of Evidence-Based Substance Abuse Prevention Interventions among the Military
NIDA 153	Products to Prevent (Lethal) Drug-induced Respiratory Depression
NIDA 154	Bundled Service for Designing Methodologically Rigorous Animal Studies

All firms that are awarded Phase I contracts originating from this solicitation will be eligible to participate in Phases II and III. HHS Components will notify Phase I awardees of the Phase II proposal submission requirements. Submission of Phase II proposals will be in accordance with dates provided by individual Component instructions. The details on the due date, content, and submission requirements of the Phase II proposal will be provided by the awarding HHS Component either in the Phase I award or by subsequent notification. **All SBIR/STTR Phase II awards made on topics from solicitations prior to FY13 will be conducted in accordance with the procedures specified in those solicitations.**

The HHS is not obligated to make any awards under Phase I, Phase II, or Phase III, and all awards are subject to the availability of funds. HHS is not responsible for any monies expended by the offeror before award of any contract.

2 PROGRAM DESCRIPTION

2.1 Objectives

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 basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive dated October 18, 2012. This SBIR Contract solicitation strives to encourage scientific and technical innovation in areas specifically identified by the NIH/CDC awarding components. 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.

2.2 Three Phase Program

The SBIR program consists of three separate phases. The award amount and duration listed below represent the guidelines of the SBIR program and, unless the research topic stating the award listed in Section 12.0 of the solicitation states otherwise.

Phase I: Feasibility; \$150,000; 6 months (See Section 12.0 for Specific Award amounts per Topic Number)

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 \$150,000 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; \$1,000,000; 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 \$1,000,000 for direct costs, indirect costs, and profit (fixed fee) for a period normally not to exceed two years. *Phase I contractors will be informed of the opportunity to apply for Phase II, if not submitted concurrently with the initial Phase I proposal under the Fast-Track procedure. Only one Phase II award may result from a single Phase I SBIR contract.*

FAST TRACK (NIH COMPONENTS ONLY) - See Research Topics for Specific award amounts/period of performance

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 12.0](#) “Research Topics,” for notation.)

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 [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](#) 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](#)".

2.3 Grant Opportunity - Phase IIB Competing Renewal Awards (INFORMATION ONLY)

Some NIH Institutes/Centers (ICs) offer Phase II SBIR/STTR awardees the opportunity to apply for Phase IIB Competing Renewal awards. These are available for those projects that require extraordinary time and effort in the R&D phase and may or may not require FDA approval for the development of such projects, including drugs, devices, vaccines, therapeutics, and medical implants related to the mission of the IC. Some ICs have announced this opportunity through the NIH Guide for Grants and Contracts (see link below), and some are using this Omnibus SBIR/STTR Grant Solicitation. Only those small business concerns who have been awarded a Phase II are eligible to apply for a Phase IIB Competing Renewal award. Prospective applicants are strongly encouraged to contact NIH staff prior to submission. Additional requirements and instructions (e.g., submission of a letter of intent) are available in the specific IC research topics section and in the specific [IC Program Funding Opportunity Announcements](#). The following NIH ICs will accept applications for Phase IIB Competing Renewal awards: NIA, NIAAA, NIAID (SBIR only), NICHD (SBIR only and only Competing Renewals of NICHD-supported Phase II awards), NIDA, NIDCD, NIDDK (only Competing Renewals of NIDDK-supported Phase II awards), NEI (SBIR only), NIGMS (SBIR only), NIMH (SBIR only), NCATS (SBIR only), and ORIP (SBIR only). NCI offers Phase IIB opportunities that focus on the commercialization of SBIR-developed technologies. Contact the NCI SBIR Development Center at 240-276-5300, NCISBIR@mail.nih.gov for additional information. NHLBI offers Phase IIB Competing Renewals that focus on the commercialization of technologies requiring regulatory approval through the NHLBI Bridge Award (RFA-HL-13-016) and the NHLBI Small Market Award (RFA-HL-14-012). Contact Kurt Marek, Ph.D., at 301-443-8778 or kurt.marek@nih.gov for additional information. NINDS accepts Phase IIB SBIR/STTR Competing Renewal applications through specific opportunities that focus on the commercialization of SBIR and STTR developed technologies. These opportunities can be found on the NINDS SBIR webpage: http://www.ninds.nih.gov/funding/small-business/small_business_funding_opportunities.htm. Contact Stephanie Fertig, M.B.A., at 301-496-1779 or fertigs@ninds.nih.gov for additional information.

2.4 Awarding Components

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

National Institutes of Health (NIH) Components:

National Cancer Institute (NCI)

National Center for Advancing Translational Sciences (NCATS)

National Heart, Lung, and Blood Institute (NHLBI)

National Institute on Aging (NIA)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

National Institute of Allergy and Infectious Diseases (NIAID)

National Institute on Drug Abuse (NIDA)

Centers for Disease Control and Prevention (CDC) Components:

Center for Global Health (CGH)

National Center for Birth Defects and Developmental Disabilities (NCBDDD)

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

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

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

National Center for Immunization and Respiratory Diseases (NCIRD)

Office of Public Health Preparedness and Response (OPHPR)

3 DEFINITIONS

3.1 General Definitions

The following definitions from the SBA Policy Directive and the Federal Acquisition Regulation (FAR) apply for the purposes of this solicitation:

8(a) Small Business Concern. A small business concern that is owned and controlled by a socially and economically disadvantaged individual and that has been approved by the U.S. Small Business Administration as part of the 8(a) Business Development Program (see [13 CFR 124](#)).

Act. The Small Business Act ([15 U.S.C. 631](#), et seq.), as amended.

Applicant. The organizational entity that qualifies as an SBC at all pertinent times and that submits a contract proposal or a grant application for a funding agreement under the SBIR Program.

Affiliate. This term has the same meaning as set forth in 13 CFR part 121—Small Business Size Regulations, section 121.103. What is affiliation? (Available at <http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr;sid=03878acee7c064a02cac0d870e00ef43;rgn=div6;view=text;node=13%3A1.0.1.1.17.1;idno=13;cc=ecfr>.) Further information about SBA's affiliation rules and a guide on affiliation is available at www.SBIR.gov and www.SBA.gov/size.

Awardee. The organizational entity receiving an SBIR Phase I, Phase II, or Phase III award.

Commercialization. The process of developing products, processes, technologies, or services and the production and delivery (whether by the originating party or others) of the products, processes, technologies, or services for sale to or use by the Federal government or commercial 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.

Cooperative Agreement. A financial assistance mechanism used when substantial Federal programmatic involvement with the awardee during performance is anticipated by the issuing agency. The Cooperative Agreement contains the responsibilities and respective obligations of the parties.

Covered Small Business Concern. A small business concern that:

- (1) Was not majority-owned by multiple venture capital operating companies (VCOCs), hedge funds, or private equity firms on the date on which it submitted an application in response to a solicitation under the SBIR program; and
- (2) Is majority-owned by multiple venture capital operating companies, hedge funds, or private equity firms on the date of the SBIR award.

Essentially Equivalent Work. Work that is substantially the same research, which is proposed for funding in more than one contract proposal or grant application submitted to the same Federal agency or submitted to two or more different Federal agencies for review and funding consideration; or work where a specific research objective and the research design for accomplishing the objective are the same or closely related to another proposal or award, regardless of the funding source.

Extramural Budget. The sum of the total obligations for R/R&D minus amounts obligated for R/R&D activities by employees of a Federal agency in or through Government-owned, Government-operated facilities. For the Agency for

International Development, the “extramural budget” must not include amounts obligated solely for general institutional support of international research centers or for grants to foreign countries. For the Department of Energy, the “extramural budget” must not include amounts obligated for atomic energy defense programs solely for weapons activities or for naval reactor programs. (Also see section 7(i) of this Policy Directive for additional exemptions related to national security.)

Feasibility. The practical extent to which a project can be performed successfully.

Federal Agency. An executive agency as defined in 5 U.S.C. § 105, and a military department as defined in [5 U.S.C. 102](#) (Department of the Army, Department of the Navy, Department of the Air Force), except that it does not include any agency within the Intelligence Community as defined in Executive Order 12333, section 3.4(f), or its successor orders.

Federal Laboratory. As defined in 15 U.S.C. § 3703, means any laboratory, any federally funded research and development center, or any center established under 15 U.S.C. §§ 3705 & 3707 that is owned, leased, or otherwise used by a Federal agency and funded by the Federal Government, whether operated by the Government or by a contractor.

Fraud, Waste, and Abuse

- a. **Fraud** includes any false representation about a material fact or any intentional deception designed to deprive the United States unlawfully of something of value or to secure from the United States a benefit, privilege, allowance, or consideration to which an individual or business is not entitled.
- b. **Waste** includes extravagant, careless or needless expenditure of Government funds, or the consumption of Government property, that results from deficient practices, systems, controls, or decisions.
- c. **Abuse** includes any intentional or improper use of Government resources, such as misuse of rank, position, or authority or resources.

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

Funding Agreement Officer. A contracting officer, a grants officer, or a cooperative agreement officer.

Grant. A financial assistance mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity. A grant is used whenever the Federal agency anticipates no substantial programmatic involvement with the awardee during performance.

HubZone Small Business Concern. A small business concern that appears on the List of Qualified HUBZone Small Business Concerns maintained by the Small Business Administration (13 CFR 126.103). HUBZone Small Business Concerns are located in historically underutilized business zones, in an effort to increase employment opportunities, investment, and economic development in those areas.

Innovation. Something new or improved, having marketable potential, including: (1) Development of new technologies; (2) refinement of existing technologies; or (3) development of new applications for existing technologies.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as “intellectual property,” including but not limited to: (1) Patents; (2) trademarks; (3) copyrights; (4) trade secrets; (5) SBIR technical data (as defined in this section); (6) ideas; (7) designs; (8) know-how; (9) business; (10) technical and research methods; (11) other types of intangible business assets; and (12) all types of intangible assets either proposed or generated by an SBC as a result of its participation in the SBIR Program.

Joint Venture. See [13 CFR 121.103\(h\)](#).

Key Individual. The principal investigator/project manager and any other person named as a “key” employee in a proposal submitted in response to a program solicitation.

Principal Investigator/Project Manager. The one individual designated by the applicant to provide the scientific and technical direction to a project supported by the funding agreement.

Program Solicitation. A formal solicitation for proposals issued by a Federal agency that notifies the small business community of its R/R&D needs and interests in broad and selected areas, as appropriate to the agency, and requests proposals from SBCs in response to these needs and interests. Announcements in the Federal Register or the GPE are not considered an SBIR Program solicitation.

Proprietary Information. Proprietary information is information that you provide which constitutes a trade secret, proprietary commercial or financial information, confidential personal information or data affecting the national security.

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

SBIR Participants. Business concerns that have received SBIR awards or that have submitted SBIR proposals/applications.

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

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

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

Small Business Concern. A concern that meets the requirements set forth in [13 CFR 121.702](#):

To be eligible for award of funding agreements in the SBA's Small Business Innovation Research (SBIR) program, a business concern must meet the requirements of paragraphs (a) and (b) below:

(a) *Ownership and control.*

(1) An SBIR awardee must

- (i) Be a concern which is more than 50% directly owned and controlled by one or more individuals (who are citizens or permanent resident aliens of the United States), other business concerns (each of which is more than 50% directly owned and controlled by individuals who are citizens or permanent resident aliens of the United States), or any combination of these; OR
- (ii) Be a concern which is more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these. No single venture capital operating company, hedge fund, or private equity firm may own more than 50% of the concern; OR
- (iii) Be a joint venture in which each entity to the joint venture must meet the requirements set forth in paragraph (a)(1)(i) or (a)(1)(ii) of this section. A joint venture that includes one or more concerns that meet the requirements of paragraph (ii) of this section must comply with § 121.705(b) concerning registration and proposal requirements

(2) If an Employee Stock Ownership Plan owns all or part of the concern, SBA considers each stock trustee and plan member to be an owner.

(3) If a trust owns all or part of the concern, SBA considers each trustee and trust beneficiary to be an owner.

(b) *Size.* An SBIR awardee, together with its affiliates, will not have more than 500 employees.

Socially and Economically Disadvantaged SBC (SDB). See [13 CFR part 124](#), Subpart B.

Socially and Economically Disadvantaged Individual. See [13 CFR 124.103](#) and [124.104](#).

Service-Disabled Veteran-Owned Small Business Concern. A small business concern not less than 51 percent of which is owned by one or more service-disabled veterans or, in the case of any publicly owned business, not less than 51 percent of the stock of which is owned by one or more service-disabled veterans; and the management and daily business operations of which are controlled by one or more service-disabled veterans or, in the case of a service-disabled veteran with permanent and severe disability, the spouse or permanent caregiver of such veteran. Status as a Service-Disabled Veteran-Owned Small Business Concern is determined in accordance with 13 CFR Parts [125.8 through 125.13](#); also see [19.307](#).

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by an awardee of a funding agreement calling for supplies or services for the performance of the original funding agreement.

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

Women-Owned SBC (WOSB). An SBC that is at least 51% owned by one or more women, or in the case of any publicly owned business, at least 51% of the stock is owned by women, and women control the management and daily business operations.

3.2 Definitions (Relating to R&D)

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.

HHS Regulations ([45 CFR 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 studies, or
- (d) development of new technologies.

(2) Epidemiologic and Behavioral Studies.

(3) Outcomes Research and Health Services Research.

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

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

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

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

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

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

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

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.*

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

Human Subjects. The HHS 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 system

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 [Guidance on Research Involving Coded Private Information on Biological Specimens.](#))

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.
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.
- 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.

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))

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

- a. 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
- b. 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 HHS 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/policy/cdebiol.html>.)

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

1. A systematic, intensive study directed toward greater knowledge or understanding of the subject studied;
2. A systematic study directed specifically toward applying new knowledge to meet a recognized need; or
3. A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

Research Institution. Any organization located in the United States that is:

- A university.
- A nonprofit institution as defined in Section 4(5) of the Stevenson-Wydler Technology Innovation Act of 1980.

Research Involving Animal Subjects

All research involving live, vertebrate animals shall be conducted in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals ([PHS Policy](#)).

In addition, the research involving live vertebrate animals shall be conducted in accordance with the description set forth in the Vertebrate Animal Section (VAS) of the contractor's technical proposal, as modified in the Final Proposal Revision (FPR), which is incorporated by reference.

Research Involving Human Subjects

All research involving human subjects, to include use of human biological specimens and human data, shall comply with the applicable federal and state laws and agency policy/guidelines for human subject protection.

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

- (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.
- (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.
- (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.
- (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- (5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which 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.
- (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.

Research Involving Recombinant DNA Molecules. Any recipient performing research involving recombinant DNA molecules and/or organisms and viruses containing recombinant DNA molecules shall comply with the National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules, dated March 2013 as amended. The guidelines can be found at: http://oba.od.nih.gov/rdna/nih_guidelines_oba.html. Recombinant DNA is defined as (i) molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in living cells or (ii) molecules that result from the replication of those described in (i) above. A listing of the cited regulations is available at: <http://www.acq.osd.mil/osbp/sbir/sb/resources/deskreference/quickref/researchrecombinantdna.shtml>.

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.

4 PROPOSAL FUNDAMENTALS

Unless otherwise specified, Section 4 applies to both Phase I and Phase II.

4.1 Introduction

The proposal must provide sufficient information to demonstrate to the evaluator(s) that the proposed work represents an innovative approach to the investigation of an important scientific or engineering problem and is worthy of support under the stated criteria. The proposed research or research and development must be responsive to the chosen topic, although it need not use the exact approach specified in the topic. Anyone contemplating a proposal for work on any specific topic should determine that (a) the technical approach has a reasonable chance of meeting the topic objective, (b) this approach is innovative, not routine, with potential for commercialization and (c) the proposing firm has the capability to implement the technical approach, i.e., has or can obtain people and equipment suitable to the task.

4.2 Offeror Eligibility and Performance Requirements

To receive SBIR funds, each awardee of a SBIR Phase I or Phase II award must qualify as an SBC at the time of award and at any other time set forth in SBA's regulations at 13 CFR 121.701-121.705. Each Phase I and Phase II awardee must submit a certification stating that it meets the size, ownership and other requirements of the SBIR Program at the time of award, and at any other time set forth in SBA's regulations at 13 CFR 121.701-705.

Each offeror must qualify as a small business for research or research and development purposes and certify to this on the Cover Sheet (Appendix A) of the proposal. For Phase I, a minimum of two-thirds of the research or analytical effort must be performed by the awardee. For Phase II, a minimum of one-half of the research or analytical effort must be performed by the awardee. The percentage of work will be measured by labor hours. Offeror's planning to subcontract a significant fraction of their work should verify how it will be measured with their HHS Component contracting officer during contract negotiations. For both Phase I and II, the principal investigator must be primarily employed with the small business firm or the research institution. Primary employment means that more than one half (50%) of the employee's time is spent with the small business. Primary employment with a small business concern precludes full-time employment at another organization. For both Phase I and Phase II, all research or research and development work must be performed by the small business concern and its subcontractors in the United States.

Phase I to Phase II Transition Benchmark. Section 4(a) of the SBIR Policy Directive calls for each Federal agency participating in SBIR to set a Phase I to Phase II transition rate benchmark in response to Section 5165 of the SBIR/STTR Reauthorization Act of 2011. The rate is the minimum required ratio of past Phase II/Phase I awards that an awardee firm must maintain to be eligible for a new Phase I award from a particular agency. The benchmark will apply to those Phase I applicants that have received 20 or more Phase I awards Program-wide. Small businesses can view their transition rate on www.sbir.gov upon completion of registration. When logging in, the Phase I to Phase II transition rate will be displayed in the welcome screen.

The HHS benchmark uses a five-year period and counts an applicant's total number of Phase I awards over the last five fiscal years, excluding the most recently completed fiscal year; and the total number of Phase II awards over the last five fiscal years, including the most recently completed year. The HHS SBIR Phase I to II Transition Benchmark as published in the Federal Register is:

For all SBIR Program Phase I contract applicants that have received 20 or more Phase I awards over the 5-year period, the ratio of Phase II awards received to Phase I awards received must be at least 0.25.

4.3 Multiple Principal Investigators

The NIH now provides offerors the opportunity to propose a multiple Principal Investigator (PI) model on research and development contracts. The multiple PI model is intended to supplement, and not replace, the traditional single PI model. The NIH chose this RFP as a candidate for the multiple PI model. Ultimately, the decision to submit a proposal using the multiple PI versus single PI is the decision of the investigators and their institutions. The decision should be consistent with and justified by the scientific goals of the project.

4.4 Joint Ventures

Joint ventures and limited partnerships are permitted, provided that the entity created qualifies as a small business in accordance with the Small Business Act, 15 U.S.C. § 631. Majority Ownership in Part by Multiple Venture Capital, Hedge Fund, and Private Equity Firms (NIH COMPONENTS ONLY)

4.5 Majority Ownership in Part by Multiple Venture Capital, Hedge Fund, and Private Equity Firms (NIH COMPONENTS ONLY)

Small businesses that are owned in majority part by multiple venture capital operating companies (VCOCs), hedge funds, or private equity funds are **eligible to submit proposals for opportunities under this solicitation to the National Institutes of Health components.**

SBIR Application Certification for small business concerns majority-owned by multiple venture capital operating companies, hedge funds, or private equity firms

Applicant small business concerns that are majority-owned by multiple venture capital operating companies (VCOCs), hedge funds, or private equity firms (e.g. majority VCOCs-owned) **are required** to submit a “SBIR Application VCOCs Certification” at time of their application submission per the [SBIR Policy Directive](#). Follow the instructions below.

1. Download the “SBIR Application VCOCs Certification.pdf” at the [NIH SBIR Forms](#) webpage.
2. Answer the 3 questions and check the certification boxes.
3. The authorized business official must sign the certification.
4. The signed SBIR Application VCOCs Certification must be submitted as part of the Pricing Proposal.

Applicant small business concerns who are more than 50% directly owned and controlled by one or more individuals (who are citizens or permanent resident aliens of the United States), other business concerns (each of which is more than 50% directly owned and controlled by individuals who are citizens or permanent resident aliens of the United States), or any combination of these (i.e. **NOT** majority VCOCs-owned) should **NOT** fill out the SBIR Application VCOCs Certification and should **NOT** attach it their application package.

4.6 Majority Ownership in Part by Multiple Venture Capital, Hedge Fund, and Private Equity Firms (CDC COMPONENTS ONLY)

Small businesses that are owned in majority part by multiple venture capital operating companies (VCOCs), hedge funds, or private equity funds are **ineligible to submit proposals for opportunities under this solicitation to the CDC components.**

4.7 Conflicts of Interest

Contract awards to firms owned by or employing current or previous Federal Government employees could create conflicts of interest for those employees which may be a violation of federal law. Proposing firms should contact the cognizant Ethics Counselor from the employee’s Government agency for further guidance if in this situation.

4.8 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.

4.9 OMB Clearance

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 any such activity for Phase I, which normal only has a six-month period of performance.

4.10 Research Involving Human Subjects

The HHS 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*

Notice to Offerors of Requirements of 45 CFR Part 46, Protection of Human Subjects, HHSAR 352.270-4(a) (January 2006)

- a. Copies of the Department of Health and Human Services (HHS) regulations for the protection of human subjects, 45 CFR Part 46, are available from the Office for Human Research Protections (OHRP), Bethesda, Maryland 20892. The regulations provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS.
- b. The regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information. The regulations extend to the use of human organs, tissue, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects. The use of autopsy materials is governed by applicable State and local law and is not directly regulated by 45 CFR Part 46.
- c. Activities in which the only involvement of human subjects will be in one or more of the categories set forth in 45 CFR 46.101(b)(1-6) are exempt from coverage.
- d. Inappropriate designations of the noninvolvement of human subjects or of exempt categories of research in a project may result in delays in the review of a proposal. The Government's Project Officer will make a final determination of whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the proposal. In doubtful cases, the Project Officer will consult with OHRP.
- e. In accordance with 45 CFR Part 46, prospective Contractors being considered for award shall be required to file with OHRP an acceptable Assurance of Compliance with the regulations, specifying review procedures and assigning responsibilities for the protection of human subjects. The initial and continuing review of a research project by an institutional review board shall assure that: the rights and welfare of the human subjects involved are adequately protected; the risks to the subjects are reasonable in relation to both the potential benefits, if any, to the subjects and the importance of the knowledge to be gained; and informed consent will be obtained by methods that are adequate and appropriate. HHS regulations for the protection of human subjects (45 CFR Part 46), information regarding OHRP registration and assurance requirements/processes, and OHRP contact information can be accessed at the [OHRP Website](#).
- f. Offerors may consult with OHRP for advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects.

4.11 Care of Live Vertebrate Animals

The following notice is applicable when contract performance is expected to involve care of live vertebrate animals:

Notice to Offerors of Requirement for Compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals, HHSAR 352.270-5(a) (January 2006)

The Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (PHS Policy) establishes a number of requirements for research activities involving animals. Before award may be made to an applicant organization, the organization shall file, with the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health (NIH), a written Animal Welfare Assurance (Assurance) which commits the organization to comply with the provisions of the PHS Policy, the Animal Welfare Act, and the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC). In accordance with the PHS Policy, applicant organizations must establish an Institutional Animal Care & Use Committee (IACUC), qualified through the experience and expertise of its members, to oversee the institution's animal program, facilities and procedures. Applicant organizations are required to provide verification of IACUC approval prior to release of an award involving live vertebrate animals. No award involving the use of animals shall be made unless OLAW approves the Assurance and verification of IACUC approval for the proposed animal activities has been provided to the Contracting Officer. Prior to award, the Contracting Officer will notify Contractor(s) selected for projects that involve live vertebrate animals that an Assurance and verification of IACUC approval are required. The Contracting Officer will request that OLAW negotiate an acceptable Assurance with those Contractor(s) and request verification of IACUC approval. For further information contact OLAW, at NIH, 6705 Rockledge Drive, RKL1, Suite 360, MSC 7982 Bethesda, Maryland 20892-7982 (E-mail: olaw@od.nih.gov ; Phone: 301-496-7163).

The PHS Policy is available on the internet at: <http://www.grants.nih.gov/grants/olaw/olaw.htm>.

4.12 Research Involving Recombinant DNA Molecules

Recombinant DNA Molecules are either 1) molecules that are constructed outside of 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). All research involving recombinant DNA molecules that is conducted at or sponsored by an entity that receives any support for recombinant DNA research from NIH shall be conducted in accordance with the [NIH Guidelines for Research Involving Recombinant DNA Molecules \(NIH Guidelines\)](#). The NIH Guidelines stipulate biosafety and containment measures for recombinant DNA research and delineate points to consider in the development and conduct of human gene transfer clinical trials, including ethical principles and safety reporting requirements (See Appendix M of the Guidelines). More information about compliance with the NIH Guidelines can be found in a set of [Frequently Asked Questions](#).

The NIH Guidelines apply to both basic and clinical research studies. Prior to beginning any clinical trials involving the transfer of recombinant DNA to humans, the trial must be registered with the NIH OBA and reviewed by the NIH Recombinant DNA Advisory Committee (RAC). If this contract involves new protocols that contain unique and/or novel issues, the RAC may recommend that the protocol also be discussed by the RAC in a public forum. Approval of the Institutional Biosafety Committee (IBC) and the Institutional Review Board (IRB) are necessary before the Contracting Officer's Representative (COR) and Contracting Officer may approve the protocol prior to the start of the research. The IBC approval may not occur before the NIH RAC has concluded its review of the protocol.

Failure to comply with the NIH Guidelines may result in suspension, limitation, or termination of the contract for any work related to recombinant DNA research or a requirement for Contracting Officer prior approval of any or all recombinant DNA projects under this contract. This includes the [requirements of the Institutional Biosafety Committee \(IBC\)](#).

As specified in Appendix M-1-C-4 of the NIH Guidelines, any serious adverse event that that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product) must be reported to the NIH OBA and IBC within 15 days, or within 7 days if the event was life-threatening or resulted in a death. A copy of the report must also be filed with the COR and Contracting Officer (See http://oba.od.nih.gov/oba/rac/guidelines_02/APPENDIX_M.htm). Such reports must also be submitted within their mandated time frames to the IRB, Food and Drug Administration, and, if applicable, the HHS Office for Human Research Protections.

4.13 Debriefing

An unsuccessful offeror that submits a written request for a debriefing within 3 days of being notified that its proposal was not selected for award will be provided a debriefing. Please note that Component-unique debriefing processes exist; in those cases, the Component debriefing instructions supersede instructions provided here. The written request should be sent to the HHS organization that provided such notification to the offeror. Be advised that an offeror that fails to submit a timely request is not entitled to a debriefing, although untimely debriefing requests may be accommodated at the Government's discretion.

4.14 Phase I Award and (FAST TRACK NIH ONLY) Information

- a. **Number of Phase I Awards.** The Topic Description indicates the number of Phase I contract awards anticipated by the HHS Component. No Phase I contracts will be awarded until evaluation of all eligible proposals for a specific topic is completed.
- b. **Type of Funding Agreement.** Each Phase I proposal selected for award will be funded under negotiated contracts. It is anticipated that the amounts negotiated for award will include a reasonable fee or profit consistent with normal profit margins provided to profit-making firms for R/R&D work. Firm fixed price contracts will be awarded for all Phase I projects.
- c. **Dollar Value.** The Phase I contract value varies among the HHS Components; it is therefore important for proposing firms to review understand Section 12.0 COMPONENT INSTRUCTIONS AND TECHNICAL TOPIC DESCRIPTIONS, for the component to which they are proposing for any specific instructions regarding award size.

4.15 Phase II/FAST TRACK Award Information

- a. **Number of Phase II (as part of FAST TRACK) Awards.** The number of Phase II awards will depend upon the results of the Phase I efforts and the availability of funds.
- b. **Type of Funding Agreement.** Each Phase II proposal selected for award will be funded under a cost, reimbursement, negotiated contract and will include a reasonable fee or profit consistent with normal profit margins provided to profit-making firms for R/R&D work.
- c. **Average Dollar Value.** The typical size of award varies across the HHS Components. Information on award size will be provided in HHS Component instructions for submission of Phase II proposals.

4.16 Registrations and Certifications

Registration in the System for Award Management (SAM)

Before the HHS Components can award a contract, proposing firms must be registered in the System for Award Management (SAM). If you were previously registered in CCR, your information has been transferred to SAM. However, it is in the firm's interest to visit SAM and ensure that all the firm's data is up to date from SAM and other databases to avoid delay in award. SAM replaced the Central Contractor Registration (CCR), Online Representations and Certifications Application (ORCA), and the Excluded Parties List System (EPLS). SAM allows firms interested in conducting business with the federal government to provide basic information on business capabilities and financial information. To register, visit [SAM.gov](https://sam.gov).

SBA Company Registry

All applicants to the SBIR and STTR programs are required to register at the [SBA Company Registry](https://sba.gov) prior to application submission and attach proof of registration. Completed registrations will receive a unique SBC Control ID and .pdf file. If applicants have previously registered, you are still required to attach proof of registration. The SBA Company Registry recommends verification with [SAM](https://sam.gov), but a SAM account is not required to complete the registration. In order to be verified with SAM, your email address must match one of the contacts in SAM. If you are unsure what is listed in SAM for your

company, you may verify the information on the SAM site. Confirmation of your company's DUNS is necessary to verify your email address in SAM. Follow these steps listed below to register and attach proof of registration to your application.

- a. Navigate to the [SBA Company Registry](#).
- b. If you are a previous SBIR/STTR awardee from any agency, search for your small business by Company Name, EIN/Tax ID, DUNS, or Existing SBIR/STTR Contract/Grant Number in the search fields provided. Identify your company and click "Proceed to Registration".
- c. If you are a first time applicant, click the [New to the SBIR Program?](#) link on lower right of registry screen.
- d. Fill out the required information on the "Basic Information" and "Eligibility Statement" screens.
- e. Press "Complete Registration" on the lower right of the "Eligibility Statement" screen and follow all instructions.
- f. Download and save your SBA registry PDF locally. The name will be in the format of SBC_123456789.pdf, where SBC_123456789 (9 digit number) is your firm's SBC Control ID.
- g. A copy of the completed SBA Company Registration for your organization must be submitted as part of your Pricing Proposal.

Life Cycle Certifications

In addition to the standard federal procurement certifications, the SBA SBIR/STTR Policy Directive requires the collection of certain information from firms at time of award and during the award life cycle.

Please go to the NIH SBIR/STTR Forms Website at: <http://grants.nih.gov/grants/forms.htm#contracts> to access the forms required to be submitted at time of the Phase I and Phase II awards and during the award life cycle.

The Life Cycle certifications that are required prior to final payment on the Phase I award, prior to receiving 50% of the total award amount on the Phase II award, and prior to final payment on the Phase II award will be identified as contract deliverables, and incorporated into the contract delivery schedule.

4.17 Promotional Materials

Promotional and non-project related discussion is discouraged and additional information provided via Universal Resource Locator (URL) links or on computer disks, CDs, DVDs, video tapes or any other medium will not be accepted or considered in the proposal evaluation.

4.18 Prior, Current, or Pending Support of Similar Proposals or Awards

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 is eligible to submit a Phase II contract or grant proposal. Phase I contractors will be informed of the opportunity to apply for Phase II.

IMPORTANT – While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work 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 prior, current, or pending support of similar proposals or awards, it must be disclosed to the soliciting agency or agencies as early as possible.

4.19 Fraud and False Statements

The [Office of Inspector General Hotline](#) accepts tips from all sources about potential fraud, waste, abuse and mismanagement in Department of Health & Human Services programs. The reporting individual should indicate that the fraud, waste and/or abuse concerns an SBIR/STTR grant or contract, if relevant.

The Contractor shall not use contract funds to disseminate information that is deliberately false or misleading.

4.20 State and Other Assistance Available

State Assistance - Many states have established programs to provide services to those small business firms and individuals wishing to participate in the Federal SBIR/STTR Program. These services vary from state to state.

Contact your State STTR Support office at <http://www.sbir.gov/state-contacts> for further information.

Technical Assistance-NIH offers distinct [technical assistance programs](#) to NIH SBIR and STTR Phase I and Phase II awardees. These programs offer specialized, strategic business training and provide access to a vast network of industry experts possible through the efficiencies of scale that under a contract deliver the best value to the government and the intended small businesses seeking such assistance.

NIH and CDC Components

If you wish to utilize your own technical assistance provider, you are required to include these costs in your budget and to provide a detailed budget justification. You may request up to \$5,000 for assistance. Refer to Section 8.1 for how to include this in your Pricing Proposal. If the amount of \$5,000 is included in your cost proposal is determined to be appropriate and allowable for technical assistance, this will be in addition to the amount negotiated per award, and as specified in the topic description.

Please note, if funds are requested to utilize your own technical assistance vendor and an award is made, the awardee is not eligible to apply for the NIH-provided technical assistance program for the phase of their award. Reimbursement is limited to services received that comply with 15 U.S.C. § 638(q):

To provide small business concerns engaged in SBIR or STTR projects with technical assistance services, such as access to a network of scientists and engineers engaged in a wide range of technologies, or access to technical and business literature available through on-line data bases, for the purpose of assisting such concerns in—

- (A) making better technical decisions concerning such projects;
- (B) solving technical problems which arise during the conduct of such projects;
- (C) minimizing technical risks associated with such projects; and
- (D) developing and commercializing new commercial products and processes resulting from such projects.

4.21 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. Offerors must access the CCR through the System for Award Management (SAM) located at www.sam.gov.

Payments on Phase I contracts may be made based on the satisfactory completion, receipt and acceptance of contract deliverables. Advance payments may be requested, and approved on a case-by-case basis, and is dependent on Agency procedures. Invoices/financing requests submitted for costs incurred under Phase II cost reimbursement contracts will be no more frequently than on a monthly basis unless otherwise authorized by the contracting officer.

4.22 Proprietary Information

Information contained in unsuccessful proposals will remain the property of the applicant. The Government may, however, retain copies of all proposals. Public release of information in any proposal submitted will be subject to existing statutory and regulatory requirements. If proprietary information is provided by an applicant in a proposal, which constitutes a trade secret, proprietary commercial or financial information, confidential personal information or data affecting the national security, it will be treated in confidence, to the extent permitted by law. This information must be clearly marked by the applicant with the term "confidential proprietary information" and the following legend must appear on the title page of the proposal:

"These data shall not be disclosed outside the Government and shall not be duplicated, used, or disclosed in whole or in part for any purpose other than evaluation of this proposal. If a funding agreement is awarded to this applicant as a result of or in connection with the submission of these data, the Government shall have the right to duplicate, use, or disclose the data to the extent provided in the funding agreement and pursuant to applicable law. This restriction does not limit the Government's right to use information contained in the data if it is obtained from another source without restriction. The data subject to this restriction are contained on pages ___ of this proposal."

4.23 Identification and Marking of SBIR Technical Data in Proposals

To preserve the SBIR data rights of the awardee, the legend (or statements) used in the SBIR Data Rights clause included in the SBIR award must be affixed to any submissions of technical data developed under that SBIR award. If no Data Rights clause is included in the SBIR award, the following legend, at a minimum, should be affixed to any data submissions under that award. These SBIR data are furnished with SBIR rights under Funding Agreement No. ___ (and subcontract No. ___ if appropriate), Awardee Name __, Address, Expiration Period of SBIR Data Rights __. The Government may not use, modify, reproduce, release, perform, display, or disclose technical data or computer software marked with this legend for four (4) years. After expiration of the 4- year period, the Government has a royalty-free license to use, and to authorize others to use on its behalf, these data for Government purposes, and is relieved of all disclosure prohibitions and assumes no liability for unauthorized use of these data by third parties, except that any such data that is also protected and referenced under a subsequent SBIR award shall remain protected through the protection period of that subsequent SBIR award. Reproductions of these data or software must include this legend."

5 CONTRACT REQUIREMENTS

5.1 Other Contract Requirements

Upon award of a contract, the contractor will be required to make certain legal commitments through acceptance of Government contract clauses in the Phase I contract. The outline that follows is illustrative of the types of provisions required by the Federal Acquisition Regulation that will be included in the Phase I contract. This is not a complete list of provisions to be included in Phase I contracts, nor does it contain specific wording of these clauses. While a Phase II contract may include some or all of the provisions below, additional provisions will be required. Copies of complete general provisions will be made available prior to award.

- a. **Standards of Work.** Work performed under the contract must conform to high professional standards.
- b. **Inspection.** Work performed under the contract is subject to Government inspection and evaluation at all reasonable times.
- c. **Examination of Records.** The Comptroller General (or a fully authorized representative) shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
- d. **Default.** The Government may terminate the contract if the contractor fails to perform the work contracted.
- e. **Termination for Convenience.** The contract may be terminated at any time by the Government 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.
- f. **Disputes.** Any dispute concerning the contract which cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
- g. **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 (that is, receives overtime pay).
- h. **Equal Opportunity.** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
- i. **Affirmative Action for Veterans.** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran.
- j. **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.
- k. **Officials Not to Benefit.** No member of or delegate to Congress shall benefit from the contract.
- l. **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.
- m. **Gratuities.** The contract may be terminated by the Government if any gratuities have been offered to any representative of the Government to secure the contract.
- n. **Patent Infringement.** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.
- o. **E-Verify.** Contracts exceeding the simplified acquisition threshold may include the FAR clause 52.222-54 "Employment Eligibility Verification" unless exempted by the conditions listed at FAR 22.1803.

- p. **Needle Distribution.** The Contractor shall not use contract funds to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.
- q. **Acknowledgement of Federal Funding.** The Contractor shall clearly state, 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: (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) the percentage and dollar amount of the total costs of the project or program that will be financed by nongovernmental sources.
- r. **Restriction on Abortions.** The Contractor shall not use contract funds for any abortion.
- s. **Continued Ban on Funding of Human Embryo Research.** The Contractor shall not use contract funds 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) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)). The term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the 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.

Additionally, in accordance with a March 4, 1997 Presidential Memorandum, Federal funds may not be used for cloning of human beings.

- t. **Limitation on Use of Funds for Promotion of Legalization of Controlled Substances.** The Contractor shall not use contract funds to support activities that promote the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established under section 202 of the Controlled Substances Act, except for normal and recognized executive-congressional communications. This limitation shall not apply when the Government determines that 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.
- u. **Dissemination of False or Deliberately Misleading Information.** The Contractor shall not use contract funds to disseminate information that is deliberately false or misleading.
- v. **Salary Rate Limitation.** None of the funds appropriated in this title shall be used to pay the salary of an individual, through a grant or other extramural mechanism, at a rate in excess of Executive Level II." In previous years, the Salary Limitation was based upon Executive Level I of the Federal Executive Pay Scale. Effective January 1 through December 31, 2010 the Executive Level I of the Federal Executive Pay Scale was \$199,700. **Effective December 23, 2011, the Salary Limitation is based upon the Executive Level II of the Federal Executive Pay Scale. That amount is \$179,700.**
- w. **Anti-Lobbying.** No part of any appropriation contained in this Act or transferred pursuant to section 4002 of Public Law 111-148 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, electronic communication, radio, television, or video presentation designed to support or defeat the enactment of legislation before the Congress or any State or local legislature or legislative body, except in presentation to the Congress or any State or local legislature itself, or designed to support or defeat any proposed or pending regulation, administrative action, or order issued by the executive branch of any State or local government, except in presentation to the executive branch of any State or local government itself.

5.2 Special Contract Requirements

Specific contract requirements relating to research involving the use of Human Subjects or Animals will be required in any contract awarded for a project involve the use of Human Subjects or Animals.

5.3 Copyrights

With prior written permission of the Contracting Officer, the awardee may copyright material developed with HHS support. HHS receives a royalty-free license for the Federal Government and requires that each publication contain an appropriate acknowledgment and disclaimer statement.

5.4 Patents

Small business firms normally may retain the principal worldwide patent rights to any invention developed with Government support. The Government receives a royalty-free license for its use, reserves the right to require the patent holder to license others in certain limited circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it domestically. To the extent authorized by 35 USC 205, the Government will not make public any information disclosing a Government-supported invention for a period of four years to allow the awardee to pursue a patent. See also Invention Reporting in Section 5.6.

Inquiries or information about additional requirements imposed by 37 CFR 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
E-mail: jpkim@nih.gov

See also Invention Reporting in Section 5.6.

5.5 Technical Data Rights

Rights in Data Developed Under SBIR Funding Agreement. The Act provides for “retention by an SBC of the rights to data generated by the concern in the performance of an SBIR award.”

- (1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the 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 (b) (3) of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR applicant. 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. 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.

5.6 Invention Reporting

The reporting of inventions may be accomplished by submitting paper documentation, including fax, or through the [Edison Invention Reporting System](#) for those agencies participating in iEdison.

Inventions must be reported promptly—within two months of the inventor’s initial report to the contractor organization—to:

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
E-mail: jpkim@nih.gov

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 U.S.C. 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.

If no invention is disclosed or no activity has occurred on a previously disclosed invention during the applicable reporting period, a negative report shall be submitted to the Contracting Officer at the address listed above.

To assist contractors in complying with invention reporting requirements of the clause, the NIH has developed "Interagency Edison," an electronic invention reporting system. Use of Interagency Edison is encouraged as it streamlines the reporting process and greatly reduces paperwork. Access to the system is through a secure interactive Web site to ensure that all information submitted is protected. Interagency Edison and information relating to the capabilities of the system can be obtained from the Web.

6 METHOD OF EVALUATION

If the NIH Component has indicated in the topic description that FAST Track proposals are accepted under a specific topic, and the offeror wishes to be considered for a FAST Track award, they must submit a Phase I and Phase II (FAST Track) proposal for concurrent peer review and evaluation. The Phase I and Fast Track Proposals will be evaluated and scored individually. Consequently, if a Phase I proposal is evaluated and found to be Technically Unacceptable; the Fast Track proposal will not be evaluated.

All proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria specified below, a panel of primarily 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 proposals or any specific number of proposals in a given topic. It may also elect to fund several or none of the proposed approaches to the same topic.

6.1 Evaluation Process

Your proposal will be peer reviewed by an external panel of experts 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
- Human Subject Protection <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
- Data Safety Monitoring Plan <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>
- Inclusion of Women and Minorities in Study Populations http://grants.nih.gov/grants/funding/women_min/women_min.htm
- Inclusion of Children <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>
- Animal Welfare http://grants.nih.gov/grants/oer_offices/olaw.htm

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 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 contract may be awarded only if the proposal has been recommended as technically acceptable by the peer review panel. *Funding for any/all acceptable proposals is not guaranteed. Proposals that are found to be technically unacceptable by the peer review panel will not be considered further for award.*

Selection of an offeror for contract award will be based on an evaluation of proposals against two factors. The factors in order of importance are: technical and cost/price. However, cost/price may become a critical factor in source selection in the event that two or more offerors are determined to be essentially equal following the evaluation of all factors other than cost or price. In any event, the Government reserves the right to make an award to that offeror whose response provides the best overall value to the Government.

6.2 Phase I Technical Evaluation Criteria

Proposals will be evaluated based on the criteria outlined below:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
<p>1. The soundness and technical merit of the proposed approach based on:</p> <ul style="list-style-type: none"> a. Identification of clear measureable goals (milestones) that have a reasonable chance of meeting the topic objective in Phase I; b. The approach is innovative and not routine, c. Offeror’s ability to implement technical approach, i.e., has or can obtain the resources (facilities, personnel and equipment) suitable to the task. <p>(Preliminary data are not required for Phase I proposals.)</p>	40%
<p>2. The qualifications of the proposed 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 expertise of each of the PDs/PIs?</p>	20%
<p>3. The potential of the proposed research for technological innovation.</p>	15%
<p>4. The potential of the proposed research for commercial application. The commercial potential of a proposal will be assessed using the following criteria:</p> <ul style="list-style-type: none"> 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 as well as method to overcome. 	15%
<p>5. The adequacy and suitability of the facilities and research environment.</p>	10%

Technical reviewers will base their conclusions only on information contained in the proposal. It cannot be assumed that reviewers are acquainted with the firm or key individuals or any referenced experiments. Relevant supporting data such as journal articles, literature, including Government publications, etc., should be contained or referenced in the proposal and will count toward the page limit.

6.3 FAST TRACK (NIH ONLY)/Phase II Technical Evaluation Criteria Evaluation Criteria

FACTORS FOR PHASE II PROPOSALS	WEIGHT
<p>1. The soundness and technical merit of the proposed approach based on:</p> <ul style="list-style-type: none"> a. Identification of clear measureable goals (milestones) that have a reasonable chance of meeting the topic objective in Phase II; b. The approach is innovative and not routine, c. Offeror’s ability to implement technical approach, i.e., has or can obtain the resources (facilities, personnel and equipment) suitable to the task. 	25%

FACTORS FOR PHASE II PROPOSALS	WEIGHT
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 I 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. 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?	25%
4. The adequacy and suitability of the facilities and research environment.	15%

Technical reviewers will base their conclusions only on information contained in the proposal. It cannot be assumed that reviewers are acquainted with the firm or key individuals or any referenced experiments. Relevant supporting data such as journal articles, literature, including Government publications, etc., should be contained or referenced in the proposal and will count toward the page limit.

6.4 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.
5. Cost/Price

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.

7 PROPOSAL SUBMISSION

7.1 Limitation on the Length of the Technical Proposal.

SBIR Phase I technical proposals (Item 1) shall not exceed 50 pages.

SBIR Phase II technical proposals (Item 1) shall not exceed 150 pages. All pages shall be single-sided, single-spaced pages for the entire proposal, all inclusive [including all pages, cover sheet(s), tables, CVs, resumes, references, pictures/graphics, and all enclosures, appendices or attachments, etc.]. Proposal pages shall be numbered “Page 1 of 50,” “Page 2 of 50,” and so on. Pages shall be of standard size (8.5” X 11”) with a font size of 11 points (or larger). Two sided pages count as two pages. There are NO exclusions to the page limit – the technical proposal shall not exceed 50 pages for Phase I, and 150 pages for Phase II. Pages in excess of the page limitation will be removed from the proposal and will not be read, considered, or evaluated.

7.2 Submission, Modifications, Revision, and Withdrawal of Proposals

- (a) Offerors are responsible for submitting proposals, and any revisions, and modifications, so as to reach the Government office designated in the solicitation by the time specified in the solicitation. Offerors may use any transmission method authorized by the solicitation (*i.e.*, regular mail, electronic commerce, or facsimile). If no time is specified in the solicitation, the time for receipt is 4:30 p.m., local time, for the designated Government office on the date that proposals are due.
- (b)
 - (1) Any proposal, modification, or revision, that is received at the designated Government office after the exact time specified for receipt of proposals is “late” and will not be considered unless it is received before award is made, the contracting officer determines that accepting the late proposal would not unduly delay the acquisition ; and—
 - (i) If it was transmitted through an electronic commerce method authorized by the solicitation, it was received at the initial point of entry to the Government infrastructure not later than 5:00 p.m. one working day prior to the date specified for receipt of proposals; or
 - (ii) There is acceptable evidence to establish that it was received at the Government installation designated for receipt of proposals and was under the Government’s control prior to the time set for receipt of proposals; or
 - (iii) It was the only proposal received under the HHS Component Topic.
 - (2) However, a late modification of an otherwise successful proposal, that makes its terms more favorable to the Government, will be considered at any time it is received and may be accepted.
- (c) 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.
- (d) If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the Government office designated for receipt of proposals by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation closing date, 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.
- (e) Proposals may be withdrawn by written notice at any time before award. One copy of withdrawn proposals should be retained in the contract file (see [4.803\(a\) \(10\)](#)). Extra copies of the withdrawn proposals may be destroyed or returned to the offeror at the offerors request. Extremely bulky proposals must only be returned at the offeror’s request and expense.

- (f) The contracting officer must promptly notify any offeror if its proposal, modification, or revision was received late, and must inform the offeror whether its proposal will be considered, unless contract award is imminent and the notice prescribed in [15.503](#)(b) would suffice.
- (g) Late proposals and modifications that are not considered must be held unopened, unless opened for identification, until after award and then retained with other unsuccessful proposals.
- (h) If available, the following must be included in the contracting office files for each late proposal, modification, revision, or withdrawal:
 - (1) The date and hour of receipt.
 - (2) A statement regarding whether the proposal was considered for award, with supporting rationale.
 - (3) The envelope, wrapper, or other evidence of date of receipt.

7.3 How To Submit Proposals

Paper copies and the Original Proposal are to be submitted by the due date and time specified in the solicitation, and to the Contracting Officer, at the address specified for their respective HHS Component or Topic in Section 10.

We do not have the technology at this time to accept electronic proposals. Nor do we have a portal through which you can track your proposal through the award process. Please keep your component contact information available so that you can contact them directly for an update on your proposal.

8 PROPOSAL PREPARATION AND INSTRUCTIONS

8.1 Introduction

It is important to read and follow the proposal preparation instructions carefully. The requirements for Phase I and FAST Track proposals are different, and are outlined below. Pay special attention to the requirements concerning Human Subjects and Animal Research if your project will encompass the use of either item.

8.2 Phase I Proposal Instructions

A complete Phase I proposal consists of four elements:

Item 1: Technical Element (1 Original, 5 Copies)

- a. Proposal Cover Sheet Appendix A
- b. Table of Contents
- c. Abstract of the Research Plan, (Appendix B)
- d. Content of the Technical Element

Item 2: Pricing Proposal (Appendix C) (1 Original, 5 copies)

Item 3: SBIR Application VCOC Certification

(See Section 4.5 to determine if this applies to your organization)

Item 4: Proof of Registration in the SBA Company Registry

(Refer to Section 4.7 for Directions)

In addition to the paper submissions, proposers are also encouraged to submit two (2) CD. One CD should contain Item 1 only and the other CD should contain Items 2-4, all in PDF format (Adobe Acrobat). This does not replace the paper copies but is in addition to them. The paper copy is the official copy for recording timely receipt of proposals. By signing the proposal, the offeror certifies that, as part of the offer, the information in the paper copy is exactly the same as that which is contained on the electronic media.

With the exception of the FAST TRACK proposals that may be submitted as specified in some NIH ONLY Research Topics, Phase II proposals may only be submitted by Phase I awardees. Submission of Phase II proposals are not permitted at this time and, if submitted, will be rejected without evaluation. Phase II proposal preparation and submission instructions will be provided by the HHS Components to Phase I awardees in a separate solicitation.

IMPORTANT -- While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work 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 as early as possible. If a proposal submitted for a Phase II effort is substantially the same as another proposal that was funded, is now being funded, or is pending with another Federal Agency, or another or the same HHS Component, you must reveal this on the Cover Sheet and provide the information required.

8.3 Fast Track Proposal Instructions

A complete Phase II as part of a (FAST TRACK) proposal consists of four elements:

Item 1: Technical Element (1 Original, 5 Copies)

- a. Technical Proposal Cover Sheet Appendix D
- b. Table of Contents
- c. Abstract of the Research Plan, (Appendix B)
- d. Content as outlined in the Technical Element Description
- e. Draft Statement of Work (Appendix E)
- f. Summary of Related Activities (Appendix F)

Item 2: Pricing Proposal (Appendix C) 1 (1 Original, 5 Copies)

Item 3: SBIR Application VCOC Certification

(See Section 4.5 to determine if this applies to your organization)

Item 4: Proof of Registration in the SBA Company Registry

(Refer to Section 4.7 for Directions)

In addition to the paper submissions, proposers are also encouraged to submit two (2) CD. One CD should contain Item 1 only and the other CD should contain Items 2-4, all in PDF format (Adobe Acrobat). This does not replace the paper copies but is in addition to them. The paper copy is the official copy for recording timely receipt of proposals. By signing the proposal, the offeror certifies that, as part of the offer, the information in the paper copy is exactly the same as that which is contained on the electronic media.

1. Technical Proposal Cover Sheet (Item One)

For Phase I Proposals complete the form identified as Appendix A and use it as the first page of the proposal. No other cover sheet should be used.

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf>)

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

For Fast Track Proposals Complete the form identified as Appendix D and use it as the first page of the proposal. No other cover sheet should be used.

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf>)

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
- **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.

- **FAST TRACK Only.** 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.

2. Table of Contents (Item One)

Layout: Include a Table of Contents. Number all pages of your proposal consecutively. Those who wish to respond must submit a direct, concise, and informative research or research and development proposal (no type smaller than 11-point on standard 8-1/2" x 11" paper with one inch margins). The header on each page of the technical proposal should contain your company name and topic number. The header may be included in the one-inch margin.

3. Abstract of Research Plan (Item One)

Complete the form identified as Appendix B

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.docx>)

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

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.

NOTE: PRIOR TO PREPARING THE RESEARCH PLAN APPLICANTS SHOULD REFER TO THE SPECIFIC RESEARCH TOPIC (SEE SECTION 12.0 OF THE SOLICITATION) TO REVIEW THE DESCRIPTION AND THE OUTLINED GOALS, ACTIVITIES AND BUDGET BEFORE PREPARING THIS ELEMENT OF THEIR PROPOSAL. ALSO, IF YOUR RESEARCH IS TO INCLUDE HUMAN OR ANIMAL SUBJECTS YOU MUST ADDRESS THE REQUIREMENTS OUTLINED IN THE ‘PROPOSAL FUNDAMENTALS’. ADD RESSE THESE ITEMS IN A SEPARATE SECTION OF YOUR TECHNICAL PROPOSAL AND LABEL AS REQUIRED.

NOTE: The Requirements for the Research Plan(s) for Phase I and Phase II are provided below. The Research Plans for Phase I have distinctly different requirements. In developing your technical proposal please make sure you are addressing the appropriate Research Plan.

4. Content of Technical Element (Item 1)

The Technical Item should cover the following items in the order given below.

(A) Research Plan for a Phase I Proposal

Discuss in the order indicated the following elements:

- 1) Identification and Significance of the Problem or Opportunity. Provide a clear statement of the specific technical problem or opportunity addressed.
- 2) Technical Objectives. State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.
- 3) **Work Plan.** Provide 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.

- 4) **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.
- 5) **Relationship with Future R&D.**
 - a) State the anticipated results of the proposed approach, assuming project success.
 - b) Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.
- 6) **Potential Commercial Applications.** Describe why the proposed project 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.
- 7) **Senior/Key Personnel and Bibliography of Directly Related Work.** Identify senior/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.

- 8) **Subcontractors/Consultants.** Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail and identified in the cost proposal. In addition, supported by appropriate letters from each individual confirming his/her role in the project must be included. Small business concerns must perform a minimum of two-thirds for Phase I of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.
- 9) **Facilities and Equipment.** Indicate where the proposed research will be conducted. One of the performance sites must be the offeror organization. Describe the facilities* to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project.

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

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

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

***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).**

(B) NIH FAST TRACK Only. Anticipated Results of the Phase I Effort

Briefly discuss and summarize the objectives of the Phase I effort, the research activities to be carried out, and the anticipated results.

(C) Research Plan for Phase II (FAST TRACK) Research Plan

- 1) **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.
- 2) **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.
- 3) **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.)
- 4) **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 [4.10](#) and [4.11](#) of this solicitation for further guidance.
- 5) **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.

- 6) 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.
- 7) **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 (for example, human subject concerns, the Small Business Act provisions, etc.), this must be explained in the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.
 - a) **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 [NIH Guide NOT-OD-04-042](#).
 - 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 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 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 [Genome-Wide Association Studies](#).
- 8) **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 12 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.
- d) 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.
- e) 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.)
- f) **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.
- g) **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:
 - i) Letter of commitment of funding.
 - ii) Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
 - iii) Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.
 - iv) Specific steps you are going to take to secure Phase III funding.
- h) **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.
- i) **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.
- j) 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.
- k) 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.

(D) **Prior, Current, or Pending Support of Similar Proposals or Awards.** If a proposal submitted in response to this solicitation is substantially the same as another proposal that was funded, is now being funded, or is pending with another Federal Agency, or another or the same HHS Component, you must reveal this on the Proposal Cover Sheet and provide the following information:

- 1) Name and address of the Federal Agency(s) or HHS Component, to which a proposal was submitted, will be submitted, or from which an award is expected or has been received.
- 2) Date of proposal submission or date of award.
- 3) Title of proposal.
- 4) Name and title of principal investigator for each proposal submitted or award received.
- 5) Title, number, and date of solicitation(s) under which the proposal was submitted, will be submitted, or under which award is expected or has been received.
- 6) If award was received, state contract number.
- 7) Specify the applicable topics for each SBIR/STTR proposal submitted or award received.

Note: If this does not apply, state in the proposal "No prior, current, or pending support for proposed work."

8.4 Human Subjects Research and Protection from Risk

Instructions and Required Information

If your project involves the use of Human Subjects as defined in Section 3.2 of this solicitation, this information must be submitted with the proposal.

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

Instructions to Offerors Regarding Protection of Human Subjects

Offerors must address the following human subjects protections issues if this contract will be for research involving human subjects (note: under each of the following points below, the offeror should indicate whether the information provided relates to the primary research site, or to a collaborating performance site(s), or to all sites:

- a. Risks to the subjects
 - Human Subjects Involvement and Characteristics:
 - Describe the proposed involvement of human subjects in response to the solicitation.
 - 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, pregnant women, children, prisoners, institutionalized individuals, or others who are likely to be vulnerable populations.
 - Sources of Materials:

- Identify the sources of research material obtained from individually identifiable living human subjects in the form of specimens, records, or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records, or data.
 - Potential Risks:
 - Describe the potential risks to subjects (physical, psychological, social, legal, or other) and assess their likelihood and seriousness to the subjects.
 - Describe alternative treatments and procedures, including the risks and benefits of the alternative treatments and procedures, to participants in the proposed research, where appropriate.
- b. Adequacy of Protection Against Risks
 - Recruitment and Informed Consent:
 - Describe plans for the recruitment of subjects and the procedures for obtaining informed consent. Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. The informed consent document for the Contractor and any collaborating sites should be submitted only if requested elsewhere in the solicitation. Be aware that an IRB-approved informed consent document for the Contractor and any participating collaborative sites must be provided to the Government prior to patient accrual or participant enrollment.
 - Protection Against Risk:
 - Describe the procedures for protecting against or minimizing potential risks, including risks to confidentiality, and assess their likely effectiveness.
 - Discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects where appropriate.
 - In studies that involve interventions, describe the provisions for data and safety monitoring of the research to ensure the safety of subjects.
- c. Potential Benefits of the Proposed Research to the Subjects and Others
 - Discuss the potential benefits of the research to the subjects and others.
 - Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.
 - Describe treatments and procedures that are alternatives to those provided to the participants by the proposed research, where appropriate.
- d. Importance of the Knowledge to be Gained
 - Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
 - Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that may reasonably be expected to result.

Note : If a test article (investigational new drug, device, or biologic) is involved, name the test article and state whether the 30-day interval between submission of offeror's certification to the Food and Drug Administration (FDA) and its response has elapsed or has been waived and/or whether the FDA has withheld or restricted use of the test article.

Collaborating Site(s)

When research involving human subjects will take place at collaborating site(s) or other performance site(s), the offeror must provide in this section of its proposal a list of the collaborating sites and their assurance numbers. Further, if you are awarded a contract, you must obtain in writing, and keep on file, an assurance from each site that the previous points have been adequately addressed at a level of attention that is at least as high as that documented at your organization. Site(s) added after an award is made must also adhere to the above requirements.

Required Education in the Protection of Human Research Participants

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for contracts for research involving human subjects. This policy announcement is found in [NOT-OD-00-039](#) in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000. Offerors should review the policy announcement prior to submission of their offers. The following is a summary of the Policy Announcement:

For any solicitation for research involving human subjects, the offeror shall provide in its technical proposal the following information: (1) a list of the names of the principal investigator and any other individuals proposed under the contract who are responsible for the design and/or conduct of the research; (2) the title of the education program completed (or to be completed prior to the award of the contract) for each named personnel; (3) a one sentence description of the program(s) listed in (2) above. This requirement extends to investigators and all individuals responsible for the design and/or conduct of the research who are working as subcontractors or consultants under the contract.

Curricula that are readily available and meet the educational requirement include the NIH Office of Extramural Research (OER) on-line tutorial, entitled "[Protecting Human Research Participants](#)/" This course is also available in Spanish under the title "[Protección de los participantes humanos de la investigación.](#)" You may take the tutorials on-line or download the information in PDF form at no cost. The University of Rochester has made its training program available for individual investigators. Completion of this program will also satisfy the educational requirement. The University of Rochester manual can be obtained through [Centerwatch, Inc.](#)

If an institution already has developed educational programs on the protection of research participants, completion of these programs also will satisfy the educational requirement.

In addition, prior to the substitution of the principal investigator or any other individuals responsible for the design and/or conduct of the research under the contract, the Contractor shall provide the contracting officer with the title of the education program and a one sentence description of the program that the replacement has completed.

Inclusion of Women and Minorities in Research Involving Human Subjects

It is NIH policy that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. The Director, NIH, may determine that exclusion under other circumstances is acceptable, upon the recommendation of an Institute/Center 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. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43), **and applies to research subjects of all ages.**

All investigators proposing research involving human subjects should read the UPDATED "[NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, Amended October 2001,](#)" published in the NIH Guide for Grants and Contracts on October 9, 2001.

These guidelines contain a definition of **clinical research** adopted in June 2001, as: "(1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes (a) mechanisms of human disease, (b) therapeutic interventions, (c) clinical trials, and (d) development of new technologies; (2) Epidemiologic and behavioral studies; and (3) Outcomes research and health services research."

Information Required for ALL Clinical Research Proposals

This solicitation contains a review criterion addressing the adequacy of: (1) the offeror's plans for inclusion of women and minorities in the research proposed; or (2) the offeror's justification(s) for exclusion of one or both groups from the research proposed.

Provide information on the composition of the proposed study population in terms of sex/gender and racial/ethnic groups and provide a rationale for selection of such subjects in response to the requirements of the solicitation. The description may include (but is not limited to) information on the population characteristics of the disease or condition being studied in the planned research, and/or described in the statement of work, national and local demography, knowledge of the racial/ethnic/cultural characteristics of the population, prior experience and collaborations in recruitment and retention of the populations and subpopulations to be studied, and the plans, arrangements and letters of commitment from relevant community groups and organizations for the planned research.

The proposal must include the following information:

- A description of the subject selection criteria
- The proposed dates of enrollment (beginning and end)
- A description of the proposed outreach programs for recruiting women and minorities as subjects
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group
- The proposed sample composition using the "Targeted/Planned Enrollment Table"(see Section J, Attachments)

NOTE 1: For all proposals, use the ethnic and racial categories and complete the "Targeted/Planned Enrollment Table in accordance with the [Office of Management and Budget \(OMB\) Directive No. 15](#).

NOTE 2: If this is an Indefinite Delivery, Indefinite Quantity (IDIQ) or Requirements contract as defined in FAR 16.5, the proposal should describe in general terms how it will comply with each bulleted item above for each task order. When the Government issues a task order request for proposal, each of the bulleted information items must be fully and specifically addressed in the proposal.

Standards for Collecting Data. When you, as a contractor, are planning data collection items on race and ethnicity, you shall use, at a minimum, the categories identified in OMB Directive No. 15. The collection of greater detail is encouraged. However, you should design any additional, more detailed items so that they can be aggregated into these required categories. Self-reporting or self-identification using two separate questions is the preferred method for collecting data on race and ethnicity. When you collect race and ethnicity separately, you must collect ethnicity first. You shall offer respondents the option of selecting one or more racial designations. When you collect data on race and ethnicity separately, you shall also make provisions to report the number of respondents in each racial category who are Hispanic or Latino. When you present aggregate data, you shall provide the number of respondents who selected only one category, for each of the five racial categories. If you collapse data on multiple responses, you shall make available, at a minimum, the total number of respondents reporting "more than one race." Federal agencies shall not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

In addition to the above requirements, solicitations for **NIH defined Phase III clinical trials** * require that: a) all proposals and/or protocols provide a description of plans to conduct analyses, as appropriate, to detect significant differences in intervention effect by sex/gender, racial/ethnic groups, and relevant subpopulations, if applicable; and b) all contractors to report annually cumulative subject accrual, and progress in conducting analyses for sex/gender and race/ethnicity differences.

(See NIH Guide: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm, Definitions - Significant Difference.)

*The definition of an "NIH-Defined Phase III clinical trial" can also be found at this website.

Offerors may obtain copies of the Updated Guidelines from the sources above or from the contact person listed in the solicitation.

Also, the proposal must include one of the following plans:

Plans to conduct valid analysis 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,

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.

Use the form entitled, "[Planned Enrollment Report](#)," when preparing your response to the solicitation requirements for inclusion of women and minorities.

Unless otherwise specified in this solicitation, the Government has determined that the work required by this solicitation does not involve a sex/gender specific study or a single or limited number of minority population groups. Therefore, the NIH believes that the inclusion of women and minority populations is appropriate for this project.

Use the form entitled, "[Cumulative Inclusion Enrollment Report](#)," for reporting in the resultant contract.

Inclusion of Children in Research Involving Human Subjects

It is NIH policy that children (defined below) must be included in all human subjects research, including, but not limited to, clinical trials, conducted under a contract funded by the NIH, unless there are clear and compelling reasons not to include them. (See examples of Justifications for Exclusion of Children below). For the purposes of this policy, contracts involving human subjects include categories that would otherwise be exempt from the HHS Policy for Protection of Human Research Subjects (sections 101(b) and 401(b) of 45 CFR 46), such as surveys, evaluation of educational interventions, and studies of existing data or specimens that should include children as participants. This policy applies to both domestic and foreign research contracts.

For purposes of this policy, a child is defined as an individual under the age of 21 years.

All offerors proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" which was published in the NIH Guide for Grants and Contracts on March 6, 1998 and is available at the following URL address: <http://www.nih.gov/grants/guide/notice-files/not98-024.html>. Offerors also may obtain copies from the contact person listed in the RFP.

Inclusion of children as participants in research must be in compliance with all applicable subparts of 45 CFR 46 as well as other pertinent laws and regulations whether or not such research is otherwise exempted from 45 CFR 46. Therefore, any proposals must include a description of plans for including children, unless the offeror presents clear and convincing justification for an exclusion. The "Human Subjects" section of your technical proposal should provide either a description of the plans to include children and a rationale for selecting or excluding a specific age range of child, or an explanation of the reason(s) for excluding children as participants in the research. This solicitation contains a review criterion addressing the adequacy of: (1) the plans for including children as appropriate for the scientific goals of the research; and/or (2) the justification of exclusion of children or exclusion of a specific age range of children.

When children are included, the plan also must include a description of: (1) the expertise of the investigative team for dealing with children at the ages included; (2) the appropriateness of the available facilities to accommodate the children; and, (3) the

inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose/objective of the solicitation.

Justifications for Exclusion of Children

It is expected that children will be included in all research involving human subjects unless one or more of the following exclusionary circumstances can be fully justified:

- The objective of the solicitation is not relevant to children.
- There are laws or regulations barring the inclusion of children in the research to be conducted under the solicitation.
- The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be redundant. You should provide documentation of other studies justifying the exclusion.
- A separate, age-specific study in children is warranted and preferable. Examples include:
 - The relative rarity of the condition in children, as compared with adults (in that extraordinary effort would be needed to include children); or
 - The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
 - Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages of different age-related metabolic processes); or
 - 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). While 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; or
 - Study designs aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children);
 - Other special cases justified by the offeror and found acceptable to the review group and the Institute Director

Definition of a Child

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

8.5 Research Involving Prisoners as Subjects

HHS Regulations at 45 CFR Part 46, Subpart C provide additional protections pertaining to biomedical and behavioral research involving prisoners or those individuals who, during the period of the contract become prisoners, as subjects. These regulations also set forth the duties of the Institutional Review Board (IRB) where prisoners are involved in the research. HHS funded research involving prisoners as subjects may not proceed until the Office for Human Research Protections

(OHRP) issues approval, in writing, as required by 45 CFR 46.306(a)(2). In addition, OHRP Guidance on the Involvement of Prisoners in Research may be found at: <http://www.hhs.gov/ohrp/humansubjects/guidance/prisoner.pdf>.

HHS Waiver for Epidemiological Research Involving Prisoners as Subjects

On June 20, 2003 the Secretary of HHS waived the applicability of certain provisions of Subpart C of 45 CFR Part 46, (Additional HHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects) to specific types of epidemiological research involving prisoners as subjects.

The applicability of 45 CFR 46.305(a)(1) and 46.306(a)(2) for certain epidemiological research conducted or funded by HHS is waived when:

The sole purposes are:

- a. to describe the prevalence or incidence of a disease by identifying all cases, or
- b. to study potential risk factor associations for a disease, **and**

The Institution responsible for the conduct of the research certifies to the OHRP that the Institutional Review Board (IRB) approved the research and fulfilled its duties under 45 CFR 46.305(a)(2 7) and determined and documented that:

- a. the research presents no more than minimal risk, and
- b. no more than inconvenience to the prisoner subjects, and
- c. prisoners are not a particular focus of the research.

For more information about this Waiver see [http://www.hhs.gov/ohrp/special/prisoners/Prisoner waiver 6-20-03.pdf](http://www.hhs.gov/ohrp/special/prisoners/Prisoner%20waiver%206-20-03.pdf)

8.6 Research Involving Human Fetal Tissue

Human Fetal Tissue means tissue or cells obtained from a dead human fetus, including human embryonic stem cells, human pluripotent stem cells and human embryonic germ cells.

The governing federal statute is the Public Health Service Act, 42 U.S.C. 289g 1 and 289g 2. Implementing regulations and guidance for conducting research on human fetal tissue may be found at 45 CFR 46, Subpart B and [NIH Guide NOT-OD-93-235](#) and any subsequent revisions to this NIH Guide to Grants and Contracts ("Guide") Notice.

By signing the face page of the proposal, the offeror (authorized institutional official) certifies that researchers using human fetal tissue are in compliance with 42 USC 289g 2. This statute specifically prohibits any person from knowingly acquiring, receiving, or transferring any human fetal tissue for valuable consideration. "Valuable consideration" is a concept similar to profit, and does not include reasonable payment for costs associated with the collection processing, preservation, storage, quality control or transportation of these tissues.

Research involving the transplantation of human fetal tissue must be conducted in accordance with applicable Federal, State and local law.

8.7 Research Involving Live Vertebrate Animals

If it is intended that live vertebrate animals will be used during performance of this contract. The Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (authority derived from the Health Research Extension Act of 1985) specifies that certain information is required from offerors in contract proposals submitted to the NIH that will use live vertebrate animals.

The following five points must be addressed in a separate section of the Technical Proposal titled "Vertebrate Animal Section" (VAS):

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.

A concise (no more than 1-2 pages), complete description addressing these five points must be provided. The description must be cohesive and include sufficient information to allow evaluation by reviewers and NIH staff. For more discussion regarding the five points in the VAS, see [NIH Guide Notice NOT-OD-10-049](#).

NIH no longer requires Institutional Animal Care and Use Committee approval of the proposed research before NIH peer review of a proposal ([NOT-OD-02-064](#)).

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 U.S.C. 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.

8.8 Content of the Pricing Proposal (Item Two).

Complete the Pricing Item in the format shown in the Pricing Proposal ([Appendix C](#)). Some items in the Pricing Proposal may not apply to the proposed project. If that is the case, there is no need to provide information on each and every item. What matters is that enough information be provided to allow us to understand how you plan to use the requested funds if a contract is awarded.

1. List all key personnel by name as well as by number of hours dedicated to the project as direct labor.
2. While special tooling and test equipment and material cost may be included under Phases I, the inclusion of equipment and material will be carefully reviewed relative to need and appropriateness for the work proposed. The purchase of special tooling and test equipment must, in the opinion of the Contracting Officer, be advantageous to the Government and should be related directly to the specific topic. These may include such items as innovative instrumentation or automatic test equipment. Title to property furnished by the Government or acquired with Government funds will be vested with the HHS Component; unless it is determined that transfer of title to the contractor would be more cost effective than recovery of the equipment by the HHS Component.
3. Cost for travel funds must be justified and related to the needs of the project.
4. 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 a Phase I proposal.
5. All subcontractor costs and consultant costs must be detailed at the same level as prime contractor costs in regards to labor, travel, equipment, etc. Provide detailed substantiation of subcontractor costs in your cost proposal. Enter this information in the Explanatory Material section of the on-line cost proposal form.
6. NIH Policy on Threshold for Negotiation of General and Administrative (G&A)/Indirect Costs (IDC) Rates for SBIR proposals - SBIR offerors who propose in the contract an G&A/IDC rate of 40 percent of total direct costs or less will not be required to provide further justification at the time of award, and G&A/IDC costs will be awarded at the requested rate. However, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for G&A/IDC rates on an *ad hoc* basis. If the SBC has a currently effective negotiated indirect cost rate(s) with a Federal agency, such rate(s) shall be used when calculating proposed G&A/IDC costs for an NIH proposal. (However, the rate(s) must be adjusted for IR&D expenses, which are not allowable under HHS awards.)

SBCs are reminded that only actual G&A/IDC costs may be charged to projects. If awarded at a rate of 40 percent or less of total direct costs, the rate used to charge actual G&A/ID costs to projects cannot exceed the awarded rate unless the SBC negotiates an indirect cost rate(s) with DFAS.

7. Offerors submitting proposals may include the amount of \$5,000 for technical assistance as discussed and outlined in Section 4.20 of the solicitation.

8.9 Proposal Checklists

Phase I Proposal:

Item 1:

- a. Proposal Cover Sheet Appendix A (1 Original, 5 Copies)
- b. Table of Contents
- c. Abstract of the Research Plan, (Appendix B) (1 Original, 10 Copies)
- d. Content of the Technical Element

Item 2: Pricing Proposal (Appendix C) (1 Original, 5 copies)

Item 3: SBIR Application VCOC Certification

(See Section 4.5 to determine if this applies to your organization)

Item 4: Proof of Registration in the SBA Company Registry

(Refer to Section 4.16 for Directions)

Phase II as part of a Fast Track Proposal

Item 1: Technical Element

- a. Technical Proposal Cover Sheet Appendix D (1 Original, 5 Copies)
- b. Table of Contents
- c. Abstract of the Research Plan, (Appendix B) (1 Original, 10 Copies)
- d. Content as outlined in the Technical Element Description
- e. Draft Statement of Work (Appendix E)
- f. Summary of Related Activities (Appendix F)

Item 2: Pricing Proposal (Appendix C) I (1 Original, 5 Copies)

Item 3: SBIR Application VCOC Certification

(See Section 4.5 to determine if this applies to your organization)

Item 4: Proof of Registration in the SBA Company Registry

(Refer to Section 4.16 for Directions)

Those responding to this solicitation should note the proposal preparation tips listed below:

1. Read and follow all instructions contained in this solicitation, including the instructions in Section 12.0 of the HHS Component to which the firm is applying.
2. Check that the cost adheres to the Component criteria specified and the price on the cover sheets matches the price in the Pricing proposal.
3. Check that the Project Abstract and other content provided on the cover sheets contain NO proprietary information.
4. Mark proprietary information within the Technical Proposal as instructed in Section 4.23.
5. That the header on each page of the technical proposal should contain the company name and topic number.
6. Ensure that if you have proposed for your research to include Human Subjects or Research on Animals that you have addressed the requirements outlined in the solicitation in the Technical proposal as necessary.

9 SUMMARY OF HHS COMPONENTS ANTICIPATED NUMBER OF AWARDS

HHS COMPONENTS	ANTICIPATED NO. OF AWARDS	ANTICIPATED TIME OF AWARD
National Institutes of Health (NIH) National Cancer Institute (NCI)	25 - 38	Scientific and Technical Merit Review: March-May 2014 Anticipated Award Date: August-September 2014
National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS)	4-8	Scientific and Technical Merit Review: February-March 2014 Anticipated Award Date: September 2014
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	10-17	Scientific and Technical Merit Review: February-April 2014 Anticipated Award Date: July-September 2014
National Institutes of Health (NIH) National Institute on Aging (NIA)	1-2	Scientific and Technical Merit Review: February-March 2014 Anticipated Award Date: August-September 2014
National Institutes of Health (NIH) National Institute on Alcohol Abuse and Alcoholism (NIAAA)	1	Scientific and Technical Merit Review: March 2014 Anticipated Award Date: August 2014
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	4-10	Scientific and Technical Merit Review: March 2014 Anticipated Award Date: August 2014
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	8-10	Scientific and Technical Merit Review: March 2014 Anticipated Award Date: August 2014
Centers for Disease Control and Prevention (CDC) Center for Global Health (CGH)	1-2	Scientific and Technical Merit Review: May-June 2014 Anticipated Award Date: August 2014
Centers for Disease Control and Prevention (CDC) National Center for Birth Defects and Developmental Disabilities (NCBDDD)	1-3	Scientific and Technical Merit Review: May-June 2014 Anticipated Award Date: August 2014
Centers for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	3	Scientific and Technical Merit Review: May-June 2014 Anticipated Award Date: August 2014
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	5	Scientific and Technical Merit Review: May-June 2014 Anticipated Award Date: August 2014
Centers for Disease Control and Prevention (CDC) National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	7	Scientific and Technical Merit Review: May-June 2014 Anticipated Award Date: August 2014

HHS COMPONENTS	ANTICIPATED NO. OF AWARDS	ANTICIPATED TIME OF AWARD
Centers for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	2	Scientific and Technical Merit Review: May-June 2014 Anticipated Award Date: August 2014
Centers for Disease Control and Prevention (CDC) Office of Public Health Preparedness and Response (OPHPR)	2	Scientific and Technical Merit Review: May-June 2014 Anticipated Award Date: August 2014

10 CONTRACTING OFFICERS AND ADDRESSES FOR DELIVERY OF CONTRACT PROPOSALS

General Questions about the NIH SBIR Program

Email: sbir@od.nih.gov

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, e-mail, 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.

NATIONAL INSTITUTES OF HEALTH (NIH)

NATIONAL CANCER INSTITUTE (NCI)

Ms. Elizabeth Shanahan

Phone: (240) 276-5432

Fax: (240) 276-5431

E-mail: eshanahan@mail.nih.gov

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

Ms. Elizabeth Shanahan

Contracting Officer

Office of Acquisitions

National Cancer Institute

9609 Medical Center Drive, 1E564, MSC9700

Bethesda, MD 20892-9700

**Change the city to Rockville and the zip code to 20850 if hand-delivered or delivered by an overnight service to the NCI.*

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

Mr. Bryan Jones

Phone: 301-594-1852

E-mail: bryan.jones@nih.gov

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

Ms. Bryan Jones

Branch Chief

Office of Acquisitions

NIDA COAC

6701 Democracy Blvd, Suite 1086

Bethesda, MD 20892-4874 *

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

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

Mr. John Taylor

Phone: (301) 435-0327

Fax: (301) 480-3338

E-mail: taylorjc@nhlbi.nih.gov

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

Review Branch
Division of Extramural Research Activities
National Heart, Lung, and Blood Institute
Rockledge 2, Room 7195
6701 Rockledge Drive, MSC 7924
Bethesda, MD 20892-7924 *

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

NATIONAL INSTITUTE ON AGING (NIA)

For inquiries about NIA's SBIR Contract Solicitation and Topic:

Max Guo, Ph.D.
Division of Aging Biology
National Institute on Aging
Office: 301-402-7747
Fax: 301-402-0010
Email: Max.Guo@NIH.GOV

NIA SBIR Contract Proposals must be mailed or delivered to:

Suzanne Stinson
NIDA COAC (COAC for NIA)
MSC 9661/NSC/8154
6001 Executive Boulevard
Rockville, MD 20892-9661*

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

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

Mr. Paul D. McFarlane
Phone: (301) 443-3041
Fax: (301) 443-3891
Email: paul.mcfarlane@nih.gov

Proposals to the NIAAA must be mailed or delivered to:

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

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

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Eileen Webster-Cissel

Chief, AIDS Research Contracts Branch
Phone: 301-496-0612
FAX: 301-480-4675
Email: webstere@niaid.nih.gov

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

Eileen Webster-Cissel
Office of Acquisitions, Division of Extramural Activities
6700B Rockledge Drive
Bethesda, Maryland 20892
Room 3214
Mail stop 7612

**Change the city to Rockville, MD and the zip code to 20817 for hand-delivery or overnight delivery service.*

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

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

Proposals to the NIDA must be mailed or delivered to:

Mr. Brian O'Laughlin
NIDA R&D Contracts Management Branch
Neurosciences Office of Acquisition
6001 Executive Boulevard
Room 4211, MSC 9559
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.*

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Office of the Director, Office of the Associate Director for Science

Juliana Cyril, Ph.D., M.P.H.
Director, Office of Technology and Innovation
Office of the Associate Director for Science
Phone: (404) 639-4639
Fax: (404) 639-4903
E-mail: JCyril@cdc.gov

Sean David Griffiths, M.P.H.
Office of Technology and Innovation
Office of the Associate Director for Science
Phone: 404-639-4641
Fax: 404-639-4903
E-mail: SGriffiths@cdc.gov

CENTER FOR GLOBAL HEALTH (CGH)

Carlos Smiley
Contracting Officer
Phone: (770) 488-1517
Fax: (770) 488-2688
E-mail: CSmiley1@cdc.gov

Proposals to CGH must be mailed or delivered to:

Carlos Smiley
Contracting Officer
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

NATIONAL CENTER FOR BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

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

Proposals to NCHHSTP must be mailed or delivered to:

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

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

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

Proposals to NCHHSTP must be mailed or delivered to:

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

NATIONAL CENTER FOR EMERGING ZOO NOTIC AND INFECTIOUS DISEASES (NCEZID)

Theresa Routh-Murphy
Contracting Officer
Phone: (770) 488.2173
E-mail: TNR3@cdc.gov

Proposals to NCHHSTP must be mailed or delivered to:

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

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

Theresa Routh-Murphy
Contracting Officer
Phone: (770) 488.2713
E-mail: TNR3@cdc.gov

Proposals to NCEZID must be mailed or delivered to:

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

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

Alan Sims
Contracting Officer, Lead
Phone: (770) 488-2647
Fax: (770) 488-2670
E-mail: ASims1@cdc.gov

Proposals to NCIRD must be mailed or delivered to:

Alan Sims
Contracting Officer
Centers for Disease Control and Prevention
Procurement and Grants Office
2920 Brandywine Road
Atlanta, GA 30341

OFFICE OF PUBLIC HEALTH PREPAREDNESS AND RESPONSE (OPHPR)

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Proposals to OPHPR must be mailed or delivered to:

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Procurement and Grants Office
2920 Brandywine Road (MS- E14)
Atlanta, GA 30341

11 SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit <http://nmlm.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/>

12 COMPONENT INSTRUCTIONS AND TECHNICAL TOPIC DESCRIPTIONS

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, and treatment of cancer, as well as the rehabilitation and continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread application, 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. The NCI SBIR program acts as NCI's catalyst of innovation for developing and commercializing novel technologies and products to research, prevent, diagnose, and treat cancer.

It is strongly suggested that potential offerors do not exceed the total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

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 IIB Bridge Award

The National Cancer Institute would like to provide notice of a recent funding opportunity entitled the SBIR Phase IIB 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 making such awards to contract awardees.

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

The NCI expanded the Phase IIB Bridge Award program in FY2011 to allow previous SBIR Phase II contract awardees to compete for SBIR Phase IIB Bridge Awards. Pending its planned continuation, it is anticipated that the Phase IIB Bridge Award program will be open to contractors that successfully complete a Phase I award as a result of this solicitation, and who are subsequently awarded a Phase II contract (or have an exercised Phase II option under a Fast-Track contract). Provided it is available in the future, NIH SBIR Phase II contractors who satisfy the above requirements may be able to apply for a Phase IIB Bridge Award under a future Phase IIB Bridge Award grant funding opportunity announcement (FOA), if they meet the eligibility requirements detailed therein. Selection decisions for a Phase IIB Bridge 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:

326 Development of Novel Therapeutic Agents that Target Cancer Stem Cells

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

Number of anticipated awards: 3 – 5

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

Cancer stem cells (CSCs) are a subset of tumor cells that possess characteristics associated with normal stem cells. Specifically, they have the ability to self-renew, differentiate and generate the diverse cells that comprise the tumor. CSCs have been identified and isolated in several human cancer types, including breast, brain, colon, head and neck, leukemia, liver, ovarian, pancreas and prostate. These CSCs represent approximately 1% of the tumor as a distinct population and cause relapse and metastasis by giving rise to new tumors. While chemotherapy and other conventional cancer therapies may be more effective at killing bulk tumor cells, CSCs may manage to escape and seed new tumor growth due to the survival of quiescent CSCs. Therefore, traditional therapies often cannot completely eradicate tumors or prevent cancer recurrence and progression to metastasis. With growing evidence supporting the role of CSCs in tumorigenesis, tumor heterogeneity, resistance to chemotherapeutic and radiation therapies, and the metastatic phenotype, the development of specific therapies that target CSCs holds promise for improving survival and quality of life for cancer patients, especially those with metastatic disease.

Project Goals

The goal of this solicitation is to provide support for the development of novel therapeutic agents that target CSCs. These small molecules or biologics should be designed to target CSCs, CSC-related biomarkers, or CSC pathways that affect fundamental processes associated with carcinogenesis, tumor progression, maintenance, recurrence or metastasis. Particular emphasis is placed on agents that target CSC self-renewal, regeneration, or differentiation processes. Proposals that combine the development of agents that target CSCs with conventional cancer therapy are encouraged. The long term goal of this contract topic is to enable small businesses to bring fully developed therapeutic agents that target CSCs to the clinic and eventually to the market.

To apply for this topic, offerors should:

- Have at least one validated target. The target can be, but is not limited to: a marker, a pathway, a set of markers or pathways, or any other molecular targets that are specifically associated with CSCs in the cancer of choice.
- Provide data or cite literature to support that the target is tightly associated with CSCs.
- Have ownership of, or license for, at least one lead agent (e.g., compound or antibody) with preliminary data showing that the agent hits the identified target.
- Have experience with a well-validated assay for CSCs.
- Describe what is known about the mechanism by which the agent acts on CSCs.

Phase I Activities and Expected Deliverables

- Demonstrate *in vitro* efficacy for the agent(s) that targets CSCs.
- Validate the effect of the agent(s) on CSCs. The offerors are required to provide evidence confirming that the agent(s) specifically targets CSCs (e.g., measurement showing reduced quantity, viability, or frequency of CSCs).
- Conduct structure-activity relationship (SAR) studies, medicinal chemistry, and/or lead antibody optimization (as appropriate).

- Perform animal toxicology and pharmacology studies as appropriate for the agent(s) selected for development.
- Develop a detailed experimental plan (to be pursued under a future SBIR Phase II award) necessary for filing an IND or an exploratory IND.

Phase II Activities and Expected Deliverables

- Complete IND-enabling experiments and assessments according to the plan developed in Phase I (e.g., demonstration of desired function and favorable biochemical and biophysical properties, PK/PD studies, safety assessment, preclinical efficacy, GMP manufacturing, and commercial assessment). The plan should be re-evaluated and refined as appropriate.
- Develop and execute an appropriate regulatory strategy. If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agents (i.e., oncologic indications for CSCs).
- Demonstrate the ability to produce a sufficient amount of clinical grade materials suitable for an early clinical trial.

327 Reformulation of Failed Chemotherapeutic Drugs

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2 – 4

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

Many promising chemotherapeutic candidates have failed to gain FDA approval due to adverse properties discovered in pre-clinical development or in human clinical trials. Such failures often occur due to unacceptable toxicity, although other limitations may also derail the development of promising anti-cancer agents. Novel drug delivery systems for cancer treatment that carry and deliver therapeutic payloads within close proximity of the tumor *in vivo* play a significant role in increasing the effectiveness of the treatment while decreasing the severity of toxicities. The successful delivery of well-established chemotherapeutics has been demonstrated previously using a number of platforms; however, such systems provide only incremental improvements in the overall therapeutic index of previously-approved drugs. An even greater opportunity is associated with reformulating once promising chemotherapeutic drugs that either failed to reach clinical trials or failed in clinical development. Among the limitations that reformulation strategies can address are poor oral bioavailability, poor solubility in biological fluids, inappropriate pharmacokinetics, and/or lack of efficacy within a tolerable dose range. To accelerate such efforts, the National Cancer Institute (NCI) requests proposals for the development of commercially-viable platforms for the reformulation of chemotherapeutic drugs that have failed previously in pre-clinical development or in human clinical trials.

Project Goals

The goal of this project is to add new agents to the current arsenal of chemotherapeutic drugs by identifying and evaluating candidate delivery systems to enable the therapeutic potential of drugs that could not otherwise be delivered to humans in free form. The focus of this topic is on the reformulation of small-molecule chemotherapeutic agents. The proposed drug-delivery platform must yield a significant improvement in properties with respect to the free drug in order to enable the re-evaluation of the chemotherapeutic drug as a potential therapy for cancer treatment.

Proposals submitted under this topic **must**:

- Name the small-molecule chemotherapeutic drug (i.e., the active pharmaceutical ingredient [API]) proposed for reformulation;
- Describe to the greatest extent possible the mechanism by which the chemotherapeutic drug acts on cancer cells (i.e., mode of action);
- Cite published literature and/or clinical data and/or other supporting evidence to clearly demonstrate that the chemotherapeutic drug is not deliverable in its free form;
- Describe the drug-delivery platform/reformulation approach that will be used to reformulate the drug, and provide a compelling scientific rationale for why the solution may reduce or eliminate the adverse properties of the free drug.

The proposed drug-delivery platform/reformulation approach may utilize any technology capable of meeting the stated goals of this contract topic. Examples include the use of multi-functional targeted drug delivery platforms or multi-chamber chips carrying encapsulated drugs, although other approaches will be favorably considered. The final drug formulation may utilize an imaging agent(s) for a combination of therapeutic and diagnostic modalities, in order to provide real-time feedback and monitoring of therapy; however, such “theranostic” approaches are NOT required. Acceptable technologies/approaches under this contract may include, but are not necessarily limited to:

- Devices involving novel tumor targeting and concentration schemes;
- Novel drug loading and releasing schemes;
- Novel drug delivery platforms, which are able to cross the blood-brain barrier, penetrate stromal barriers, overcome multi-drug resistance or treat metastatic cancer;
- Novel therapeutic nanoparticle systems;
- Antibody-drug conjugates;
- Biomimetic constructs;
- Virus-like particles (VLPs);
- Combination therapies utilizing at least one chemotherapeutic agent meeting the above criteria.

Please note that the following approaches are NOT acceptable under this contract topic:

- Chemical entities that have received FDA approval for any indication (cancer or otherwise) are NOT acceptable chemotherapeutic drug candidates under this topic.
- Chemically-modified, failed chemotherapeutic agents are NOT acceptable drug candidates for this topic (i.e., traditional medicinal chemistry approaches are considered non-responsive).

Phase I Activities and Expected Deliverables

- Identification of appropriate cancer indication(s) for the proposed reformulated drug, and a detailed description of experimental strategy towards developing and delivering the construct containing the candidate chemotherapeutic agent;
- Proof-of-concept attachment, encapsulation or incorporation of the candidate chemotherapeutic agent to the delivery vehicle;
- *In vitro* stability of the drug-delivery construct, and drug release profile of the candidate chemotherapeutic agent from delivery vehicle (i.e., appropriately designed studies for the technology under development);
- Proof-of-concept cell culture studies demonstrating efficacy in relevant tumor cell lines and lack of toxicity in relevant non-tumor cell lines;
- Proof-of-concept small animal studies demonstrating therapeutic efficacy and improved therapeutic index, bioavailability, solubility, pharmacokinetics, and/or other relevant drug property as compared to the use of free drug, utilizing an appropriate animal model;
- Plan and timeline for filing an IND with the FDA, including a strategy for scale-up of the reformulated chemotherapeutic drug construct.

Phase II Activities and Expected Deliverables (include at least three of the following)

- Biodistribution studies in tumor-bearing animals (required);
- Toxicology studies in small mammals (required);
- Toxicology studies in second animal species (e.g., large mammals);
- Pharmacokinetic/pharmacodynamics studies;
- IND-enabling studies carried out in a suitable pre-clinical environment.

328 Validation of 3D Human Tissue Culture Systems that Mimic the Tumor Microenvironment

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 5 – 7

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

There is a critical need to improve the accuracy of preclinical drug efficacy screening and testing through the development of *in vitro* culture systems that more effectively mimic the *in vivo* environment. Currently, two-dimensional (2D) *in vitro* culture systems or *in vivo* animal models are the primary tools used to test cancer cell responses to drugs. However, drug sensitivity data obtained via 2D culture systems can be misrepresentative, while animal models are expensive, time-consuming, and not always predictive of the effects on human tumors in their native environment. Three-dimensional (3D) culture systems using human tissue could be a better tool for drug screening by providing a more accurate, *in vivo*-like structure and organization than 2D culture systems, and better informing drug efficacy testing in animal models. In addition, culture systems based on human tissue may produce responses more predictive of human cancers than non-human model systems.

Advances in bioengineering, biomaterials, and 3D cell culture models have led to *in vitro* systems that better replicate the structure, physiology, and function of tissues seen *in vivo*. 3D models more accurately mimic the *in vivo* milieu than current 2D *in vitro* culture systems by recreating the morphology and architecture of cellular relationships, gradients of signaling molecules, therapeutic agents, interstitial pressure, oxygen, and the composition, structure, and mechanical forces of extracellular matrix (ECM) proteins. The use of 3D systems that recreate the human tumor microenvironment and reflect tumor heterogeneity could improve the development of therapeutic strategies (e.g., treatment combinations, dose, timing) and the feasibility of chemo-sensitivity assays in at least two ways: 1) better inform decision-making for whether a particular therapeutic agent is worth pursuing in an animal model, reducing the time and cost of development; 2) lead to fewer clinical trial failures because of earlier, more relevant results from human tissue.

Properly representing the tumor microenvironment as can be done using 3D systems is particularly critical for testing the effectiveness of anti-cancer therapeutic agents. For example, extravascular transport in solid tumors is a fundamental determinant of the efficacy of both locally and systemically administered cancer agents. Large diffusion distances in tumor tissues, elevated interstitial fluid pressure, and interactions between anti-cancer drugs, tumor tissue, and normal tissue are factors that significantly limit drug diffusion in the extravascular compartment. Additionally, due to rapid proliferation and poor perfusion of tumors, the tumor microenvironment is often acidic and hypoxic, which can lead to the resistance of tumor cells to both drug and radiation therapy. Thus, 3D systems to properly recreate the tumor microenvironment are essential to advance the discovery and development of effective anti-cancer agents.

Project Goals

The focus of this topic is the validation of 3D human tissue model culture systems that accurately mimic the tumor microenvironment, including factors affecting tumor cell responses such as vascularization, interstitial pressure, physiochemical factors, and interactions with heterogeneous cell types. The project goal is to validate a 3D human

tumor culture system against anti-cancer agents with known effects to demonstrate the system's utility as a predictive tool, a pre-clinical screening assay, and/or a chemo-sensitivity assay. It is anticipated that the development of 3D systems representative of human tumor microenvironments will lead to an increase in the quality and accuracy of drug screening, along with reductions in the associated timelines and costs, leading to enhancement in the efficacy of producing information for regulatory decisions.

Essential characteristics of an *in vitro* tumor microsystem should include all or some of the following features:

1. multicellular architecture that represents physiologically relevant characteristics of the tumor and tissue of origin;
2. reproducible and viable operation with simple and clear protocols;
3. ability to examine multiple aspects of cancer, such as tumor growth, angiogenesis, cell proliferation and cell death, migration, and/or invasion; and
4. compatibility with high content screening platforms that include multiple molecular read-outs, such as genomic, proteomic, metabolomic, or epigenomic analyses.

System development should permit scale-up production such that the system can be reliably reproduced at a cost with reasonable expectation for market success. An eventual goal for such systems may include the ability to incorporate individual patient tumor biopsies to test patient-specific responses to available agents.

It is important to note that full 3D tumor microenvironment systems will consist of more than an extracellular matrix (ECM) containing tumor cells and will facilitate the inclusion of various cell types to mimic cancer cell interaction and paracrine signaling from surrounding non-malignant cells to model their effects on cancer aggressiveness and response to anti-cancer agents. Examples include stromal cells that can induce chemoresistance and encourage metastasis, as well as endothelial cells that can carry chemotherapeutics to the tumor. Systems of particular interest will incorporate perfusion, interstitial, and/or immune components.

This topic is not intended to fund microphysiological organ systems for the study of toxicity, though tumor culture systems developed under this topic may be combined as a module with systems such as those being developed through the [collaborative program between NIH, FDA, and DARPA](#).

Phase I Activities and Expected Deliverables

- Validate a reproducible 3D culture system that mimics the tumor microenvironment and appropriate pre-clinical or chemo-sensitivity assays to screen response to therapeutics.
 - Culture system should include:
 - Incorporation of human tumor cells (cell lines, primary tumor cells, or biopsy tissue) that are readily available and well-characterized *in vivo* or in a 2D system
 - Multiple cell types (e.g., stromal cells, leukocytes, endothelial cells, etc.)
 - Structural components to mimic ECM topology, mechanical cues/gradients, and/or chemical cues/gradients found *in vivo*
 - Method to deliver and control necessary growth factors and/or therapeutics
 - Adaptability for use with high-content screening platforms for sample analysis

- Systems of particular interest will incorporate perfusion, interstitial, and/or immune components
 - Pre-clinical or chemo-sensitivity assay should quantitatively examine at least two of the following aspects of cancer in response to therapeutics: tumor growth, angiogenesis, cell proliferation, cell death, migration, and/or invasion.
 - Quantify reproducibility of culture system SOP and corresponding assay SOP using a statistically relevant number of samples.
- Submit a statement to NCI that specifies metrics used and criteria for prediction of clinical efficacy prior to demonstration of accurate prediction of clinical efficacy.
 - Identify specific biomarkers (e.g. gene expression patterns, cell surface proteins, soluble factors) that characterize cell types and tumors used.
 - Specify criteria for assessing that tumor microenvironment is representative of human physiological environment.
 - Specify markers of tumor activity.
 - Specify metrics that will be used to evaluate efficacy and milestones for desired efficacy.
- Demonstrate accurate prediction of clinical efficacy or chemo-sensitivity in the culture system.
 - Test at least one anti-cancer agent with a known clinical profile using the validated prototype. For example, agent used may be from the [NCI Developmental Therapeutics Program \(DTP\) Approved Oncology Drugs Set](#).
 - Benchmark performance in developed system against 2D (e.g. NCI-60 Human Tumor Cell Line) and currently available 3D culture systems (e.g. tumor spheroids, hollow-fiber bioreactors).

Phase II Activities and Expected Deliverables

- Benchmark performance in developed system against applicable in vivo animal model(s) and known clinical performance.
 - Test multiple agents, at least four, with known clinical profiles in the prototype validated in Phase I.
 - Include at least one agent that demonstrated significant efficacy in animal trials but could not recapitulate that efficacy in clinical trials.
 - Include at least one agent that did not demonstrate significant efficacy in 2D systems and either was not tested in animal trials, or demonstrated efficacy in animal trials.
 - Measure profile of tumor prototype system and applicable in vivo animal model(s) using high content analysis (i.e. at least 6 different measurements per sample). Measurements may include, but are not limited to: genomic, proteomic, morphological, metabolomic, and epigenomic profiles of tumor system.
 - Use validated markers and/or evaluative criteria from in vivo histologic analysis.
 - Genomic data may be compared to that acquired by [The Cancer Genome Atlas](#).

- Compare dose-response relationships of known anti-cancer agents with available clinical performance data.
- Demonstrate ability to scale-up system for use in high-throughput therapeutic agent screening assays.
 - Demonstrate ability to perform high-throughput quantitative analysis on samples, such as simple harvesting and/or automated imaging. High throughput assays must still be considered high content (i.e. measurement capabilities of at least 6 different parameters)

OR

- Demonstrate potential clinical utility of chemo-sensitivity assay
- Compare dose-response relationships using high content analysis across a subset of clinical biospecimens to assess sensitivity of assay and relevance to alter standard-of-care treatments on an individual patient basis.

329 Proteomic Analysis of Single Cells Isolated from Solid Tumors

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 4

Budget (total costs): Phase I: \$160,000 for 9 months; Phase II: \$1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

The isolation and proteomic mapping of single cells are essential to understanding cancer disease processes at both the molecular and systems levels. In a given tissue, whole cell populations pose the issues of heterogeneity and a lack of synchronicity, which can be overcome with analysis performed at the single cell level. The ability to monitor and analyze signaling events in individual cells would enhance our knowledge of disease biology in cancer cells. Furthermore, protein changes can occur in both graded and binary fashions in response to differing environmental conditions, but bulk measurements obscure such cellular responses. Thus, identifying single cell variation is necessary for understanding how cells exist as autonomously functioning dynamic systems. While imaging techniques currently exist, it is not possible to analyze a whole proteome or differences in protein expression between individual cells as these methods are low-throughput with limited scope. New advances have been made in mapping a single cell's proteome using flow cytometry, transition element isotopes, and mass cytometers, each of which relies on viable cells. Single cell approaches that can capture living cells from solid tumors *in vivo*, *ex vivo*, or from fixed/frozen solid tumor tissues, combined with innovative proteomic engineering technologies and computational analytic tools, will substantially expand the single cell proteomics field and provide novel insights into cancer biology.

Project Goals

The goal of this contract topic is to advance the field of single cell proteomics through the optimization of single cell isolation from tumors, and the validation and benchmarking of proteomic analytical methods. Single cell approaches that can effectively and reliably isolate single cells, without the use of an artificial construct or overexpression system, from solid tumor tissues *in vivo*, from fresh solid tumor tissue *ex vivo*, or from fixed/frozen solid tumor tissues require improvements in yield, ease-of-use, and reproducibility. Current methods for isolating, manipulating, and tracking cells are limited to either bulk techniques that lack single cell accuracy, or manual methods that provide single cell accuracy, but at significantly lower throughputs and repeatability. Additionally, sensitivity of current single cell technologies does not allow for in depth analysis spanning the whole proteome. Therefore, the integration of medium to high throughput single cell acquisition from solid tumors with whole proteome analysis will enhance

our biological understanding of post-translational modifications, signaling circuitries, aberrations and other cancer proteome-related information at both the single cell and global levels. Proposals for single cell isolation technologies from circulating tumor cells, hematological non-solid cancers or blood immune cells will not be considered. Contractors will be expected to work with the [Clinical Proteomic Technologies for Cancer \(CPTC\) community](#), as well as stakeholders in the private and public sectors, during development to ensure that appropriate unmet needs in the field are addressed.

Phase I Activities and Expected Deliverables

- Design the system and identify the interacting components.
- Build cell isolation prototype.
- Test prototype to demonstrate proof-of-concept functionality using solid tumor clinical samples for proteomic analysis applications including, but not limited to, mass spectrometry, flow cytometry, transition element isotope analysis, and mass cytometry.
- Fusing fresh unfrozen tumors, demonstrate that cell viability following isolation is >90%.
- Establish a protocol to integrate the single cell isolation technique into a proteomic platform such as mass spectrometry.
- Validate above integrated platform by demonstrating enhanced proteomic analysis coverage compared to current technologies such as mass cytometry. Criteria include, but are not limited to, number of proteins detected, and the limit of detection or detectability of low abundant proteins.
- Present findings to an NCI CPTC Evaluation Panel.
- Research should be proposed with quantitative feasibility milestones.

Phase II Activities and Expected Deliverables

- Demonstrate medium to high-throughput single cell isolation capacity of the prototype and integrate all of the modules in the proteomic platform.
- Test integrated platform operability.
- Benchmark system by comparing and contrasting the competitive advantage of the new prototype over existing products or services using whole tissue analysis.
- Perform requirement and actual use analysis in such a way that it can be translated into a viable commercial opportunity.
- Verify the scope and application of the single cell analysis system and derived data analysis by using a designed cohort of samples with a specified biological question or application.
- Deploy the system in the production environment and correct any errors that are identified in this phase. Add or modify functionality based on updated requirements.

330 Generation of Site-Specific Phospho-Threonine Protein Standards for use in Cancer Assays

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3 – 5

Budget (total costs, per award): Phase I: \$150,000 for 9 months; Phase II: \$1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

As phosphorylated proteins play a significant role in normal and abnormal cellular function, there is a critical need for the production of pure, analytically characterized phospho-proteins/polypeptides for use in assays designed to capture the phosphorylation signatures of different cancers. Phospho-protein/polypeptide standards can serve as reference controls for quantitative immunoassays, immunogens for generating phospho-specific antibodies, and can

be utilized in kinase inhibitor screens as well as protein-protein interaction studies. Technologies for generating phospho-serine and –tyrosine proteins are currently progressing, whereas the production of phospho-threonine (pThr) proteins has been unsuccessful due to imprecise chemical, enzymatic, and recombinant techniques. For example, biological systems that generate pThr-reagents are lacking, and those that exist provide poor control over site-directed phosphorylation and the phosphorylation percentage at each site. Additionally, commercially available reagents often do not meet purity guidelines for specific analytic applications. Therefore, the development of an appropriate methodology for the production of high quality and analytically verified pThr-protein/polypeptide standards will be a valuable step toward the commercialization of assays that detect target proteins associated with disease and drug action. The identification of such phosphorylated biomarkers has significant potential for the development of safer and more effective targeted cancer therapies.

Project Goals

The primary goal of this contract topic is to develop innovative site-directed phospho-threonine protein synthesis technologies for the production of marketable pThr protein/polypeptide standards that enhance the analytic capacity of cancer assays. Technologies must demonstrate the reproducible generation of high quality, analytically verified phosphorylated threonine protein standards with 50 – 80% modification of the specified site. Protein standards listed below are of particular interest to the NCI; however, any phospho-protein target of clinical relevance to cancer may be developed. Peptide domains should contain 100 – 1000 amino acid residues that span the phospho-site of interest. A minimum of 30 amino acids in length may be acceptable, specifically if both a capture and detection antibody can bind to the peptide fragment.

Ultimately, the development of robust, quantitative, phospho-threonine specific assays will require:

1. production of phosphorylated polypeptide standards;
2. verification of the specific phospho-sites;
3. quantification of site-specific phospho-residues.

PRIORITY	NAME	PHOSPHO-SITE(S)
1	ATR (ataxia telangiectasia and Rad3-related protein)	pT1989
2	mTOR (mechanistic target of rapamycin)	pT2446
3	Akt/PKB (v-akt murine thymoma viral oncogene homolog)	pT308
4	Chk2 (CHK2 checkpoint homolog)	pT68
5	53BP1 (tumor suppressor p53-binding protein)	pT543
6	XRCC1 (X-ray repair complementing defective repair in Chinese hamster cells 1)	pT519/T523/T488

Phase I Activities and Expected Deliverables

- Develop proof-of-concept methodology to reliably produce threonine site-directed, high content (>50%), pThr-protein/polypeptide standards for at least two NCI-approved targets. Full length protein is desired, but if too difficult to produce, polypeptides of 100-1000 amino acid domains will be acceptable. Under certain circumstances, shorter peptides with a minimum 30 amino acids in length may also be acceptable, pending NCI approval.

- Provide data that demonstrates reproducibility and accuracy of the methodology that includes analytic (quantitative) measurements of the produced pThr-calibrators, including but not limited to site of phosphorylation and level of phosphorylation.
- Demonstrate preliminary product stability (<10% degradation of the phospho-content) for at least 1 month when stored at company-determined optimized conditions (e.g., -80oC)
- Deliver to NCI a minimum of 0.5 mg each of two NCI-approved pThr-protein/polypeptide standards selected for production. A corresponding Certificate of Performance that contains the analytic characterization strategy and measurements for each protein must also be submitted.
- Provide the written methodology for the generation of the pThr-calibrators using a Standard Operating Procedure (SOP) template to be provided by NCI.
- If requested, provide NCI with sufficient reagents to perform ten test runs for independent validation of the methods used for phospho-protein production and characterization.
- Provide technical support, and if requested, one on-site training session for the NCI.

Phase II Activities and Expected Deliverables

- Processes should be optimized to reproducibly generate quantitative, threonine site-specific phosphorylation with the highest level of modification feasible (>80% preferred) for six NCI-approved targets.
- Demonstrate preliminary product stability (<10% degradation of the phospho-content) for at least 6 months when stored at company-determined optimized conditions (e.g., -80oC)
- Perform full validation of the method with three runs for all designated pThr-protein targets, and provide data that characterizes reproducibility, variability, and accuracy of the optimized methods with Quality Control measures implemented.
- Deliver to NCI:
 - A minimum of 1 mg each of all of the specified pThr-recombinant proteins/peptides
 - All data
 - Final versions of the Certificate of Performance for each polypeptide
 - An ISO- and CLIA- quality SOP of method
- If requested, provide NCI with sufficient reagents to perform ten test runs for independent validation of the methods used for phospho-protein production and characterization.
- Provide technical support, and if requested, one on-site training session for the NCI.
- Provide the program and contract officers with a letter of commercial interest.

331 Development of a Biosensor-Based Core Needle Tumor Biopsy Device

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3 – 5

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

Analysis of dynamic biomarkers in tumor biopsies is being performed with increasing frequency to help physicians in diagnosis, selecting and assessing treatment, and understanding disease recurrence. Current biopsy techniques

were developed to acquire specimens with sufficient numbers of malignant cells for histopathologic diagnosis. However, the tumor content of a biopsy specimen required for pathological analysis is much lower than what is required for molecular profiling of low prevalence mutations or biomarker quantification, which would aid in determining therapeutic options for the patient. Even with Positron Emission Tomography/Computed Tomography (PET/CT) or ultrasound guidance, current biopsy methodology may not yield specimens with sufficient tumor for molecular biomarker profiling. PET/CT and ultrasound methods lack the resolution to direct the biopsy needle into areas with high viable tumor content, resulting in a high failure rate of 25 – 50% due to the heterogeneity of tumor architecture within a biopsy area. The incorporation of biosensor technology into the tip of the biopsy needle, in conjunction with currently utilized imaging and ultrasound guidance, could increase the probability of sampling high tumor content areas through providing real-time feedback that identifies optimal regions for biopsy. Collection of high quality tumor biopsies with sufficient material for biomarker profiling is essential for full implementation of precision medicine for cancer patients. Biosensor/biofeedback devices designed to complement existing radiologic methods will improve current biopsy procedures by increasing viable tumor recovery, and thus, allow for a more thorough molecular assessment of patient tumors.

Project Goals

The goal of this solicitation is to advance the development of biopsy needle-based biosensor technology that can determine regions of maximum tumor cellularity within the biopsy region. The biosensor technology should be designed for use in conjunction with current image-guided and biopsy devices to detect high tumor content regions, and provide real-time feedback that indicates to the radiologist where the needle should be placed for optimal sample selection. Real-time feedback from the tip of the biopsy needle to the physician should be based on visual, sensory, or chemical parameters.

Malignant transformation is associated with structural, genotypic/phenotypic cellular modifications, and biochemical changes in the extracellular environment, which consequently alters spectroscopic, metabolic and microscopic properties. The biosensor should be able to detect such alterations and extract information about the physiological and/or morphological properties in the biopsy region surrounding the needle that distinguish normal from malignant areas. Properties include, but are not limited to, measurement of redox potential, pH, extracellular matrix elasticity/stiffness, dielectric properties (electrical bio-impedance), glucose metabolism (anaerobic glycolysis), and various blood vessel parameters such as tissue color, microvascular saturation, blood volume fraction, bilirubin concentration, and average vessel diameter.

Phase I Activities and Expected Deliverables

- Manufacture and optimize a needle-based biosensor device with the following features:
 - a. adaptability for use with existing imaging/ultrasound needle placement methods and needle biopsy procedures.
 - b. real-time signal generation indicative of physiological and/or morphological parameters that distinguish between tumor and non-tumor tissue, and if possible, between necrotic and viable tumor.
 - c. does not significantly damage or change tissue biology in regions surrounding the needle placement site.
- Show preliminary proof-of-concept of the sensor-guided biopsy in a relevant animal model.
- Produce written methodology for the sensor manufacturing with quality assurance and control measures using the Standard Operating Procedure (SOP) template to be provided by NCI.
- Provide device and training in use to NCI. The device and associated methodology will undergo independent validation at NCI.

Phase II Activities and Expected Deliverables

- Optimize the sensor design and performance for a clinical setting, and refine the manufacturing process.
- Show the feasibility of this novel technique to complement current radiologic and biopsy procedures.
- Demonstrate the performance of the device as designed and intended in fit-for-purpose studies in relevant clinical veterinary models (NCI will identify appropriate models during Phase I).
- Deliver to NCI final versions of the manufacturing methodology and Certificate of Performance using recommended templates (to be provided in Phase I).
- Provide at least one optimized device, technical support, and if requested, one on-site training session for NCI in order to perform independent validation.
- Provide to NCI staff two letters of commercial interest at the end of year 1, and two letters of commercial commitment to buy the developed product at the end of year 2.

332 Development of Radiation Modulators for Use During Radiotherapy

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 3 – 5

Budget (total costs, per award): Phase I: \$200,000 for 9 months; Phase II: \$1,500,000 for 2 years.

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded

Summary

Radiotherapy is employed in the treatment of over half of all cancer patients. Many of those patients, however, suffer adverse effects during and/or after treatment. Additionally, tumors recur in approximately half the patients treated with curative intent. Enhancing specific tumor killing and minimizing normal tissue damage from radiotherapy would improve tumor control and patient quality of life. An ideal intervention would both enhance radiation effects in tumors and protect the normal tissues.

Radiosensitizers are agents that are intended to enhance tumor cell killing while having a minimal effect on normal tissues. Two radiation sensitization drugs have recently proven clinically effective: Temozolomide treatment with radiotherapy for glioblastoma and Cetuximab treatment combined with radiation for head and neck squamous cell cancers. There is significant potential for further development of novel radiosensitizing agents.

Conventionally, *radioprotectors* are defined as agents given before radiation exposure to prevent or reduce damage to normal tissues, while *mitigators* refer to those agents given during or after a patient's prescribed course of radiation therapy to prevent or reduce imminent damage to normal tissues. Both radioprotectors and mitigators are being developed as potential countermeasures against radiological terrorism and several have shown promise in pre-clinical testing. In order for these to be developed and useful in clinical radiation therapy applications, it is imperative to demonstrate that they do not protect cancer cells.

The importance of developing agents that sensitize tumor cells, protect or mitigate radiation-induced damage in normal tissue, improve survival, quality of life, and palliative care in cancer patients was emphasized in an NCI workshop on *Advanced Radiation Therapeutics - Radiation Injury Mitigation* held on January 25th 2010 (Movsas B, et al. [Decreasing the adverse effects of cancer therapy: National Cancer Institute guidance for the clinical development of radiation injury mitigators](#). Clin Cancer Res. 2011 Jan 15;17(2):222-8. Epub 2010 Nov 3. PMID: 21047979), and in a workshop on *Radiation Resistance in Cancer Therapy: Its Molecular Bases and Role of the Microenvironment on its Expression* held Sept 1-3, 2010. Prior workshops have dealt with sensitization, protection, or radiation effects assessment (Colevas AD, et al. Radiation Modifier Working Group of the National Cancer Institute. [Development of investigational radiation modifiers](#). J Natl Cancer Inst. 2003 May 7;95(9):646-51. Review. PMID:12734315; Stone HB, et al. [Models for evaluating agents intended for the prophylaxis, mitigation and treatment of radiation injuries. Report of an NCI Workshop, December 3-4, 2003](#). Radiat Res. 2004 Dec;162(6):711-28. PMID: 1554812.)

This contract topic encourages the development of innovative and promising radioprotectors, mitigators, or sensitizers that either selectively protect normal tissues but not tumors against ionizing radiation, or selectively sensitize tumors, thereby increasing the therapeutic ratio of radiation. Proposals for radiation modulators are solicited that include preclinical and/or early phase clinical studies demonstrating safety, efficacy, dose, schedule, pharmacokinetics (PK), pharmacodynamics (PD), and metabolism. Proposals should also demonstrate a clear understanding of regulatory requirements, and should include a regulatory plan including key steps such as a pre-IND meeting with FDA, submission of an investigational new drug (IND) application, approval of clinical trial design, and ultimately drug registration.

Project Goals

The goal is to stimulate collaboration among small businesses, academic institutions, and contract research organizations to promote the rapid development of innovative radioresponse modifiers that will decrease normal tissue injury and/or enhance tumor killing, thereby improving radiotherapy outcomes. The long-term goal is to enable small businesses to fully develop, license, and/or market radioresponse modifiers for clinical use.

The contract proposal must describe:

Phase I:

- A quantitative estimate of the patient population that will benefit from the availability of such radioresponse modifiers.
- A plan for generating evidence that the proposed compound(s) protects at least one relevant normal tissue from radiation-induced injury, and/or sensitizes at least two relevant tumor models.
- Either:
 - a. A plan for generating evidence that the proposed radioprotector(s)/mitigator(s) does not significantly protect cancer cells, **OR**
 - b. A plan for generating evidence that the proposed radiosensitizer(s) does not significantly sensitize normal cells and tissues.
- The plans must include the methodologies proposed to evaluate the preferential effects on normal tissues or tumors by the compound(s) *in vivo* (including appropriate biomarkers and endpoints as determined during early interactions with the FDA).
- Determination of the optimal dose and schedule *in vivo* based upon preclinical pharmacodynamic and pharmacokinetic studies.
- Statistical validation of the proposed study endpoints including where appropriate, power calculations and rationale for proposed sample sizes.
- Phase II:
- The approach to early-phase human trials designed to take into account relevant molecular pathways and targets, and aim to gather pharmacodynamic and pharmacokinetic data to confirm the compound's observed behavior in animal studies.
- The approach and experiments to assess the safety and efficacy of the compound(s) in early-phase human trials employing, as appropriate, physician-reported endpoints as well as patient-reported outcomes.

Activities and Expected Deliverables

Phase I may include primarily preclinical studies. Phase II or Fast-Track proposals must contain a section entitled "Regulatory Plan" detailing plans for early involvement of the FDA. There should be a description of how the applicant plans on meeting the requirements to: 1) define suitable biomarkers and endpoints, 2) file IND and 3) design and perform phase 0-2 clinical trials in preparation for product transition to phase 3 clinical trials by groups such as the [Radiation Therapy Oncology Group](#).

Where cooperation of other partners is critical for implementation of the proposed methodology, the applicant should provide evidence of such cooperation (through partnering arrangement, letters of support, etc.).

The following deliverables may be required depending on a compound's maturity in the developmental pipeline:

Phase I

- Selection and approval of cell line panels for *in vitro* testing.
- Demonstration of drug solubility and uptake using cultured normal and transformed cells.
- Study design for determining clonogenic survival or approved alternative tailored to the mechanism of each tested compound.
- Clonogenic survival data or approved alternative validating lack of drug toxicity in normal cells, efficacy and specificity of radioprotection for normal cells and/or efficacy and specificity of radiosensitization for tumor cells.
- Preliminary evidence for lack of *in vivo* toxicity in normal cells or organisms.
- Documentation providing a top-level description of the protocols and the testing results should be provided to NCI as part of the Phase I progress report.

Phase II

For advanced pre-clinical work:

- Design of NCI and Institutional Animal Care and Use Committee (IACUC)-approved *in vivo* experimentation plan including statistical validation of experimental design, and sample size determination including power calculations.
- Selection and approval of tumor cell panel and normal tissues for *in vitro* testing.
- Demonstration of bioavailability PK and PD in rodent model.
- For radiation protectors / mitigators: demonstration by physiologic testing and histological assessment that irradiated normal tissues are spared over a 6-month period.
- Demonstration of effects (sensitization or lack of protection as appropriate) on tumors using *in vivo* radiation regrowth delay assays.
- Collection of data validating lack of drug toxicity, efficacy, and specificity for normal cells over tumor cells in the case of radiation protectors/mitigators.

Documentation of the testing protocol and testing results should be provided to NCI as part of the Phase II progress report for pre-clinical studies.

For proposals advancing to early phase human trials:

- Identify GMP drug source.
- Obtain IND approval.
- Provide evidence of established clinical collaboration.
- Submitted protocol for IRB approval.
- Define suitable clinical endpoints and patient-oriented outcomes.

333 Software Tools for the Development of Environmental Measures Related to Cancer Health Behaviors and Resources

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2 – 3

Budget (total costs, per award): Phase I: \$200,000 for 9 months; Phase II: \$1,000,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded

Summary

The NCI Division of Cancer Control and Population Sciences aims to reduce risk, incidence, and deaths from cancer, as well as enhance the quality of life for cancer survivors. A key to achieving these goals is to improve health behaviors and access to health services. Because environmental factors affect health behavior, it is critical to develop robust measures of the natural, commercial, policy, and man-made environments to better understand and improve health quality. In the past 20 years there has been an explosive growth in the availability of data related to these environmental features. The federal government has recently increased public access to high value, machine readable data through Data.gov, and HHS has specifically encouraged innovators to utilize health data through the Health Data Initiative at HealthData.gov. Improved data access and geographic linkages have created a growing interest in the development of indices of aggregate measures of the environments related to diet, physical activity, access to health care, and other health-related behaviors. Better methods and access to software tools to easily develop such indices are required for accelerating progress towards NCI's mission of cancer control, and also have potential applications in other areas of health, policy and the commercial sector.

The skills required to efficiently collect the data underlying potential environmental indices related to cancer risk factors, health services, and diverse aspects of behavior cut across diverse disciplines and require mastery of disparate concepts and technologies. An especially pressing problem is the need to gain efficient access to the 'digital environment' in order to collect data from map resources, online archives, and crowd sourced resources related to walking, running routes, commercial venues, street and transit characteristics, and many other data resources. Many potentially interested parties lack the technical capacity required to automate access to diverse data resources from interactive and frequently updated web sources. This lack of capacity is a barrier to the development, evaluation and utilization of environmental indices in the public health field. IT professionals have the ability to collate needed data, but the health community does not always have access or resources to work with IT teams. An appropriate software tool could be useful to facilitate the development of environmental metrics across different areas of expertise.

Project Goals

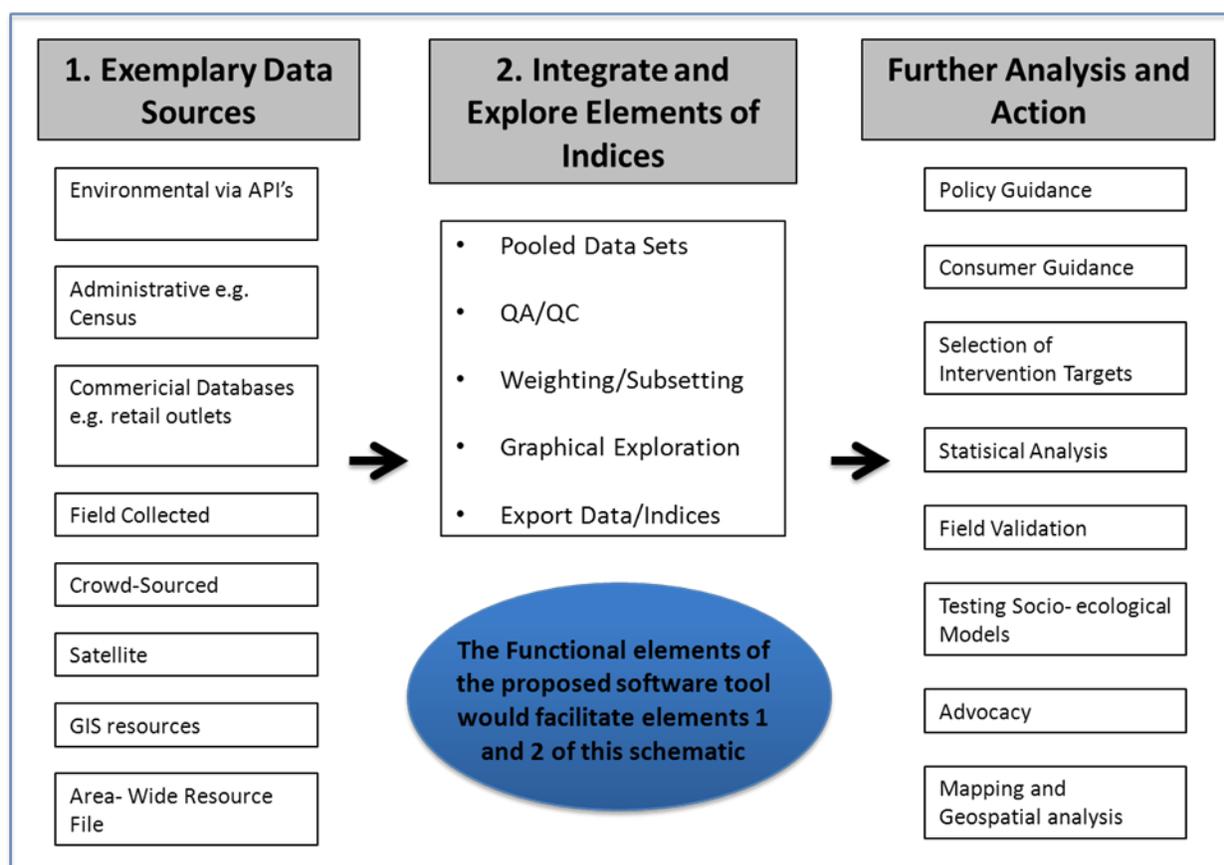
The purpose of this solicitation is to support the development of an efficient, user-centered software tool that connects diverse data sources to enable the creation of metrics describing the environment related to health behaviors and services. This software tool could accelerate and improve decision making-related planning and policy for cancer prevention and control, cancer related risk factors, decision-making about geographic locales for consumers, and site selection issues for businesses and government organizations.

The products called for are specifically related to cancer prevention and control across the cancer control continuum. For example, improving cancer prevention via fostering positive health behaviors, reducing disparities in early detection and ensuring access to appropriate treatment and end-of-life support all require integration of individual and socio-ecological factors to achieve improvements in health. Notably, construction of environmental metrics could play a key role in guiding efforts to reduce health disparities by facilitating efforts to characterize regions or communities with combinations of interacting characteristics that could lead to disparities in health behaviors and health outcomes.

The developed platform should:

- automate data aggregation from diverse sources to allow users to efficiently obtain data
- use a non-expert graphical user interface that allows the design and implementation of environmental indices
- support evaluation of environmental indices' ability to rank locations such as specific addresses, neighborhoods, census tracts, counties, or states in accord with features of interest
- support access to or dissemination of data from environmental indices imported or developed by users.

Figure 1. Schematic of capacity and data cycle that enables enhanced development and use of indices of environmental characteristics related to health behaviors and health resource access and use.



Responses to this topic are expected to address the development of efficient methods and platforms to:

1. Collect data via open data Application Programming Interfaces (API's), Data.gov, online web search engines, mobile app data housed on servers, screen scraping, and map resources concerning environmental correlates of health behaviors such as retail outlets, exercise facilities, and other community related venues including schools, churches, and hospitals.
2. Allow the efficient import of additional relevant data from diverse sources such as physiological data, survey results, field-collected information, and mobile devices.
3. Compile data at multiple geo-located scales such as point addresses, buffers, and administrative boundaries including but not limited to census elements.
4. Allow the compilation of data into matrices easily transferable into relevant analytical software packages, including statistical and graphics packages.
5. Supply scripts or protocols to allow visualization of the correlation structure among collated variables.
6. Demonstrably allow the recreation of existing metrics related to the food and physical activity environments.
7. Contain plans for extending these tools into products useful for specific clients such as those in government and public sectors, foundations, and other non-governmental organizations.

8. Recreate existing indices, replicate their estimates, and then modify them with new data elements or new weighting schemes.

Completed projects could be on-line or stand-alone resources, or they could be applications that work with existing spreadsheet, GIS or other software products, but the product should be usable without high-level expertise in the underlying software platform. Vitality, these tools must allow users to efficiently obtain current, up-to-date data automatically from diverse data resources, as many elements of the environment change rapidly, particularly man-made commercial and retail environments.

Phase I Activities and Deliverables

- Establish a project team including proven expertise in software development and methods for obtaining data from web, survey, and commercial sources as well as one or more subject matter experts in environmental determinants of topic areas such as the food, physical activity, or health care access environment. Inclusion of topic matter experts will help ensure that the product is developed with the capacity to integrate key topic specific data resources.
- Provide a report including detailed description and/or technical documentation of the proposed:
 - Software/Online tool(s)
 - Description of additional software and hardware required for use of the tool
 - Specific approach to interacting with API's and integrating data from diverse commercial and governmental sources – Data.gov is a key target, as is the Google Places API, which currently features over 80 million businesses and points of interest
 - Data standards for collection, transport, importation, and storage of such data
 - Proposed built in methods for constructing indices and weighting procedures from imported data sets. These should include a variety of mathematical functions aimed at transforming and rescaling individual elements of the metric and combinations of metrics. They are not expected to implement complex statistical analyses such as factor analysis and other multivariate approaches. Simpler descriptive statistics could be included, such as correlation matrices, and the capacity to visualize distributions, box-plots and other exploratory graphics.
 - Data visualization, feedback, and reporting systems for environmental indices and their elements
 - Developing a linked data library describing and documenting resources that can be imported automatically or manually into the software for use in constructing environmental metrics
- Develop a functional prototype system that:
 - Facilitates use of existing API's with salient data sources
 - Allows import and export of data to and from existing tabular datasets
 - Uses geographic identifiers compatible with major GIS software
 - Allows the recreation and modification of an existing metric from the web or a scientific publication
- Prepare a tutorial session for presentation at NCI and via webinars describing and illustrating the use of the system.

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

Phase II Activities and Deliverables

- Further test and finalize interface with online data via diverse API's and other approaches developed in Phase I.
- Further test and finalize methods for combining data into candidate metrics
- Develop, beta-test, and finalize data integration and visualization tools developed in Phase I
- Conduct usability testing of all stages of use of the environmental metric data acquisition and development tool
- Develop systems documentation where applicable
- 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

NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

The National Center for Advancing Translational Sciences (NCATS) was officially established in fiscal year 2012. The Center strives to develop innovations to reduce, remove or bypass costly and time-consuming bottlenecks in the translational research pipeline in an effort to speed the delivery of new drugs, diagnostics and medical devices to patients. NCATS is interested in the development of innovative tools, technologies and intervention (drug, device, diagnostic) platforms that would support the creation of novel therapeutics and/or diagnostics, especially for rare and neglected diseases.

It is strongly suggested that potential offerors not exceed the total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

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.

005 Development of biomarkers for rare diseases as endpoints for clinical trial measurements

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

Number of anticipated awards: 1-2

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

In rare a disease, affecting less than 200,000 patients in the US, there are often heterogeneity in the age of onset, symptoms and progression of the disease that make clinical endpoint assessments difficult in small patient populations. Conducting long-term clinical trials in these patients is not feasible and often requires prospective natural history studies to better understand disease progression and identify potential biomarkers that correlate with disease progress. The development of well characterized and relevant biomarkers to be used as clinically meaningful endpoints, or as surrogate endpoints, that likely predict clinical benefit are needed to successfully provide new therapies to patients with rare diseases. It is important that the measured changes in these biomarkers are quantifiable and statistically meaningful representation of the specific disease process. These tools can be furthered be applied to the development of new diagnostic tests for these diseases.

Main requirements

The outcome of this contract is expected to be a biomarker to monitor disease progression in a rare disease population targeting a specific rare condition. The biomarker could be developed for the analysis of blood, urine, and cerebral spinal fluid markers. This biomarker would have a large impact on patients if banked tissue and blood samples could be examined as well. This biomarker must be capable of discriminating between the normal volunteers and diagnosed rare disease patient population. This assay designed for the biomarker needs to be robust and amiable to medium throughput format.

Deliverables Phase 1

Phase I Activities and Expected Deliverables

A biomarker assay that meets the requirements listed above and also meets the following:

- Develop a validated assay for a biomarker that is specific for a rare disease. Some rare diseases of specific interest but to which the offeror is not limited are: creatine transporter deficiency (CTD), duchenne muscular dystrophy (DMD), LEOPARD syndrome (LS), hereditary inclusion body myopathy (HIBM), retinitis pigmentosa (RP), and fibrodysplasia ossificans progressiva (FOP).
- Characterize the sensitivity, specificity, variability, reproducibility, and accuracy of the method in detecting the biomarker
- Perform proof of concept pre-clinical pilot studies in a validated animal disease model if feasible
- Demonstrate the utility of the assay by characterizing differences between normal volunteer and the diagnosed rare disease patient population
- Deliver the SOP of the biomarker assay to be evaluated by NCATS

Deliverables Phase 2

Phase II Activities and Expected Deliverables

- Demonstrate clinical utility by testing a large number of patient samples or banked tissue or plasma samples
- Establish a relationship with companies developing therapeutics for the rare disease population of biomarker target
- Deliver final SOP to NCATS for evaluation

006 Development of Neurocognitive Pediatric Tools for Measuring and Analyzing Clinical Study Endpoints in Rare Neurocognitive Disorders

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

Number of anticipated awards: 1-2

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

One of the challenges in developing drugs for children with neurological diseases is the limited availability of age-appropriate and validated endpoints to be used in clinical trials as a measure of meaningful therapeutic effect. In neurocognitive disorders, the extrapolation of adult endpoints into pediatric studies is usually not applicable due to the lack of age-dependent normative data necessary to sample normal brain development. NCATS invites SBIR proposals that will facilitate the development of neurocognitive pediatric tools for rare diseases as suitable endpoints for pediatric clinical trials; capable of generating regulatory compliant data. A rare disease is defined as affecting fewer than 200,000 patients in the US.

Main requirements

The outcome of this contract is expected to be neurocognitive tools, a combination of instrumentation and software, capable of generating regulatory compliant data that can be developed into endpoints for clinical trials involving the pediatric population for rare disease. The neurocognitive measurements in clinical studies are critical for understanding the natural history of the rare disease, and the development of clinical endpoints in determining drug efficacy in therapeutic trials.

Deliverables Phase 1

Phase I Activities and Expected Deliverables

- Develop new instrumentation or establish the feasibility of existing tools and technologies that can be implemented in children 1-18 years of age with moderate to severe cognitive impairment,
- Characterize the variation, reproducibility, and accuracy of the neurocognitive measurements and that the tool is amenable to generate developmental appropriate normative data across age groups
- Demonstrate the suitability of the neurocognitive measurements for use in a clinical setting and that the instrumentation used is devoid of patient discomfort and meets patient safety requirements
- All offerors must demonstrate that the instrumentation and software is user friendly and support is readily available for instrumentation, software training, data interpretation and analysis.
- All offerors must establish a collaboration or partnership with a diagnostic and/or pharmaceutical company and/or clinical/research institution that can provide rare disease patients for a pilot study to validate the technology; offerors must provide a letter of support from the partnering organization in the Phase II application
- Deliver an SOP of the instrument and protocol for cognitive measurement to be evaluated by NCATS

Deliverables Phase 2

Phase II Activities and Expected Deliverables

- Demonstrate clinical utility and value of the neurocognitive pediatric tool by testing sufficient numbers of patients to unequivocally prove statistical significance with regards to neurocognitive impairment in a particular neurocognitive disease population
- Establish a marketing partnership or alliance with a company developing a therapy for a neurocognitive rare disease or validate that this neurocognitive tool monitoring changes in neurocognition in an approved therapy
- Deliver the final SOP to NCATS for evaluation

007 Exploring the Potential of CRISPR/CAS Genome-editing Tools

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

Number of anticipated awards: 1-2

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

The adaptation of CRISPR/CAS systems for genome editing is increasingly being reported, and holds much promise for a host of applications. One such area includes the possible use of CRISPR/CAS tools for large-scale loss of function studies given their scalability compared to more established, yet complex, genome-editing tools such as ZFNs and TALENs. However, much needs to be learned about the efficiency CRISPR/CAS reagents and their potential for off-target editing. An improved understanding of CRISPR/CAS tools will greatly advance their utility

in terms of creating model systems, cell therapy, gene therapy, and their potential use for rapid, genome-wide interrogations of gene function; much like RNAi is used currently.

Main requirements

The main outcome of this contract is to explore the commercial potential of CRISPR/CAS genome editing tools for large-scale loss of function studies. Phase 1 will focus on evaluating reagent efficiency and potential for off-target editing, especially in mammalian systems. Phase 2 will focus on translating Phase 1 findings into a deliverable library of CRISPR/CAS reagents for large-scale loss of function studies.

Deliverables Phase 1

- Make general observations regarding the knockout efficiency of CRISPR/CAS reagents that target ~20 genes.
 - Evaluate multiple reagents per gene to understand effective design principles.
 - Evaluate endonuclease inactive counterparts for their ability to repress transcription of target genes.
- Compare reproducibility of reagent efficiency in the same and different cell backgrounds, including those that may have different copy numbers of target genes.
- Rigorously characterize the off-target effects of several (~6) different CRISPR/CAS reagents that are effective at genome editing.
- Evaluate results to determine feasibility for use in screening and deliver to NCATS.

Deliverables Phase 2

- Explore the potential use of CRISPR/CAS tools for large-scale screening in microplate format (e.g. 384 well plate).
 - Develop strategies within the framework of a typical screen workflow to maximize target editing while minimizing potential off-target effects.
 - Develop strategies within the framework of a typical screen workflow that enrich for edited populations.
 - Evaluate the effects of CRISPR/CAS reagents directed at a series of positive control genes (~12) in a phenotypic assay.
 - Evaluate correlation in phenotypes between different reagents designed to target the same control genes.
 - Evaluate cell line variation with common cell types.
 - Construct a library of CRISPR/CAS reagents directed against a broad set of genes (e.g., the human kinome) for pilot screening.
 - Deliver the library and protocols for further evaluation by NCATS.
- Explore partnerships with large vendors to produce off-the-shelf that incorporate insights gained during the course of this contract.

008 Droplet Detection System

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

Number of anticipated awards: 1

Budget (total costs, per award): Phase I: \$225,000 for 9 months; Phase II: \$1,500,000 for 2 years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary:

This initiative seeks to develop a low cost, real time droplet detection system to market that can be integrated on a variety of common low volume liquid dispensers used in many laboratories for both screening and diagnostic applications. One of the most common problems during high throughput screening (HTS) is errors in dispensing reagents into microplates. This is typically due to a failure of the dispense instrumentation itself (often a clogged tip) or incorrect calibration of the dispenser. These errors can cause plates to fail quality control and rescreening compounds costs additional screening resources and time. The system would immediately respond to detected dispensing errors, and thus allow microplates to be run without loss and thus increase the robustness of HTS. In addition to HTS applications, low volume liquid dispensers are widely used in many diagnostics laboratories. The ability to monitor and potentially quantify the volume of critical reagents that are dispensed could provide valuable quality assurance data in addition to preventing the loss of these reagents due to dispenser failure.

Given the potential for cost savings and the large amount of low volume liquid dispensers used in biological laboratory and diagnostic settings, any system developed to detect dispense errors could have a commercial market.

Project Goals:

The preliminary goal of this project is to develop a functional prototype of a device capable of detecting droplets dispensed from commercially available low volume liquid dispensers that utilize the standard 8 tip format, with 9mm tip to tip spacing. The final product will be device that could be integrated on a variety of existing commercially available low volume liquid dispensers; assuming they utilize the standard 8 tip with 9mm tip to tip spacing, and could allow for real time droplet detection. The long term goal of this project is to bring this device to market to meet the needs of laboratories using low volume liquid dispensers and providing real time droplet detection for dispense failure notification and quality assurance purposes.

Phase I Activities and Expected Deliverables:

- Develop a prototype device that meets the following specifications:
 - Has the ability to detect dispensed droplets with volumes as low as 1uL and upwards of 1mL
 - These droplets can be a variety of liquids, from buffers such as PBS to cells suspended within media.
 - There should be no limitation to the color of liquid that can be detected, including clear liquids.
 - Can count drops dispensed from each tip.
 - Can measure the length of each drop dispensed and calculate the average drop length.

- Can report the total number of drops dispensed from each tip.
- Can report the average drop length of drops dispensed from each tip.
- Can report the total number of drops dispensed for all tips.
- Can report the average drop length of drops dispensed from all tips.
- Design a fixture that will mount to at least one commercially available low volume liquid dispenser that utilizes the 8 tip, 9mm tip to tip spacing.
- Provide a detailed requirements and design document for the device, including mechanical and electrical drawings, in addition to hardware specifications and communications protocols used.
- Cost estimates to manufacture a device capable of meeting the specifications listed above.
- Provide NCATS with all data resulting from Phase I Activities and Deliverables.

Phase II Activities and Expected Deliverables:

- Build a prototype instrument that meets the Phase I specifications in addition to several others:
 - Has a flexible mounting fixture that can be adapted to several different commercially available low volume liquid dispensers;
 - Has a remote programmatic interface allowing the device to be controlled and monitored by an external software application through standard laboratory communication protocols (RS-232, TCP/IP, etc.);
 - Ideally, the device should be able to start and stop monitoring dispensing based upon commands sent to it through a remote command interface that matches the structure of whatever dispenser it is integrated with. For example, if the run command is normally sent to the dispenser, instead it should be sent to the device; which captures the run command and starts the dispense monitoring, and then sends the command along to the dispenser to actually start the dispense. In this way only one piece of software will be required to monitor a dispense, instead of having to synchronize two different software applications running; one for the dispenser itself and one for the monitoring device attached to it.
 - Can reliably operate for extended periods of time in an automated fashion (overnight usage with a constant plate throughput limited by the duration of the load/unload time of the dispenser the device is integrated with).
- Develop detailed procedures to be able to quantify the ability to monitor droplets in real time:
 - Provide detailed protocols to show the effectiveness of the device in monitoring a dispense in real time;
 - Provide detailed protocols to show the effectiveness of the device in capturing dispensing errors in real time;
- Develop a robust manufacturing plan for the device, using off the shelf OEM components where possible to minimize expense.
- Provide NCATS with all data resulting from Phase II Activities and Deliverables.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts and supports research, clinical trials and demonstration and education projects related to the causes, prevention, diagnosis, and treatment of heart, blood vessel, lung, and blood diseases and sleep disorders. It also supports research on the clinical use of blood and all aspects of the management and safety of blood resources. The NHLBI SBIR/STTR program fosters basic, applied, and clinical research on all product and service development related to the mission of the NHLBI.

For more information on the NHLBI SBIR/STTR program, visit our website at:
<http://www.nhlbi.nih.gov/funding/sbir/index.htm>

SBIR Phase IIB Programs

The National Heart, Lung, and Blood Institute would like to provide notice of two SBIR Phase IIB funding opportunities. This notice is for informational purposes only and is not a call for Phase IIB proposals. This informational notice does not commit the government to making such awards to contract awardees.

The NHLBI offers Phase IIB opportunities through the NHLBI Bridge Award and the NHLBI Small Market Award using separate funding opportunity announcements (Bridge Award: [RFA-HL-13-016](#). Small Market Award: [RFA-HL-14-012](#)). The purpose of the NHLBI Bridge and Small Market Awards is to accelerate the transition of SBIR Phase II projects to the commercialization stage by promoting partnerships between SBIR Phase II awardees and third-party investors and/or strategic partners. The Small Market Award is designed to support technologies addressing rare diseases or pediatric populations. The Bridge and Small Market Awards encourage business relationships between applicant small business concerns and third-party investors/strategic partners who can provide substantial financing to help accelerate the commercialization of promising new products and technologies that were initiated with SBIR funding. In particular, applicants are expected to leverage their previous SBIR support, as well as the opportunity to compete for additional funding through the NHLBI Bridge Award or Small Market Award programs, to attract and negotiate third-party financing needed to advance a product or technology toward commercialization.

Budgets up to \$1 million in total costs per year and project periods up to three years (a total of \$3 million over three years) may be requested. Development efforts may include preclinical R&D, which is needed for regulatory filings (e.g., IND or IDE) and/or clinical trials.

An SBIR Phase IIB Bridge or Small Market Award application must represent a continuation of the research and development efforts performed under a previously funded SBIR Phase II award. The NHLBI welcomes applicants previously funded by any NIH Institute or Center or any other Federal agency, as long as the proposed work applies to the NHLBI mission. Applications may be predicated on a previously funded SBIR Phase II grant or contract award. Applicants with Phase II contracts or awards from another Federal agency must contact the NHLBI to ensure their application can be received.

Applicants are strongly encouraged to contact Kurt Marek, Ph.D., at 301-443-8778 or kurt.marek@nih.gov for additional information.

Limited Amount of Award

For budgetary, administrative, or programmatic reasons, the NHLBI may not fund a proposal or may decrease the length of an award and/or the budget recommended by a review committee. The NHLBI does not intend to fund proposals for more than the budget listed for each topic.

This solicitation invites proposals in the following areas.

081 Passive MRI Cardiovascular Guidewire

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

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

Summary

MRI-guided catheter procedures can avoid radiation and may allow surgery to be avoided in a range of applications. A safe clinical guidewire is not commercially available. A complex “active” electronic MRI guidewire is being developed by the NHLBI Division of Intramural Research (DIR). However, a more simple and versatile “passive” MRI guidewire also is valuable to be used as part of multi-step procedures (such as catheter exchange), but is neither commercially available nor attractive to manufacture in DIR. Mere avoidance of radiation in pediatric catheterization using a passive MRI cardiovascular guidewire would be attractive or even fundamentally enabling. Several prototypes have been reported in the literature but none have been commercialized. Such a device would have utility in cardiovascular and in non-cardiovascular applications.

This contract solicitation is to obtain an exchange-length guidewire that is safe for operation during MRI.

Project Goals

The goal of the project is to develop an exchange-length guidewire that is safe for operation during MRI. First a prototype would be developed and tested in animals, and ultimately a clinical-grade device would undergo regulatory development for clinical testing. NIH offers to perform clinical testing at no charge to the contractor.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a guidewire prototype. The awardee deliverable would be tested in vivo in the contracting DIR lab (cardiovascular intervention program).

The specific deliverable would be:

- 0.035” outer diameter x 2.6-3.0 meters length allowing unencumbered catheter exchange
- Mechanical properties matching up to two commercially available X-ray guidewires, in descending priority order: (1) Wholey {steerable and torquable angled guidewire}, (2) Supra-Core {steerable and torquable shapeable soft-tip and stiff-shaft}
- Shapeable tip is strongly preferred over a J tip
- Free from clinically-important heating (2°C at 1W/kg SAR) during MRI at 1.5T
- Visibility during MRI. If using individual susceptibility markers, they should be positioned at the tip and along the shaft in a pattern that allows the operator to delineate/differentiate them. Susceptibility markers should be > 3mm in diameter using commonly used steady state free precession or fast gradient echo MRI techniques
- Proposals for alternative visualization strategies, such as “active” or “inductively-coupled” receiver coils, are welcomed, but such solutions must be testable using the NHLBI DIR contracting laboratory equipment (currently Siemens Aera 1.5T).
- A report of test results, including *in vivo* test results if not performed at NHLBI

Phase II Activities and Expected Deliverables

A phase II award would allow mechanical and electrical testing and regulatory development for the device to be used in human investigation, whether under Investigational Device Exemption or under 510(k) marketing clearance. The contracting DIR lab offers to perform an IDE clinical trial at no cost to the awardee.

The specific deliverable would be:

- 0.035” outer diameter x 2.6-3.0 meters length allowing unencumbered catheter exchange

- Mechanical properties matching up to two commercially available X-ray guidewires, in descending priority order: (1) Wholey {steerable and torquable angled guidewire}, (2) Supra-Core {steerable and torquable shapeable soft-tip and stiff-shaft}
- Shapeable tip is strongly preferred over a J tip
- Free from clinically-important heating (2°C at 1W/kg SAR) during MRI at 1.5-3.0T
- Visibility during MRI. If using individual susceptibility markers, they should be positioned at the tip and along the shaft in a pattern that allows the operator to delineate/differentiate them. Susceptibility markers should be > 3mm in diameter using commonly used steady state free precession or fast gradient echo MRI techniques
- Proposals for alternative visualization strategies, such as “active” or “inductively-coupled” receiver coils, are welcomed, but such solutions must be testable using the NHLBI DIR contracting laboratory equipment (currently Siemens *Aera* 1.5T).
- A complete report of prior investigation along with all other elements of the IDE application and accompanying regulatory correspondence.

082 MRI Myocardial Needle Injection Catheter

(Fast-Track proposals will be accepted.)

Number of anticipated Phase I awards: 1-2

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

Summary

Myocardial catheter ablation is commonly performed for the treatment of rhythm disorders, using radiofrequency energy, typically guided using X-ray and/or electromagnetic positioning. Available non-surgical technologies do not allow clear depiction of myocardium being ablated. MRI-guided needle catheter chemo-ablation, for example using focal injection of ethanol, may allow targeted disruption of small segments of myocardium in the treatment of rhythm disorders such as ventricular tachycardia and in the treatment of structural heart disease such as hypertrophic cardiomyopathy. No commercial options are available.

An MRI myocardial needle injection catheter system may enable a new family of non-surgical cardiovascular treatments for rhythm and structural heart disease. This contract solicitation is to obtain a catheter-based endomyocardial injection needle that is safe for operation during MRI.

Project Goals

The goal of the project is to develop an endomyocardial injection needle catheter that is safe for operation during MRI, to allow targeted myocardial delivery of liquid agents. First a prototype would be developed and tested in animals, and ultimately a clinical-grade device would undergo regulatory development for clinical testing. NIH offers to perform clinical testing at no charge to the contractor.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a myocardial injection needle prototype. The contracting NHLBI Division of Intramural Research (DIR) lab is willing to provide feedback about design at all stages of development. The contracting DIR lab will test the final deliverable device for success in vivo in swine.

Specific Phase I deliverables would be

- 9Fr or smaller.
- Suitable for use via femoral artery retrograde across aortic valve and via jugular and femoral venous access to the right sided cardiac chambers.

- A needle that can delivered to multiple endomyocardial targets, achieve stable positioning, and that can penetrate the myocardium without causing significant harm while delivering injectate. Solutions should allow a user-selected injection depth and may be spring-loaded or offer alternative penetration capabilities.
- Sufficient radius of curvature to access all parts of left ventricle endocardial surface including left ventricle outflow tract, and all parts of right ventricle including septum and outflow tract. Suitable solutions may be deflectable, may have multiple coaxial curved catheters, or alternative approaches.
- Visibility during MRI: (1) “Active” design incorporating MRI receiver coils for shaft, tip, and needle visibility during MRI; (2) Receiver coils should be conspicuous under MRI using “profiling” or “tracking” techniques as described in publications from the contracting NHLBI DIR laboratory; (3) The “active” receiver coils must operate for testing on a Siemens *Aera* 1.5T MRI scanner installed at contracting NHLBI DIR laboratory.
- There should be a characteristic imaging signature that distinguishes the needle from the rest of the catheter. One suitable option is a separate receiver channel for the needle.
- Free from clinically-important heating (2°C at 1W/kg SAR) during continuous MRI at 1.5T.
- Proposals for alternative visualization and heat-mitigation strategies, such as “active” or “inductively-coupled” receiver coils, are encouraged, but must operate for testing on a Siemens *Aera* 1.5T MRI scanner installed at contracting NHLBI DIR laboratory.
- A report of test results, including in vivo test results if not performed at NHLBI.
- Sufficient devices to test the final device in vivo at the contracting NHLBI DIR laboratory.

Phase II Activities and Expected Deliverables

A phase II award would allow mechanical and safety testing and regulatory development for the device to be used in human investigation, whether under Investigational Device Exemption or under 510(k) marketing clearance. The contracting DIR lab offers to perform an IDE clinical trial at no cost to the awardee. IDE license or 510(k) clearance, along with twenty clinical investigational prototypes, would constitute the deliverable.

Offerors are encouraged to include concrete milestones in their proposals, along with detailed research and development plans, risk analysis, and contingency plans.

Specific Phase II deliverables would be

- All characteristics of Phase I deliverable, and in addition:
- 8Fr or smaller in phase II
- A complete report of prior investigation along with all other elements of the IDE application and accompanying regulatory correspondence.
- Suitability of the injection system for delivery of viable cells, while outside the scope of this contract, is encouraged.

083 Transcatheter Pulmonary Artery Resistor

(Fast-Track proposals will be accepted.)

Number of anticipated Phase I awards: 1-2

Budget (total costs): Phase I: up to \$225,000 for 1 year; Phase II: up to \$1,500,000 for 2 years

Summary

Certain congenital heart defects require restriction of pulmonary blood flow by a pulmonary artery band (PAB) to support life and development for months before surgical repair. Current surgical pulmonary artery bands are difficult to tailor to individual patient needs, especially as they grow. Not only do surgical pulmonary artery bands require an additional major open heart procedure on small children, they also confer major complications that interfere with later surgical treatment. A catheter-based non-surgical alternative would be attractive, but is not available. The highly elastic main pulmonary artery imposes unique challenges to development of such a device.

Classes of congenital heart disease that would benefit from such a device include: (1) Biventricular repair candidates or largely non-mixing left to right shunt lesions as ventricular septal defect (single or multiple), atrioventricular canal, double outlet right ventricle, congenitally corrected transposition of the great arteries (2) Single ventricle candidates or largely mixing non-ductal dependent as double outlet right ventricle, double inlet left ventricle, tricuspid atresia (3) hypoplastic left heart syndrome (branch pulmonary arteries) as part of hybrid first stage palliation (4) rare clinical scenarios as *d*-transposition of the great vessels requiring late arterial switch

In one embodiment, a catheter-based pulmonary artery resistor would allow small children with, for example, ventricular septal defect, to survive and grow to allow completely non-surgical repair, first by placing a resistor and at a later date once the child is big enough, by transcatheter repair of the ventricular septal defect combined with transcatheter reversal (balloon crush) of the pulmonary artery resistor. Another embodiment, a catheter-based pulmonary artery resistor could be removed or occluded as needed during the subsequent surgical palliation or follow-on catheterization.

Finally, in the developing world, a majority of children with treatable congenital heart disease develop irreversible pulmonary vascular disease before they grow large enough to undergo “austere” surgical procedures. A transcatheter pulmonary artery resistor would be sufficiently simple to implant that unsophisticated medical centers could perform the procedure as a temporary palliative procedure awaiting later definitive surgical repair.

Project Goals

The goal of the project is to develop a temporary or permanent transcatheter pulmonary resistor device as an alternative to surgical pulmonary artery banding. First prototypes would be developed and tested in animals, and ultimately a clinical-grade device would undergo regulatory development for clinical testing. NIH offers to perform clinical testing at no charge to the contractor.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a transcatheter pulmonary artery resistor prototype. The final awardee deliverable would be tested for success *in vivo* in the contracting NHLBI Division of Intramural Research (DIR) lab (cardiovascular intervention program). Offerors are asked to specify R&D and contingency plans.

The specific deliverable devices would have the following characteristics:

- Transcatheter operation with introducer size no larger than 7 Fr
- Designed specifically to accommodate elastic main pulmonary artery.
- Designed specifically to avoid chronic injury to the MPA bifurcation or proximal branch pulmonary arteries, especially after surgical revision/removal/replacement.
- Designed to resist migration away from implantation site.
- Design features should be justified including the choice to employ a fixed flow reducer, an adjustable or variable flow reducer, and embodiments that allow remote or transcatheter modification after implantation.
- A desirable embodiment would allow transcatheter reversal of the obstruction, such as balloon dilatation of deformable implant at the time of definitive repair.
- Range of nominal (deployed) length and diameter of 12-20mm in width and length 10-15mm, mindful of marked elasticity of the main pulmonary artery.
- Expected age range of target clinical population: 0-3 months.
- Expected duration of implantation 3-6 months.
- Implant is MRI compatible. A MRI-safe delivery system would be attractive.
- A report of test results, including *in vivo* test results if not performed at NHLBI

Phase II Activities and Expected Deliverables

A phase II award would allow mechanical and safety testing and regulatory development for the device to be used in human investigation under Investigational Device Exemption. The contracting DIR lab offers to perform an IDE

clinical trial at no cost to the awardee. IDE license and a supply of required devices would constitute the deliverable. Offerors are encouraged to include concrete milestones in their proposals, along with detailed research and development plans, risk analysis, and contingency plans.

The specific deliverable devices would have the following characteristics:

- Transcatheter operation with introducer size no larger than 7 Fr
- Designed to resist migration away from implantation site.
- Designed specifically to avoid chronic injury to the MPA bifurcation or proximal branch pulmonary arteries, especially after surgical revision/removal/replacement
- Design features should be justified including the choice to employ a fixed flow reducer, an adjustable or variable flow reducer, and embodiments that allow remote or transcatheter modification after implantation.
- A desirable embodiment would allow transcatheter reversal of the obstruction, such as balloon dilatation of deformable implant at the time of definitive repair.
- Range of nominal (deployed) length and diameter of 12-20mm in width and length 10-15mm, mindful of marked elasticity of the main pulmonary artery.
- Expected age range of target clinical population: 0-3 months.
- Expected duration of implantation 3-6 months.
- Implant is MRI compatible. A MRI-safe delivery system would be attractive.
- A complete report of prior investigation along with all other elements of the IDE application and accompanying regulatory correspondence.

084 Value of Information Models for Clinical Trial Assessment

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 2-4 Phase I awards, 1-2 Phase II awards.

Budget (total costs): Phase I: up to \$225,000 for one year; Phase II: up to \$1,500,000 for two years

Summary

Clinical research is time consuming and expensive, with major trials costing tens of millions of dollars over many years. Assessment of research needs has relied on information from the scientific literature, systematic reviews, meta-analyses, and expert opinion. To maximize the impact of NHLBI clinical research investment on public health, Value of Information (VOI) modeling may provide an additional tool to help to predict the potential impact of studies under consideration, evaluate study design, estimate optimal sample size, and prioritize where additional investment may have maximal benefit. VOI is a modeling-based approach that quantifies knowledge and uncertainty and that evaluates the value of information that might be derived from a potential study or a particular investment in research.

The objective of this contract solicitation is to support the commercial development of VOI models for application to heart, lung, blood, and sleep research. Organizations or individuals who have VOI tools will receive resources to incorporate NHLBI mission-specific parameters and to test their performance against real-life scenarios based on retrospective data from completed clinical trials and hypothetical scenarios based on contemporary issues of interest to the Institute.

Project Goals

This contract would support VOI modeling services to help proposed major clinical trials and studies refine study designs and study populations, evaluate economic potential of targeted new priority research areas, and promote cost effectiveness by providing predictions of clinical applicability of research results. First a prototype would be developed by a collaboration of VOI modelers and clinical research experts, and then it would be validated against

an initial, self-defined use-case. The final objective is to develop a product that will be useful to the extramural research community and the NHLBI for a broader range of clinical trial topics than the original use-case.

Phase I Activities and Expected Deliverables

Phase I activities are expected to be aimed at demonstration of the method's feasibility. This will be demonstrated through application of the VOI model to a use case, identified by the offeror. It is expected that the Phase I award will develop a model that is focused on a specific disease area or need, and as such, it is expected that the Phase I will include both modeling and clinical expertise.

The scientific focus of the Phase I award will be on some aspect of heart, lung, blood, or sleep research and may include, but are not restricted to the following examples:

- VOI analyses to assess the study design, effectiveness, and economic impact of a potentially controversial interventional, randomized clinical study of drugs to treat heart failure.
- VOI analysis of the need for and design of additional ECG screening studies in the young.
- VOI models that include patient and consumer input, in addition to standard health care and economic parameters.

Deliverables in Phase I would include

- Functional VOI software focused on a well-defined use case for validation.
- Validation data of the VOI model against its initial use case.
- Proof of feasibility (including costs and time) of adapting the VOI model for clinical research to a related family of diseases or conditions (for example, atherosclerosis, diabetes, or peripheral vascular disease). This would include information on data or methods that would be required to adapt this model to these additional use cases and inform a more general use of the VOI model.
- Feedback of usability and usefulness from users of the VOI model.
- Access to the VOI model by NHLBI staff.

Phase II Activities and Expected Deliverables

Phase II awards would develop the commercial VOI model to be more broadly applicable across HLB diseases.

- Expansion and application of the VOI model to additional disease areas and study designs. The targeted areas will be identified, along with a timeline of development, validation methods, and clinical experts to support model refinement and validation.
- Proof of feasibility of applying VOI modeling to these expanded areas, including time and cost of adapting the model to new areas.
- Feedback of usability and usefulness from users of the VOI models.
- Access to the VOI models by NHLBI staff.

085 Development of Molecular Imaging Agents and Methods to Detect High Risk Atherosclerotic Plaque

(Fast-Track proposals will be accepted)

Number of anticipated awards: 3 - 5 Phase I awards and 1 - 3 Phase II or fast-track awards

Budget (total costs): Phase I: up to \$225,000 for one year; Phase II: up to \$1,500,000 for two years

Summary

Imaging has become an essential tool in preclinical and clinical research of cardiovascular diseases. Current imaging methods in clinical use are primarily focused on detecting the morphological and physiological changes that occur once disease has developed. Molecular imaging may help clinicians identify alterations at an early stage of the disease process to enhance efforts to prevent or retard disease progression. This will go beyond the conventional measurements like plaque burden, calcification, perfusion, and cardiac function to identify and quantify the molecular and cellular changes such as inflammation, apoptosis, cellular metabolism, endothelial dysfunction, and thrombogenesis.

Project Goals

This initiative will support the development of target-specific molecular imaging agents in combination with existing imaging modalities to detect high risk atherosclerotic plaque. Rupture of such plaques is responsible for the majority of acute cardiovascular events. The ultimate goals are clinical translation of molecular imaging techniques and their ultimate adoption into clinical decision making. The specific focus of this contract will be on the design and synthesis of targeted molecular probes, in vitro characterization and in vivo imaging studies in animal models.

Phase I Activities and Expected Deliverables

Synthesis and characterization of molecular imaging probes, with the development of lead candidate probe

Phase II Activities and Expected Deliverables

Lead optimization by in vivo small animal imaging studies, scale-up synthesis of the optimized probes for large animal studies. Development of toxicology studies and large animal imaging studies that is required for regulatory filing.

086 Tools for Educating Children about Clinical Research

(Fast-Track proposals will be accepted. *Potential contractors submitting Fast-Track proposals should include concrete milestones for both Phase I and II.*)

Number of anticipated awards: 2-3

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

Summary

Validated materials and tools, for children to learn about pediatric research and participating in such research, are lacking. We seek educational materials, demonstrated to be effective in diverse pediatric populations (race, ethnicity, culture, age, health status). The goal is to educate children via materials and tools offered to the public as an open-source product on the NHLBI's [Children and Clinical Studies](#) website to reside within the "Kids Clubhouse" space, currently being developed.

Project Goals

To develop innovative and validated tools tailored to children (for purposes of this solicitation, "children" is defined as reading-age and older) that will:

- increase awareness of pediatric clinical research among children and adolescents;
- enhance knowledge, empathy and acceptance of pediatric research participants;
- educate about general clinical research information (should not be trial or disease-specific) in an engaging, culturally sensitive and age-appropriate way.
- Tools that are of particular interest include, but are not limited to:
 - Electronic and/or animated comic books

- YouTube video campaign of children and adolescents sharing their personal clinical research experiences. Children want to hear from other children enrolled in research to help them understand what it means to be part of a study. (The widely heralded projects such as [It Gets Better](#) to end bullying of GLBT youths and [The Trevor Project](#) addressing youth suicide prevention, demonstrate the accessibility and public health benefit of using these technology resources.)
- Interactive and/or serious learning games
- Crowd-sourcing challenges that foster collaboration among children/teens to address the goals for this project

Phase I Activities and Expected Deliverables

Development of a prototype of the proposed tool will be delivered with evaluation results that demonstrate the effectiveness of the proposed message, content and mode of delivery in the proposed target population. Parent, educator and other expert evaluations should be conducted as appropriate. Adherence to all Federal Regulations pertaining to pediatric human subject research is mandatory. Paperwork Reduction Act (PRA) clearance by the Office of Management and Budget (OMB) will be required for the effective evaluation of sufficient numbers of subjects and must be reflected in the project timeline. When developing the prototype in Phase I, investigators should be aware that Section 508 compliance will be required if selected to proceed to Phase II. Proposals must include a summary of a commercialization plan that describes how the “framework” for developing the open source product may be used to develop a commercial or “like” product. For example, after development of a comic book on clinical trials, the programming, technology, or evaluation might be used to create a comic book on a different topic (asthma or sickle cell disease) for a commercial product. Proposals should contain a description of the potential market and how the proposed product would compete in that marketplace. Proposals should describe if the tool will be developed in Spanish also for inclusion in the Spanish version of the Children and Clinical Studies website’s [Niños y Estudios Clínicos](#) “Pagina de Niños”, which is currently under development.

Phase II Activities and Expected Deliverables

Phase II will begin with modifications to the tool based on the evaluation results in Phase I. Additional testing may be required during Phase II to ensure that the tool is effective in educating/raising awareness of clinical research in a diverse group of children, is developmentally appropriate for the age ranges of the proposed target population, validates the learning method proposed as effective and is technically feasible to exist within the [Children and Clinical Studies](#) website, which includes Section 508 compliance. Adherence to all Federal Regulations pertaining to pediatric human subject research is mandatory. PRA clearance will be required for the effective evaluation of sufficient numbers of subjects and must be reflected in the project timeline. The proposal must include a detailed commercialization plan with discussion of financing efforts if additional resources beyond the Phase II award will be needed. The plan should describe how the “framework” for developing the open source product may be used to develop a commercial or “like” product. For example, after development of a comic book on clinical trials, the programming, technology, and/or evaluation might be used to create a comic book on a different topic (asthma or sickle cell disease) for a commercial product. Proposals should describe whether the tool will be developed in Spanish also for inclusion in the Spanish version of the Children and Clinical Studies website, [Niños y Estudios Clínicos](#), “Pagina de Niños”, which is currently under development.

NATIONAL INSTITUTE ON AGING (NIA)

NIA’s mission is to support and conduct genetic, biological, clinical, behavioral, social, and economic research on aging; foster the development of research and clinician scientists in aging; provide research resources; and disseminate information about aging and advances in research to the public, health care professionals, and the scientific community, among a variety of audiences.

This solicitation invites proposals in the following area:

087 Development of Calorie-restricted and Nutrient-balanced Medicinal Food Products for Mitigation of Age-related Diseases or Conditions

(Fast-track proposals will be accepted.)

Number of anticipated awards: 2

Budget (total costs): Phase I: \$200,000 for 9 months; Phase II: \$1,500,000 for 3 years

(Note: It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.)

Background

Americans are living longer than ever before. Life expectancy nearly doubled during the 20th century with a 10-fold increase in the number of Americans age 65 or older. The older population age 65 and over is projected to grow to 72 million in 2030, representing nearly 20% of the total U.S. population. As life expectancy increases, diseases and conditions that are associated with older age become a major health burden. The stresses caused by the medical interventions of these diseases and conditions are also a major issue for older Americans. Large proportions of older Americans report a variety of chronic health conditions such as obesity, type 2 diabetes, chronic lower respiratory disease, Alzheimer's disease, cardiovascular diseases, and cancers. A major risk factor for the development and progression of some of the most prevalent chronic diseases is the excessive intake of food rich in calories and poor in nutrients (e.g., some high energy food lacking adequate amounts of vitamins and phytochemicals). In contrast to the detrimental effects caused by over-consumption of such foods, a reduction in calorie intake without malnutrition has a wide range of benefits which may prevent, delay, or ameliorate a number of age-related diseases or conditions and improve the healthspan of older Americans. It could also enhance the effectiveness of some medical interventions or decrease the stresses caused by treatments of these age-related diseases or conditions.

Caloric restriction (CR), a diet that is lower by a specific percentage of calories than the normal diet, is considered one of the most robust life-extending interventions. CR increases lifespan in many species studied so far, from yeast to mammals. In addition, data from studies in animal models have found that CR without malnutrition increases healthspan by preventing or delaying the occurrence of a wide range of chronic diseases. CR has been shown to inhibit spontaneous, chemically-induced or radiation-induced tumors in several murine models of cancer. CR has also been shown to prevent, delay, or decrease the occurrence of chronic nephropathies, cardiomyopathies, autoimmune and respiratory diseases, neurodegeneration, and amyloid deposition in the brain. In addition, CR enhances neurogenesis in animal models of Alzheimer disease, Parkinson disease, Huntington disease, and stroke. Studies in nonhuman primates found that CR protects against diabetes, cancer, hypertension and cardiovascular diseases. Although it is difficult to determine the effects of CR on aging and lifespan in humans, data from some epidemiological studies suggest that CR may have beneficial effects on human longevity and aging. These studies include "natural experiments" such as a study on the residents of Okinawa who are known to consume fewer calories than those living on the main Japanese islands. The effects of CR have also been examined in normal-weight individuals in a more controlled environment. During the course of the Biosphere 2 project which took place from 1991 to 1993 in a closed ecosystem in Arizona, four men and four women experienced a forced decrease in calorie intake for 18 months, due to an unanticipated decrease in food availability. Measurements obtained from individuals practicing long-term CR showed a reduction of metabolic and hormonal factors associated with increased cancer risk. Early findings of the "Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy" (CALERIE) study have found that slightly overweight adults who cut their calorie consumption by about 20 percent lowered their fasting insulin levels and core body temperature.

These results in animal models and the limited data from humans suggest that novel modalities that mimic caloric restriction, including certain ratios of carbohydrate, protein, and lipids in the calorie-restricted and nutrient-balanced diets, can be effective to prevent, delay, or ameliorate age-related diseases or conditions. The goal of this SBIR contract topic is to support small businesses to develop novel calorie-restricted and nutrient-balanced diet formulations for prevention and/or treatment of age-related diseases or conditions.

Project Goals:

The aim of this project is to stimulate the development of novel medicinal food products with balanced nutrients but restricted calories for mitigation of age-related diseases and conditions. These include products containing specific combinations of carbon sources, vitamins and minerals as well as sugar and amino acid substitutes that produce the similar apparent benefits of caloric restriction; i.e., prevent, delay, or ameliorate age-related diseases or conditions. These medical food products may also enhance the effectiveness of treatments or improve patients' abilities to withstand stresses of medical interventions (such as chemotherapy or surgery) while providing the necessary nourishment to patients.

Phase I Activities and Expected Deliverables:

- Develop one or more medical food products with the potential to improve a number of physiological measurements and prevent, delay, or ameliorate age-related diseases or conditions.
- Develop one or more medical food products with the potential to allow patients to better withstand stress induced by clinical interventions such as chemotherapy or surgery.
- Develop one or more medical food products with the potential to improve the effectiveness of medical interventions for age-related diseases and conditions.
- Provide compelling pre-clinical data for the feasibility in developing the proposed products, as well as proof that the products do not cause detrimental side-effects.
- Phase I efforts should include animal studies aimed at demonstrating a statistically significant effect on various markers or measurements (such as glucose levels, IGF, inflammatory and metabolic markers) as a result of the administration of the developed medical food product.
- The development plan for the medical food products should be formulated in consultation with NIA.

Phase II Activities and Expected Deliverables:

- Complete the development of the medical food products for one or more age-related disease or conditions.
- Perform animal studies demonstrating utility of the medical food product for preventing, delaying, or ameliorating one or more age-related disease or condition; improving the effectiveness of treatments or decreasing the stresses caused by treatment of these age-related disease or conditions.
- Appropriate preclinical data should be accumulated to support a Phase I clinical trial.
- Perform human studies to determine safety.
- Provide NIA with updates on a comprehensive IP and development plan, outlining how the small business will develop and commercialize the products.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

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

088 Development of a Database of Non-English Measures and Instruments for Use in Alcohol Research

(Fast-Track proposals will be accepted.)

Number of anticipated awards: 1

Budget (total costs): \$225,000 for 6 months; Phase II: \$1,000,000 for two years

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background

In the NIH Revitalization Act of 1993 (PL 103-43) Congress has mandated monitoring of successful inclusion of women and members of minority groups and their subpopulations in NIH-funded clinical research. The 1993 Act also mandates that special attention be given to Phase III clinical trials in order to allow minority representation in sufficient numbers for valid analyses of differences in intervention effects by race/ethnic and gender whenever possible.

Disparities in participation in NIAAA sponsored extramural clinical trials were identified and reported to the 2013 NIAAA National Advisory Council indicating a decreasing order in participation from White, Black/African American, Hispanic/Latino, and Asian populations. For FY2011 the total minority enrollment was 43.7% and for FY2012 it was 45%. Further, the minority enrollment in Phase III clinical trials has varied greatly, for example, the representation of Hispanic and Asian participants decreased from FY2011 to FY 2012 (Hispanic 11.8 to 6.7%; Asian 3.3 to 0%). Disparities in participation in research may reflect language issues, local demographics, and/or the diversity of study staff although data to understand under-representation of racial and ethnic minorities in research is not available. One means to expand the numbers of under-represented minorities is to have study assessments available in languages other than English in order to allow non-English speaking racial and ethnic minority participants into the subject population.

Expanding the knowledge base about ethnic minority alcohol use is among the priorities outlined in the NIAAA Health Disparities Strategic Plan (FY2009-2013). Increased research on under-represented minority populations, such as Asian Americans and Pacific Islanders, and increased efforts to document differences within groups among minority populations are identified as high priorities. The availability of research measures in languages in addition to English, such as Spanish, Chinese, Japanese, Korean, etc., would be likely to enhance the participation of Hispanic and Asian Americans in NIAAA funded research. Having Hispanic and Asian language measures would also increase the recruitment of recent immigrants with low level of acculturation for whom completing measures in English would be a problem. Level of acculturation has been shown to influence alcohol use among Hispanics and it is likely to play a similar role among Asians.

There may be examples of alcohol-related assessment tools that have been rigorously translated and back translated into languages other than English. As an initial step toward increasing outreach to non-English speakers NIAAA proposes to survey available measures already available in Spanish and Asian languages. These may include but are not limited to: (1) NIAAA Intramural Laboratory of Epidemiologic and Biometry field research in Spanish and some of the major Asian languages, (2) NIAAA funded extramural awards, including Phase III Clinical trials such as COMBINE (Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence), that received

funds to produce translations of their measures into one or more languages and (3) studies conducted internationally by groups such as the World Health Organization and the Pan American Health Organization.

Deliverables:

The contractor will conduct a literature review including published research since 1990 to identify published alcohol research that has employed non-English measures. The contractor will further create a data base including the non-English language measures where possible; authors, sources, and contact information relevant to such measures where copies of the measures are not available; references to published research that has employed the translated measures; and psychometric data for the measures where available. The contractor will develop an application suitable for use on smart phones such as iPads, Android based systems and other tablet devices to facilitate access. The contractor will make the data base 508 compliant in order to allow posting of the product by NIAAA on its website. Marketing of the app generated as a result of this contract at professional meetings and to researchers and health care professionals would enhance the utilization of the database generated and provide a revenue stream for the developer beyond the initial sale of the app. Updating of the database and continued marketing of updated versions could be used as a business model.

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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 60 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. To learn more about the NIAID, please visit our web page at <http://www.niaid.nih.gov/about/whoWeAre/Pages/moreWhoWeAre.aspx>.

025 Biomedical Methods To Quantify Adherence To Prevention Clinical Trial Study Products and Strategies

Fast Track proposals will not be accepted.

Number of anticipated awards: 1-2

Budget (total costs): Phase I: \$225,000 for up to 1 year; Phase II: \$1,500,000 for up to 3 years

Background: The critical role of adherence in providing reliable estimates of product and / or strategy efficacy in preventing HIV transmission was recently highlighted by the outcome of the VOICE trial. This 5 arm trial, (oral Tenofovir, oral Truvada, oral placebo, 1% Tenofovir vaginal gel and gel placebo), required the daily use of products by women at risk for HIV infection. As reported at CROI 2013, the VOICE study failed to confirm the efficacy of 1% Tenofovir gel and oral Truvada observed in previous clinical trials. Multiple measures of adherence (self-reports, pill and applicator counts) were incorporated into the VOICE trial and they suggested high overall adherence (>90%). However, less than 30% of the women had detectable levels of drug in their plasma at study visits. The results suggest that current approaches to measuring adherence are not capturing product use accurately. Although many biological, behavioral and social factors may influence adherence, there is a critical need for accurate, real-time methods to quantify product adherence independent of trial participant bias.

Project Goal: The goal of this SBIR contract solicitation is to support small businesses interested in developing novel and innovative technologies to quantify the adherence to the clinical trial strategy used in HIV prevention clinical trials. Applicants may propose to develop innovative biomedical, electronic, and/or analytical technologies that are independent of subject reporting biases to determine clinical trial product/ strategy adherence. Proposed approaches should be accurate and reproducible and, ideally, able to quantify a subject's adherence when used either remotely by trial participants, during clinical study visits, or within 1 week of a study visit. Technologies must quantify adherence to the placebo(s) and the study drug(s). Proposals to further develop or optimize MEMS caps, Wisebags™, and applicator staining methods are not responsive to this solicitation. Behavioral/social determinations of product use/adherence as comparators to demonstrate efficiency, accuracy and/or fidelity of the methods under development are appropriate for incorporation into proposals. The developed methods, strategies and/or instrumentation should be cost effective and have a defined regulatory pathway, and should not significantly increase participant or site personnel burden.

Based on the stage of development, Phase I activities may include one or more of the following:

- Initial design and testing of innovative biomedical, analytical and/or electronic-based detection technologies to quantitatively measure product/strategy adherence without subject bias in real time.
- Demonstration of sensitivity and specificity of the proposed innovation(s).
- Demonstration of the robustness of the proposed technologies in human secretions, i.e. vaginal, rectal, and semen. If active pharmaceutical ingredients (API) are to be detected as part of the adherence measurement, then robustness of the detection method should be demonstrated in the presence of these secretions.
- Iterative optimization of a detection technology already under development, such as studies to increase the sensitivity and specificity of the technology.

Phase II activities may include one or more of the following:

- Process development for the manufacturing of components, including Quality Assurance/Quality Control for the proposed product.
- Expanding testing on human samples.
- Comparative studies of the developed methods with current behavioral –based adherence measuring/monitoring technologies.
- Address applicable FDA preclinical approval requirements.

026 Simple, Inexpensive Assay for Five Common HIV Resistance Mutations

Fast-Track proposals will not be accepted.

Number of anticipated awards: 1-2

Budget (total costs): Phase I: \$225,000 for up to 1 year; Phase II: \$1,500,000 for up to 3 years

Background: Antiretroviral therapy in resource limited countries generally includes two NRTI and one NNRTI. While these HAART regimens are very potent and reduce viral load to undetectable levels in most patients, drug resistance occurs in some patients after long term therapy. The WHO has published a report of HIV resistance including data from 40 surveys conducted in 12 countries from 2006 to 2012. These surveys indicate that there are resistance mutations that predominate among patients failing therapy after 12 months. These mutations include the NNRTI resistance mutations K103N and Y181C, the tenofovir and d4T resistance mutation K65R, the 3TC/FTC resistance mutation M184V, and the most common thymidine analog resistance mutation D67N. The ability to quickly and easily detect these five mutations after virological failure could help optimize second line therapy regimens.

Project goal: The goal of this solicitation is to develop an inexpensive, easy to use assay that will detect the presence or absence of five common HIV drug resistance mutations in blood samples from patients failing HAART regimens in resource limited countries.

Phase I activities:

- Development of a method for detecting five mutations
- Development of an inexpensive, easy to use assay platform
- Initial testing on laboratory isolates, including several HIV subtypes

Phase II activities:

- Validation testing to include precision, accuracy, sensitivity, and specificity for detection of each mutation, with comparison to FDA-approved HIV resistance test methods
- Development of a well-defined test platform under good manufacturing practices (GMP)
- Development of a quality control program to ensure lot-to-lot consistency
- Scale-up and production for multi-site evaluations using clinical isolates

027 Capreomycin: Formulation for Oral Delivery

Number of anticipated Phase I awards: 1-3

Fast-Track proposals will not be accepted

Budget (total costs): Phase I: \$225,000 for up to 1 year; Phase II: \$1,500,000 for up to 3 years

Background: Multidrug-resistant tuberculosis (MDR-TB) is an increasing challenge for the treatment of TB. Currently existing drugs for the treatment of MDR TB are only moderately potent, show restrictions with absorption or oral bioavailability, and have toxicity profiles that make patient management difficult. Current international guidelines for the treatment of MDR-TB include at least one second-line agent administered by injection. There are two important classes of injectable drugs: the aminoglycosides (amikacin and kanamycin) and the polypeptide capreomycin. Capreomycin is specifically recommended for use in cases of known or suspected resistance to the aminoglycosides. Capreomycin also seems to have activity against non-replicating persisters bacilli, unlike aminoglycosides. The drug is painful to receive by injection and is associated with severe systemic side effects, including nephrotoxicity and ototoxicity.

Project goal: The goal of this solicitation is to develop novel formulations or modifications of capreomycin that can be orally administered, maintain efficacy, possibly decrease adverse events (nephrotoxicity and ototoxicity), and used as part of a drug regimen for the treatment of MDR-TB.

Phase I activities:

- Development of methodologies to be used to formulate capreomycin for oral administration
- Development and implementation of a plan for a biological testing component to quantitatively assess the product(s) for:
 - In vitro activity in an existing standardized, reproducible, and validated in vitro culture and intracellular test systems, and provide quantitative assessment of efficacy and cytotoxicity of the formulated products(s) and/or
 - In vivo efficacy in an existing standardized, reproducible, and validated small animal model of infection which detects statistically valid differences between formulated and non-formulated products for drug efficacy, toxicity and pharmacokinetics

Phase II activities

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

028 Adjuvant Development

Fast-Track proposals will not be accepted.

Number of anticipated awards: 1-3

Budget (total costs): Phase I: \$225,000 for up to 1 year; Phase II: \$1,500,000 for up to 3 years

Background: Adjuvants stimulate innate and/or adaptive immune responses. For the purpose of this SBIR, adjuvants are defined according to the U.S. Food and Drug Administration (FDA) as “agents added to, or used in conjunction with, vaccine antigens to augment or potentiate (and possibly target) the specific immune response to the antigen.” The adjuvant products targeted in this program must be developed as components of antigen-specific vaccines against infectious disease, and may not be developed as stand-alone agents. Currently, only two adjuvants have been approved for use in the United States - aluminum hydroxide/aluminum phosphate (alum), and 4'-monophosphoryl lipid A (MPL), a component of lipopolysaccharide, adsorbed to alum. Additional efforts are needed to address limitations of current adjuvant:vaccines and to more fully develop the potential capabilities of adjuvants.

Project Goal: The goal of this project is to accelerate pre-clinical development of a single lead adjuvant candidate for prevention of human disease caused by non-HIV disease pathogens.

Phase I Activities

- Depending on the developmental stage at which an adjuvant is entered into the
- Program, the offeror may choose to perform one or more of the following:
- Optimization of one candidate compound for enhanced safety and efficacy; this may include structural alterations or modifications to formulation.
- Establishment of an immunological profile of activity and immunotoxicity that can be used to evaluate the capability of the adjuvant to advance to human testing.
- Preliminary studies in a suitable animal model to evaluate the protective efficacy of a lead adjuvant:vaccine combination.

Phase II Activities

- Extended pre-clinical studies that may include IND-enabling studies such as:
- Additional animal testing of the lead adjuvant:vaccine combination to evaluate immunogenicity and protective efficacy.
- Pilot lot or cGMP manufacturing of adjuvant or adjuvant:vaccine.
- Advanced formulation and stability studies.
- Toxicology testing.
- Establishment of quality assurance and quality control protocols.
 - Pharmacokinetics/absorption, distribution, metabolism and excretion studies.

This SBIR will not support:

- The further development of an adjuvant that has been previously licensed for use with any vaccine.
- The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial>) for the NIH definition of a clinical trial). For SBIR phase II clinical trial support, see the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#).
- The discovery and initial characterization of adjuvant candidates.

- The discovery or development of adjuvants or vaccines to prevent or treat cancer, allergic diseases or autoimmunity.
- Platform development such as vehicle or delivery systems.
- The development and/or optimization of a pathogen-specific vaccine component.
- The development of therapeutic adjuvant:vaccines.

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:

151 Web Resource System for Prescription Drug Providers, Researchers and Users: The Prescription Drug Abuse Policy System (PDAPS)

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

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

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

The RFP requests applications for the creation of Prescription Drug Abuse Policy System (PDAPS), that would provide user-searchable access to authoritative, detailed, and comparable information on prescription drug abuse related laws and policies in the United States at the State and Federal levels. It would primarily be a tool for researchers to encourage and facilitate analyses on the effects and effectiveness of prescription drug-related policies.

Background

The harm to the country's public health attributed to the misuse and abuse of prescription drugs is substantial. In the United States, the rate of drug overdose deaths has more than tripled over the last decade, fueled largely by increases in unintentional deaths involving prescription drugs, especially opioid analgesics and sedative/ hypnotics. Morbidity has also increased with the non-medical usage of opioid analgesics and benzodiazepines, doubling between 2004-2008. The prevention of prescription drug misuse and abuse, and the mitigation of its negative consequences both feature prominently in the NIDA's research portfolio and within the Office on National Drug Control Policy's strategic objectives. Though the implementation of sound public policies across the nation has the potential to prevent prescription drug abuse, little research has been conducted to evaluate the influence and effectiveness of these policies.

As such, there is a need for accessible data on the laws, policies and public health outcomes related to prescription drug misuse and abuse. With thousands of jurisdictions around the country, ranging from county and city police to state poison control centers, professional medical associations governing the conduct of prescribers, and the federal government's multifaceted efforts at curbing these abuses, obtaining a measured lay of the legal landscape is difficult. Public policies and laws that affect prescription drug misuse and abuse can also impact morbidity, mortality and a range of health and social outcomes. Public health research in this area has been severely limited by the availability and quality of policy and law information which has been established by governments at many levels. A foundational law and policy source is needed that can stimulate new research on prescription drug policy to

inform public health strategies for law enforcement, prevention advocates, researchers, policy makers, medical practitioners and their associations, and the general public.

Prescription drug policy has been formed using a complex array of laws, policies, and regulations designed to address a variety of aspects like restrictions on practitioners, the chemical makeup of controlled medical substances, and the judicial rights of overdosed citizens and those who help them. Advances in scientific research depend on well-measured indicators of these laws and policies. This RFP requests applications for the creation of Prescription Drug Abuse Policy System (PDAPS), that would provide user-searchable access to authoritative, detailed, and comparable information on prescription drug abuse related laws and policies in the United States at the State and Federal levels. It would primarily be a tool for researchers to encourage and facilitate analyses on the effects and effectiveness of prescription drug-related policies.

Project Goals

This contract will create and maintain PDAPS, including the web site (or another alternate information technology platform) and the associated data structures and repositories, to provide detailed, reliable, comparable and timely information on prescription drug abuse related public policies adopted by governments at the State and Federal levels in the United States. This contract will also provide for technical assistance and related support activities. PDAPS would feature compilations and tabulations of prescription drug abuse related statutes and regulations and should be designed to simplify the process of ascertaining the status of the law for researchers who wish to study the impacts and effectiveness of prescription drug abuse related policies.

Phase I Activities and Expected Deliverables

- Establish a project team including proven expertise in: prescription drug abuse, public health policy/ law, website design and data visualization that will effectively address all objectives of the current topic. Other alternate information technology platforms are also encouraged like Service Oriented Architecture (SOA), mobile computing applications, etc.
- Provide a report including detailed description and/or technical documentation of the proposed PDAPS project elements and procedures including (but not limited to) data standards, database structures, data harmonization procedures, website platform (or other alternate information technology platform) information, etc.
- Develop and test a functional prototype system that includes:
 - Identifying, assessing and acquiring accurate and detailed information on two prescription abuse related policies adopted and implemented at the Federal and State levels through appropriate electronic resources; Two policy topics must be selected in conjunction with the project officer after a rigorous feasibility analysis is conducted on the identified potential prescription drug abuse policies (which should include analysis of the public health significance, legislative activity across states, high relevance to identified research gaps areas, complexity of legal research required to attain variables)
 - Establish formal procedures for summarizing two prescription drug abuse related policies at multiple levels of detail, including descriptive overviews and detailed variables that effectively characterizes specific policy provisions (which does not mask meaningful heterogeneity needed for research by aggregating data); Examples of variables to be included are name of policy/law and identifying numbers in legal code, specific dates on which such provisions became or ceased to be effective, history of legislative/regulatory activity, jurisdiction, administrative and enforcement authorizes, etc.
 - Storing the policy information, including all related descriptions, keywords, indicators, and variables in an electronic system that permits on-line search and retrieval of policy information by a variety of flexible criteria;
 - Operating and maintaining the PDAPS web site (or another alternate information technology platform). In addition, a web site platform must: (a) conform to all relevant Federal, HHS, and NIH regulations and requirements, including those pertaining to accessibility, privacy, and security; (b) provide introductory information about prescription-related policy and about PDAPS; (c) provide user-

friendly access to summary policy information; (d) permit users to search PDAPS for detailed policy information according to various criteria; (e) generate search results in suitable display formats (e.g., tables, graphs, maps, etc.); (g) provide access to other policy-related information generated or maintained by PDAPS.

- Implement and employ rigorous quality assurance procedures to ensure the utility, reliability and integrity of the system and its various components.
- Finalize database formats and structure, data collection, transport, and importation methods for targeted data inputs.
- Include funds in budget to present Phase I findings and demonstrate the final prototype to a NIDA evaluation panel.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.

Phase II Activities and Expected Deliverables

- Beta-test and finalize the functional PDAPS system developed in Phase I.
- Develop, beta-test, and finalize data integration and visualization tools developed in Phase I.
 - Include several more prescription drug abuse related policies at several levels of detail, including descriptive overviews and detailed characterizations of specific policy provisions, (including the specific dates on which such provisions became or ceased to be effective) in addition to the ones identified in the Phase I pilot;
- Perform legal research and all related tasks to maintain and update policy and related information provided through the web site. Create maintenance stand operating procedures (and possibly explore automation procedures) to constrain costs while keeping data relevant to research.
- Conduct a usability assessment to make improvements in the clarity, format, accessibility, graphic appeal, intuitiveness, ease of use, and ease of navigation of the PDAPS web site.
- Conduct outreach to relevant organizations and research to promote utility of the developed service.
- Respond to inquiries from users of the PDAPS web site and provide technical assistance to researchers and others utilizing the information.
- Monitor and report on publications and abstracts that make use of the PDAPS system.
- Develop further systems documentation where applicable.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

152 Technological Tools to Facilitate Implementation of Evidence-Based Substance Abuse Prevention Interventions among the Military

(Fast-Track proposals will be accepted only if it existing effective interventions are selected and it can be argued that these can be readily implemented in technological formats – e.g. some prior piloting of this approach has begun).

Number of anticipated awards: 1

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

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Summary

This solicitation invites researchers to use technology to facilitate implementation of evidence-based drug abuse prevention and health promotion interventions (the entire intervention, key components of them, or as an adjunct to the intervention) for use with military personnel, veterans and their families. In response to this solicitation, applicants should assess the types of technology that are currently in use in the military and consider how these do or do not link to prevention interventions. The applicants should assess the types of technology-based tools for substance abuse, or other health issues, that are currently in use in the military and consider how these may be linked to other prevention interventions to provide an integrated continuum of services for the target population. Beyond web-based tools already in use in many military settings, applicants are encouraged to promote the use of telephone, telephone interactive voice response (TIVR), mobile applications, and other modern technologies that they can demonstrate are appropriate for the context and population.

Background

U.S. military personnel and their families have endured many challenges since September 11, 2001. More than 2.5 million service members have been deployed in support of the war efforts Operation Enduring Freedom (Afghanistan), Operation Iraqi Freedom (Iraq) (OEF/OIF), and/or Operation New Dawn (OND). These sustained combat operations have resulted in military personnel experiencing increased numbers and lengths of deployments and greater exposure to stressors, including death or risk to life, sustained threat of injury or actual injury, and the day-to-day and family stress inherent in all phases of the military lifecycle (to include the deployment cycle) and transitions. Negative life stress has been shown to be a major contributor to both the onset and exacerbation of substance abuse and psychological health problems and to be related to a variety of negative physical health outcomes including cardiovascular disease, cancer and asthma. Moreover, positive health behaviors such as physical activity, proper nutrition, adequate sleep, and improvements to social relationships, all have been shown to both reduce stress and improve physical and psychological health outcomes. Alcohol and drug use, especially prescription drug abuse, and suicides among military personnel who have served in OEF/OIF, are reaching epidemic proportions (Institute of Medicine, 2012, 2013). For example, rates of active duty personnel reporting prescription drug misuse have increased from 2% in 2002 to 11% in 2008 (Bray et al., 2009). Binge drinking among active duty personnel increased from 35% in 1998 to 47% in 2008 (Bray et al., 2009). The injuries sustained by active duty service members in theater differ from those of other conflicts in that they often involve explosions that can maim, cripple and cause traumatic brain injuries (TBI); many of these injuries would have been fatal in previous wars.

Effective prevention efforts for military personnel, veterans and their families are needed to address these serious health issues and the on-going stress associated with them. Access to effective prevention among the military has been identified as a major public health gap. Numerous factors support the value, and the timing, of bringing existing efficacious prevention interventions to the military. First, many current prevention interventions lend themselves readily to the issues faced by the military and their families. Two examples are the Video Doctor (Humphreys, Tsoh, Kohn, & Gerbert, 2011) and the Family Check-up (Dishion & Kavanagh, 2003). The Video Doctor is now available online for use with military personnel, veterans, and their families. Second, the military is already quite advanced in its use of technology, and is leading technology development in many areas. Increasingly, the military is embracing web-based technology as an intervention platform, to address issues of access/distance (reaching military personnel, veterans and their families who are living in rural areas and do not have easy access to care, especially those who are reservists and National Guard members who do not live on a base), and stigma (substance use, misuse and abuse is a complex issue in the military, due to lack of confidentiality, potential command notification and impact on one's career). Third, and not unusual in the field of prevention, the majority of interventions being utilized in the military are not evidence-based. Fourth, the focus on prevention interventions may be the "safest" approach to take with the military; prevention can benefit entire families, and veterans, and it can help to circumvent issues of stigma by addressing, and ameliorating, an entire social context (e.g. the family), suggesting that the affected military personnel member is not singled out. Finally, prevention interventions in military settings have great potential for commercialization. The Department of Defense and Veterans Affairs Administration have actively expressed both a desire and a need for prevention interventions. Specific recommendations of the Committee on the Assessment of Readjustment Needs of Military Personnel, Veterans, and their Families (IOM Report, 2013, p. 476. p. 479) include:

- The committee recommends that the Department of Defense use evidence-based primary prevention programs and treatments that have been specifically evaluated in service members and their families and that are focused on preventing and treating mental-health and relationship problems.
- The committee recommends that the Department of Defense continue to promote an environment that reduces stigma and encourages treatment for mental-health and substance-use disorders.

In addition, the many individual military bases and military hospitals and clinical settings would benefit from the availability of these interventions, and may be expressly encouraged to adopt (and pay for) them.

Given the numbers of past, current and future service members, veterans and their families, there is a great need for prevention and health promotion interventions to reduce the incidence and prevalence of health risking behaviors such as substance use disorders (SUD). Drug abuse prevention refers to the prevention of initiation of drug use and prevention of progression from drug use to drug abuse and dependence, including the misuse and abuse of prescription drugs. Prevention of tobacco use refers to the prevention of initiation of tobacco use alone. This solicitation invites researchers to use technology to facilitate implementation of evidence-based drug abuse prevention and health promotion interventions (the entire intervention, key components of them, or as an adjunct to the intervention) for use with military personnel, veterans and their families. In response to this solicitation, offerors should assess the types of technology that are currently in use in the military and consider how these do or do not link to prevention interventions. Offerors should assess the types of technology-based tools for substance abuse, or other health issues, that are currently in use in the military and consider how these may be linked to other prevention interventions to provide an integrated continuum of services for the target population. Beyond web-based tools already in use in many military settings, offerors are encouraged to promote the use of telephone, telephone interactive voice response (TIVR), mobile applications, and other modern technologies that they can demonstrate are appropriate for the context and population.

In preparing their proposals, offerors are expected to indicate strategies for penetrating the military marketplace, including gaining command leadership buy-in and support, with particular attention to deployment cycle, combat experience, and command readiness. Special consideration should be given to how to build upon existing military systems infrastructure and platforms. Additionally, strategies for protecting the confidentiality of the target audience, particularly in a military context, should be addressed clearly. To ensure that military women and military spouses are adequately included, offerors should propose strategies for recruiting military and civilian personnel and their families, including those on active duty, veterans, and National Guard/Reservists.

Though in-depth commercialization plans are not required of Phase I SBIR contract proposals, offerors are encouraged to consider plans for product commercialization aside from the product development, as these are very different capabilities made more distinct by the military context. Phase II activities and deliverables will include explicit language about commercialization plans, including identification of the target audience and ways to reach this audience with the developed product(s). For instance, the target audience (e.g. specific military branch), and the actual need for services within the identified target audience, is key to a successful implementation.

Project Goals

This contract will support development of technological tools to facilitate implementation of effective prevention interventions for military personnel, veterans and their families. Offerors are invited to consider all forms of technology that may be of value in these environments. Successful contracts will suggest specific interventions and specific technological formats to be utilized and specific populations to be targeted. In addition, offerors must describe initial plans for marketing to and reaching the target population.

Phase I Activities and Expected Deliverables

- Conduct a review of evidence-based prevention interventions – those addressing substance abuse and co-occurring disorders, and which promote healthy behaviors (e.g. sleep, nutrition) and relationships – to determine those with greatest applicability to military settings, and those which lend themselves to technological implementation. This task may include convening a team of experts in prevention research to provide guidance on the most applicable and ready-to-use interventions for the military, veterans and their families.

- Provide recommendations of the most suitable evidence-based prevention interventions and technological tools for implementation with military personnel, veterans and their families.
- Develop and test a functional prototype of the intervention in the technology(ies) chosen. The prototype should include:
 - the named intervention(s) or its/their components to be incorporated in the proposed technological tool;
 - the technological formats to be used and a preliminary design (mock-ups acceptable) for each;
 - if feasible, design plans for the completed technological product(s).
 - Test the functional prototype, using appropriate methods. Examples may include:
 - user testing;
 - focus groups;
 - small controlled studies.
- Produce a report of findings and Phase II plans.

Phase II Activities and Expected Deliverables

- In Year 1, beta-test and finalize the functional technological tool(s) developed in Phase I.
- Simultaneous to the technological tool development in Year 1, prepare materials for approval of an OMB clearance package to allow for conduct of a research study.
- In Year 2, conduct a rigorous research study of the finalized product. Details of the proposed study will be determined by the offeror, and must consider the military setting(s) and the tools to be tested. A randomized, controlled trial (RCT) is ideal but offerors may propose alternative formats if the research environment lends itself to such studies.
- As part of the in-depth commercialization plan to be included in the Phase II proposal, include measures or potential strategies to assess the market appeal of the final product.
- Complete a Final Report detailing the technological product(s) completed as a result of the contract, and the findings of the research study to be conducted. Also share knowledge gained about the market's responsiveness to the resulting tool(s).

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153 Products to Prevent (Lethal) Drug-induced Respiratory Depression

(Fast-Track proposals will be accepted.)

Number of anticipated Phase 1 awards: 2-3

Number of anticipated Fast Track awards: 1

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

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Objectives

To develop a medication or a delivery device to be used by a non-medically trained individual (patient, or caregiver) that will be effective in reversing the lethal depressive consequences arising out of the use or abuse of a pharmacological agent or combination of agents. This formulation and/or device could be prescribed by a treatment provider who may be an addiction specialist, primary care physician, pain specialist, anesthesiologist, etc.

Background

Drug overdose is currently the second leading cause of unintentional death in the United States, second only to motor vehicles crashes, which prompted the Centers for Disease Control and Prevention to label pharmaceutical opioid overdose as a national epidemic. (National Center for Injury Prevention and Control. Centers for Disease Control and Prevention. Unintentional drug poisoning in the United States (July 2010) <http://www.cdc.gov/homeandrecreationalafety/pdf/poison-issue-brief.pdf>.) The population at risk for opioid overdose is diverse and includes, for example, the more than 3% of U.S. adults currently receiving long-term opioid therapy for chronic noncancer pain, in addition to the drug/substance abusing population. Opioids are the primary drug group associated with lethal drug overdose because of their respiratory depressive effects (reduced breathing) and vomiting which can lead to death by aspiration at high doses. However, other sedating drugs and substances such as barbiturates, propofol and alcohol can also dangerously depress respiration and even sedatives such as benzodiazepines can magnify the effects of opioids and so induce respiratory depression at lower than expected opioid doses.

There are more than 300,000 heroin users, nearly 5 million prescription opiate users, plus millions of chronic pain patients receiving end-of-life opiate analgesic pain care. The number of poisoning deaths and the percentage of these deaths involving opioid analgesics increase each year. From 1999 through 2006, the number of fatal poisonings involving opioid analgesics more than tripled from 4,000 to 13,800 deaths (Substance Abuse and Mental Health Services Administration. (2010). *Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings*. Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4586 Findings. Rockville, MD).

Opioid analgesics are among the most effective medications for pain management, but emergency department visits related to pharmaceutical opioids more than doubled between 2004-2008 (from 144,644 to 305,885) and unintentional opioid-related overdose deaths increased from about 3,000 in 1999 to 12,000 in 2007. (ND Volkow and TA McLellan).

Pain is among the most common diagnoses in medicine, with prevalence estimates for chronic noncancer pain ranging from 4% to 40% in primary care settings. (MC Reid et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med*. 2002; 17(3): 173-179). Opioids are now more often being prescribed for patients with moderate to severe pain. Thus effective measures that would prevent/avert opioid overdoses are needed as overdoses and death often occur inadvertently in private settings where no one is present to offer assistance. Furthermore, data show an alarming number of fatalities caused by co-ingestion of alcohol, opioids, benzodiazepines and/or other central depressant medication (<http://www.samhsa.gov/data/2k13/DAWN127/sr127-DAWN-highlights.pdf>).

There is a need for development of new medications and/or a device that would help prevent respiratory depression. There are existing programs with Naloxone nasal sprays that reported successes (Walley et al., 2013). However, it is desirable that new compounds or medications that alter analgesia and sedation less than Naloxone will be developed (see Greer & Ren, 2009 as an example). This medication could work to reverse the effect of one or more drug classes or substances in a combination so long as the overall effect is to prevent the otherwise expected lethal outcome.

There is also a need for a device with a sensor that can detect respiratory depression. This device will be able to alert bystanders that a patient is experiencing respiratory depression due to the use of a pharmacological agent or combination of agents.

Phase I Activities and Expected Deliverables

- Develop and test new or existing compounds, formulations and/or technologies suitable to prevent respiratory depression in patients using medication, substances of abuse or their combination that cause or contribute to respiratory depression and death;
- Scale up production of the successful formulations and/or medical device prototype capable of supporting nonclinical and clinical studies of safety;
- Conduct the initial clinical testing to inform Phase II;
- Field-test the research idea of formulation development and/or the device prototype by conducting focus groups.

Phase II Activities and Deliverables

(Phase II information is provided for informational purposes to assist Phase I offerors with their long-term strategic planning even when only Phase I applications are requested).

- Develop detailed plans for formulation development and initial production model with cost projections;
- Plan regulatory strategy;
- Establish an FDA-compliant medication or medical device development;
- Provide clinical testing necessary for FDA approval.

References

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154 Bundled Service for Designing Methodologically Rigorous Animal Studies

Fast-Track or Phase I proposals will be accepted. The Fast-Track process allows Phase I and Phase II contract proposals to be submitted and reviewed together.

Number of Anticipated Awards: 2

Budget (total costs): Phase I: \$150,000 for one year; Phase II: \$1,000,000 for 2 years. Total budget for Fast-Track: \$1,150,000 for three years.

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods will not be funded.

Objectives

To improve quality of scientific exploration and to set standards in addiction research, NIDA is taking action to ensure methodological rigor in animal (*in vivo*) research studies by inviting offers from qualified small business concerns (SBCs) to research and develop a bi-modular bundle to assist addiction and other life science investigators in designing *in vivo* animal experiments. The service bundle should include 1) an animal study design interface based on a core set of research parameters (described below), and 2) personalized (e.g., face-to-face, on-line chat) access module allowing direct interactions with experimental design professionals and statisticians. Upon implementation by successful SBC, the customer (a life science researcher from academia or industry) would purchase SBC's bundled service to generate a proper *in vivo* study design and to obtain a certificate of assurance. This readily accessible web-based experimental design assistant is envisioned as one of the components of the efforts to improve the conduct and reporting of *in vivo* research. It is understood that this bundled service is not intended to fully replace critical thinking and years of scientific training.

Description

In addiction research, as in other life sciences, laboratory animals are used to develop and test putative medications, to elucidate normal biological processes, and to study genes/mutations found in both animals and humans, among others. Animals are used because research often cannot be conducted using human subjects for practical or ethical reasons. Animal studies play a vital role in science. National Institutes of Health (NIH) is diligent in following the guidelines for ethical conduct in the care and use of animal in research. Minimizing the use of animals in research is not only a requirement, but also an ethical obligation for NIH-funded researchers. However, insufficient numbers of animals utilized in underpowered experiments with an inadequate animal study design often leads to the failure to detect meaningful differences and to the needless use of animals in subsequent studies that build upon the incorrect results. Unnecessary repetition is unethical and results in waste of funds and resources. Unfortunately, the current reality is that in the US many graduate students (and others who are receiving training in the life sciences) receive little formal instruction in experimental design and variable training in statistics. Although life scientists are advised by the funding agencies to seek assistance of professional statisticians at their home institutions, this professional help is often not available or easily accessible.

In 2012, during the meeting with academic researchers and educators, reviewers, journal editors and representatives from funding agencies, disease advocacy communities and the pharmaceutical industry, NIH/NINDS identified poor experimental design associated with poor reporting as a significant issue contributing to irreproducibility of animal studies and that the universal core set of research parameters/key elements exists which should be addressed when designing and reporting the results of animal experiments. At the same time, the agreement was reached that raising

awareness of the importance of rigorous study design would contribute to the scientific progress and the development of new therapies.

It appears self-evident that the design quality of an animal experiment affects its scientific validity, but this problem has received little attention in translational medicine research. NIDA is looking to fund a SBC's research and development activities leading to the creation of a fee-for-service "bundle" to guide, assist or even educate the addiction and other life science investigators on the design, execution and, optionally, interpretation of animal experiments. Expected product is a bundled service, including a subscription to on-line software for animal study design with user-friendly interface (e.g., *Experimental Design Module*), and "real time" access to additional technical/professional support (e.g., *Personal Assistance Module*). Although some statistical packages (SPSS, SAS, Epi-6) are commercially available, their use without practical understanding of animal study design and methodological rigor is often inappropriate and misguided. The availability, assistance and participation of highly trained statistical staff in experimental designs is universally accepted as imperative; however, this type of support is not commonly available or accessible. Thus, the personal technical assistance component in this service "bundle" to be developed by the offeror(s) is absolutely required.

Experimental Design Module (EDM). This user-friendly, on-line, practical, step-by-step interface will guide and assist scientists to properly design animal studies. It must be focused on important steps involved in animal study designs and key features of experimental design. For example, all experiments should clearly inform the aim, the reasons for choosing specific animal models, the species, strain and source. As a rule, EDM must be constructed so that the final experimental designs/descriptions present enough information to allow other investigators to repeat the study elsewhere. Components that are considered essential to the design of most clinical trials, such as randomization, blinding, and sample size calculation, appear to be much less widespread in animal research. While SBC-offerors will be responsible for research and determination of all features of experimental design for animal studies to be included as a part of the on-line interface, the interface must introduce the important steps involved in experimental designs, and must allow for addressing of the certain key elements. When animal experiments are not carefully designed and interpreted, those key elements are known to result in studies that are un-interpretable and irreproducible. Those key elements are:

- Inadequate sample size
- Inadequate repetition
- Limited data sets and over-fitting the data
- Retrospective primary end-point selection
- Randomization and blinding
- Losses and exclusions after randomization
- Data handling.

Thus, *Experimental Design Module* is envisioned to help scientists to think and address, at a minimum, the following:

Selection of the model system: Factors contributing to selection (e.g., phylogenic scale, adequacy to the planning procedures and study aims, similarity to both human anatomy and physiology, animals' life span, cost), definition of study population, including the importance of strains and individual commercial stocks; designations of animal provider; developmental stage; diet, housing conditions, microbial status and handling; age, gender, health status, etc. It is useful to include the (pop-up) reminders that, for example, restricting experiments to male animals could limit their generalizability to female patients, or that the choice of inbred vs. outbred animals will affect the sample size calculations. Interspecies variances should be allowed to be taken into consideration in case the cross reactivity of the compounds with the target in the rat or mouse differs.

Adequate Controls: Negative, positive, systems, assumption, etc.

Repetitions and Extensions

Randomization and blinding: Methods of animal randomization to the various experimental groups, as well as on random (or appropriately blocked) sample processing and collection of data (blinded to the allocation sequence,

blinded to group allocation, blinded to the intervention, etc. It is useful to include the (pop-up) reminders that, for example, “to improve the reliability of the proposed studies, the investigator must use randomization to eliminate systematic differences between treatment groups, and induce the condition under investigation without knowledge of whether or not the animal will get the drug of interest; and assess the outcome in a blinded fashion” or similar.

Selecting the dose, timing and route of administration of pharmacological agents: a drug administration and dose regimen must be adapted to the pharmacokinetic properties of the drug, and to the duration of the study; the rationale for dosing the animal must be evident from appropriate pharmacodynamic and pharmacokinetic assays; the route of administration.

Sample Size Estimation: interface should allow demonstrating the reconciliation between statistical needs for detection of biological/behavioral effects and constraints of animal welfare, cost and time. To guard against 'underpowered' studies, the proposed platform must calculate the number of animals required to have a reasonable chance of detecting the anticipated effect given the expected variance of the data. Sample size estimation should take into consideration the study type (exploratory vs. confirmatory), the issues of gender and strain selections, types of variables collected and the number and “type” of control groups.

Effect Size: It should be recognized and explained that a statistically significant effect or difference is not necessarily biologically or clinically significant.

Overall, *Experimental Design Module* will benefit from curation of the relevant literature by the offeror. Preferably, each of the key elements of experimental design (for example, selecting the dose or model system) would have a list (links) of relevant behavioral literature. At a minimum, alerts such as “Consult previous relevant behavioral literature” should be included when appropriate.

In addition to a practical, computer interface-based step-by-step guidance, a personal, in real-time, assistance component (*Personal Assistance Module (PAM)*), including the availability of statistical consultations, must be proposed. Personal assistance may manifest itself as a detailed discussion about the use of appropriate statistics, the sufficient group size, and statistical methods used in analysis and interpretation of results.

It is understood that this bundled service is not intended to fully replace critical thinking and years of scientific training. It is also understood that establishing an “out of the box” web-based solution which meets all probable situations is challenging. Real-person (statistician/behavioral scientist) back-up should make it possible to get a service bundle that works in majority of the cases.

The offerors are strongly encouraged to consult published generic and model-specific guidelines for designing *in vivo* animal experiments, such as the [ARRIVE](#) guidelines for reporting animal research and FDA’s [Guidance for Industry: Animal Models — Essential Elements to Address Efficacy Under the Animal Rule](#) to assist them in research and development of both *Experimental Design and Personal Assistance Modules*.

Commercial Potential:

Expected product is a bundled service, including a subscription to on-line software for animal study design with user-friendly interface, and “real time” access to additional technical/professional support. Customers will access software through the on-line portal via user accounts. In addition, other business development models may be proposed.

The customer (a life science researcher from academia or industry) is expected to receive a customized assistance to generate a proper *in vivo* study design and to obtain a certificate of assurance. This dated certificate/study design can be used both as a study protocol for depositing any future registry of preclinical research and to allow scientists to demonstrate that the analyses they performed and the outcomes they measured were pre-specified rather than post hoc (the issues of choosing the test and the outcome measure which supports the proposal’s argument and ignoring the rest).

Phase I Activities and Expected Deliverables

- Establish a project team including proven expertise in: animal behavior studies and experimental design; statistics; software engineering, data visualization, and systems architecture that will effectively address all objectives of the current topic.
- Phase I research should generate data confirming the potential of the proposed bundle. Some of the expected activities are:
 - Design and development of an “experimental design work flow”. The offerors are encouraged to take advantage of the existing tools, numerous publications, validated statistical programs and technologies whenever possible as opposed to developing their own approaches. The choices must be justified, analyzed, and well documented with advantages and limitations of every source. **The experimental design work flow must be designed to contain enough information/entries to allow other investigators to repeat the experiment elsewhere.**
 - Development of software algorithms.
 - Initial demonstration of the capabilities of the software that should:
 - Assist the user in understanding complex concepts of experimental study design;
 - Create personalized view that enable interactive learning;
 - Have Application Programming Interface (API) that does not require programming skills;
- Final Phase I report should include plans for future work and commercialization.

Phase II Activities and Expected Deliverables

- Conduct usability testing of consumer-facing “real-life professional support” (PAM) applications.
- Beta-test the capabilities of the associated web portals, including system management, analyses, and reporting applications, that should:
 - Assist the user in understanding complex concepts of experimental study design;
 - Create personalized view that enable interactive learning;
 - Have Application Programming Interface (API) that does not require programming skills;
 - (Optional) Enable data exploration and analysis following the experimental procedures.
- Design and development of a functional prototype of a customer-ready bundle, including the software package with user-friendly interface (EDM) and PAM.
- Develop systems documentation, including user manual.
- Beta-test the complete system (bundled service).
- Include funds in budget to present Phase II findings and demonstrate the final prototype to an NIDA evaluation panel

References:

ARRIVE guidelines for reporting animal research
<http://www.plosbiology.org/article/info%3Adoi%2F10.1371%2Fjournal.pbio.1000412>

FDA's Guidance for Industry: Animal Models — Essential Elements to Address Efficacy Under the Animal Rule
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078923.pdf>

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155 Affordable Care Act (ACA) Web Platform to Integrate Behavioral Health & Prevention with Primary Care

(Fast-Track proposals will not be accepted.)

Budget (total costs): Phase I: \$150,000 for one year; Phase II: \$1,000,000 for 2 years. Ph II budget provided for future planning purposes only.

Number of awards – 2-3

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods will not be funded.

Background

Screening and assessment are currently covered services by the Affordable Care Act (ACA), including screening for substance use and related problem behaviors. It is unclear how referral to additional services, such as substance abuse prevention interventions, will be covered; yet prevention is a goal of the ACA landscape. Primary care providers have not integrated known effective substance abuse and related behavioral health prevention models. Providers may be unaware of the evidence base around substance abuse prevention interventions that may be reimbursable under ACA. We expect that it will be easier to justify charges for substance abuse prevention services if the services are known to be effective, if these services are already packaged and ready for use, and if the cost per item seems reasonable (generally true with higher volume purchases). Tools that can facilitate this process for primary care providers may increase the likelihood of uptake of effective prevention interventions, ultimately generating improved outcomes and greater incentive for ongoing use of these services.

Systems to help providers manage the referral process, locate and make use of assessment tools, and identify substance abuse prevention services are needed to increase the likelihood that providers will see these services as worthwhile. The primary goal of this solicitation is to encourage the development of web-based platforms that guide providers and payors through the maze of available tools and services, ultimately to increase utilization of evidence-based substance abuse prevention approaches. The web tools should incorporate at least one of the components listed below. Offerors are invited to suggest alternative or additional component.

- Screening instruments that are generally available but may be copyrighted (e.g. depression and anxiety scales, measures of school behavior problems)
- Risk scoring tools to determine need for services
- Referral tools and resources
- Prevention interventions that have an evidence base (publically available; available directly from the program developer, etc.), including associated materials, web formats, costs, etc. (e.g. Family Check-up, Video Doctor).

Most importantly, this component would allow providers to determine “what fits” in the way of prevention services and any specific patient’s need.

- Cost/reimbursement tracking tools, including information about billable services
- Links to information resources and practical guides (Table 1 below provides an example of some covered service areas the tools to be developed might include. However, any tools developed through this solicitation must include substance abuse as an outcome and substance abuse prevention as the primary service approach).

These tools could help providers to know how best to offer needed services to thereby meet demand, which should enhance the efficiency of their service provision.

Table 1: Example Information Resource for ACA Web Platform

COVERED SERVICE AREA	TARGET POPULATION(S)	WHAT’S COVERED?
Alcohol Misuse	Adults; Pregnant Women	Screening
Alcohol and Drug Use	Adolescents	Assessment
Behavioral Assessments	Children of all ages	Assessment
Depression	Adults; Adolescents	Screening
Developmental Screening	Children	Screening under age surveillance throughout childhood
HIV	Adults; Adolescents	Screening for individuals at high risk
Obesity	Adults; Children; Adolescents	Screening and counseling
Sexually Transmitted Disease	Adults; Adolescents	Prevention counseling for adults; Infection counseling and screening for adolescents at higher risk
Tobacco Use	Adults; Pregnant Women	Prevention counseling screening for all women; expanded counseling for pregnant women
Syphilis	Adults; Pregnant Women	Screening for adults at higher risk; screening for all pregnant women or other women at higher risk

Though a detailed commercialization plan is not required of a Phase I proposal, offerors should consider how their planned system can help overcome barriers associated with using new technologies, primarily current payment mechanisms. For example, the fee-for-service reimbursement mechanism requires face-to-face services. Although tele-psychiatry is often a covered service, it still requires a clinician interacting with a patient in real time. Many of the new technology services can be used independently of a provider and therefore are not eligible for the existing billing codes even though the provider may access and review the results and progress of the utilization of the systems and use this information to guide treatment. While provider time is not necessary for every service, there are the costs of licensing, hardware, software and maintenance and improvement of the system.

Project Goals

This SBIR contract solicitation invites proposals to produce web platforms that increase the knowledge and use of evidence-based substance abuse prevention intervention services for health care settings. Alternative technology platforms, such as mobile tools, may also be proposed, as well as those that promote greater interaction. Such platforms should make it easier for primary care providers and payors to see the benefits of substance abuse prevention services, and how to better navigate the Affordable Care Act to bill charges for these services. The

prospective customers for systems such as those proposed in this solicitation are many. Large health care systems (e.g. Children's Hospitals, University Hospital systems, networks of providers, partnerships between hospital provider systems and state financing systems) are likely the biggest users.

Given the increasing integration of health care services, the potential for more integration of prevention and care, and, the potential increase in screening and assessment for drug use, there are new opportunities to increase the uptake of evidence-based substance abuse prevention services. Web systems and tools should facilitate integration at the patient, provider, and systems levels.

Phase I Activities and Expected Deliverables

Phase I tools that demonstrate efficacy among professionals working in these settings include: 1) screening and assessment tools that address multiple, related problems (inclusion of drug/alcohol use screening); 2) tools to support referrals and linkages between providers who screen and those who provide prevention services, who may be in different settings (automated algorithms – prevention or care needs, cost and reimbursement at the client level and location and configuration of services); and 3) tools and systems to facilitate planning and evaluation of integrated service systems that provide assessment, care, and substance abuse prevention, with particular attention to the financing of services.

- Assess Produce a summary document (paper or electronic or both) that assesses the current state of available tools and resources to be considered for, and built into, the proposed technological tools. Conduct thorough reviews of, and assemble, materials related to each of the core domains identified in the web platform to be built. Domains and information resources may include:
 - screening and assessment resources
 - evidence-based prevention services (EBPS)
 - means of access to these EBPS
 - cost information associated with EBPS
 - relevance to particular health care outcomes.

Offerors should specify if all of these will be incorporated into the planned web system, or which ones and why those if including selected ones is considered a better approach.

- Provide recommendations for organization of modules of the web system to be relevant to various subgroups of health care providers, to include primary care physicians, nurse practitioners, social workers, education specialists, etc.
- Develop a functional prototype of the web platform.
- Assess feasibility of the platform with representatives of as many of the relevant subgroups as is practical in an SBIR Phase I contract. Offerors should specify the planned approach to assessing feasibility, e.g. whether focus groups, interviews, user testing, or some other approach(es) will be utilized, and specify the types of resulting reports that will be delivered to NIDA. As part of this assessment, some types of information offerors should seek might include :
 - how the planned system can be made to fit into the busy primary care workflow
 - what providers know about the current billability of these services and under ACA; how to create a system to fit within their current billing procedures

- whether meeting other identified needs would facilitate primary care providers' (PCPs') conduct of substance abuse prevention services (e.g. coaching substance abuse screening within a larger health risk assessment or mental health screening)
- what medium would be best suited for the delivery of web-based tools (i.e., desktop computer, tablet, or other device); etc.
- Specify how women and minorities will be incorporated into the research strategy, to include both women and minority primary care providers and women and minority primary care patients. Tools and platforms developed for the proposed project should be vetted and demonstrated with women and minority representatives of these groups.
- Produce a report of findings and Phase II plans.

Phase II Activities and Expected Deliverables (for future planning purposes only)

- In Year 1, beta-test and finalize the web platform and all its components designed in Phase I.
- Simultaneous to the technological tool development in Year 1, prepare materials for approval of an OMB clearance package to allow for conduct of a research study.
- In Year 2, conduct a rigorous research study of the finalized product. Provide a detailed plan for the proposed study. A randomized, controlled trial (RCT) is ideal but Offerors may propose alternative formats if the research environment introduces significant obstacles to such a study.
- Specify outcomes to be targeted by the web system, and how the research study will help inform our understanding of the system's ability to track these outcomes. Details will be needed in Phase II but as early as the Phase I proposal, Offerors should be considering which outcomes will be the primary targets of the tools to be developed.
- As in Phase I, specify how women and minorities will be incorporated into the research strategy, to include both women and minority primary care providers and women and minority primary care patients. Tools and platforms developed for the proposed project should be vetted and demonstrated with women and minority representatives of these groups.
- As part of the in-depth commercialization plan to be included in the Phase II proposal, include measures or potential strategies to assess the market appeal of the final product.
- Complete a Final Report detailing the technological product(s) completed as a result of the contract, and the findings of the research study to be conducted. Also share any knowledge of the market's responsiveness to the resulting tool(s).

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

CENTER FOR GLOBAL HEALTH (CGH)

The Center for Global Health (CGH) leads the execution of the CDC's global strategy; works in partnership to assist Ministries of Health to plan, manage effectively, and evaluate health programs; achieves U.S. Government program and international organization goals to improve health, including disease eradication and elimination targets; expands CDC's global health programs that focus on the leading causes of mortality, morbidity and disability, especially chronic disease and injuries; generates and applies new knowledge to achieve health goals; and strengthens health systems and their impact.

CGH Internet site: <http://www.cdc.gov/globalhealth/>

For this solicitation CGH invites Phase I proposals in the following areas:

006 Development of Novel Malaria Parasite Metabolite-based Non-invasive Diagnostic Biosensor

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Malaria is a mosquito-borne parasitic disease and remains a significant cause of morbidity and mortality in humans worldwide, particularly in African countries and among children under 5 years of age. Current malaria diagnostic tools include: 1) parasite detection by microscopic examination of blood smears, 2) antigen-based rapid diagnostic tests (RDTs), and 3) sensitive DNA-based assays. All these diagnostic methods require blood sampling by finger-prick and their implementation has been limited by either their labor/time intensive nature and requirement for specialized training and skills (microscopic method), moderate sensitivity (RDTs), or high cost of sample preparation and supporting infrastructure needed (DNA-based methods). For programs aiming to further decrease the parasite reservoir and reduce transmission rates with an ultimate goal of the elimination of malaria, the large-scale/real-time screening of persons with asymptomatic and low density malaria infection using a sensitive, low-cost, simple, field-deployable non-invasive diagnostic tool at the community level (as opposed to clinical cases in hospitals) is increasingly important. However, our current malaria diagnostic tools are limited in addressing this challenge. Recent metabolome analysis of *Plasmodium falciparum* parasite has identified several parasite-specific low-molecular-weight metabolites. In addition, inexpensive and simple biosensor platforms have been used for detection of small molecules, such as a microfluidic-based Origami Paper Analytical Device (oPAD) for detection of adenosine. Based on biochemical principles, the concentration of naturally-eliminated malaria parasite metabolic small molecule wastes (end products) should be higher in urine and/or saliva than in blood, making them ideal biomarkers for detection of malaria infection in these body fluids. Therefore, it is potentially feasible to use simple and inexpensive biosensors for, first, detection of malaria parasite metabolites, and second, to further develop sensitive non-invasive malaria diagnostic tools.

Project Goal: The long term goal of the project is to use malaria parasite specific low-molecular-weight metabolites as biomarkers for development of sensitive, low-cost and field-deployable urine or saliva diagnostic biosensor for detection of malaria infection. Specific aims in Phase I are: 1) to generate the biopolymer receptors against four malaria parasite-specific metabolites (3-Methylindole, Succinylacetone, S-Methyl-L-thiocitrulline, O-Arachidonoyl Glycidol) which were recently identified by our metabolome analysis, and 2) to provide proof of concept in the use of inexpensive and simple biosensor platforms for detection of the target compounds. Specific aims for phase II include: 1) to enhance the sensitivity and limit of detection (LOD) of the simple and inexpensive biosensors for detection of the four metabolites in urine and saliva samples from malaria patients to meet the LOD equaling malaria PCR diagnosis by blood samples, and 2) to design a fully-functional prototype of a battery operated, portable and data transmissible biosensor device that can be deployed for field evaluation.

Phase I Activities and Expected Deliverables: The detection of the above four malaria parasite-specific metabolites requires generation of biopolymer receptors, aptamers or antibodies, specific for the assay of these compounds. Once the receptors against the four compounds are ready, they are respectively applied to various simple and inexpensive biosensors for detection of these compounds. By the end of the Phase I, expected deliverables are: 1) the results of affinities and specificities of receptors against the four compounds, and 2) evidence that shows an inexpensive and simple biosensor with different readout devices that can detect the four compounds, their sensitivity, and limit of detection (LOD).

Impact: CDC provides substantial technical support to various malaria control programs globally and is a key partner in the President's Malaria Initiative (PMI), a vital component of the CDC priority to increase global health impact. Development of a novel malaria parasite metabolite-based non-invasive field-applicable diagnostic biosensor for detection of malaria infection will have an enormous impact on monitoring current control efforts and future global malaria elimination programs.

NATIONAL CENTER ON BIRTH DEFECTS AND DEVELOPMENTAL DISABILITIES (NCBDDD)

The mission of the CDC's National Center on Birth Defects and Developmental Disabilities (NCBDDD) is to promote the health of babies, children and adults and enhance the potential for full, productive living. To achieve its mission, NCBDDD works to: Identify the causes of birth defects and developmental disabilities; helps children to develop and reach their full potential; and, promotes health and well-being among people of all ages with disabilities, including blood disorders.

NCBDDD Web site: <http://www.cdc.gov/ncbddd/index.html>

For this solicitation NCBDDD invites Phase I proposals in the following area:

018 Developing Rapid Test for the Diagnosis of Sickle Cell Disease

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: It is estimated over 300,000 babies are born with severe forms of hemoglobinopathies, such as sickle cell disease (SCD), worldwide each year. Sub-Saharan Africa carries the greatest global burden of SCD, accounting for 71% of the over 300,000 annual births with SCD worldwide. In sub-Saharan Africa, up to 2% of all children are born with the condition and the proportion of the population with sickle-cell trait ranges between 10% and 40%. In some areas where SCD prevalence is highest, estimates derived from the age structure of populations attending clinics suggest that 50 to 90% of children with SCD die during childhood usually from infectious diseases like malaria or from the associated anemia itself. According to the World Health Organization (WHO), SCD may be responsible for approximately 5% of under-five deaths on the African continent, more than 9% of such deaths in West Africa and up to 16% of under-five deaths in specific West African nations. However, there is strong evidence to support that neonatal screening for SCD, when linked to regular administration of prophylaxis and vaccinations to prevent infections, along with parental education and comprehensive care, significantly reduce SCD-related morbidity and mortality in infancy and early childhood. In fact, evidence from the United States and European countries has demonstrated that almost all sickle-cell disease-related childhood mortality can be eliminated with the use of low-cost interventions. However, because of the cost, the need of laboratory infrastructure, and the delays in delivery of test results that may lead to loss-to-follow-up, traditional methods of neonatal screening for SCD are not ideal for resource-poor settings. Thus, there is need for the development of a simple, low-cost, rapid, point of care device for diagnosis of SCD that could be used for newborn screening or diagnosis in resource-poor settings like Sub-Saharan Africa. The implementation of a low-cost and accurate point-of-care diagnostic device would allow earlier SCD diagnosis and acute and long term treatment of children, thereby reducing mortality, especially under-five mortality.

Project Goal: To develop a sensitive and specific device for rapid point-of-care screening to identify individuals with the most common forms of sickle cell disease (SS, SC and S-Bthalassemia) in sub-Saharan Africa or other regions with high prevalence of the disease. The device should be easy to operate and maintain. Additionally, the results should be easy to interpret with minimal training. The device should allow for accurate distinction between sickle cell carriers (AS) and those with disease (SS, SC and S-Bea-thalassemia) among newborns. The device should be able to be marketed for significantly less cost than current "gold-standard" screening (i.e., IEF and HPLC) methods.

Phase I Activities and Expected Deliverables:

- Determine which scientific technologies will be used for to develop a point-of-care device for screening sickle cell disease and trait in low resource setting
- Develop a detailed timeline, plan, and budget for device development
- Develop device and demonstrate functionality of point of care device for screening sickle cell disease and trait

Impact: Sickle Cell Disease (SCD) is a leading cause of under-five mortality in Sub-Saharan Africa and often remains unaddressed. The key to reducing mortality is early diagnosis (preferably during the newborn period) and prophylaxis to prevent infections, which are the leading causes of childhood deaths due to SCD. Unfortunately, many countries do not have universal newborn screening to identify children with SCD and many of the methods of screening and diagnosis that are the gold-standard in the US are prohibitively expensive to establish and maintain in resource poor settings. The development of a rapid point-of-care diagnostic or screening test could lead to expansion of newborn screening for sickle cell disease to resource-poor settings that have a high burden of SCD that are not currently screening and reduce loss to follow-up and program costs in areas that are currently screening, allowing for more resources to be directed toward care and counseling. The overall impact would be a reduction in mortality and morbidity related to sickle cell disease.

019 Development of Rapid, Point-of-care Tests for Cytomegalovirus (CMV)

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 2

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Congenital CMV is a leading cause of birth defects and developmental disabilities in the U.S. Each year more than 5,000 children are born with or develop hearing loss, vision loss, intellectual disability (i.e., mental retardation) or other serious sequelae caused by congenital CMV.

Two promising approaches for reducing the public health burden caused by congenital CMV are 1) Prevent infections in pregnant women through screening and brief intervention (SBI); and 2) Improve secondary outcomes in children born with congenital CMV through early detection and intervention. Both approaches are evidence-based and feasible. It has been demonstrated that a SBI provided during prenatal care lowered rates of CMV infection among pregnant women. Similarly, early interventions can improve language development in children identified with hearing loss by age 9 months, which would include children with congenital CMV who pass their newborn hearing screen but develop delayed hearing loss.

Maternal prenatal screening and newborn screening for CMV are not routinely done in the U.S. One of the major barriers to screening is the availability of accurate, inexpensive, and high-throughput screening assays. For maternal screening, a rapid, point-of-care assay (similar to a rapid Strep test) that could detect anti-CMV IgG in blood would facilitate on-the-spot prevention counseling for pregnant women so that the behavioral intervention would not have to be delayed until the next prenatal visit. For newborn screening, a rapid, point-of-care assay that could detect CMV DNA or proteins in urine or saliva would allow for immediate counseling and additional specimen collection for confirmatory testing, and would avoid having to create new laboratory infrastructure for widespread urine or saliva testing.

Project Goal:

1. To develop a sensitive and specific device for a rapid, point-of-care test to identify anti-CMV IgG antibody. The device should be easy to operate and maintain. Additionally, the results should be easy to interpret with minimal training. The device will have potential for use in screening pregnant women for evidence of having been infected with CMV at some time in the past.

2. To develop a sensitive and specific device for a rapid, point-of-care test to detect CMV DNA or proteins in urine or saliva. The device should be easy to operate and maintain. Additionally, the results should be easy to interpret with minimal training. The device will have potential for use in screening newborns for congenital CMV infection.

Phase I Activities and Expected Deliverables:

Determine which scientific technologies will be used to develop a point-of-care device for testing for -

1. anti-CMV antibody in a prenatal care setting or (2) CMV DNA or protein screening in a hospital newborn nursery setting
 - Develop a detailed timeline, plan, and budget for device development
 - Develop device and demonstrate functionality of point-of-care device for -
2. IgG screening or (2) CMV DNA or protein screening

Impact: These point-of-care assays are not currently commercially available. If they were available, they would significantly lower the barriers to widespread screening and timely prevention interventions. For example, if CMV SBI were a routine part of clinical prenatal care, and had similar effectiveness to the France intervention, more than 10,000 new CMV infections could be prevented in pregnant women each year in the U.S. This could result in 1,000 fewer annual cases of CMV-related disabilities. Similarly, if routine CMV newborn screening were implemented and infected children were actively followed for hearing loss, 500 children each year would have improved secondary outcomes. If prenatal or newborn screening became routine, there would be a need for up to 4,000,000 of these tests each year.

020 Nutrition Support for Group Homes Serving Individuals with Intellectual Disabilities

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: In 2009, 379,911 individuals with intellectual or developmental disability (I/DD) received residential care in group homes with capacities of 1 to 15 people. Data from the National Core Indicators Project indicates that 29% of group home residents are overweight and 33% are obese (HSRI, 2013; <http://www.nationalcoreindicators.org/charts/?i=35>). Direct service providers (DSPs) in these facilities are often poorly educated and poorly paid. A 2006 HHS report to Congress indicated that annual turnover rate among residential and in-home DSPs averaged 53.6% (<http://aspe.hhs.gov/daltcp/reports/2006/DSPsupply.htm#table3>, accessed May 13, 2013).

Nutrition is a leading health indicator for individuals with I/DD. Research shows that diet is related to many of their most limiting secondary conditions and better nutrition may prevent or reduce limitations. The diets of residents of congregate care facilities have been characterized as “high in fat and empty calories and deficient in fruits and vegetables, whole grains and dairy products.” For these individuals, overweight and obesity are particularly critical problems that must, in part, be addressed through nutrition intervention.

Project Goal: The goal of this project is the development of an easily understood and interactive menu planning system designed to provide nutritious and economically neutral meals for people (adults) with intellectual or developmental disabilities (I/DD). The menu planning system must include education and good nutrition guidance

that will improve the diets of people in congregate living arrangements, by providing needed support and education for both clients and support staff. In addition, the program should include education and guidelines related to nutrition and food safety, adherence to standards of care and relevant regulations, menu and meal planning, grocery shopping, and cooking guidelines designed for the special needs of individuals with I/DD as well as group home staff. Attention must be paid to portion size and menu planning must be scalable for group homes housing varying numbers of people.

Phase I Activities and Expected Deliverables: Activities during this phase are expected to include the conceptual development of a web-based system for menu planning for group homes serving 1-15 residents. The nutritional program is expected to comply with all USDA Food Guidelines (i.e., www.ChooseMyPlate.gov) related to portions of fruits, vegetables, grains, protein foods, dairy products, and oils. The program should be developed using participatory action research (PAR) design and also designed to address the very limited experience and skill level of direct service staff in group homes. This will require a comprehensive review and summary of available menu planning guidelines for group homes, an assessment of nutritional needs for group home residents relative to recommended activity levels, and piloting of a menu-driven system. PAR will be utilized by recruiting a small number (< 10) of group home administrators representing a range of resident demographics to provide active and informed feedback and guidance for each developmental step. Emphasis will be on commercialization of the menu planning system and viability in the current marketplace. Materials to implement the program should be conceptually and practically coordinated to cover menu and meal planning, shopping, and cooking, with a focus on effective environmental supports, processes, and procedures rather than staff training (due to large turnover) and should encourage increased resident engagement and participation in food systems, to include decision making and operations. Menus should not be rigid but flexible to reflect consumers' strong preferences, individual special dietary needs, food availability, grocery store sales, and the ethnic and cultural background of residents.

Impact: The market for this intervention is strong and the need unmet. States and private organizations are in need of cost effective straightforward nutritional interventions to control costs, improve nutrition, weight status and health of residents, and provide needed training to support to staff who have limited or no knowledge of good nutrition/dietary practices.

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

The mission of 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. The vision is all people living healthy lives free from the devastation of chronic diseases.

Strategic Priorities

Focus on Well-Being: Increase emphasis on promoting health and preventing risk factors, thereby reducing the onset of chronic health conditions.

Health Equity: Leverage program and policy activities, build partner capacities, and establish tailored interventions to help eliminate health disparities.

Research Translation: Accelerate the translation of scientific findings into community practice to protect the health of people where they live, work, learn, and play.

Policy Promotion: Promote social, environmental, policy, and systems approaches that support healthy living for individuals, families, and communities.

Workforce Development: Develop a skilled, diverse, and dynamic public health workforce and network of partners to promote health and prevent chronic disease at the national, state, and local levels.

NCCDPHP's Web site: <http://www.cdc.gov/chronicdisease/index.htm>

For this solicitation NCCDPHP invites Phase I proposals in the following areas:

034 Promoting Regular Physical Activity for Older Adults through “Wayfinding” Technology

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Walking is currently the most commonly reported form of physical activity among U.S. adults, yet walking can be challenging for older adults or people with functional limitations, especially in the face of environmental barriers or hazards. Route selection is potentially more complex for older adults because it necessitates taking into account many more factors, such as lack of street crossing aids, pathway quality, and availability of places to rest. Moreover, what is regarded as safe and accessible by one person may be viewed very differently by another because of variability in peoples’ functional capacities and preferences and tolerance for risk.

Currently, there are a growing number of mobile applications for phones, tablets and other special devices that are intended to promote walking, facilitate wayfinding or enable people to find destinations of interest. Most provide information about environmental factors that influence walking behavior and route decision-making, such as access to amenities, residential density, street connectivity, land use diversity, traffic safety and crime safety. Few, if any, current applications address issues critical for support mobility for older adults, such as falls risk, environmental barriers or hazards, or comfort and other amenities. Additionally, they often do not take into consideration cognitive decline or impairment that an older person may be experiencing.

Developing new uses for technology to provide environmental cues for older adults will likely increase their ability to remain engaged in physical activity longer, thereby enhancing their health and quality of life. According to the Administration on Aging, the number of adults aged 65 or older is expected to more than double to a projected 72 million by 2030. The implications for population aging in the marketplace are getting greater attention as the baby boom generation began turning age 65 in 2011. Already aging-related products have seen a tremendous increase in the marketplace, and transferability of such products benefits other populations with similar concerns, such as people with disabilities or traumatic brain injuries.

Project Goal: This project aims to support the development SmartPad and SmartPhone applications designed to assist with orientation and choosing a path within the built environment (i.e., wayfinding) for older adults to assist in navigating outdoors and promote physical activity.

Phase I Activities and Expected Deliverables:

- Obtain input from a small number of selected expert informants to identify and prioritize a comprehensive set of environmental factors that influence typical situational route decision-making;
- Conduct an environmental audit, using an existing audit tool that incorporates factors of importance to older adults. The audit tool should be found in published academic literature, or could be an audit tool that has been used and tested for relevance of factors of importance to older adults (if evidence of testing can be provided). The environmental audit may be conducted in a smaller geographic area, such as a neighborhood with a high concentration of adults aged 60 or older to adhere to the 6-month project period.
- Collect or identify existing GIS data for the same geographic area to be used in the prototype, described below.
- Develop a prototype of the application. As a minimum this would include a) integrating the environmental factors obtained from expert opinion and audit tool with other data fields to develop the database structure for a mobile application and 2) populate the database with GIS data for the location where the environmental audit took place.

- Propose a plan for developing backend capability to collect real-time data to customize preferences for individual users and to create an evidence base to inform policy and planning decisions about priorities for improving community accessibility; and to make the application usable and accessible by older adults in a larger geographic area.

035 Development of Pills or Tablets to Expedite Water Fluoridation

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: In order to achieve the HP2020 objective for community water fluoridation (79.6% of the population on public water supplies having access to fluoridated water), it will be necessary both to address persistent technical impediments to initiating community water fluoridation among the many small water systems that remain unfluoridated and to improve the consistency of fluoride concentration over time in these smaller systems. Both goals might be met by developing alternate methods for handling fluoride additives, to replace those that have been available for many decades. Through development of fluoride products in pill or tablet form that would use existing technology for water treatment, small water systems could implement community water fluoridation more easily and safely and maintain its quality more consistently.

Project Goal: Most other dry additives (particularly sodium hypochlorite) are now processed using new pill/tablet feeder equipment that reduces hazard exposure for personnel and proves simpler to operate at smaller water treatment facilities. Creation of a new fluoride product for the standard feeder system could extend water fluoridation to smaller communities that remain reluctant to utilize older legacy equipment, and better maintain quality among all small water systems that choose to fluoridate. Anecdotally, some smaller systems that add fluoride have expressed concerns about potential exposure of personnel to fluoride product dust during handling of granular crystalline salts. These salts also can be difficult to measure. Alternatively, some small systems use fluorosilicic acid, which is difficult to control accurately without appropriate instrumentation. Smaller systems often cannot afford more sophisticated instrumentation and thus their installations may have more limited safety features for operators. Simpler delivery using pill or tablet products would be consistent with equipment and appurtenances familiar to water system operators and would suit the technical capability of operators employed by small water systems, who often have less experience with more sophisticated equipment.

The market for this new product already exists. Of the 6,000 public water systems (PWS) currently adding fluoride, 4,000 are small systems (serving 15 million persons) that would likely want a pill/tablet feeder to replace their current equipment. Of the 40,000 PWS not fluoridating, 40 percent (16,000 PWS serving 24 million persons) would be candidates for fluoride addition if delivery via pill or tablet feeder proves feasible. A typical small system uses multiple wells, strongly suggesting that a meaningful market exists, since each well requires a feeder.

Phase I Activities and Expected Deliverables: Develop tablet/pill prototype for the adjustment of fluoride in drinking water to prevent tooth decay

- Prototype should achieve concentrations of fluoride in drinking water consistent with recommended concentrations and accepted operating tolerances
- Prototype should be appropriate, feasible, and of acceptable cost for use in smaller systems serving no more than 5000 customers
- Prototype should be furnished in one or two sizes
- Develop standard written protocol documenting materials, procedures, and equipment necessary to produce tablet/pill prototypes

036 Application for Improving Embryo Transfer Practices at Fertility Clinics

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: The United States has one of the highest rates of preterm birth in the world. Due to the transfer of multiple embryos during in vitro fertilization (IVF) procedures, assisted reproductive technology (ART) is one of the major contributors to multiple and preterm births, with ART accounting for 20% of all multiple-birth infants and 3.9% of all preterm infants in the U.S during 2009. While national clinical guidelines for embryo transfer practices exist, variations in clinic and physician practices as well as patient preference influence decisions about how many embryos are transferred. ART providers would benefit from an interactive tool for use during individualized counseling to advise patients on the recommended number of embryos to transfer during an ART cycle in order to get an optimal outcome: a healthy singleton live birth.

Project Goal: The goal of this project is the design and development of an application for tablets, smartphones, and desktop/laptop computers that will promote the goal of a healthy, singleton live birth by providing estimates of the likelihood of this outcome at a population level according to the number of embryos transferred during a given treatment cycle. Use of tablet, smartphone, and web-based technology has the potential to allow ART providers to harness current national data to facilitate individualized counseling to patients about the risks and effectiveness of ART based on certain maternal and treatment characteristics. The development of the application should include a plan for small-scale pilot testing, during which feedback will be solicited from ART providers, as well as evaluating the utility and effectiveness of the final application. The application should be interactive – allowing ART providers to enter patient-specific information in order to obtain individualized embryo transfer recommendations. The application should be designed so that patients or the general public could also use it outside of the clinical setting to estimate their chances of giving birth to a healthy child using ART, and to locate nearby ART clinics.

Phase I Activities and Expected Deliverables:

- Months 1-3
 - Activity: Design application prototype for iPad
 - Deliverable: Application prototype package
- Months 4-6
 - Activities:
 - Develop application for iPad
 - Draft protocol for small-scale pilot testing of iPad application
 - Deliverables:
 - Fully functioning, working prototype application for iPad
 - Final protocol for small-scale pilot

NATIONAL CENTER FOR EMERGING ZOOONOTIC AND INFECTIOUS DISEASES (NCEZID)

The mission of the National Center for Emerging and Zoonotic Infectious Diseases aims to prevent disease, disability, and death caused by a wide range of infectious diseases. NCEZID focuses on diseases that have been around for many years, emerging diseases (those that are new or just recently identified), and zoonotic diseases (those spread from animals to people). NCEZID's work is guided in part by a holistic "One Health" strategy, which recognizes the vital interconnectedness of microbes and the environment. Through a comprehensive approach involving many scientific disciplines, NCEZID can attain better health for humans and animals and improve our environment.

NCEZID's Web site: <http://www.cdc.gov/ncezid>

For this solicitation NCEZID invites Phase I proposals in the following areas:

006 Distinguishing Infection, Colonization, and Recurrence in Patients with *Clostridium difficile*

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: *Clostridium difficile* infection (CDI) results in excess of 14,000 deaths and over \$1 billion in excess healthcare costs annually. Major host defenses include the development of serum antibodies to toxins A and B in addition to an intact lower intestinal microbiome that is often disrupted by antibiotic use. Currently there are no serologic assays for *C. difficile* toxins A and B for either research or clinical use despite their utility for defining the epidemiology of CDI and selecting patients in whom to target future vaccines. Moreover, early and reliable diagnosis is key for both improving treatment outcomes and instituting precautions to prevent transmission. Nucleic acid amplification tests (NAAT) have improved detection of the organism in feces but cannot differentiate between infection and asymptomatic colonization that may occur in patients with diarrhea from other causes. In addition, recurrent CDI occurs in as many as 20% of patients and the ability to reliably predict which patients are at most risk for recurrence, as defined by a lack of early immunologic response to toxins A and B, could help direct use of newly available therapies that prevent recurrence (i.e. more expensive antibiotics, monoclonal antibodies, probiotics, intestinal microbiota transplantation).

Project Goal: To develop a research grade serologic assay to measure circulating IgG and IgA antibodies to *C. difficile* toxins A and B as well as a research grade diagnostic assay that can detect early and specific immunologic responses (i.e. newly proliferated plasma cells that secrete antibodies in the blood) to these toxins. Intended research use would be for determining who among a population: 1) is susceptible for primary infection (i.e. asymptomatic with low IgG/IgA levels to toxin A and B); 2) has diarrhea and a positive NAAT due to colonization only (i.e. low IgG/IgA levels, no newly proliferated plasma cells secreting antibody); 3) has diarrhea and a positive NAAT due to acute CDI that is unlikely to recur (i.e. low IgG/IgA levels but presence of newly proliferated plasma cells secreting antibody); and 4) has diarrhea and a positive NAAT due to acute CDI that is likely to recur (i.e. low IgG /IgA levels and no newly proliferated plasma cells secreting antibody).

Phase I Activities and Expected Deliverables:

1. Develop a quantitative or semi-quantitative serologic assay for IgG and/or circulating IgA, using either purified whole-toxin A and/or B *C. difficile* antigens or recombinant hybrid toxins (i.e. with demonstrated improved antigenicity).
2. Perform the quantitative serologic assay on 30-paired acute and convalescent sera from patients with clinical and laboratory documentation of incident (i.e. non-recurrent) CDI to set cutoffs for quantitative levels.

3. Develop an assay to interrogate *C. difficile* toxin A and/or B antibodies from newly proliferated, circulating antibody-secreting cells in the blood (e.g. circulating plasmablasts).
4. Perform interrogation of circulating antibody-secreting cells and trace quantitative IgG/IgA levels specific for *C. difficile* toxin A and/or B on serially collected samples, beginning on the day of CDI diagnosis and between daily and weekly until 12 weeks post infection, from at least 10 individual patients with acute, incident (i.e. non-recurrent) CDI, to trace the humeral immune responses of acute CDI.

Impact: It is anticipated that development of fully functional research grade diagnostics in this area would support a sustainable business model and also spawn further development into fully FDA-approved clinical assays.

007 Development of Reagents for Diagnosis of Fungal Infections in Formalin-fixed Paraffinized (FFPE) Tissue Blocks

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: The introduction of several antifungal drugs with varying mechanisms of action has resulted in an important need to detect and diagnose fungal infections at the genus and species level. However, the failure to suspect fungal infections has resulted in collection of diagnostic samples which are placed immediately into formalin rather than being submitted for fungal culture, thus preventing identification of the specific fungal agent. Direct recovery of fungal DNA from FFPE tissues is not always successful due to formalin-mediated destruction of DNA. Hence there is an increasing need for non-nucleic acid-based reagents that can identify specific fungal agents in FFPE tissues.

Project Goal: Immunohistochemistry reagents useful for the detection and identification of fungal agents in FFPE tissues are sought. A very small number of immunohistochemistry reagents have been described for *Aspergillus* and *Mucormycetes* and are available commercially, but many more reagents need to be developed. Particular categories of interest are reagents for detecting *Fusarium* and *Scedosporium* species, *Histoplasma*, and *Blastomyces*, as well as individual genus-specific *Mucormycete* reagents. Monoclonal antibody or other novel reagents for either immunohistochemistry or for in situ hybridization methods of testing are sought. Reagents should show sensitivity and specificity in detecting fungal agents at the genus and/or species level.

Impact: Development of rapid fungal diagnostics is a market that should be of particular interest to small business concerns. The number of humans and animals susceptible to fungal infection is increasing in the United States and globally. The number of patients who are suspected to have cancer or other diseases but who actually have fungal infections continues to increase. Public health authorities and clinical laboratories have either no alternative methods to fungus culture, or only indirect and inefficient methods for diagnosis of fungal infections at this time. Innovative approaches to develop rapid fungal diagnostics can be incorporated into clinical and histopathology practices in the future. Specific diagnosis and therapy of fungal infections will enhance public health by providing a mechanism to save lives through preventing death and serious disease.

008 Rapid Detection of Endemic Fungal Infections in the United States

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: The increase in prevalence of endemic fungal infections in the United States (coccidioidomycosis, blastomycosis, histoplasmosis) has resulted in an acute need for rapid tools to detect and diagnose these infections. The lack of specific symptoms has made it difficult to distinguish these infections from influenza, Lyme disease, or tuberculosis by clinical examination. The treatment with specific antifungal therapy has made it imperative that these fungal infections be rapidly distinguished from others with similar symptoms. Coccidioidomycosis is endemic in the Southwest US, while histoplasmosis and blastomycosis are endemic in the Midwest US. Because they are acquired by inhalation, these diseases can infect otherwise healthy individuals in these areas who do not have immunity.

Project Goal: Reagents and devices useful for the detection and diagnosis of the endemic fungal diseases are sought. Although some serologic and antigen tests have been described, rapid detection of these diseases is not available at this time. Reagents should show sensitivity and specificity in detecting these fungal agents. Novel reagents and devices such as lateral flow technology are of particular interest. Devices/systems for detection of these organisms in environmental samples are also sought. Demonstrate proof of concept with reagent/device

Impact: Development of rapid fungal diagnostics is a market that should be of particular interest to small business concerns. The number of humans and animals susceptible to endemic fungal infection continues to increase in the United States, as larger numbers of susceptible individuals continue to move into endemic regions. At this time the methods and tests available for diagnosis of fungal infections lack timeliness and the ability to make rapid and specific diagnosis, resulting in the implementation of inappropriate, ineffective and expensive treatment in many cases. Specific diagnosis and therapy of fungal infections will enhance public health by providing a mechanism to save lives through preventing death and serious disease.

009 Development of Anti-Japanese Encephalitis Virus Human Monoclonal Antibodies Using Humanized Rodent Models

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: The development of human monoclonal antibodies (hMAbs) that can be used in the prevention and treatment of Japanese encephalitis (JE) specifically aligns with CDC's strategic public health priorities by reducing the burden of disease caused by Japanese encephalitis virus (JEV), improving health security at home and around the world, and increasing the CDC's impact on global public health.

The geographic expansion of arboviruses causing human disease continues to be a global public health concern. In recent years, Japanese encephalitis virus (JEV) has expanded geographically into Pakistan, western Indonesia, Papua New Guinea and northern Australia. Like West Nile virus, JEV has the potential to become introduced and endemic in the United States causing widespread outbreaks of disease in unvaccinated populations. Japanese encephalitis (JE) is the most common viral encephalitis in South East Asia. According to the WHO, 50,000 cases of JE are reported annually, although this number may be inaccurate due to inadequate laboratory-based surveillance and reporting. Of the cases reported 25-30% result in death, while 50% result in permanent neurologic sequelae. Most of the cases occur in children under the age of 15 in rural areas. Unvaccinated travelers, expatriates and military personnel deployed overseas may also be at risk of infection with JEV.

HMAbs are a rapidly growing class of human therapeutics representing approximately 25% of drugs under development. Thirty-four therapeutic MAbs are predicted to be on the market for treating cancer, auto-immune, and infectious diseases by 2014. The use of hMAbs in prophylaxis and treatment of arboviral diseases like JE is

applicable for a number of reasons. While several vaccines are available and vaccination campaigns are successful in endemic countries, their use is often limited due to cost. Post-vaccinal adverse events have been reported, making it unsuitable for certain at-risk populations. Alternatives to traditional vaccines are needed and would complement prevention and treatment of JE.

Project Goal: There is a need to develop hMAbs for prophylactic and therapeutic treatment of JEV that can be administered during an outbreak to susceptible populations or given prophylactically to travelers and military personnel. The first objective of the project will be to determine an appropriate antigen and vaccination schedule to produce hMAbs in the humanized rodent model. The second objective will be to immortalize activated B cells and produce fully human anti-JEV MAbs. The final objective will be to test these hMAbs for their ability to neutralize virus in vitro and determine the best candidates for development as prophylactic or therapeutic hMAbs by in vivo testing in mice. Lastly, it will be important to determine if this technology can be utilized to produce hMAbs to other medically important arthropod-borne viruses like dengue viruses, yellow fever virus, chikungunya virus and Venezuelan equine encephalitis virus. At the end of this project, anti-JEV hMAbs that have the potential to be used as a therapeutic antibody will be identified. Further study such as testing in non-human primates and human clinical trials will need to be conducted in order for these hMAbs to lead to a marketable product.

Phase I Activities and Expected Deliverables:

1. Determine antigen/adjuvant and vaccination schedule in humanized rodent model to produce a high anti-JEV antibody response.
2. Vaccinate animals, isolate activated B cells to JEV antigen, and immortalize or engineer cell lines capable of constitutively expressing anti-JEV MAbs.

010 Formulation of Nootkatone in Soaps and Lotions for Lyme Disease Prevention

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Tick-borne Lyme disease spirochetes affect >30,000 people annually and is the number one reported vector-borne disease in the United States. The frontline method to combat tick-borne illness is the use of insect repellents effective against ticks, but the public is reluctant to use synthetic chemical repellents. Initial tests at CDC have indicated that the botanical product nootkatone is an effective repellent of ticks with activity comparable to DEET in the duration and efficacy of its repellent properties. The next step in the development of this natural product as an insect repellent is to design formulations that can be used as sprays, soaps, or lotions that will have extended repellency properties when applied to human skin.

Project Goal: The goal of this project is the formulation of lotions, soaps, and sprays designed to be a long acting repellent product containing 2.5 – 5% nootkatone. Initial tests by CDC have indicated that technical grade nootkatone is an effective repellent of ticks comparable to DEET in the duration and efficacy of its repellent properties. It is used in the flavor and fragrance industry and is considered “food grade” and therefore safe for human consumption and topical application. Consumer data suggest that safety concerns are among the central factors inhibiting use of currently available products. The next step in the development of this natural product as an insect repellent is to design formulations that can be used as sprays, soaps, or lotions that will have extended repellency properties when applied to human skin.

Phase I Activities and Expected Outcomes: A deliverable will be the development of all natural candidate soaps, lotions, and sprays containing nootkatone. Once candidate products are formulated they will be screened for repellent activity against nymphal deer ticks using approved laboratory bioassays as suggested by CDC scientists.

Sources of nootkatone will include plant derived extracts as well as novel yeast fermented product derived from natural precursor compounds that are less expensive than direct plant derived products.

Impact: The availability of novel botanically based repellent formulations that are perceived by the public as safe, effective, and pleasant to use are desperately needed in order to increase the proportion of the public mitigating their risk from tick-borne pathogens. In the field of Lyme disease in particular, a soap based repellent could interrupt the ability of infected ticks to attach to people and stay attached for the 48 hour period required to transmit the Lyme disease spirochete.

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

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

NCHHSTP Web site: <http://www.cdc.gov/nchhstp/>

For this solicitation NCHHSTP invites Phase I proposals in the following areas:

037 Development of a Rapid Test for detection hepatitis C core antigen in clinical samples.

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Hepatitis C is the most common chronic blood borne infection in the United States, affecting an estimated 4.1 million of Americans, of whom 3.2 million are living with the infection. Most persons are unaware of their infection status. It is estimated that 30% of HIV-infected individuals are also infected with hepatitis C virus (HCV) and 60-90% of individuals who were infected with HIV by injecting drugs are also infected with HCV. The majority (80%) of individuals with HCV infection develop chronic hepatitis and are at risk for substantial morbidity and mortality. HCV infection is the leading indication for liver transplantation in the United States. Identification of active infection is of particular importance given the continued HCV transmissions and availability of improved therapeutic options for HCV infected persons.

Recently, CDC recommended a one-time test for everyone born between 1945 and 1965 to help identify people who are not aware of their infection status. Then, CDC updated hepatitis C testing guidelines recommending identification of the HCV viremic state as indication of current HCV infection.

At present, there are two serological markers available in the United States for the laboratory diagnosis of HCV infection for which assays are approved by the FDA – HCV antibody by rapid or laboratory-conducted testing and HCV RNA by Nucleic Acid Testing (NAT). HCV RNA is the marker of current HCV infection. HCV antigens can also be markers of current HCV infection. Although an immunoassay for the detection of hepatitis C core antigen has been developed and is available for clinical use in Europe and Asia, it is not yet available in the United States. Furthermore, it requires to be conducted in a laboratory. Rapid test technologies have tremendously facilitated the speedy diagnosis of viral infections and have proven their mark in HIV and hepatitis B diagnostics. Rapid tests for detection of hepatitis B surface antigen are widely used for the diagnosis of current hepatitis B virus infection. Development of a rapid assay for HCV antigens with view to have it marketed for wider and more economical testing of HCV viremia is called for.

Project Goal: Develop, validate and market a rapid test for detection of hepatitis C core antigen for diagnosis of active HCV infection.

- Identify a panel of monoclonal antibodies that have the potential to detect HCV core antigen in clinical samples.
- Validate and develop a serological assay for detection of HCV core antigen.
- Validate the assay with small cohorts of retrospective human serum samples with high sensitivity and specificity.
- Validate the assay with large cohorts of retrospective human serum samples with high sensitivity and specificity.
- Establish and validate prototype for the diagnostic assay kit.
- New technology application for HCV diagnostics can lead to a marketable, scalable product for commercial and state and public health diagnostic laboratories.

Phase I Activities and Deliverables:

Technology Innovation:

- Deliverable: Design and develop a simple, rapid test for detection of HCV core antigen in serum/plasma from patients with acute and chronic HCV infection
- Activity: Identify a panel of monoclonal antibodies that have the potential to detect HCV core antigen
- Activity: Evaluate the assay using commercially available seroconversion panels

038 Development of a Laboratory Test for Detection of Serum Biomarkers Associated with Hepatocellular Carcinoma

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Hepatocellular carcinoma (HCC) is the third most lethal cancer worldwide and the ninth most lethal cancer in the United States. HCC is the fifth most common cancer in men and the seventh in women and it is diagnosed in more than half a million people worldwide, including approximately 20,000 new cases in the United States. HCC related to hepatitis C virus (HCV) infection has become the fastest-rising cause of cancer-related death in the United States. During the past two decades, the incidence of HCC in the United States has tripled, while the 5-year survival rate has remained below 12%. Currently, the diagnosis of HCC is primarily based on changes detected from contrast-enhanced imaging and histopathological assessment. These methods are costly, onerous, and may not be definitive until the disease has reached advanced stages, when remediation options become limited.

Laboratory-based assays in body fluids for early detection and staging of HCC have not been developed. Early diagnosis of HCC will have a significant impact on survival by implementation of effective treatment strategies, including hepatic resection, locoregional ablative therapy, and liver transplantation. The development of novel biomarkers in serum for HCC, proteomics, and other techniques may significantly improve noninvasive for early detection of HCC. For example detection of highly conserved segments of DNA/RNA/protein, with specific association to HCC in blood samples derived from HCC infected patients seems achievable.

Project Goal: Development of a laboratory test for detection of serum biomarkers associated with hepatocellular carcinoma.

- Identify a panel of biomarkers that have specific association with HCC – these may include all or some of the following markers - Glypican 3 (GPC3), Golgi membrane protein 1 (GP73), fucosylated kininogen (Fc-Kin), dickkopf WNT signaling pathway inhibitor 1 (DKK1) and Des-gamma carboxyprothrombin (DCP).
- Validate and develop a combination of serum biomarkers in a single assay for detection of HCC
- Design and develop a simple, non-invasive and cost-effective method to detect HCC using serum/plasma from infected patients.
- Validate the assay with small cohorts of retrospective human serum samples with high sensitivity and specificity.
- Validate the assay with large cohorts of retrospective human serum samples with high sensitivity and specificity.
- Establish and validate prototype for the diagnostic assay kit.
- New technology application for HCC diagnostics can lead to a marketable, scalable product for commercial and state and public health diagnostic laboratories.

Phase I Activities and Deliverables:

Technology Innovation -

- Deliverable: Design and develop a simple, non-invasive and cost-effective assay for detection of HCC in serum/plasma.
- Activity: Identify a panel of serum biomarkers associated with HCC. Determine the expression levels of Glypican 3 (GPC3), Golgi membrane protein 1 (GP73), fucosylated kininogen (Fc-Kin), dickkopf WNT signaling pathway inhibitor 1 (DKK1) and Des-gamma carboxyprothrombin (DCP) and compare these levels with appropriate normal controls.
- Activity: Develop appropriate experimental controls to check the expression of biomarkers in normal versus infected patient samples.
- Activity: Establish cut-off values and standardize the assay.

039 Text my EOB: The Innovative Delivery of Confidential Medical Information

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: The confidentiality of adolescents and young adults is often unintentionally violated through health insurance billing procedures. When patients insured under their parents' plans receive sensitive healthcare services, such as STD/HIV screening or contraception, explanation of benefit (EOB) forms are typically sent to their parents. This lack of confidentiality causes adolescents and young adults to avoid sensitive, necessary services. Furthermore, this issue has become more urgent and concerning due to provisions of the Affordable Care Act. One provision requires insurers to allow young adults up to age 26 to remain on their parents' insurance plans (implemented in 2010), and another requires that non-grandfathered private insurance plans cover USPSTF grade A and B recommendations (which include chlamydia, gonorrhea, and HIV screening for various populations) and HRSA Women's Preventive Service Guidelines (which include all FDA approved contraceptive methods) without copay or cost sharing to the patient. Thus, the number of individuals at risk of inadvertent disclosure, as well as the probability of a disclosure occurring due to increased utilization of sensitive preventive services, can be expected to increase. The avoidance of sensitive services due to parental notification, as well as the potential legal liability of insurers under HIPAA, would be eliminated if EOBs were instead sent directly to the young adult patient. Furthermore, this could feasibly occur through electronic means which are widely used and generally private for adolescents and young adults, such as text messaging.

Project Goal: The immediate goal of this project is to facilitate the development of platform for sending EOBs through text message, first by determining its feasibility and identifying means to facilitate this solution. Longer term (Phase II), as informed by the feasibility study, a platform for sending text message EOBs would be developed and evaluated. Ultimately, the goal of this project is to encourage best practices with regard to the communication of sensitive medical services, which should decrease morbidity related to insured dependents forgoing sensitive services.

During Phase I, a feasibility study for sending EOBs via text messaging or other mobile means is expected. This would involve a series of interviews or roundtable/focus group discussions with nine or fewer relevant stakeholders, including but not necessarily limited to insurance company representatives, providers, attorneys who specialize in healthcare privacy and confidentiality, and health information technology experts. Different questions would be asked of each group (e.g., gain a better understanding of how this solution would fit within current insurance company procedures and information technologies in use, how to ensure legal and regulatory compliance, the technological feasibility and/or necessary investment of the solution, and what would best facilitate the development and adoption of this solution, etc.). Phase I is not a data collection phase; rather, it is a critical first step to addressing this solution as the details of the solution must be informed by relevant stakeholders before development can begin.

Impact: Texting EOBs would facilitate efficiencies in the private healthcare insurance market and its potential for commercialization is high. Widespread changes in the way health insurance companies handle this situation seem increasingly likely in the near future. In the absence of a single solution from a third party outside of industry for adoption by health insurers, the prospect of industry-wide collaboration seems unlikely. Thus, resources would be wasted through duplication of effort and implementation of solutions may be delayed.

040 Development of a Mobile Application for Homeless Youth and Providers

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: An estimated 2.5 million youth ages 16-24 experience homelessness in the U.S. each year. Homeless youth are significantly affected by sexual health issues including Human Immunodeficiency Virus (HIV), sexually transmitted infections (STI), and teen pregnancy. Homeless youth are at higher risk for contracting HIV, HIV-related diseases, and other STDs; and many are pregnant or become pregnant. LGBT (Lesbian, gay, bisexual, and transgender) youth are overrepresented in the homeless population and are at an increased risk for physical and sexual exploitation. Moreover, homeless youth have unmet physical health and mental health needs. To reach homeless youth and provide appropriate services, targeted interventions need to address gaps in basic needs, access to healthcare, and instill attitudes and beliefs that are consistent with HIV/STI/pregnancy prevention. Healthcare providers, in turn, need to be prepared to provide care for homeless (LGBT) youth and link them to appropriate services and care. Finally, there is increasing recognition of the role of health systems in STD/HIV screening and treatment (i.e., the need to better integrate STD/HIV prevention and care into primary care and the broader health system).

Studies have shown that 62% of homeless youth have cell phones or mobile devices. Because these youth move frequently, their cell phones are often their main connection to people and resources. Recently, the Veterans Administration (VA) began piloting locality-based mobile applications “apps” on cell phones for homeless individuals to link them with resources and care including healthcare, and food and employment services. Based on positive findings from the pilot, the VA is now supporting development of a linked mobile app with resources for homeless persons and the caregivers and case workers who serve them. Recent research indicates over 81% of physicians use tablets or smart phones with mobile apps and 30% of physicians access medical information using a mobile device. Many healthcare providers are already using mobile apps to help them provide care to specific

populations. Studies suggests these apps can improve decision making; provide diagnostic capabilities; decrease medical errors; and facilitate learning of new skills for practicing providers, as well as students.

The proposed project is to develop an interconnected, dual-purpose mobile application for homeless and unstably housed youth, and their providers. This is a marketable, scalable, innovative, modifiable, technology-based project to design a mobile app, built in way that can be easily expanded and populated with local resources. To meet the needs of youth, the app will: 1) link homeless and unstably housed youth to local health related resources including sexual health care, mental health services, family planning/condoms, general health services and other services such as food, housing and work force training; and 2) increase health promotion and disease prevention knowledge and awareness (to include HIV, STI and pregnancy prevention and other lifestyle information, as appropriate) To meet the needs of providers, the app will: 1) assist healthcare providers in identifying and linking homeless and unstably housed youth to local resources and referrals; and 2) promote the provision of integrated, holistic health services by offering tools (e.g., guide to sexual history taking) and resources (e.g., how to integrate STI/HIV/pregnancy screening and care into primary care practices).

Project Goal: Develop a mobile app with two distinct, but interconnected modules: Module I for homeless and unstably housed youth, and Module II for providers. Module I will deliver prevention information for youth, with particular relevance to homeless/unstably housed youth and LGBT homeless youth; and link these youth to sexual health services and other health/social services in relation to their location. Module II will provide resources, tools, and guidance and referral suggestions for healthcare providers serving homeless youth.

- Create an innovative, useful mobile app product with the potential for commercialization and scalability that has demonstrated ability to improve healthcare access and provision of care.
- Evaluate the mobile app based on feasibility, acceptability, ease-of-use and impact on uptake of care and healthcare provision and make recommendations for related technology projects in the future.
- Strengthen the integration of public health approaches within primary care and broader health systems.

Phase I Activities and Expected Deliverables:

1. Activity: Use existing mobile apps, research, and resources, to inform the app's appearance, content and resources to enhance its relevance, appeal and appropriateness for homeless/unstably housed youth and their providers. Review health services research, particularly around primary care management and social services to explore ways the app could help strengthen the integration of public health/STI/HIV/teen pregnancy services into primary care.
2. Activity: Develop and input content for youth, particularly content relevant to homeless youth, including critical HIV/STI/pregnancy prevention information and nearby health care and social services; and for providers including up-to-date information on providing care to youth, both homeless and LGBT youth; and integrating public health into practice and making referrals etc.
3. Activity: Explore ways to link Module I and II so that resources can remain up to date and service providers can best serve youth. Develop a way for each population (youth or providers) to see only their respective module when using the app.
4. Activity: Consider piloting the initial versions of the app with members of the target audience in a nearby area to gauge their experience with services, as well as their impressions of the app, to improve the design.
5. Deliverable (pilot mobile app): Develop a proof of concept mobile app for homeless youth, homeless LGBT youth and providers for use on a variety of mobile devices and platforms (smart phones; tablets; computers; gaming systems etc.) Equip the mobile app with the ability for youth to track, record and rate use of services and their locations to help healthcare settings reach homeless youth with reminders, and/or keep track of them in the system, and improve their service offerings. Consider a youth "check-in" feature to gauge mobility patterns to better provide services/mobile services.

041 Leveraging Technology to Prevent STIs Using High-Intensity Behavioral Counseling

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Since 2008, the U.S. Preventive Services Task Force has recommended high-intensity behavioral counseling (HIBC) for adolescents and adults at high-risk for STIs. Rigorously controlled studies and meta-analysis of interventions suggest that high-risk adolescents and adults benefit from HIBC, with outcomes including increased patient condom use and significant reduction in new STIs (e.g., chlamydia, gonorrhea, syphilis, and HIV) at both 6 and 12 months post-intervention.

However, to date, there have been significant barriers to the delivery of HIBC due to a lack of clarity on session content and appropriate duration. Moreover, the field lacks a way in which to successfully integrate HIBC into time-restricted provider visits and ways in which to confirm that HIBC is sustainable and universally-assured for those patients for whom HIBC is indicated.

Most recently, the Affordable Care Act (ACA) has offered cost coverage of HIBC for high-risk adolescents and adults in primary care settings. The Centers for Medicare and Medicaid Services (CMS) stipulates that it will reimburse up to two 20-30 minute sessions delivered by clinical staff in a primary care setting. Although this eliminates much of the financial burden of providing HIBC, successful integration into a pre-existing primary care system remains an impediment to care. Given ACA requirements and USPSTF recommendations, the timing is critical to (1) delineate an evidence-based and effective HIBC intervention which meets the new standards of reimbursement and care and (2) design a sustainable technological platform that can be integrated into an existing health care electronic management system to facilitate HIBC content delivery.

Project Goal: Develop a technology application and platform for provider delivery that can be transportable and flexible to accommodate the pre-existing technology in primary care offices

- Evaluate the new technology application for ease of use and acceptability for providers and facility of integration into existing health care electronic management system
- Use technology application to deliver CDC-developed HIBC module for primary care settings. For the trial, patient effectiveness measurement on key STI outcomes will also be included.
- Produce recommendations for future technology application use and integration into primary care offices beyond HIBC
- Further strengthen the relation between public health and health care settings in order to reduce STI risk behaviors and negative health outcomes
- New technology application for primary health care interventions can lead to a marketable, scalable product for health care offices that has the ability to facilitate evidence-based practice

Phase I Activities and Deliverables:

Technology Innovation -

- Deliverable: Develop a technology application and platform that can be transportable and flexible to be used with a variety of devices (smartphone, tablet, laptop, etc.) in order to meet (1) the diverse needs of primary care doctors and (2) accommodate the pre-existing technology in primary care offices
- Activity: Input and integrate content into the newly developed application that will incorporate (1) the new CDC-developed HIBC intervention, (2) baseline and follow-up sexual risk surveys to patients, (3) key STI

patient outcomes in follow-up survey and (4) feasibility and tool satisfaction for clinicians into follow-up survey in order to ensure the application is useful and meaningful for providers amidst a changing health care climate

- Activity: Explore Meaningful Use (MU) incentive program to introduce newly developed application into diverse yet interoperable Health IT and EMR platforms

042 Assessing the Feasibility of e-measure Adoption in an EHR Environment

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: It has become quite clear that required data elements should be available in electronic health records (EHRs) or other electronic sources connected to an EHR, to be imported on demand for quality related e-measures calculations (e-measures are clinical quality measures designed to be generated automatically from EHRs); the Centers for Medicare and Medicaid Services (CMS) have published [guidance](#) for e-measures)

The promise of EHRs as a tool for quality reporting will rest on the ability of providers, payers, public health agencies, vendors and patients to know that e-measures provide valid and reliable data, which would in turn be based on the quality of the data being input into the rules engines. The National Quality Forum (NQF) has endorsed Chlamydia Screening in Women as an e-measure. This represents an opportunity to test the readiness of an EHR system to provide relevant data input for the e-measure-related computations. However, a lot of work is needed to assess the feasibility of e-measure adoption in an Electronic Health Record (EHR) environment. Widespread EHR data are not yet available for measure development and testing. There is a lack of comparability across vendor products and data elements needed for advanced measures currently may not be available. However, NQF-endorsed e-measures, with a relatively simple burden of calculation, such as the chlamydia screening measure, have a better chance to succeed.

Project Goal: The goal of this project is to foster the development of an application or other tool that can gather the required data elements from a broad variety of EHR systems needed to report the chlamydia e-measure. The application or tool should do this with little or no customization required across EHR platforms to improve acceptability among end-users.

During Phase I, the awardee(s) will conduct a feasibility assessment and construct a prototype chlamydia e-measure that will work with at least one EHR system. The e-measure will conform to HEDIS specifications for both numerator and denominator. The deliverables will include the feasibility assessment and prototype e-measure.

Impact: Demonstration that the data collection strategy (e.g., source, timing, frequency, sampling, patient confidentiality) can be implemented will be a key ingredient in making a case for widespread adoption of the relevant e-measure.

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

The mission of the National Center for Immunization and Respiratory Diseases (NCIRD) is the prevention of disease, disability, and death through immunization and by control of respiratory and related diseases. Our challenge is to effectively balance our efforts in the domestic and global arenas as well as accommodate the specific needs of all populations at risk of vaccine preventable diseases from children to older adults.

NCIRD Web site: <http://www.cdc.gov/ncird/>

For this solicitation NCIRD invites Phase I proposals in the following areas:

027 Thermostable Dry Vaccine Formulation for Microneedle Administration

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 2

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Vaccines are one of the most powerful tools available for preventing disease. However, the logistic difficulties inherent in vaccination by injection create barriers to high vaccine coverage. Vaccination by injection requires highly skilled vaccinators, maintenance of an expensive cold-chain, vaccine reconstitution with risks of contamination and bio-waste disposal of millions of syringes and needles to prevent reuse or injuries. Microneedle vaccine delivery would lower these barriers and provide the benefits of vaccination to many more people.

Project Goal: Develop and test a prototype thermostable microneedle vaccine formulation.

Phase I Activities and Expected Deliverables -

- Development of a thermostable vaccine formulation.
- Process thermostable vaccine into microneedle format which has no residual sharps.
- Assess thermostability of vaccine microneedle at 37 C over 6 months.
- Test microneedle vaccine delivery in small animal model.

Impact: A thermostable microneedle measles vaccine would lower barriers to vaccination, especially in the developing world, by reducing the skill level required to vaccinate, eliminating cold chain requirements and the risks associated with reconstitution and injection. Dry microneedle vaccine would reduce shipping costs, cold chain costs and the direct cost of syringe and needles as well as many hidden costs (costs of vaccinator training, sharps disposal, disease from needle reuse or injury).

028 Development of Anti-diphtheria Antibodies for Use in Humans

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: Despite the availability of an effective vaccine against diphtheria, the disease continues to be endemic particularly in developing countries. Large outbreaks were reported in the past few years in countries having inadequate diphtheria vaccine coverage. With the increase in global travel and the occurrence of outbreaks, the existence of diphtheria anywhere in the world represents a threat to susceptible persons (unimmunized persons and those with low levels of immunity) in the United States and other developed countries. The mortality rate from disease is about 10% (even with the best treatment available) but can exceed 25% during outbreaks. Specific treatment for diphtheria is early administration of diphtheria antitoxin to prevent life-threatening complications. This drug is an equine product and is no longer manufactured in developed countries. Currently, there are very few known manufacturers/suppliers of diphtheria antitoxin (India, Croatia, and Brazil) and production is limited globally. In the USA, imported diphtheria antitoxin is made available to healthcare providers under an FDA-

approved Investigational New Drug (IND) protocol that is managed by the Centers for Disease Control and Prevention (CDC). Hypersensitivity reactions occur in about 20% of persons who receive equine diphtheria antitoxin.

Monoclonal antibody technology is used successfully to produce antibodies against other toxins such as botulinum and tetanus, and is widely used in treating human disease. The development of human monoclonal antibodies against diphtheria could offer a commercially viable alternative to equine antitoxin for treatment of human diphtheria with a number of potential advantages including higher potency per unit dose, a greater margin of safety, and a sustainable supply.

Project Goal: To produce a prototype diphtheria antitoxin using a human monoclonal antibody or equivalent approach, with a path to IND or licensure.

Phase I: Establish a proof of concept and an appropriate system for production of a monoclonal diphtheria antitoxin or comparable product. Demonstrate in vitro potency of neutralizing antibodies against diphtheria toxin.

Impact: The issues highlighted in the Background section stress the importance of having an uninterrupted supply of specific diphtheria antitoxin available for patient management, both in industrialized and developing countries.

OFFICE OF PUBLIC HEALTH PREPAREDNESS AND RESPONSE (OPHPR)

The Office of Public Health Preparedness and Response (OPHPR)'s mission is to strengthen and support the nations' health security to save lives and protect against public health threats. OPHPR has primary oversight and responsibility for all programs that comprise CDC's public health preparedness and response portfolio. Through an all-hazards approach to preparedness-focusing on threats from natural, biological, chemical, nuclear, and radiological events-OPHPR helps the nation prepare for and respond to urgent threats to the public's health. PHPR carries out its mission by emphasizing accountability through performance, progress through public health science, and collaboration through partnerships.

OPHPR's Web site link: <http://www.cdc.gov/phpr/about.htm>

For this solicitation OPHPR invites Phase I proposals in the following area:

003 "Plug and Play" Global Health Security Initiative (GHSI) Response Tool

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

It is strongly suggested that proposals adhere to the above budget amounts and project periods. Proposals with budgets exceeding the above amounts and project periods may not be funded.

Background: There are a variety of commercial software products that support Incident Management System (IMS) general staff sections (logistics, plans, operations, situation awareness (SA), joint information center (JIC)) for use by emergency operations centers (EOCs) regardless of their focus (e.g., fire or law enforcement). However, there are none that address the specific organizational requirements of those essential public health roles, responsibilities, and functions needed to respond to an emergency public health event. Because public health response is organized to address specific public health requirements of the disease outbreak or emergency incident, specific software based on the IMS is needed to organize and support response functions in such areas as epidemiology, surveillance, medical countermeasures, and community health across a variety of public health response scenarios.

This effort is to support the GHSI and target the needs of international partners' Ministries of Health with under-resourced IT capability. In addition to the public health functions, the deliverable would maximize the utilization of

existing Commercial Off the Shelf (COTS) software and provide standard general staff EOC functionality and capability, including task tracking, virtual operations, section breakout, data integration, meeting scheduling, and staff rhythm with sufficient capacity to handle numerous multidisciplinary staff members in distributed locations. Interoperability with other information and public health surveillance systems is also a deliverable requirement. The plug and play requirement is essential as there will be very limited IT support for end-users and an adaptive, expandable, user-friendly, menu-driven, COTS-based software platform for public health EOC response is the goal. In addition to English, the final deliverable would have versions in two other official UN languages: Arabic and Spanish.

Project Goal: A plug and play software tool that supports emergency response management and integrates standardized response concepts as part of the general staff IMS with those specific to public health incident functional designs and requirements would significantly facilitate the global acceptance and success of the response portion of GHSI.

Activities

1. Kickoff meeting and one follow-up meeting with the SBIR awardee to discuss the specific statement of work and proposed times lines to meet Phase 1 Deliverable
2. Monthly progress report meetings to monitor progress or work issues and problems.

Deliverable: Phase 1 prototype integrated COTS tool

004 Improved Rapid Antimicrobial Susceptibility Testing from Primary Specimens

(Fast-Track proposals will not be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: \$150,000 for 6 months

Background: The effect of antimicrobial resistance (AMR) continues to be a major public health threat. The World Health Organization estimates there are around 440,000 new multi-drug resistant tuberculosis cases per year that cause an estimated 150,000 fatalities. Additionally, new resistance mechanisms continue to be discovered such the beta-lactamase NDM-1 demonstrating the continued need for advanced diagnostics for rapid AMR detection. The ability to rapidly determine AMR in infectious agents may lead to a reduction in AMR seen in foodborne and healthcare associated infections. Additionally, rapid AMR testing could save thousands of lives by informing which antimicrobials should be deployed from the Strategic National Stockpile during a large scale bioterrorism event.

The extensive use of antimicrobial compounds has resulted in the emergence of some nearly pan-resistant strains of pathogens. Much of this antimicrobial use is inappropriate. For example, in the healthcare setting it is estimated that nearly 50% of antimicrobials are used improperly. One of the barriers to improving the proper use of antimicrobials is the lack of diagnostic tests for rapid and accurate detection of antimicrobial susceptibility for pathogens causing infection. Rapid diagnostics to detect antimicrobial susceptibility are also critical during bioterrorism events where exposed individuals may be given antimicrobials to prevent disease. Traditional techniques require obtaining a pure culture isolate from a clinical or environmental specimen and growing the organism in the presence of antibiotics to assess growth inhibition. Since these methods take up to 36 hours to perform (or longer for fastidious organism), patients must begin treatment or prophylaxis before knowing whether the antimicrobial drug is effective in treating the infection. Physicians and public health officials need access to rapid antimicrobial susceptibility assays that guide appropriate treatment decisions to minimize the risks associated with inappropriate or ineffective antimicrobial use. Unfortunately, AMR mechanisms are diverse and complex (i.e., multiple mechanisms may exist in one isolate) creating significant challenges in developing rapid antimicrobial tests.

Project Goal: The development/improvement of culture-independent, rapid diagnostic methods/technologies that are able to (a) accurately detect clinically relevant resistance of pathogens to the available antimicrobial agents

within 8 hours or less (inclusive of specimen processing time) (b) reliably assign the resistance to the specific pathogen causing the patient's infection, and (c) predict whether presence of the mechanism(s) correlates with clinical resistance within 8 hours or less (inclusive of specimen processing time) to inform treatment and post exposure prophylaxis.

Phase I Activities and Expected Deliverables: Development of rapid, culture-independent methods/technologies that can detect phenotypic resistance or susceptibility to ciprofloxacin, doxycycline, penicillin, gentamicin, and/or ceftazidime in agents of bioterrorism such as *Bacillus anthracis*, *Francisella tularensis*, and *Yersinia pestis*, *Burkholderia mallei* and *Burkholderia pseudomallei*, *Brucella* spp., and *Coxiella burnetii*.

Of particular interest will be 1) rapid, culture-independent methods/technologies that can detect phenotypic resistance or susceptibility to antimicrobials in both microorganisms routinely found in clinical specimens such as, *Acinetobacter* spp, *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, Group B *Streptococcus*, *Escherichia coli*, *Salmonella*, *Shigella*, *Neisseria gonorrhoeae*, *Staphylococcus aureus*, *Clostridium difficile*, and in microorganisms that have the potential for use as agents of bioterrorism (see previous list); and 2) Rapid antimicrobial susceptibility tests that use methods, technology, and equipment that are not pathogen specific (e.g., mass spectrometry, enzymatic assays), but can assess antimicrobial susceptibility in a variety of pathogens.

13 APPENDICIES

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf>)

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.docx>)

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

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf>)

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf>)

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf>)

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf>)

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

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf>)

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

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

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