

**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 2015-1 - Amendment 1

Closing Date: November 5, 2014, 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 5, 2014, 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.

This solicitation is for Phase I, and in some cases, FAST TRACK and/or Direct Phase II proposals only. Some NIH Components utilize a 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. Some NIH Components utilize a mechanism called Direct to Phase II which allows for the submission of a Phase II proposal where the small business has performed the Phase I stage-type of research through other funding sources. FAST TRACK AND DIRECT TO PHASE II PROPOSALS WILL ONLY BE SUBMITTED UNDER THE FOLLOWING TOPICS AND ALL OTHER PHASE II PROPOSALS WILL NOT BE CONSIDERED.

TOPIC NUMBER	FAST TRACK ALLOWED?	DIRECT TO PHASE II ALLOWED?	TOPIC TITLE
NCI 334	Yes	No	Vacutubes to Preserve the Viability of Circulating Tumor Cells
NCI 335	Yes	No	Development of Advanced Culture Systems for Expansion of Cancer Stem Cells
NCI 336	Yes	No	Development of Novel Therapeutic Agents That Target Cancer Stem Cells
NCI 337	Yes	No	Cell-Free Nucleic Acid-Based Assay Development for Cancer Diagnosis
NCI 338	Yes	No	Predictive Biomarkers of Adverse Reactions to Radiation Treatment
NCI 339	Yes	No	Systemic Targeted Radionuclide Therapy For Cancer Treatment
NCI 340	No	Yes	Validation of Mobile Technologies for Clinical Assessment, Monitoring, and Intervention
NHLBI 087	Yes	Yes	Transcatheter Cerclage Mitral Annuloplasty (SBIR-TT)
NHLBI 088	Yes	Yes	Closure Devices for Transcaval Access to the Abdominal Aorta
NHLBI 089	Yes	Yes	In-bore Defibrillation for Invasive MRI Cardiology Procedures
NHLBI 090	Yes	No	Devices to Close Ductus Arteriosus in Premature Infants
NHLBI 092	Yes	Yes	Selective Silencing of Stat3 Signaling to Treat Relapsed Disease After Transplantation
NHLBI 093	Yes	Yes	Cellular Immunotherapy After Stem Cell Transplantation
NIAID 030	Yes	No	Methods of Clinical Sample Preparation for Rapid Detection of Bacterial Pathogens

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 research or research and development (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 February 24, 2014. 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, 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 Section 12.0 for specific award amounts / periods of performance per Topic Number)

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.)

Direct to Phase II (NIH COMPONENTS ONLY) (See Section 12.0 for specific award amounts / periods of performance per Topic Number)

The SBIR/STTR Programs were recently reauthorized by the United States Congress with the SBIR/STTR Reauthorization Act of 2011 (P.L. 112-81). One change that was made to the SBIR program in this reauthorization was the authority for certain participating federal agencies to issue a Phase II award to a small business concern that did not receive a Phase I award for that research/research & development through FY 2017. This is a so-called ‘Direct to Phase II’ SBIR award. This authority would permit SBCs to submit Direct to Phase II SBIR proposals, if the small business had performed the Phase I stage-type of research through other funding sources. The legislative rationale for permitting the Direct to Phase II award is to allow a SBC that has already built a technology prototype and tested its feasibility (i.e. completed Phase I type R&D) to move directly into a Phase II type R&D that tests the functional viability of the prototype according to scientific methods and

potential for commercial development. The Direct to Phase II SBIR mechanism eliminates the need for the SBCs to propose additional small feasibility studies, if the technology is ready for the Phase II stage of development. This pilot is applicable only to NIH and only if an awarding component indicates it is accepting Direct to Phase II 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 grant 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 Jennifer Shieh, Ph.D., at 301-443-8785 or jennifer.shieh@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 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 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)

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.

Direct to Phase II. A new pilot authority under P.L. 112-81 that allows NIH to issue a Phase II award to a small business concern that did not receive a Phase I award for that research/research & development, if the small business had performed the Phase I stage-type of research through other funding sources (non SBIR/STTR). Certain NIH topics will allow Direct to Phase II SBIR proposals in this solicitation.

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.

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 [FAR 19.307](#).

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 small 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 (for agencies electing to use the authority in 15 U.S.C. 638(dd)(1)); 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 (a)(1)(ii) of this section must comply with § 121.705(b) concerning registration and proposal requirements

- (2) No single venture capital operating company, hedge fund, or private equity firm may own more than 50% of the concern.
- (3) If an Employee Stock Ownership Plan owns all or part of the concern, each stock trustee and plan member is considered an owner.
- (4) If a trust owns all or part of the concern, each trustee and trust beneficiary is considered an owner.

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

Small Disadvantaged Business (SDB). See [13 CFR part 124](#), Subpart B.

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

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.

DHHS 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 trials, or

- (d) development of new technologies.
- (2) Epidemiologic and behavioral studies.
- (3) Outcomes research and health services research. Note: Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

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

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

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

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

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

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial.* For the purpose of the Guidelines an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or 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. 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.*

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.

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

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)).

Investigational Device Exemption (IDE). An IDE is a regulatory submission that permits clinical investigation of devices. This investigation is exempt from some regulatory requirements. The term “IDE” stems from the description in 21Code of Federal Regulations (CFR) 812.1.

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 Vertebrate Animals

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 or Synthetic Nucleic Acid Molecules. Any recipient performing research involving recombinant or synthetic nucleic acid molecules and/or organisms and viruses containing recombinant or synthetic nucleic acid molecules shall comply with the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, dated November 2013 as amended. The guidelines can be found at:

http://oba.od.nih.gov/rdna/nih_guidelines_oba.html. Recombinant or synthetic nucleic acid molecules are defined as:

- (i) molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell, i.e., recombinant nucleic acids
- (ii) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids; or,
- (iii) molecules that result from the replication of those described in (i) or (ii) above.

Sex/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 sex/gender composition cannot be accurately determined (e.g. pooled blood samples or stored specimens without sex/gender designation). In addition, sex/gender classification is based on the self-reporting of participants enrolled in the research study. Investigators should consider the scientific goals of their study when requesting this information, particularly if the research may include individuals whose gender identity differs from their sex assigned at birth.

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 a small business concern (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 total contract costs. 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 (VCOC), hedge funds, or private equity firms (e.g. majority VCOC-owned) **are required** to submit a “SBIR Application VCOC Certification” at time of their application submission per the [SBIR Policy Directive](#). Follow the instructions below.

1. Download the “SBIR Application VCOC 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 VCOC 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 VCOC-owned) should **NOT** fill out the SBIR Application VCOC 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 **eligible to submit proposals for opportunities under this solicitation to the Centers for Disease Control and Prevention 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 (VCOC), hedge funds, or private equity firms (e.g. majority VCOC-owned) **are required** to submit a “SBIR Application VCOC Certification” at time of their application submission per the SBIR Policy Directive. Follow the instructions below.

1. Download the “SBIR Application VCOC 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 VCOC 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 VCOC-owned) should **NOT** fill out the SBIR Application VCOC Certification and should **NOT** attach it their application package.

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 (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), 1101 Wootton Parkway, Suite 200, Rockville, MD 20852. 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 (see section 3.2 above).
- 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 the Office of Extramural Programs (OEP).
- 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 Vertebrate Animals

The following notice is applicable when contract performance is expected to involve 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 (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 or Synthetic Nucleic Acid Molecules

Recombinant or synthetic nucleic acid molecules are either (i) molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell, i.e., recombinant nucleic acids; (ii) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids; or, (iii) molecules that result from the replication of those described in (i) or (ii) above. All research involving recombinant or synthetic nucleic acid molecules that is conducted at or sponsored by an entity that receives any support for recombinant or synthetic nucleic acid molecules research from NIH shall be conducted in accordance with the [or Synthetic Nucleic Acid Molecules \(NIH Guidelines\)](#). The

NIH Guidelines stipulate biosafety and containment measures for recombinant or synthetic nucleic acid molecules 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 or synthetic nucleic acid molecules 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 or synthetic nucleic acid molecules research or a requirement for Contracting Officer prior approval of any or all recombinant or synthetic nucleic acid molecules 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. 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 are anticipated for 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/Direct to Phase II Award Information

- a. **Number of Phase II (as part of FAST TRACK and including Direct to Phase II) Awards.** The number of Phase II awards will depend upon the results of the Phase I (or Phase I-like) efforts and the availability of funds.

- b. **Type of Funding Agreement.** Each Phase II proposal selected for award will be funded under negotiated contracts. Phase II contracts may be either firm fixed price or a cost type and will include a reasonable fee or profit consistent with federal and HHS acquisition regulations and policies regarding 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.

SBA Company Registry

All applicants to the SBIR and STTR programs are required to register at the SBA Company Registry 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, 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.

Funding Agreement Certification & 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.

A Funding Agreement Certification is required at the time of award and may also be required at any other time that has been identified and incorporated into the contract delivery schedule.

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 8.8 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 System for Award Management before the award of a contract. Offerors must access (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 under Phase II 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 clauses required by the Federal Acquisition Regulation that will be included in the Phase I contract. This is not a complete list of clauses 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 clauses below, additional clauses will be required. Copies of complete general clauses 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 certain classes of employees 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. 289(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." **Effective January 17, 2014, the Salary Limitation is for Executive Level II of the Federal Executive Pay Scale is \$181,500.**
- 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.
- x. **Gun Control.** The Contractor shall not use contract funds in whole or in part, to advocate or promote gun control.
- y. **Restriction on Pornography on Computer Networks.** The Contractor shall not use contract funds to maintain or establish a computer network unless such network blocks the viewing, downloading, and exchanging of pornography.

5.2 Special Contract Requirements

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

Each 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. Reviewers will 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 http://grants.nih.gov/grants/funding/women_min/women_min.htm
- Inclusion of Children <https://grants.nih.gov/grants/funding/children/children.htm>
- 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 protection and inclusion 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
1. The soundness and technical merit of the proposed approach based on:	40%

FACTORS FOR PHASE I PROPOSALS	WEIGHT
<ul style="list-style-type: none"> a. The identification of clear measurable goals (milestones) that have a reasonable chance of meeting the topic objective in Phase I; and, b. The approach is innovative and not routine, c. The 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, supporting staff and consultants.</p> <p>The leadership approach (including the designated roles and responsibilities, governance, and organizational structure) being 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 in 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/Phase II (NIH ONLY) & Direct to Phase II (NIH ONLY) Technical Evaluation Criteria

FACTORS FOR PHASE II PROPOSALS	WEIGHT
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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. The identification of clear, measureable goals (milestones) that have a reasonable chance of meeting the topic objective in Phase II; b. The approach being innovative and not routine, c. The Offeror's ability to implement technical approach, i.e., has or can obtain the resources (facilities, personnel and equipment) suitable to the task. d. NIH Direct to Phase II only: How well did the Offeror demonstrate feasibility of the methodology or technology equivalent to meeting Phase I-level objectives, providing a solid foundation for the proposed Phase II activity? 	30%
<p>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.</p>	30%
<p>3. The qualifications of the proposed PDs/Pis, supporting staff and consultants.</p> <p>The leadership approach (including the designated roles and responsibilities, governance, and organizational structure) being consistent with and justified by the aims of the project and expertise of each of the PDs/Pis.</p>	25%
<p>4. The adequacy and suitability of the facilities and research environment.</p>	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);
4. Availability of funds, and.
5. Cost/Price

The government anticipates that prospective offerors will develop unique proposals in response to the topics of research set forth in this solicitation. 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. SBIR contract projects do not require establishing a competitive range but an order of merit ranking and cost analysis is performed before reaching source selection decisions.

7 PROPOSAL SUBMISSION

7.1 Questions

Offerors with questions regarding this solicitation must submit them in to the Contracting Officer point of contact identified below in Section 10 in sufficient time for receipt no later than **SEPTEMBER 19, 2014**. The Government may issue an amendment to this solicitation including responses to submitted questions. The Government anticipates that responses would be published in sufficient time for interested offerors to consider them prior to submission of a proposal.

7.2 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 considered or evaluated.

7.3 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 an award is made under the research topic for which the proposal was submitted, 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 will 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 will only be returned at the offeror's request and expense.
- (f) The contracting officer shall promptly notify any offeror if its proposal, modification, or revision was received late, and shall 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 shall 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.

7.4 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 use of Vertebrate Animals if your project will encompass 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) CDs. 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, and for topics specifically designated at Direct to Phase II, Phase II proposals may only be submitted by Phase I awardees. Submission of Direct to Phase II proposals is allowed for designated topics. Submission of regular or standard Phase II proposals are not permitted at this time and, if submitted, will be rejected without evaluation. Regular or standard 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 and Direct to Phase II Proposal Instructions (NIH Only)

A complete Phase II as part of a FAST TRACK or Direct to Phase II 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 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 1)

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 or Direct to Phase II 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 or Direct to Phase II 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 1)

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 1)

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/CDC. 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 SUBJECTS OR VERTEBRATE ANIMALS YOU MUST ADDRESS THE REQUIREMENTS OUTLINED IN THE 'PROPOSAL FUNDAMENTALS'. ADDRESS 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.
- 8) **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.
- 9) **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.
- 10) **Facilities and Equipment.** Indicate where the proposed research will be conducted. One of the performance sites must be the offeror organization. Describe the facilities* to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of

availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project.

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

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

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

***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 or Direct to Phase II Only. Anticipated or actual Results of the Phase I/Phase I-like Effort

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

For Direct to Phase II: Summarize the specific aims of the preliminary work that forms the basis for this Direct Phase II proposal, quantitative milestones (a quantitative definition of success) for each aim, the importance of the findings, and emphasize the progress made toward their achievement. Describe the technology developed, its intended use and who will use it. Provide data or evidence of the capability, completeness of design, and efficacy along with the rationale for selection of the criteria used to validate the technology, prototype, or method Describe the current status of the product (e.g., under development, commercialized, in use, discontinued). If applicable, describe the status of FDA approval for the product, process, or service (e.g., continuing pre-IND studies, filed on IND, in Phase I (or II or III) clinical trials, applied for approval, review ongoing, approved, not approved). List the generic and/or commercial names of products.

(C) Research Plan for Phase II (FAST TRACK or Direct to Phase II) 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 vertebrate 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 or Direct Phase II proposals. The Phase II portion of Fast-Track proposals and all Direct Phase II proposals must include a 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.

- 9) **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 one half for Phase II 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.

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 Human Subjects

■ Human Subjects Involvement, Characteristics, and Design

- Describe and justify the proposed involvement of human subjects in the work outlined in the Research Strategy section.
- Describe the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.
- Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.
- Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
- If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, describe and justify the selection of an intervention's dose, frequency and administration.
- List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.

■ Sources of Materials

- Describe the research material obtained from living individuals in the form of specimens, records, or data.
- Describe any data that will be collected from human subjects for the project(s) described in the application.
- Indicate who will have access to individually identifiable private information about human subjects.
- Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.

■ Potential Risks

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

- Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.
- b. Adequacy of Protection Against Risks
 - Recruitment and Informed Consent
 - Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.
 - Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.
 - Protections Against Risk
 - Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
 - Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:
 - Additional Protections for Pregnant Women, Human Fetuses and Neonates: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb>
 - Additional Protections for Prisoners: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc>
 - OHRP Subpart C Guidance: <http://www.hhs.gov/ohrp/policy/index.html#prisoners>
 - Additional Protections for Children: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>
 - OHRP Subpart D Guidance: <http://www.hhs.gov/ohrp/policy/index.html#children>
 - Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of the clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.
- c. Potential Benefits of the Proposed Research to Human Subjects and Others
 - Discuss the potential benefits of the research to research participants and others.
 - Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.
- 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 reasonably may be expected to result.

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

e. Data and Safety Monitoring Plan

- If the proposed research includes a clinical trial, create a heading entitled "Data and Safety Monitoring Plan."
- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (<http://www.fda.gov/>) and also see the following Web sites for more information related to IND and IDE requirements:

http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)

http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)

- The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:
 - PD/PI (required)
 - Institutional Review Board (IRB) (required)
 - Independent individual/safety officer
 - Designated medical monitor
 - Internal Committee or Board with explicit guidelines
 - Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.
- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. For additional guidance on creating this Plan see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>.

f. ClinicalTrials.gov Requirements

- Public Law 110-85 (also known as the FDA Amendments Act (FDAAA) of 2007) mandates registration and results reporting of "applicable clinical trials" in ClinicalTrials.gov. Under the statute

these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Review the statutory definition of applicable clinical trial to identify if registration is required to comply with the law (See PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)).

- NIH encourages registration of ALL clinical trials whether required under the law or not.
- Registration is accomplished at the ClinicalTrials.gov Protocol Registration System Information Web site (<http://prsinfo.clinicaltrials.gov/>). A unique identifier called an NCT number, or ClinicalTrials.gov registry number, will be generated during the registration process.
- The NIH implementation of FDAAA requires:
 - the registration of applicable clinical trials in ClinicalTrials.gov no later than 21 days after the first subject is enrolled,
 - the reporting of summary results information (including adverse events) no later than 1 year after the completion date for registered applicable clinical trials involving drugs that are approved under section 505 of the Food, Drug and Cosmetic Act (FDCA) or licensed under section 351 of the PHS Act, biologics, or of devices that are cleared under section 510k of FDCA, and
 - if an “applicable clinical trial” is funded in whole or in part by an NIH grant or cooperative agreement, grant and progress report forms shall include a certification that the responsible party has made all required submissions to ClinicalTrials.gov.
- For competing new and renewal applications that include applicable clinical trials which require registration and results reporting under FDAAA, provide the NCT number/s in the human subjects section of the Research Plan under a section heading entitled ClinicalTrials.gov. Supplemental Instructions for PHS 398 and SF424 (R&R) II-11
- The entity responsible for registering the trial is the “responsible party”. The statute defines the responsible party as:
 - the sponsor of the clinical trial (as defined in 21 CFR 50.3) (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3>), or
 - the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (provided that “the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements” for submitting information under the law) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).
- For the complete statutory definitions of "responsible party" and "applicable clinical trial," refer to Elaboration of Definitions of Responsible Party and Applicable Clinical Trial.
- The signature on the application of the Authorized Organization Representative assures compliance with FDAAA.
- Additional information can be found on the ClinicalTrials.gov Web site (http://grants.nih.gov/ClinicalTrials_fdaaa/).

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.

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

NIH policy requires that women and members of minority groups and their subpopulations 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 Federal law (Public Health Service Act sec. 492B. 42 U.S.C. sec. 289a-2), **and applies to research subjects of all ages.**

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, race, and ethnicity, and provide a rationale for selection of 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. Such a plan should contain a description of the proposed outreach programs for recruiting women and minorities as participants.

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, racial, and/or ethnic group
- The proposed sample composition using the "Planned Enrollment Report"(see Section J, Attachments)
- If the clinical study(s) involves US and non-US sites, the US sites and non-US sites should be provided on separate Planned Enrollment Reports.

NOTE 1: All contractors must also report at least annually cumulative subject accrual by sex/gender, race, and ethnicity. If the clinical study(s) involves US and non-US sites, the US sites and non-US sites should be reported on separate Cumulative Inclusion Enrollment Reports.

NOTE 2: For all proposals, use the ethnic and racial categories and complete the "PLANNED Enrollment Report" in accordance with the [Office of Management and Budget \(OMB\) Directive No. 15](#).

NOTE 3: 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 Racial and Ethnic 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. Collect ethnicity information first, followed by the question on race and provide participants with the option to select more than one racial category. Participants also have the option not to identify. When you present aggregate data, you shall provide the number of respondents who selected only one category, for each of the five racial categories. Participants who self-identify with more than one racial category should be reported to the NIH under the "More than one race" category of the report. Federal agencies shall not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

In addition to the above requirements, solicitations for [NIH defined Phase III clinical trials](#) * require that offerors must address whether clinically important sex/gender, racial, and/or ethnic differences are expected from the intervention effect. The discussion may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies as well as observational, natural history, epidemiology and/or other relevant studies. The discussion of expected sex/gender, racial, and ethnic differences in intervention effect must include selection and discussion of one of the following analysis plans:

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

All contractors must also report at least annually cumulative subject accrual by sex/gender, race, and ethnicity, and progress in conducting analyses for sex/gender, racial, and/or ethnic differences.

Additional Guidance for Specific Scenarios

Research Conducted with Existing Datasets: Any application (New, Renewal, Resubmission, Revision) using existing datasets or specimens that meet the NIH definition for clinical research, you should complete the Cumulative Inclusion Enrollment Report(s) rather than the Planned Enrollment Report, even if the entire sample is unknown/not reported. Please note in the Comment field that you are working with an existing dataset. For additional guidance on working with existing datasets see: http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Research Conducted with Non-US Participants: If conducting NIH-defined clinical research outside of the United States, design culturally appropriate data collection instruments that allow participants to self-identify their ethnic and/or racial affiliation in a way that is meaningful in the cultural and scientific contexts of the study. However, investigators must use the OMB-defined categories for reporting sex/gender, race and ethnicity to NIH, which will allow completion of the inclusion enrollment forms(s). Since the OMB categories reference world-based geographic origin, this should facilitate completion of the form(s). **Enrollment of participants at non-U.S. sites should be reported to NIH on a separate NIH inclusion enrollment form from that for reporting participants at U.S. sites, even if they are part of the same study.** For additional guidance and FAQs related to this topic, please refer to: http://grants.nih.gov/grants/funding/women_min/women_min.htm or [contact the program officer](#).

Delayed-Onset Human Subjects Research: If the proposed research includes studies that meet the definition for delayed-onset human subjects research described in the Human Subjects section of the instructions, and it is not possible to describe the proposed study and provide planned enrollment on sex/gender, race, and ethnicity, then enter a comment on the Planned Enrollment Report(s) indicating this is a delayed-onset study. For study title, you may enter the Project Title along with the words "Delayed Onset Study." If you expect that more than one study will be delayed onset, it is acceptable to provide only one Planned Enrollment Report indicating delayed onset, but you may wish to indicate in the comments section of the Planned Enrollment Report that more than one study is anticipated under this scenario.

Use the form entitled, "Planned Enrollment Report or Cumulative Inclusion Enrollment Report," when preparing your response to the solicitation requirements for inclusion of women and minorities. See this webpage for additional information in determining which form is appropriate to use: http://grants.nih.gov/grants/funding/women_min/women_min.htm

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 and the proposed distribution of the sample by sex/gender, race, and ethnicity should be justified in the context of the scientific goals of the proposal.

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

Inclusion of Children in Research Involving Human Subjects

Research involving children (see definition of "child") must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. For purposes of the NIH Inclusion of Children policy, a child is defined as an individual under the age of 21 years. This is a separate consideration from the protection of children (described above in the Human Subjects Protections section). The involvement of children as subjects in research must also be in compliance with all applicable subparts of 45 CFR part 46 as well as with other pertinent Federal laws and regulations.

NIH policy requires that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH (including contracts) unless there are clear and compelling reasons not to include them. (See examples of Justifications for Exclusion of Children below). Therefore, proposals involving [NIH-defined clinical research](#) must include a description of plans for including children. When children are included, the plan also must include a description of: (1) the age ranges to be included (or excluded); (2) the expertise of the investigative team for dealing with children at the ages included; (3) the appropriateness of the available facilities to accommodate the children; and, (4) the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose/objective of the solicitation.

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 US and non-US research contracts.

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.

For additional details and guidance, please refer to <http://grants.nih.gov/grants/funding/children/children.htm>.

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

8.5 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.

8.6 Research Involving 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.

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

- 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.
- 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.
- Provide information on the veterinary care of the animals involved.
- 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.
- 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](#).

The *PHS Policy on Humane Care and Use of Laboratory Animals* (PHS Policy) 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.

8.7 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.

- List all key personnel by name as well as by number of hours dedicated to the project as direct labor.
- 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.
- Cost for travel funds must be justified and related to the needs of the project.
- 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.
- 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.
- 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 negotiate Final Indirect Rates with the NIH Division of Financial Advisory Services (DFAS), or other cognizant auditing agency. However, awarding Contracting Officers may require offerors to document how they calculated their IDC rate(s) in order to determine that these costs are fair and reasonable. Furthermore, 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.

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

8.8 Reminders

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 or Direct Phase II 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:

- 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.
- Check that the cost adheres to the Component criteria specified and the price on the cover sheets matches the price in the Pricing proposal.
- Check that the Project Abstract and other content provided on the cover sheets contain NO proprietary information.
- Mark proprietary information within the Technical Proposal as instructed in Section 4.23.
- That the header on each page of the technical proposal should contain the company name and topic number.
- Ensure that if you have proposed for your research to include Human Subjects or Vertebrate Animals that you have addressed the requirements outlined in the solicitation in the Technical proposal as necessary.
- If you intend to propose surveys or other data collections in a Phase I project, you should refrain from proposing more than 9 respondents.

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)	20-31	Scientific and Technical Merit Review: March-May 2015 Anticipated Award Date: August-September 2015
National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS)	4-8	Scientific and Technical Merit Review: March-May 2015 Anticipated Award Date: September 2015
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	11	Scientific and Technical Merit Review: February-April 2015 Anticipated Award Date: July-September 2015
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	4-7	Scientific and Technical Merit Review: March 2015 Anticipated Award Date: August 2015
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	3-4	Scientific and Technical Merit Review: March 2015 Anticipated Award Date: August 2015
Centers for Disease Control and Prevention (CDC) Center for Global Health (CGH)	1-2	Scientific and Technical Merit Review: May-June 2015 Anticipated Award Date: August 2015
Centers for Disease Control and Prevention (CDC) National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)	1	Scientific and Technical Merit Review: May-June 2015 Anticipated Award Date: August 2015
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	1	Scientific and Technical Merit Review: May-June 2015 Anticipated Award Date: August 2015
Centers for Disease Control and Prevention (CDC) National Center for HIV/AIDs, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	3	Scientific and Technical Merit Review: May-June 2015 Anticipated Award Date: August 2015
Centers for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	4	Scientific and Technical Merit Review: May-June 2015 Anticipated Award Date: August 2015

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. Victoria Cunningham

E-mail: ncioasbir@mail.nih.gov

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

Ms. Victoria Cunningham

Contracting Officer

Office of Acquisitions

National Cancer Institute

9609 Medical Center Drive, 1E558, 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. Sean Dalenberg

Phone: 301-827-1017

E-mail: sean.dalenberg@nih.gov

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

Mr. Sean Dalenberg

Contracting Officer

Office of Acquisitions

NIDA COAC

6701 Democracy Blvd, Suite 1084

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:

Office of Scientific Review
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 OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

Eileen Webster-Cissel
Chief, AIDS Research Contracts Branch
Office of Acquisitions, DEA
National Institute of Allergy and Infectious Diseases
National Institutes of Health, DHHS
5601 Fishers Lane, Room 3D10, MSC 9821
Bethesda, MD 20892-9821*

**If using hand delivery or overnight delivery service, please change the city to Rockville, MD and the zip code to 20852*

Email: webstere@niaid.nih.gov

Phone Number: 301-496-0612

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

Mr. Brian O'Laughlin
Phone: (301) 443-6677
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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

Sean David Griffiths, M.P.H.
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CENTER FOR GLOBAL HEALTH (CGH)

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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 CHRONIC DISEASE PREVENTION AND HEALTH PROMOTION (NCCDPHP)

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

Proposals to NCCDPHP 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)

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E-mail: TNR3@cdc.gov

Proposals to NCEZID must be mailed or delivered to:

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

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E-mail: TNR3@cdc.gov

Proposals to NCHHSTP must be mailed or delivered to:

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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
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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

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 or the topic(s) are classified as Direct to Phase II, 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:

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-002.html>.

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 and Direct to Phase II) proposals in the following areas:

334 Vacutubes to Preserve the Viability of Circulating Tumor Cells

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 3 – 5

Budget (total costs, per award): Phase I: \$300,000 for 9 months; Phase II: \$2,000,000 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

A vacutainer blood collection tube is a septum-sealed sterile tube with an internal vacuum that facilitates drawing of blood into the tube. Specialized vacutainers containing additives or stabilizers enable many important clinical measurements: vacutainers containing heparin or sodium citrate for plasma isolation; EDTA-containing vacutainers for isolating blood cells; sodium polyanethol sulfonate for blood culture specimens; acid-citrate-dextrose for blood banking studies; and cell preparation tubes (CPTs) with anticoagulant and a density gradient or gel for isolating peripheral blood mononuclear cells.

Several decades ago, clinical metastasis of solid tumors was linked to blood-borne dissemination of tumor cells in the circulation, and clinical instrumentation is now available to isolate and enumerate these circulating tumor cells (CTCs) in a venous blood draw. One of the first instruments cleared by the FDA for in vitro diagnostic use in enumerating CTCs is the CellSearch™ system from J&J/Veridex, which enumerates CTCs that are positive for a cell surface marker called EpCAM.

CTCs are fragile and tend to degrade within a few hours when collected in standard evacuated blood collection tubes, so Veridex developed a proprietary vacutainer called a CellSave Preservation Tube that stabilizes CTCs up to 96 hours at room temperature, which allows shipment of samples to central reference laboratories for analysis. However, the proprietary chemistry of the CellSave Preservation Tube preserves the CTCs for analysis by fixation, so the cells are no longer viable or proliferative and are not suitable for many downstream applications that depend on the ability of the tumor cells to proliferate (i.e., in vitro culture and/or xenograft development).

In addition to the CellSearch technology, several other CTC isolation platforms are now on the market such as the ApoStream device which separates tumor cells based on their dielectric potential which allow for the capture of viable circulating tumor cells some of which have the capacity to proliferate.

Project Goals

The goal of this SBIR topic is the refinement of existing CTC preparation tubes or new development of vacutainers for commercialization that are capable of preserving the viability of solid tumor-derived cancer cells in venous blood for up to 96 hours of transit. Emphasis should be given to developing conditions that promote the survival of tumor cell populations that retain some degree of proliferative capacity. Such a product will enable derivation of new cell lines and patient-derived xenograft (PDX) models from clinical blood specimens that are more readily available than tumor biopsies.

Emergent needs in medical testing and blood-based cell measurements drive development of vacutainer chemistries that preserve cell viability, and once these clinical measurements become important for medical practice, the new vacutainer chemistry is readily commercialized.

There is a great demand for the development of patient-derived models (PDMs) – both cell lines and xenografts – for a number of clinical translational applications. Importantly, these models will need to reflect both the evolution and heterogeneity of a solid tumor, which implies that multiple longitudinal samples of tumor will be needed over the course of an individual patient’s therapies, responses and relapses. Because of high biopsy-associated risk, it is unlikely that tumor biopsies or resections will be able to meet this need, but the low risk of venous blood draws makes circulating cancer cells an attractive alternative for collecting tumor material that likely retains the proliferative ability required to establish cell lines and xenograft tumors.

The key to successful use of circulating tumor cells for establishing PDMs is maintaining cell viability and function (especially proliferative function) during the collection, handling and shipping of the blood specimen to central laboratory sites that have the capability to establish PDMs.

Viability of cancer cells in general depends on stimulation of the survival pathways often shared with the normal stem cell counterpart that are not already activated via mutations and other abnormalities. For example, Clevers and colleagues showed that in vitro survival and proliferation of normal gastrointestinal stem cells into organoids require the addition of cell culture supplements that cover six critical signaling pathways, all of which were similarly altered in selected tumors:

Supplied Factor	Pathway	Potential Mechanism of Cancer Cell Addiction and/or Dependence
EGF	activates RAS/RAF/MEK/ERK signaling	mutant KRAS
Noggin	blocks BMP signaling	mutant BMPRIA or SMAD4
R-spondin	activates WNT signaling	mutant APC or CTNNB1
WNT3A	activates Wnt signaling pathway(s)	abnormal Frizzled signaling
Jagged-1 peptide	Notch signaling	mutant Notch/upregulation of Jagged-1
Matrigel w/Y-27632	Cell adhesion	Modulated expression of cadherins, selectins, and integrins
N-acetyl-cysteine	Protection from oxyradical damage	Induced protective enzymes

Whereas normal GI stem cells require all of these factors to survive and function in vitro, malignant GI stem cells can harbor mutations and other abnormalities (shown in the table above) that confer factor-independence to one or more of these essential pathways. Each individual carcinoma may harbor a different set of these abnormalities, so each case may require its own specific set of supplied factors for promoting cancer survival in blood during transport. In the absence of genomic information to identify pathways that are factor-independent, multiple pro-survival factors may be needed to maximize viability of different types of tumor specimens during collection, processing and shipment.

The current understanding of normal stem cell survival and of tumor culture growth conditions may identify pro-survival factors that will maximize recovery of circulating tumor cells out of a vacutainer. The analogy may be anatomic, e.g., the cocktail of factors promoting survival of normal GI stem cells or cultured GI tumor cells may promote survival of circulating cancer cells from colorectal carcinomas (or subtypes). The analogy could also be embryologic, e.g., the cocktail that promotes survival of stem cells in endoderm-derived tissues or cultured endodermal tumors may promote survival of circulating tumor cells from malignancies of endoderm-derived tissues.

The short-term goal is identification of the minimum cocktail of survival factors for circulating tumor cells, possibly using knowledge of survival factors of corresponding normal stem cells or cultured tumor cells. In addition to protein factors, other important variables in the cocktail may include extracellular matrix, metabolic substrates (e.g. glucose, glutamine), small molecule metabolites, pH, dissolved gases, and alternative anti-coagulants. It is preferred that general viability of the tumor cells be assessed with the MTT assay and functionality be assessed via a spherogenic assay (other assays may be used with NCI approval). Once recovery, viability, and function are established in the in vitro assays, then NCI will initiate xenograft mouse studies to generate data that further

supports the maintenance of tumor cells with proliferative capacity in the presence of the customized tumor cell survival cocktails.

The long-term goal is the adaptation of the survival cocktails to the vacutainer environment either with new configurations or using current CTC prep tubes, including proof of tumor cell recovery, survival, and function in prototype vacutainers containing blood for up to 96 hours of storage. Note that the vacutainer tubes should contain an anti-coagulant with the use of K3EDTA which is recommended by NCI.

References

Bendas et al (2012) Cancer Cell Adhesion and Metastasis: Selectins, Integrins, and the Inhibitory Potential of Heparins. International Journal of Cell Biology 2012: 1 – 10

Rodilla et al (2009) Jagged1 is the pathological link between Wnt and Notch pathways in colorectal cancer. PNAS 106: 6315–6320

Avila et al (2013) Notch signaling in pancreatic cancer: oncogene or tumor suppressor? Trends in Molecular Medicine 5: 320–327

Sato et al (2009) Single Lgr5 stem cells build crypt–villus structures in vitro without a mesenchymal niche. Nature 459:262-265

Sato and Clevers (2013) Primary Mouse Small Intestinal Epithelial Cell Cultures. Methods in Molecular Biology 945:319-328

Sato and Clevers (2013) Growing Self-Organizing Mini-Guts from a Single Intestinal Stem Cell: Mechanism and Applications. Science 340:1190-1194

Yin et al (2013) Niche-independent high-purity cultures of Lgr5+ intestinal stem cells and their progeny. Nature Methods Dec 1. doi: 10.1038/nmeth.2737 [Epub]

Reference (Spheroid Assays)

Human Breast mammosphere

Residual breast cancers after conventional therapy display mesenchymal as well as tumor-initiating features. Creighton CJ, Li X, Landis M, Dixon JM, Neumeister VM, Sjolund A, Rimm DL, Wong H, Rodriguez A, Herschkowitz JI, Fan C, Zhang X, He X, Pavlick A, Gutierrez MC, Renshaw L, Larionov AA, Faratian D, Hilsenbeck SG, Perou CM, Lewis MT, Rosen JM, Chang JC. Proc Natl Acad Sci U S A. 2009 Aug 18;106(33)

Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy.

Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu MF, Hilsenbeck SG, Pavlick A, Zhang X, Chamness GC, Wong H, Rosen J, Chang JC. J Natl Cancer Inst. 2008 May 7;100(9):672-9

GBM neurospheres

In vitro Analysis of Neurospheres Derived from Glioblastoma Primary Culture: A Novel Methodology Paradigm. Pavon LF, Marti LC, Sibov TT, Malheiros SM, Brandt RA, Cavalheiro S, Gamarra LF. Front Neurol. 2014 Jan 7;4:214.

Prostate Cell line spheroids

Propagation of human prostate cancer stem-like cells occurs through EGFR-mediated ERK activation. Rybak AP, Ingram AJ, Tang D. PLoS One. 2013 Apr 19;8(4)

Colorectal Carcinoma cell line spheroids

NANOG modulates stemness in human colorectal cancer. Zhang JI, Espinoza LA, Kinders RJ, Lawrence SM, Pfister TD, Zhou M, Veenstra TD, Thorgeirsson SS, Jessup JM. Oncogene. 2013 Sep 12;32(37):4397-405.

Phase I Activities and Deliverables

The offeror will identify the minimum cocktail of survival factors for circulating tumor cells for one type of solid carcinoma malignancy. The offeror may use knowledge of survival factors for stem cells of the normal tissue counterpart and of tumor cell culture conditions. NCI will provide the appropriate cell line.

The cocktail should enable at least 50% recovery and maintain the viability and function of cancer cells spiked into fresh human blood from normal subjects of appropriate blood types for up to 96 hours under typical temperature conditions of transport. The viability, MTT, and functional spherogenic assays are to be performed on the recovered tumor cells after 96 hours.

Activities and deliverables include the following:

- Presence of an anti-coagulant in the blood that is spiked with tumor cells will be required and the preferred anti-coagulant is K3EDTA
- Preferred blood volume draw per tube is 4 mL; a second preferred volume draw is 1.0 mL (neonatal equivalent tube)
- Develop and provide the SOP methods for enriching the tumor cells from blood to analyze for recovery, viability, and function (i.e., mechanism to withdraw blood from the collection tube and transfer to a Ficoll Gradient)
- Deliver to NCI 100 tubes of cocktail to perform independent testing of the effect of the cocktail on viability/function of tumor cells spiked into blood for up to 96 hr
- Provide final report to NCI, and travel to NCI to present final results.

Phase II Activities and Deliverables

- Optimize additives to support cancer cell viability and function in two types of solid carcinoma malignancy (the type chosen for Phase I, and one additional distinct type) for up to 96 hrs in blood under conditions expected during transport. NCI will provide the appropriate cell lines for these studies.
- Adapt the two survival cocktails to the vacutainer environment, including proof of at least a minimum of 50% viable tumor cell recovery (MTT assay) from vacutainers after 96 hours and the demonstration of the maintenance of spherogenicity (or use of other tests approved by NCI).
- Develop proof-of-concept methodology to reliably manufacture the two tumor type cocktails in blood vacutainers to optimize the recovery, viability, and function of cancer cells for up to 96 hours under temperature conditions of transport.
- Perform small scale quality-control studies of the reproducibility of cancer cell viability in freshly drawn blood for 96 hours under temperature conditions of transport, e.g. the recovery, viability, and function measurements between at least 3 runs should fall within 2 standard deviations.
- Optimize manufacturing processes to generate cost-effective vacutainer tubes that 1) maintain the viability/function of cancer cells during transport in blood for up to 96 hours, and 2) that are stable for a minimum of 3 months. The manufactured tubes must meet Federal and International standards for blood vacutainer tubes.
- Optimize specifications of product for manufacture to include developing quality control and assurance measures to insure consistency in the lots of tubes produced.
- Deliver to NCI a pilot lot of 1000 vacutubes for independent validation, along with Certificates of Performances/Quality Documents and a Standard Operating Procedure for Manufacturing. Tubes must be manufactured under optimized conditions.
- Provide at the end of year one at least one letter of commercial interest from an organization potentially interested in buying the product(s).

- Provide at the end of year two at least two letters of commercial commitment from customers stating their commitment to buy the product(s).

335 Development of Advanced Culture Systems for Expansion of Cancer Stem Cells

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 4 – 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

Tumors consist of heterogeneous cell populations in which only a small fraction, less than 1%, is able to seed new tumors by transplantation, functionally defined as cancer stem cells (CSCs). There is growing interest in identifying markers and therapeutically targeting the CSC population in tumors. Recent studies have shown that CSCs have different drug sensitivities compared to the bulk population and represent an attractive therapeutic target. Studying these cells, however, has been a challenge due to their low abundance in vivo and the phenotypic plasticity they exhibit during expansion. Using current methods, isolated CSCs lose the expression of CSC markers and tumor initiating capacity when cultured in vitro or in vivo in xenograft animal models. The proportion of CSCs tends to an equilibrium level of less than 1% over time, and the cell population derived from CSC cultures typically recapitulates the heterogeneous nature of the original population. Thus, the goal of this contract topic is to meet the critical need to develop cell culture systems that can specifically grow CSCs for basic and translational research.

Developments in stem cell engineering and tissue engineering have generated new culture systems to accelerate the expansion of embryonic, induced pluripotent, and adult stem cell populations in vitro. These systems include technologies such as three dimensional (3D) culture systems containing extracellular matrix components and topological features, or bioreactors for large scale culture of cell spheroids. Preliminary data suggest that these technologies or similar culture systems may be applicable for quick and reproducible expansion of CSCs. Thus, commercial development of these culture systems specifically for CSC culture may have a significant impact in basic research and drug screening applications.

Project Goals

The purpose of this topic is to develop cell culture systems that can effectively grow cancer stem cells in vitro without the loss of cancer stem cell markers or tumor initiating potential.

The specific goals are to demonstrate that the cell culture system can expand the population of cancer stem cells isolated from established cancer cell lines, derived from either human or animal model systems (Phase I), and primary tumors from appropriate animal models or patient biospecimens (Phase II) that can then be harvested for use in downstream assays.

To successfully meet this goal, applicants will need to demonstrate that cancer stem cells grown using their system: 1) maintain the same tumor initiating potential using an established methodology; 2) maintain the same expression characteristics of accepted cancer stem cell markers; 3) can be easily and effectively harvested by a protocol that maintains the viability and tumor initiating phenotype of cancer stem cells; 4) can be readily used in downstream assays including, but not limited to, molecular read-outs (such as genomic, proteomic, metabolomic, or epigenomic analyses) or cell based read-outs (such as proliferation, migration, invasion, or apoptosis).

It is anticipated that applicants will employ innovative 3D cell culture or bioreactor systems in combination with defined media and growth factor conditions. However, applicants are free to employ any approach that will generate the desired results and meet the criteria listed above. Applicants may utilize feeder cells or co-culture conditions, provided the cancer stem cells can be effectively separated from other cell types at the point of harvest. Applicants are not restricted to specific cancer types, but should justify the choice of cancer type to study from both a scientific and commercial perspective.

Systems of particular interest will be amenable to scale up, demonstrate reliability and robustness at a price point that is compatible with market success and widespread adoption by the research community. Further, systems that can demonstrate success in expanding cancer stem cells from patient derived samples will also be of particular interest.

The focus of this contract concept is not to develop a screening platform for agents that selectively kill or arrest cancer stem cells, though a screen for such agents could be used to demonstrate the proof of principle that cancer stem cells grown using this technology can be used in downstream applications. Additionally, this contract is not intended to develop systems to expand non-cancer derived stem cells, though applicants may propose the use of such systems provided they can demonstrate effectiveness with cancer stem cells.

Phase I Activities and Expected Deliverables

- Develop a culture system and corresponding SOP that reproducibly expands cancer stem cells (CSCs) isolated from a heterogeneous cell population while maintaining the CSC phenotype.
 - Culture system should include physical (i.e. scaffold, hydrogel, or matrix) and chemical (i.e. media, oxygen tension, pH) components
 - Culture system should be able to expand population up to 10⁷ cells
 - Live cells should be able to be extracted and re-seeded from the culture system
 - Systems of particular interest will incorporate methods for freezing and long-term storage of expanded cells.
- Validate culture system and SOP using a cancer cell line known to contain a CSC population.
 - Using an appropriate cell line model system, isolate the CSC subpopulation using established protocols and markers. Applicants should clearly outline the evidence for CSC subpopulations in the chosen cell line(s).
 - Culture the isolated CSC population using the developed culture system. Examples of cancer cell lines include MCF-7 breast cancer cells or HCT116 colorectal cancer cells.
 - Identify the sustainability of CSC markers and tumor initiating phenotype after culture in system using established protocols (e.g. CSC-specific cell surface markers, Hoechst 33342 exclusion, colony formation, tumor transplantation).
- Submit a statement to NCI that specifies metrics and criteria used to evaluate the CSC population and phenotype, and justification from both a scientific and commercial perspective for why the specific cancer type or cell line is being used.
 - Specify SOP and biomarkers (cell marker or assays) used to identify CSC population.
 - Specify SOP for assays used to define CSC phenotype.

Phase II Activities and Expected Deliverables

- Demonstrate ability of developed culture system to expand CSCs isolated from in vivo samples for at least one cancer type.
 - Culture CSC population isolated from tumor biospecimens (human or mouse) to a minimum of 107 cells.
 - Compare genomic, proteomic, metabolomic, and epigenomic profile of original CSC population and expanded population.
 - Demonstrate reproducibility by expanding CSC populations from 10 different biospecimens.
- Test tumor initiating capacity of expanded CSC population using appropriate established in vivo assays.

336 Development of Novel Therapeutic Agents That Target Cancer Stem Cells

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2 – 3

Budget (total costs, per award): Phase I: \$300,000 for 9 months; Phase II: \$2,000,000 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

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 material suitable for an early clinical trial.

337 Cell-Free Nucleic Acid-Based Assay Development for Cancer Diagnosis

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 3 – 5

Budget (total costs, per award): Phase I: \$300,000 for 9 months; Phase II: \$2,000,000 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 evidence that cell-free circulating DNA is present in cancer patient's blood was first reported over half century ago. Since then, studies that addressed the clinical significance of the cell free DNA quantification in plasma/serum for cancer diagnosis have grown steadily. Research findings indicate that most patients with solid tumors in lung, breast, prostate, colon, cervix, ovary, testes, and bladder have increased DNA levels that allow for discriminating patients with malignancies from those with non-malignant disease. The first application of cell-free circulating nucleic acids (cfNA) in the diagnosis and prognosis of cancer was demonstrated in 1977, when a higher level of

circulating DNA was detected in the serum of cancer patients; these levels decreased in response to radiation therapy.

In recent years, it has been recognized that circulating DNA may be altered in fragmentation pattern, microsatellite stability, and DNA methylation. In addition, the cfDNA sequences may be mutated and tumor-specific, allowing for increased sensitivity and specificity in evaluation and detection of cancer compared to mere quantification of cfDNA levels. Besides circulating cell-free DNA, evidence has indicated that tumor-derived RNA, (especially the quantification of the tumor-derived microRNA in plasma/serum) may be an excellent biomarker for the diagnosis and prognosis of cancer. Furthermore, alterations of cfDNA are also found in other sources of body fluids or effusions such as urine or sputum. Clearly, using cfDNA as a biomarker, which is easily accessible, reliable, and reproducible, can offer many advantages in their implementation into clinical use.

To date, however, there are no currently effective cfDNA-based assays that are approved for clinical use in the diagnosis or prognosis of cancer. The low abundance of cfDNA from all body fluids and effusions remains a major challenge in assay development. Many early developments need to be further verified and validated before they can be translated to clinical use. With the latest technology advancement in sample collection, processing, and analysis for nucleic acids, the likelihood of clinical utilization of cfDNA becomes more feasible.

The purpose of this initiative is to provide much needed support for the development of a cfDNA-based assay for cancer diagnosis and/or prognosis. The selected applicants will develop an assay for detection of cancer or its subtype, so that cancer or subtypes can be identified specifically. Since a single alteration in cfDNA may not be sufficient to detect a specific cancer, offerors are encouraged to use a panel of cfDNA alterations that could be more robust for their assay development. The cfDNA alterations may include, but are not limited to, cfDNA concentration, fragmentation pattern, microsatellite stability, DNA methylation, tumor-specific sequences, DNA mutations, or tumor-derived RNA. The sources of cfDNAs can be from plasma, serum, urine, sputum, or other types of body fluids or effusions. In Phase I, the development of a molecular diagnostic assay should focus on proof of concept. In Phase II, the assay developed in Phase I will be validated in the clinical setting under a plan developed with the NCI project officer.

Project Goals

The goal of the project is to develop a cfDNA-based assay for clinical use in the evaluation of cancer diagnosis, prognosis, and/or response to therapy. The levels of sensitivity and specificity required will depend on the clinical question and the unmet need(s) that will be addressed with the proposed assay. The assay may also be used to provide a better mechanistic understanding of tumor development and progress with the idea that this knowledge may lead to better therapeutic targets and improve patient outcome. Preference will be given to the assays that are platform driven, meaning that the technology platform should be portable and easily used for diagnosis of multiple cancer types.

To apply for this topic, offerors should outline and indicate the clinical question and unmet clinical need that their assay will address. Offerors are also required to use validated cfDNA markers. This solicitation is not intended for biomarker discovery.

Phase I Activities and Expected Deliverables

- Select one or a set of validated cfDNA markers with samples of choice (e.g., plasma, serum or/and urine) for detection of a cancer or cancer subtype (e.g., breast cancer or triple negative breast cancer). If novel or proprietary markers are used, offerors must show that the markers have been validated.
- Develop an assay to identify these markers effectively to distinguish the cancer samples from healthy samples. The offerors should also demonstrate that the assay is able to differentiate the cancer from other cancer types.
- Demonstrate high reproducibility and accuracy with the assay.
- Demonstrate high specificity and sensitivity of the assay. Specificity and sensitivity will depend on the application (e.g., high specificity will be required if the assay is used to provide specific molecular information for a lesion that was detected via CT imaging).
- Deliver to NCI the SOPs of the cfDNA-based assay for cancer diagnosis, prognosis, and/or response to therapy.

- Demonstration of a plan that is necessary to file a regulatory application.

Phase II Activities and Expected Deliverables

- Demonstrate that the assay enables a test to be finished within one day.
- Validate the assay in the clinical setting.
- Submit a regulatory application to obtain approval for clinical application.

338 Predictive Biomarkers of Adverse Reactions to Radiation Treatment

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2 – 3

Budget (total costs, per award): Phase I: \$300,000 for 9 months; Phase II: \$2,000,000 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

Radiotherapy is an important definitive and palliative treatment modality for millions of patients with cancer and is used alone or in combination with drug therapy. However, a variety of patient, tumor, and treatment-related factors will influence its outcome. Currently, treatment decisions in radiotherapy and radio-chemotherapy are primarily defined by disease stage, tumor location, treatment volume, and patient co-morbidities. However, treatment planning does not take into account individual patient's (or a cohort of patients') sensitivities to radiation. This is an important limitation in personalized care, as there are known variations in individual patients' normal tissue sensitivities to radiation, but treatments are based on population normal tissue complication probabilities. In an era of precision medicine, as molecularly targeted therapy is being integrated into radiotherapy and chemotherapy, selecting the "right type of treatment" is critical to improve outcomes.

A substantial number of patients treated with radiotherapy suffer from severe to life-threatening adverse acute effects, as well as debilitating late reactions. A biomarker-based test that can predict the risk of developing severe radiotherapy-related complications will allow delivery of suitable alternative treatments. Further, such stratification may also allow dose escalation to the tumor in less sensitive patients. However, discovery, development, and validation of predictive biomarkers of radiation hypersensitivity are challenging, particularly due to a low incidence of normal tissue complications observed in the clinic, the potential need for lengthy, long-term studies for predicting late effects (e.g., predicting risk of fibrosis), and complexities arising from the combination of chemotherapy with radiation.

Several SBIR companies, in partnership with academia, have been working in this field, and some have developed prototype products serving the needs of radiation dose assessment in accidental radiation exposures. Much of this work has been accomplished in response to Requests for Proposals for developing radiation counter-measures (e.g., Biomedical Advanced Research Development Authority (BARDA), and NIAID Centers for Medical Countermeasures for Radiation Injury (CMCR)). The most promising among these technologies can be leveraged by the NCI SBIR program, as they could be quickly and readily translatable to radiation oncology applications for stratifying patients based on their radiation sensitivity. Products coming out of this solicitation may ultimately allow radiation oncologists to determine whether or not certain patients are suitable for treatments involving radiotherapy due to a high degree of normal tissue radiosensitivity.

Project Goals

The goal of this contract topic is to identify, develop, and validate simple and cost-effective biomarker-based test(s) to rapidly assess inter-individual differences in radiation sensitivity, and to predict early and late complications among patients prior to radiation therapy. These predictive biomarker-based test(s) should ideally be: (i) able to predict heterogeneity of radiation responses among patients, (ii) specific to radiation therapy, (iii) sensitive, (iv) able to show signal persistence as applicable to radiation therapy, or have known time-course kinetics of signal, (v) amenable for non-invasive or semi-invasive sampling, (vi) amenable to automation to improve quality control and assurance, (vii) quick in turnaround time between sampling and results (though speed is not as critical as in the countermeasures scenarios), and (viii) cost effective.

This contract topic aims to encourage discovery, development and validation of predictive radiation biomarkers for clinical applications. However, the regulatory pathway to bring biomarkers to market is inherently different than that for drugs, and depends on the clinical setting and intended use. Both the FDA and the Centers for Medicare and Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendment (CLIA) regulate diagnostic tests. A reasonable predictive radiation biomarker development process for identifying likely “over-responders” to radiation treatment may involve biomarker discovery, assay design and validation, determination of assay feasibility, assay optimization and harmonization, assessing the assay performance characteristics (reproducibility, sensitivity, specificity etc.), determining the effect of confounders, if any, determination of suitable assay platforms, and clinical validation with a locked-down assay before regulatory submission and commercialization. Early interaction with FDA is therefore essential.

The contract proposal must describe:

Phase I

- A quantitative estimate of the patient population that will benefit from the availability of the proposed predictive radiation biomarker for the applicable cancer type/organ site.
- A plan for generating evidence that the proposed biomarker is relevant in the prediction of radiation hypersensitivity among patients with cancer, and a logical approach in the developmental pathway to from discovery to the clinic.
- The plans must have a description of assay characteristics and the effect of known confounders, if any.
- Level of technological maturity
- Analytical validation
- Demonstration of feasibility

Phase II

- Must describe the setting and intended use of the predictive biomarker in retrospective or prospective studies using human tissue samples (frozen or fresh)
- Logical approach to regulatory approval
- Determination of assay platform and platform migration, if necessary
- Demonstration of clinical utility and clinical validation
- A proposed schedule for meeting with the FDA regarding a regulatory submission

The following activities and deliverables are applicable to both biomarkers for acute early effects and surrogate endpoints for late effects.

Phase I Activities and Deliverables

- Discovery and early development
- Demonstrate biomarker prevalence
- Preliminary data demonstrating feasibility
- Preclinical development and technical validity

- Assay characteristics, performance, reproducibility, specificity and sensitivity using frozen samples or retrospective clinical study.
- Determine the effect of confounders, such as any induction or concurrent chemotherapy regimens.

Phase II Activities and Deliverables

- Early-trial development
 - Retrospective or prospective tests using archived, frozen, or fresh human samples.
- Full development
 - Demonstrate clinical utility
 - Demonstrate clinical validity in a large prospective randomized clinical trial

339 Systemic Targeted Radionuclide Therapy For Cancer Treatment

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2 – 3

Budget (total costs, per award): Phase I: \$300,000 for 9 months; Phase II: \$2,000,000 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

Systemic targeted radionuclide therapy (STRT) combines the advantages of radiation's cytotoxic potential with the specificity of tumor-targeting agents. Typically, antibodies, antibody fragments, or peptides that have no significant effector function serve as a delivery vehicle, and a therapeutic effect is achieved by tissue absorption of the energies from continuous, low-dose, radiation emitted from the radionuclides. The exact choice of radionuclide used for STRT depends on the radiation characteristics of the nuclide, the radiolabeling chemistry, and type of malignancy or cells targeted. Two radioimmuno-conjugates targeting CD20 (Bexxar and Zevalin) have been approved previously for the treatment of non-Hodgkin's Lymphoma. Unfortunately, the clinical adoption of these agents was not successful due to: (1) the lack of randomized clinical trial data on overall survival following the treatment with these radiopharmaceuticals; and (2) the logistic and financial disadvantages faced by medical oncologists while using the radiolabeled antibodies. At a recent workshop on Targeted Radionuclide Therapy, jointly hosted by National Cancer Institute and the Society of Nuclear Medicine and Molecular Imaging, experts in the field and other stakeholders concluded that the availability of convincing survival data, combined with a multidisciplinary, patient-centric approach and evidence of cost-effectiveness, will prove to be effective in enhancing this field. In addition, the recent success of radium-223 chloride (Alpharadin®/Xofigo®) in patients with castration-resistant prostate cancer bone metastases has led to recent FDA approval and reinvigorated interest in STRT both in academia and in industry. Targeted drugs and proteins used for delivery of chemotherapeutic agents or imaging agents to cancer cells may be applied for targeted delivery of therapeutic radionuclides. This approach can extend the usefulness of current drugs and improve their efficacy, as the radiation can kill cancer cells resistant to the parent drug. To accelerate such efforts, NCI requests proposals for the development of innovative, molecularly targeted radiotherapeutics to treat cancer.

Project Goals

This contract solicitation seeks to stimulate research, development, and commercialization of innovative technologies that could fully utilize the potential of STRT, which will improve its safety and efficacy, leading to a reduction of overall treatment costs. Although, theranostic imaging might be required for identifying the suitable patients and tumors, imaging is NOT the principal objective of this solicitation. Particularly, the proposals addressing the following technology areas are encouraged:

- Design, synthesis, and evaluation of innovative radiotherapeutics
- Identification of an optimal choice of a radionuclide or mixture of radionuclides to treat individual tumor types
- Targeted radiotherapy by adding a therapeutic radionuclide to clinical-stage or FDA-approved imaging agents
- Targeted radiotherapy by adding a therapeutic radionuclide to FDA-cleared or targeted chemotherapy drugs or antibodies that are currently used in the clinical practice
- Development of an innovative targeted radionuclide therapy by conjugating a radionuclide with molecules characterized by high binding affinity to a well-validated target
- New treatment strategies
- Combination of STRT with more conventional treatment modalities

The short-term goal of the project is to perform feasibility studies for development and use of new STRT strategies for the treatment of cancer. The long-term goal of the project is to enable a small business to bring a fully developed STRT approach to the clinic and eventually to the market.

Phase I Activities and Expected Deliverables

- Phase I activities should support the technical feasibility of the innovative approach. Targets should be well-validated. If not, applicants are strongly encouraged to show proof of targeting using imaging techniques.
- If using existing drugs, then a letter of support or interest from the company that owns the drug should be included in the SBIR proposal.

Specific activities and deliverables during Phase I should include:

For new radiopharmaceuticals and treatment strategies

- Proof-of-concept of the conjugation or attachment of the radioisotope to the targeting agent.
- Physico-chemical characterization of the new radioconjugates, including stability, target specificity and affinity, etc.
- Pharmacokinetics and radiodosimetry studies in an appropriate animal model
- Assessment of toxicity to normal tissues.

Phase II Activities and Expected Deliverables

Where cooperation of other vendors or collaborators is critical for implementation of proposed technology, the offeror should provide evidence of such cooperation (through written partnering agreements, or letters of intent to enter into such agreements) as part of the Phase II proposal.

Specific activities and deliverables during Phase II should include:

For new radiopharmaceuticals and treatment strategies

- Demonstration of the manufacturing and scale-up scheme.
- IND-enabling studies carried out in a suitable pre-clinical environment.
- Proof-of-concept pre-clinical studies demonstrating improved therapeutic efficacy utilizing an appropriate animal model.
- When appropriate, demonstration of similar or higher specificity and sensitivity of the technology when compared to other technologies.

- Offerors are encouraged to demonstrate knowledge of appropriate FDA regulations and strategies for securing insurance reimbursement.

340 Validation of Mobile Technologies for Clinical Assessment, Monitoring, and Intervention

(Phase I proposals will **not** be accepted).

(Fast-Track proposals will **not** be accepted. Only Direct-to-Phase II proposals will be accepted)

Number of anticipated awards: 3 – 5

Budget (total costs, per award): 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

Mobile and wireless health technologies have grown exponentially in the past few years. Nearly 90% of U.S. adults have a cell phone and smartphone usage is above 60%. The ubiquity of mobile phone use has provided a platform for the delivery of health assessment, monitoring and interventions previously unavailable to health research and practice. The penetration of mobile phone use, even in remote areas, has provided a vehicle for the delivery of health care to people who have little to no other access to care. Wireless sensor technologies also have rapidly expanded in availability and function in the past few years. When paired with mobile and wireless devices, these sensor technologies provide passive, real-time data on a variety of physiological, behavioral, and environmental variables.

The range of health research and clinical practice affected by this mobile/wireless revolution is quite broad. Preventive health assessment and intervention applications for cancer associated behavioral risk factors including smoking, diet, and physical activity have increased dramatically. Mobile and wireless technologies have been employed for medical screening and diagnostic purposes, providing low cost and portable diagnostic tools that can be used in rural and underserved settings. Mobile and wireless technologies also have been used to improve chronic disease management for cancer risk factors such as obesity and diabetes, allowing healthcare providers to more intensively monitor patient status and intervene as needed while giving patients the tools to more effectively self-manage their disease.

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. Emerging mobile and wireless health technologies provide an opportunity to support innovation and progress towards NCI's mission of cancer prevention & control by 1) improving quality or access & reducing cost or burden of screening, diagnostic, treatment and follow-up care for cancer and related chronic diseases; and 2) improving lifestyle intervention efficacy and scalability for cancer related behavioral risk factors. The number of mobile and wireless health tools grows each year, but the majority of these tools have been inadequately validated in clinical research and practice. Adoption of these technologies requires more evaluation in clinical or behavioral research settings.

This topic encourages validation of mobile/wireless tools to support cancer prevention & control in clinical or behavioral applications. Technologies may include wireless sensors, smartphone applications, behavioral analytics and decision support software or integrated platforms for health assessment, monitoring or intervention delivery. This topic is not intended to support new technology development, but instead to clinically validate recently developed but not yet validated tools, in order to expand evidence of commercial potential and value.

Project Goals

The purpose of this topic is to support validation of mobile/wireless tools (including sensor technologies, smartphone applications, behavioral analytics and decision support software, or integrated platforms) for health assessment, monitoring or intervention delivery which focus on clinical or behavioral cancer prevention and control

objectives. In the short term, the topic aims to develop research evidence to support adoption of innovative mobile and wireless health technologies which support cancer prevention, treatment, disease management, or survivorship. Longer term goals are the integration of these technologies into clinical assessment and care, intervention delivery within health systems and accountable care organizations (ACOs), and health research.

Within the context of this topic, "mobile/wireless" health technologies are defined broadly to include any health technologies that wirelessly transmit data and that are intended for portable use. While the focus of these technologies are primarily devices worn on or carried by the individual throughout the day, devices that provide a level of portability not previously available (e.g. smaller and more portable version of a diagnostic scanner that transmits data wirelessly to the healthcare provider) is consistent with the scope of this initiative.

As noted previously, this topic is not intended to support the development of new technologies. Some additional programming may be required to customize or integrate the technology into the target clinical, health system, or related software environments, but these efforts should be sufficiently limited to retain a focus on validation and expanded evidence of commercial potential and value for health assessment or outcomes.

Responses to this topic are expected to address one or more of the following areas of mobile/wireless health research;

- Evaluation of the reliability of mobile/wireless screening, diagnostic, assessment or monitoring technologies & methods
- Evaluation of the validity of mobile/wireless screening, diagnostic, assessment or monitoring technologies & methods
- Evaluation of the efficacy and effectiveness of mobile/wireless technology and systems for behavioral analytics, clinical decision support, or intervention delivery.

Although extension of existing usability, acceptability, and feasibility of the mobile/wireless health tool may be considered as secondary research questions, they should not be the primary objectives of proposals submitted in response to this topic.

This topic will prioritize research that will rapidly validate an existing mobile/wireless tools in clinical care & monitoring, clinical decision support or intervention applications. It is anticipated that the clinical screening, diagnostic, assessment and monitoring technologies will provide the "gold standard" comparator for the new mobile or wireless tool being evaluated, but additional clinical measures may be needed to validate the new tool. However, in some instances, novel measures may not directly translate to existing clinical "gold standard" measures/technologies and alternative validation approaches may be required. Validation analyses could include but are not limited to agreement rates, sensitivity/specificity, and receiver operating curves (ROCs). Research evaluating the reliability of the technology is consistent with this topic. For outcome monitoring purposes, assessment of sensitivity to change is also appropriate for inclusion in proposals submitted under this topic.

Validation of mobile and wireless technologies and systems for intervention delivery or decision support are particularly encouraged. Dependent on the research question and technology under evaluation, research designs may include randomized controlled trials (RCTs), a series of single case designs, optimization designs (e.g. factorial, sequential) or quasi-experimental approaches such as interrupted time series and stepped-wedge designs. Projects that integrate and automate ongoing validation and/or outcomes evaluation (e.g. automated RCTs) in the commercial product are particularly encouraged. For additional information on evaluation of mHealth technologies please see ([http://www.ajpmonline.org/article/S0749-3797\(13\)00277-8/abstract](http://www.ajpmonline.org/article/S0749-3797(13)00277-8/abstract)). Primary clinical or behavioral outcomes may be supplemented with cost-effectiveness analyses where appropriate.

Pre-Submission Milestones for Direct-to-Phase II SBIR Technologies

All proposals submitted under this topic must provide evidence that significant development milestones for a specific mobile/wireless technology or system (detailed below) have already been achieved to demonstrate readiness for a Direct-to-Phase II SBIR contract. These milestones will be evaluated in addition to standard review criteria for all submissions.

- Provide evidence that a working prototype, including all major functional components of the technology, is ready for formal validation in a Phase II SBIR with minimal further development other than that required to perform the validation or outcomes research.
 - Products in beta version are particularly appropriate for this effort although recently released commercial products that do not have adequate validity or efficacy support are also encouraged.
- Provide documentation that the product to be evaluated has been developed based on theory and/or empirical evidence.
- Present evidence that appropriate focus groups, interviews, cognitive or user testing with potential end-users of the device/software tool, etc have been conducted to demonstrate that the feasibility, acceptability, and usability of the product have been established.
- Provide evidence that an established project team with appropriate expertise for the scope of work is in place to advise and support the small business on Phase II activities and outcomes. This team should include, but will not be limited to, personnel with training and research experience in clinical or intervention design, implementation, and statistical methods for validation/evaluation as appropriate for the proposed project.

Phase II Activities and Deliverables

- Provide documentation that the established project team with appropriate expertise for the scope of work is in place to advise and support the small business on Phase II activities and outcomes. This team should include, but will not be limited to, personnel with training & research experience in clinical trial or intervention design, implementation, and statistical methods for validation/evaluation as appropriate for the proposed project. Provide a report outlining team member credentials, specific project roles, and timelines for performance.
- Evaluate specific IT customization requirements to support hardware, software, or communications system integration of the technology into the target clinical setting, health system or service, or other relevant software environment in preparation for validation. Provide a report documenting the specific IT customization requirements and timelines for implementation.
- Test the integration of the technology into the target clinical setting, health system or service, or other relevant software environment in preparation for validation. Provide a report documenting the results of system testing and timelines for problem mitigation.
- Develop user support documentation to support all applicable potential users of the technology, including but not limited to patients/consumers, family/caregivers, and providers. Provide a report documenting user support resources including, but not limited to, links to online resources and copies of electronic or paper user support resources as appropriate.
- Prior to evaluation, provide a final report of the research plan including at a minimum:
 - Appropriate human subjects protection / IRB submission packages and documentation of approval for your research plan;
 - Final study design including aims, participant characteristics, recruiting plans, inclusion and exclusion criteria, measures, primary and secondary endpoints, design and comparison conditions (if appropriate), power analyses and sample size, and data analysis plan. Publication plan outlining potential research and whitepaper publications resulting from the research, including anticipated lead and co-author lists.
- Provide study progress reports quarterly, documenting recruitment and enrollment, retention, data QA/QC measure, and relevant study specific milestones.
- Prepare a tutorial session for presentation at NCI and/or via webinars describing and illustrating the technology and intended use.
- Include funds in budget to present Phase II findings and demonstrate the technology to an NCI evaluation panel.
- 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) 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.

009 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 use of CRISPR/CAS systems for genome editing is rapidly being adopted, 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. In fact, a number of large-scale screens using CRISPR/CAS tools have already been reported. However, much still needs to be learned about the efficiency CRISPR/CAS reagents such as their potential for off-target editing and in arrayed screening formats (i.e. single gene per well) as opposed to pooled screens. 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 in arrayed formats. 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 in arrayed format.

Deliverables Phase 1

- Make general observations regarding the knockout efficiency of CRISPR/CAS reagents that target ~20 genes with the intention of translating these constructs into arrayed screening applications.
 - 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., 96 or 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 strategic partnerships with large vendors to produce off-the-shelf CRISPR/CAS tools that incorporate insights gained during the course of this contract.

010 Assay Development for High-Throughput Screening of Chemicals of Toxicological Concern

(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

Adverse human health outcomes – a.k.a., “toxicity” – caused by pharmaceutical or environmental compounds are a major cause of drug development failure and public health concern. Methods to evaluate the potential of chemical compounds to induce toxicity are based largely on animal testing, are low-throughput and expensive while giving little insight into mechanisms of compound toxicity, and have not changed appreciably in the last 50 years despite enormous advances in science. Multiple efforts, including Tox21 in the U.S., REACH in the E.U., and multiple industrial collaborations, are attempting to develop in vitro methods to assess chemical toxicity. These programs must assess toxicity potential in every organ system and identify pathways and/or targets affected. Given the protean nature of these effects, it is likely that hundreds of in vitro assays will need to be developed and tested for their ability to read out chemical effects on particular cell types and pathways. Progress in the field is currently limited by the relatively small number of pathways and cell types that have been developed into high-throughput screening

(HTS)-ready assays, and the artificial nature of many of the assays that have been developed (e.g., immortalized/transformed cell lines, heterologous expression with lack of physiologically accurate regulation).

The development of HTS-ready assays which can report on particular pathways and cellular phenotypes across the full spectrum of pathway space and toxicological outcomes is needed. Such assays would need to meet strict performance criteria of robustness, reproducibility, and physiological relevance. The assays developed would need to be capable of being run in 384-well or (ideally) 1536-well format and must allow the testing of >100,000 samples per week.

Main Requirements

The outcome of this contract is expected to be one or more novel assays for targets, pathways, and cellular phenotypes related to any type of xenobiotic toxicity. These assays would utilize human cells, including immortalized cell lines, primary cells, and stem cell derived cells, and must be functional in multi-well format with characteristics suitable for automated high-throughput screening. Such assays should be novel, having metabolic capability, reflecting new pathways or cellular endpoints than are currently available, and be clearly connected to some type of human toxicological response. Such assays could find utility as in chemical assessment and risk management after validation.

Deliverables Phase 1

An assay that meets the requirements listed above and also meets the following:

- Develop a working assay in 96-well or denser (384, 1536) micro-well format
- Characterize the sensitivity, specificity, variability, reproducibility, signal: background, dynamic range, and accuracy of the assay, utilizing standard positive and negative controls, Z' values >0.5
- Demonstrate the utility of the assay by characterizing its ability to detect the effects of compounds known to affect the pathway/cellular phenotype, with a throughput of at least 10,000 samples/day with workstation automation
- Are not duplicative of assays already available commercially
- Deliver the assay/SOP to NCATS for evaluation

Deliverables Phase 2

- Demonstrate miniaturization of assay to work in at least 384-well (preferably 1536-well) format with same technical specifications as listed above
- Demonstrate amenability for HTS by successful testing of >100,000 samples/day in fully automated robotic format with maintenance of assay performance
- Deliver final assay/SOP to NCATS for evaluation.

011 Simple and Robust Reaction Progress Analyzer

(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

Process Analytical Technologies (PAT) that allow the progress of chemical reactions to be monitored over time are becoming increasingly important in the chemical and pharmaceutical industry. Online spectroscopic and chromatographic PAT technologies have emerged as valuable tools for monitoring and understanding chemical

reactions, however, the complexity and cost of these approaches limits their deployment and utilization in day to day chemical laboratory operations. While PAT technologies ideally afford a complete understanding of the growth and disappearance of all of the individual species formed or consumed during a chemical reaction, simpler approaches that record changes in easy to measure bulk properties of the reaction medium (e.g. conductivity, capacitance, viscosity, etc.) may also be useful in understanding reaction profiles. A simple, robust and affordable tool could enable the broader utilization of PAT by academic synthetic chemists as well as industrial chemists working in areas of discovery and early drug development (who are typically a significant subset of practicing chemists) that do not use PAT tools. Ideally, the integration of several inexpensive sensors technologies into a small probe, ideally with a smart-phone interface, could provide a useful and affordable tool for enabling the broader use of PAT by practicing chemists.

Main requirements

Robust, affordable and broadly applicable Reaction Progress Analyzer with a small footprint, integrating several inexpensive sensor technologies into a small probe, possibly with a smart-phone interface.

Deliverables Phase 1

Meets requirements listed above and also meets the following:

- Demonstration of the proof of concept of Reaction Progress Analyzer
- Demonstration of broad applicability to reaction monitoring
- Demonstration of cost and ease of use advantages compared to current state of the art
- Are not duplicative of instruments already available commercially
- Deliver the results to NCATS for evaluation

Deliverables Phase 2

- Miniaturization of the instrument if not achieved in Phase 1
- Development of user friendly interface
- Prototype instrument that meets all requirements listed above
- Deliver the results to NCATS for evaluation
- Explore strategic partnerships with larger vendors to produce off-the-shelf analyzer that incorporates insights gained during the course of this contract.

012 Online Real Time Metals Analysis at Low ppm Level

(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

The ability to rapidly measure metals at the low ppm levels is becoming increasingly important in pharmaceutical manufacturing. Ensuring the removal of metal impurities arising from residual organometallic catalysts is required to avoid toxicity associated with heavy metals. Current approaches (e. g. ICP MS) rely on the use of expensive equipment that cannot be conveniently co-located with the reaction and purification equipment where metal removal is performed, thus resulting in the need to transport laboratory samples for testing and adding time and cost to the drug development process. An improved approach would allow low ppm metals analysis to be performed at point of use, employing affordable, robust equipment that would be easy to operate by any lab technician (not requiring specialized training). Ideally, such an instrument could be used for the continuous monitoring of metal impurities associated with continuous processing operations. Finally, a technique that would be amenable to detect low ppm

levels of the entire suite of metals commonly used in modern synthetic organic chemistry (Pd, Rh, Cu, Zn, Fe, Ir, etc.), or at least a few metals, would be preferable to a technique that is specific to a single metal.

Main requirements

The outcome of this contract is expected to be an inexpensive and easy to use instrument that will be capable of measuring low ppm levels (at least <5 ppm) of a range of metals typically used in the pharmaceutical industry. The instrument would be co-located with the reaction and purification equipment where metal removal is performed, and preferably, amenable to continuous monitoring of metal impurities associated with continuous processing operations.

Deliverables Phase 1

Meets requirements listed above and also meets the following:

- Demonstration of a proof of concept metal analysis method
- Demonstration of required sensitivity, reproducibility and accuracy of the method
- Are not duplicative of methods that are already commercially available
- Demonstration of cost and ease of use advantages compared to current state of the art
- Deliver the results to NCATS for evaluation.

Deliverables Phase 2

- Miniaturization of the instrument if not achieved in Phase 1
- Prototype instrument that meets all requirements listed above
- Deliver the results to NCATS for evaluation
- Explore strategic partnerships with larger vendors to produce off-the-shelf instrument that incorporates insights gained during the course of this contract.

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, lung, and blood (including blood vessel), 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 programs, visit our website at: <http://www.nhlbi.nih.gov/sbir>

NHLBI Phase IIB Programs

The NHLBI 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 or STTR 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/STTR funding. In particular, applicants are expected to leverage their previous SBIR/STTR 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 or STTR 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 or STTR 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 Jennifer Shieh, Ph.D., at 301-443-8785 or jennifer.shieh@nih.gov for additional information.

Limited Amount of Award

For budgetary, administrative, or programmatic reasons, the NHLBI may not fund a proposal and does not intend to fund proposals for more than the budget listed for each topic.

This solicitation invites proposals in the following areas.

087 Transcatheter Cerclage Mitral Annuloplasty (SBIR-TT)

(Fast-Track proposals will be accepted.)

(Direct-to-Phase II proposals will be accepted.)

Number of anticipated awards: 2

Budget (total costs): Phase I: up to \$300,000 for 18 months; Phase II: up to \$3,000,000 for 3 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

Secondary mitral valve regurgitation is a common contributor to heart failure, and is caused by annular expansion and papillary muscle traction. Secondary mitral valve regurgitation may be amenable to surgical annuloplasty, which reduces mitral valve annular size to enhance coaptation of the otherwise normal leaflets.

The NHLBI Division of Intramural Research (DIR) laboratory of Dr. Robert Lederman has developed a novel non-surgical catheter-based approach to annuloplasty called “cerclage annuloplasty.” Using X-ray fluoroscopy, catheter tools traverse a trajectory including the coronary sinus, a basal septal perforator vein, a short transmural pathway through the interventricular septum, and the right ventricular inflow tract. Once this pathway is established, circumferential tension is applied to reduce annular dimensions.

The NHLBI DIR lab has established the potential utility of cerclage annuloplasty in a porcine model of ischemic cardiomyopathy. To translate the project into humans will require development of commercial-grade interventional tools to make a clinical procedure simple and safe, including device and regulatory development, followed by early clinical testing.

A catheter-based annuloplasty-like cerclage may have value as a primary therapy for secondary mitral regurgitation. Alternatively, cerclage annuloplasty may have value as an adjunctive therapy combined, for example, with leaflet clip procedures. It may also have value in less-severe disease not justifying surgical morbidity, or to relieve symptoms accompanied by severe comorbidity precluding surgical therapy.

Project Goals

The goal of the project is to develop a system of devices to test the safety and feasibility of transcatheter cerclage mitral annuloplasty in patients to treat secondary mitral regurgitation. Phase I activities include the development and test of working prototypes in vivo. Phase II activities include further refinement of the system and complete regulatory development to allow clinical testing in patients, including an Investigational Device Exemption (IDE) and production of sufficient prototypes for a clinical trial.

Additional Project Information

Investigators are expected to have prior success in developing catheter-based structural heart implants from concept into first-in-human clinical testing, and preferably into clinical marketing. Investigator teams need to have advanced capabilities and working experience in design, prototyping, and manufacturing using metallic components such as nitinol and/or cobalt-chromium, and thermoplastics, and their interaction, with attention to mechanical durability and biocompatibility as permanent implants. Principal investigators are expected to contribute at least 25% effort, and preference will be given to projects with even greater investigator effort.

Offerors are advised to plan for travel to NHLBI in Bethesda Maryland, and are expected to plan meetings at project initiation, mid-project to determine what iteration is necessary, and at project completion.

This is an SBIR Technology Transfer (TT) contract topic from the NHLBI. This is a program whereby inventions from the NHLBI Division of Intramural Research are licensed on an exclusive or non-exclusive basis to qualified small businesses with the intent that those businesses develop these inventions into commercial products that benefit the public. The contractor funded under this NHLBI SBIR TT contract topic shall work closely with the NHLBI inventor(s) of this technology, who will assist in pre-clinical experiments and will perform a clinical trial using the offeror's product. The NHLBI inventor(s) will provide assistance in a collaborative manner with catheter designs, procedure techniques, clinical considerations, and discussions during the entire award period.

An SBIR TT contractor will automatically be granted a royalty-free, non-exclusive license to make and use, but not to sell or offer to sell, for background inventions covered by the NIH-owned patent rights only within the scope and term of the award. However, an SBIR offeror or SBIR contractor can apply for an exclusive or non-exclusive commercialization license to make, use, and sell products or services incorporating the NIH background invention(s). Offerors submitting an SBIR contract proposal in response to this solicitation are strongly encouraged to concurrently submit an application for a commercialization license to such background invention(s). Under the NHLBI SBIR TT program, the SBIR contract award process will be conducted in parallel with, but separate from, the review of any applications for a commercialization license. The criteria to determine eligibility of an offeror to receive a commercialization license will depend on their technical eligibility to receive the SBIR award but will be assessed independently of the SBIR process.

To apply for a license to commercialize this NIH invention, an SBIR offeror or contractor must submit a license application to the NIH Licensing and Patenting Manager: Michael Shmilovich, shmilovm@mail.nih.gov or (301) 435-5019. A license application and model license agreements are available at <http://www.ott.nih.gov/sites/default/files/documents/pdfs/licapp.pdf> and <http://www.ott.nih.gov/forms-model-agreements#MLA>

This license application provides NIH with information about the potential licensee, some of the terms desired, and the potential licensee's plans for development and/or commercialization of the invention. License applications will be treated in accordance with Federal patent licensing regulations as provided in 37 CFR Part 404. A further description of the NIH licensing process is available at <http://www.ott.nih.gov/licensing-process>. NIH will notify an

SBIR offeror who has submitted an application for an exclusive commercialization license if another application for an exclusive license to the background invention is received at any time before such a license is granted.

NHLBI will share any unpublished patent applications with offerors subject to their agreement to the terms and execution of a confidential disclosure agreement.

Any invention developed by the contractor during the course of the NIH TT contract period of performance will be owned by the contractor subject to the terms of Section 5.5 Technical Data Rights in this Request For Proposals.

Relevant NIH Publications and Patent applications

- Kim JH, Kocaturk O, Ozturk C, Faranesh AZ, Sonmez M, Sampath S, Saikus C, Kim AH, Raman VK, Derbyshire JA, Schenke WH, Wright VJ, Berry C, McVeigh ER, Lederman RJ, *Journal of the American College of Cardiology*. 2009;54(7):638-651, Pubmed ID 19660696, posted at <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3034128>.
- Device for protecting coronary arteries against compression during transcatheter mitral valve annuloplasty (“Transcatheter Coronary Sinus Mitral Valve Annuloplasty Procedure and Coronary Artery and Myocardial Protection Device”). JH Kim, RJ Lederman, O Kocaturk. Assignee: The United States of America. U.S. Provisional Patent Applications 60/858,716 and 60/932,611 filed November 14, 2006 and May 31, 2007 respectively (expired); International Patent Application PCT/US2007/023876 filed November 13, 2007 (expired), U.S. Patent Application 12/514,990 filed May 15, 2009, European Patent Application 07861997. NIH reference no. E-249-2006.
- Cerclage locking device and delivery system (“Tensioning Device and Methods of Use”). O Kocaturk. Assignee: The United States of America. U.S. Provisional Patent Application 61/157,267 filed March 4, 2009 (expired), International Patent Application PCT/US2010/026245 filed March 4, 2010 (expired), U.S. Patent Application 13/254,160 filed August 31, 2011. NIH reference no. E-048-2009.
- An expandable mesh target and capture device for transcatheter cerclage annuloplasty. (“Method and Devices for Transcatheter Cerclage Annuloplasty”). RJ Lederman, O Kocaturk. Assignee: The United States of America. U.S. Provisional Patent Application 61/383,061 filed September 15, 2010 (expired), International Patent Application PCT/US2011/51748 filed September 15, 2011. NIH reference no. E-108-2010.

Phase I Activities and Expected Deliverables

Phase I deliverables include a mature system of purpose-built devices that allow transcatheter cerclage annuloplasty in a large animal model, and that is sufficiently mature to serve as the basis for a pre-IDE meeting with FDA.

Transcatheter cerclage annuloplasty is a new procedure requiring purpose-built devices. It uses devices and techniques typical of transcatheter arterial interventional procedures, such as catheter guides, subselective vascular instrumentation, target tissue traversal, and target-capture-recovery devices.

Several purpose-built component devices will be needed for serial procedural steps including:

- A device to engage a target septal perforator coronary vein via the coronary sinus. One option would be a coronary sinus catheter with an outer balloon to pressurize the coronary veins, to be used along with a coaxial microcatheter selectively to identify, navigate to, and engage the desired septal perforator vein.
- A device or system positioned in the right ventricular outflow tract to serve as a target for septal traversal and to capture the traversal device, while preventing trabecular or subvalvar entrapment of the traversal device. One option would resemble a retrievable self-expanding stent shaped to match the right ventricular infundibulum, and should accommodate variable reentry sites. Both the coronary sinus traversal and right ventricular target-recovery elements probably should return through a common introducer sheath, for example through a single jugular, axillary, or femoral vein and therefore should be 10-12Fr or smaller.
- A device to traverse the myocardium between the target septal perforator vein and the right ventricular target and capture device. This has been accomplished using coronary guidewires. The myocardial traversal system should be small enough that inadvertent venous perforation would be well tolerated, and therefore ideally

approximately 0.014” before larger devices are introduced. The device should be visible to the operator using the selected image guidance modality. A successful traversal device must accommodate reliable and safe capture/ensnarement/retrieval, without mechanical disruption, once it has reentered the right heart. A desired embodiment would readily transition from myocardial traversal to delivery of the tension device (below) in a single device and procedure step.

- A permanent cerclage tension or suture device. This includes a system to exchange the captured traversal device for the permanent tension device or suture. The device or suture must not erode through myocardium after deployment. The myocardial tension device or suture should distribute erosive radial forces and should probably be at least 1mm in width. Novel biocompatible materials/ solutions are invited, that are suitable for permanent implantation. The tension or suture device must have a mechanism to apply graded tension interactively under imaging guidance, and should be completely reversible at all times. A preclinical performance criterion is the ability to impart 800g linear cerclage tension force without causing angiographic obstruction of an entrapped coronary artery. A second preclinical performance criterion is the ability to reduce the septal-lateral dimension of a dilated mitral annulus by 20% in vivo. This tension should be reversible during the procedure, and should be fixed at the conclusion of the procedure. The tension fixation system should assure no circumferential displacement or loss of tension during application of fixation. The choice of a flexible versus rigid tension element or suture should be justified. Solutions are invited that can operate safely despite previous coronary sinus-based left ventricular pacing leads.
- A device deployed along the tension device to protect entrapped coronary arteries against unintended compression during application of cerclage tension, and a mechanism to deploy it and to guard against inadvertent displacement.

Key user requirements include (1) Non-surgical procedure conduct. (2) A procedure that can be completed in less than approximately one hour after vascular access is obtained. Solutions are encouraged to minimize the number of procedural steps and reduce procedural complexity. For example, the myocardial traversal system could be combined with the tension delivery/exchange device. (3) Clear imaging/visual targets for skill-driven procedure steps such as myocardial tissue traversal. (4) Reversibility of tension delivery until the conclusion of the procedure to assure success and freedom from immediate complications, and preferably even after conclusion of the procedure. (5) Freedom from immediate complications including coronary artery compression, tricuspid valve regurgitation, and iatrogenic atrioventricular conduction block.

The NHLBI Division of Intramural Research laboratory is prepared to teach the awardee how to perform the procedure, and is willing to perform in vivo proof-of-principal experiments in up to six non-survival NHLBI swine experiments. The offeror is expected independently to perform animal testing as needed to meet phase I requirements.

Individual prototypes shall include solutions for all of the procedure steps outlined above. Offerors shall include a timeline with milestones in order to produce the specific Phase I deliverables, in sequence, which include each of the following:

- Concept development and prototype devices for initial review. These may be preceded by refined concept drawings. A strategy for final concept selection shall be outlined clearly.
- Prototypes for simulated use testing in an anatomic model, and for tissue testing if applicable.
- Prototypes for simulated use in ex vivo tissue specimens such as pig hearts.
- Prototypes that undergo non-survival large animal testing, with attention to materials biocompatibility. The offeror must independently demonstrate device requirements in vivo.
- Iteration re-design and testing is expected.
- Final proof-of-concept devices.
- Detailed report of pre-Investigational Device Exemption (IDE) interaction with the US Food and Drug Administration (FDA) to establish an initial plan for clinical device development. This plan shall include a comprehensive description of the proposed Bill of Materials, Quality System, plan for addressing clinical development issues raised in interactions with the FDA, and the summary of mutual understanding with FDA

NIH operators will assess completion of Phase I by testing in swine a complete and mature system of purpose-built devices able to successfully and reliably complete cerclage annuloplasty procedure within a reasonable period of time (such as 30 minutes). This shall be a complete procedure including myocardial traversal, septal-lateral dimension reduction 30%, coronary artery protection, reversibility of tension, and fixation of tension with a biocompatible permanent implant that is near final clinical design lock. The result shall be durable as demonstrated in animal survival for at least 4 weeks, and the results should be sufficient to support a meaningful pre-IDE meeting to plan phase II. The results will be used in deciding whether to proceed to a phase II award.

Final payment is contingent on meeting all of the above requirements.

Phase II Activities and Expected Deliverables

The final deliverable is an awarded Investigational Device Exemption for first-in-human testing, as well as a supply of devices required to perform the IDE clinical trial in at least 10 subjects.

The NHLBI Division of Intramural Research lab offers to teach the contractor how to perform the procedure, how to evaluate the procedure results, and is willing to design the IDE clinical trial. The NHLBI Division of Intramural Research laboratory offers to perform the clinical trial at no additional cost to the offeror, immediately after Phase II is concluded.

Award of an IDE, including complete documentation, and a suitable supply of clinical materials would constitute the final Phase II deliverable.

The offeror should provide clear project milestones that trigger review and payment. Representative project milestones include, not necessarily sequentially

- a device build and short-term survival study to identify additional failure modes
- elements of a quality system including product specification, design and failure mode analysis, design verification and test plan, biocompatibility and sterility assessment and plan, design review, design freeze
- manufacturing plan
- iterative ex vivo testing in human cadaver explants and animal explants
- iteration for unexpected design or device failure
- FDA pre-IDE meeting #1 and #2
- modeling and fatigue study for chronic implant
- chronic GLP animal studies
- design of clinical protocol including informed consent, risk analysis for early feasibility, and case report form, whether or not conducted in collaboration with NHLBI Division of Intramural Research laboratory
- preparation of IDE
- submission and resubmission of IDE
- manufacturing of test articles.

The offeror is expected to conduct animal experiments and provide care as required to obtain the IDE. The offeror is advised to propose how to proceed in case of hold from FDA.

088 Closure Devices for Transcaval Access to the Abdominal Aorta

(Fast-Track proposals will be accepted)

(Direct-to-Phase II proposals will be accepted)

Number of anticipated awards: 2

Budget (total costs): Phase I: up to \$300,000 for 18 months; Phase II: up to \$3,000,000 for 3 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

Transcaval access is a new catheter technique that enables non-surgical introduction of large devices, such as transcatheter heart valves, into the abdominal aorta. It has been performed successfully in dozens of patients to date. The resulting aorto-caval fistula is closed with commercial nitinol occluder devices, off-label, that have important limitations such as residual bleeding. This contract solicitation is intended to support a purpose-built closure device for transcaval access to the abdominal aorta.

Project Goals

The goal of the project is to develop a purpose-built closure device to enable safe and reliable transcaval aortic access for procedures such as transcatheter aortic valve replacement. Phase I would develop and test working prototypes in vivo. Phase II would further refine the system and complete regulatory development to allow clinical testing in patients, including an Investigational Device Exemption and sufficient prototypes for a clinical trial.

Additional Project Information

Investigators are expected to have prior success in developing catheter-based structural heart implants from concept into first-in-human clinical testing, and preferably into clinical marketing. Investigator teams need to have advanced capabilities and working experience in design, prototyping, and manufacturing using metallic components such as nitinol and/or cobalt-chromium, and thermoplastics, and their interaction, with attention to mechanical durability and biocompatibility as permanent implants. Principal investigators are expected to contribute at least 25% effort, and preference will be given to projects with even greater investigator effort.

Offerors are advised to plan for travel to NHLBI in Bethesda Maryland, and are expected to plan meetings at project initiation, mid-project to determine what iteration is necessary, and at project completion.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a working prototype successfully tested in vivo in swine. The NHLBI Division of Intramural Research laboratory is willing to participate in the prototype evaluation, and is willing to perform six non-survival porcine experiments to test prototype iterations. The NHLBI Division of Intramural Research laboratory will test the final prototype in vivo. The offeror is expected to perform additional animal testing if necessary.

Device requirements include:

- Transcatheter delivery from the vena cava to the abdominal aorta through the interventional therapy introducer sheath
- Safe and reliable hemostasis of the aorto-caval fistula created by the caval aortic access sheath despite anticoagulation
- Traverse and occlude the transaortic mural rent created by caval-aortic access using introducer sheaths that are 7mm, 8.2mm, and 9.3mm in outer diameter and perhaps other sizes as well
- Immediately and hemostatically appose to the aortic endoluminal wall after deployment. Must enable complete apposition of the closure device against the aortic surfaces and aortic mural hole despite a range of unpredictable adverse geometries caused by calcification, atheroma, ectasia, angulation, etc.
- Must resist inadvertent pull-through during deployment and apposition, which would be associated with hemorrhage and aortic injury
- Conform to the aortic lumen during deployment without injury or disruption to the aorta
- Telescope to accommodate variable and even unpredictable aorto-caval distances, typically 3-14mm, with an average of 8mm.

- Must accommodate disparate crossing angle (near horizontal) and deployment angles (nearly vertical) yet close a tract closer to horizontal. A desirable delivery system imposes horizontal tension from the percutaneous caval catheter.
- Must be repositionable and retrievable, and delivers through a system not larger than 14Fr
- Allow uninterrupted guidewire access between the cava and aorta during and after deployment until after release
- Conspicuous under X-ray fluoroscopy
- Does not significantly interfere with MRI afterwards
- The offeror must independently demonstrate device requirements in vivo.

NIH operators will assess completion of Phase I, by testing in swine a complete and mature system of purpose-built devices for closure of transcaval aortic access ports, before proceeding to Phase II. This shall include a biocompatible permanent implant that is near final clinical design. The result shall be durable as demonstrated in animal survival for at least 2 weeks, and the results should be sufficient to support a meaningful pre-IDE meeting with FDA to plan phase II. The offeror must report a detailed summary of pre-IDE interactions with FDA, including the summary of mutual understanding.

Final payment is contingent on meeting all of the above requirements.

Phase II Activities and Expected Deliverables

In addition to meeting all requirements for Phase I, a phase II award would allow all testing and regulatory development for the device to be used in human investigation in the United States, under Investigational Device Exemption (IDE).

The NHLBI Division of Intramural Research lab offers to teach the contractor how to perform the procedure, how to evaluate the procedure results, and is willing to design the IDE clinical trial at no cost to the awardee. The NHLBI Division of Intramural Research lab offers to perform an IDE clinical trial at no cost to the awardee immediately after phase II is concluded. Award of an IDE, including complete documentation, and a suitable supply of clinical materials would constitute the final Phase II deliverable.

The offeror should provide clear project milestones that trigger review and payment. Representative project milestones include, not necessarily sequentially

- a device build and short-term survival study to identify additional failure modes
- elements of a quality system including product specification, design and failure mode analysis, design verification and test plan, biocompatibility and sterility assessment and plan, design review, design freeze
- manufacturing plan
- iterative ex vivo testing in human cadaver explants and animal explants
- iteration for unexpected design or device failure
- FDA pre-IDE meeting #1 and #2
- modeling and fatigue study for chronic implant
- chronic GLP animal studies
- design of clinical protocol including informed consent, risk analysis for early feasibility, and case report form, whether or not conducted in collaboration with NHLBI Division of Intramural Research laboratory
- preparation of IDE
- submission and resubmission of IDE
- manufacturing of test articles.

The offeror is expected to conduct animal experiments and provide care as required to obtain the IDE. The offeror is advised to propose how to proceed in case of hold from FDA.

089 In-bore Defibrillation for Invasive MRI Cardiology Procedures

(Fast-Track proposals will be accepted.)

(Direct-to-Phase II 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 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 seeks a prototype external defibrillator for operation inside the MRI bore, especially during invasive MRI cardiology procedures.

Project Goals

The goal of the project is to develop an external cardiac defibrillator system for operation inside the MRI bore. Phase I would develop and test a working prototype in vivo. Phase II would further develop the system and complete regulatory development to allow clinical testing in patients.

Phase I Activities and Expected Deliverables

A phase I award would develop and test a working prototype suitable for in vivo testing in large mammals such as swine. The NHLBI Division of Intramural Research laboratory will test the final prototype in vivo. The offeror should obtain animal care assurances.

Device requirements include:

- Operation on a 1.5T MRI scanner, including specifically the interventional MRI systems installed at NHLBI (Siemens Aera)
- Operation in tandem with standard anterior and posterior body surface array coils (ie Siemens Body array 18).
- Operation in tandem with standard surface ECG electrodes to allow cardiac monitoring and MRI gating, or provision of suitable alternatives that provide the same functionality
- Includes affixed disposable defibrillator electrodes, analogous to “R2” type multifunction electrodes used in standard external defibrillation systems. Electrodes must be MRI-compatible and not cause significant image artifacts.
- External pacing capability is highly desirable
- Consideration must be made to mechanical displacement forces induced in the patient during defibrillation and pacing operation inside the MRI bore
- Incorporates a controller, defibrillator, detector, power supply, and all electrodes and cabling suitable for safe deployment inside the MRI system with regarding to patient use and the magnetic field. Use of modified or unmodified commercial systems or subsystems is acceptable, as would situating components or subsystems outside the scanner connected through a penetration panel.
- Safe connection outside the suite for remote technologist operation is desirable
- Freedom from important electromagnetic interference with MR imaging, and from electromagnetic coupling with MRI surface coils, except during defibrillation
- Rapid re-charge for repeat defibrillation within 15 seconds repeated at least 10 times, with current, waveform, and user operation characteristics resembling contemporary commercial external pacing/defibrillator systems used in clinical cardiac electrophysiology laboratories
- Successful operation in a large mammal model of ventricular fibrillation, such as naïve swine, performed independently by the offeror.

- A detailed report of pre-IDE interactions with the Food and Drug Administration to identify requirements for IDE development under Phase II, including the summary of mutual understanding.

Phase II Activities and Expected Deliverables

In addition to meeting all requirements for Phase I, a phase II award would allow electrical and 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 NHLBI Division of Intramural Research lab offers to perform an IDE clinical trial at no cost to the awardee after the conclusion of Phase II. Award of an IDE license or 510(k) clearance, including disclosure of all accompanying documentation, and a supply of clinical devices necessary to complete the IDE or use in patients (under 510k), would constitute the Phase II deliverable.

The offeror is expected to conduct animal experiments and provide care as required to obtain the IDE. The offeror is advised to propose how to proceed in case of hold from FDA.

090 Devices to Close Ductus Arteriosus in Premature Infants

(Fast-Track proposals will be accepted.)

(Direct-to-Phase II proposals will **not** be accepted.)

Number of anticipated awards: 1

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

Premature infants with hemodynamically significant patent ductus arteriosus suffer increased mortality and significant morbidity. A minimally invasive, catheter based treatment strategy would be attractive.

Project Goals

The goal of the project is to develop an implantable patent ductus arteriosus closure device to be safely delivered through the peripheral vasculature of a premature infant. First, a prototype would be developed and tested in animals, and ultimately a clinical-grade device would undergo regulatory development for clinical testing at NIH.

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

It is recognized that available animal models may not match the desired human in vivo geometry of the device.

Offerors are advised to plan for travel to NHLBI in Bethesda Maryland, and are expected to plan meetings at project initiation, mid-project to determine what iteration is necessary, and at project completion.

Phase I Activities and Expected Deliverables

Phase I activities would include the development and test of a patent ductus arteriosus closure device prototype suitable for premature infants. An NHLBI Division of Intramural Research (DIR) laboratory will test the final prototype in vivo, at no expense to the offeror. The offeror is expected independently to perform animal testing as needed to meet Phase I requirements.

Device requirements include:

- Premature infant patent ductus arteriosus closure device must be delivered through a 3 or 4 French delivery system. Strong preference will be given to smaller delivery systems.
- Release must be controllable including ability to reposition and retrieve.
- The system must assure freedom from device migration and embolization.
- The delivery system and device must be conspicuous under a proposed image-guidance modality, whether ultrasound, X-ray, MRI, or all. Preference will be given to combined X-ray and ultrasound conspicuity.
- Devices must be occlusive. Devices need to be tailored to work in a “tubular” ductus.
- Devices must not obstruct pulmonary artery or aortic blood flow, and must not contribute to stenosis of neighboring vessels.
- Devices should be suitable for antegrade (transjugular or transfemoral) or retrograde (transfemoral) aortic approach.
- The offeror must independently demonstrate device requirements in a ductus arteriosus in vivo.
- The results of a pre-IDE meeting with FDA CDRH, which indicates a sufficiently mature device and which will guide Phase II activities.
- Final payment is contingent on meeting all of the above requirements.

Phase II Activities and Expected Deliverables

In addition to meeting all requirements specified for Phase I, Phase II activities include mechanical and safety testing and regulatory development for the device to be used in human investigation, whether under Investigational Device Exemption (IDE) or under 510(k) marketing clearance. The NHLBI DIR laboratory offers to perform an IDE clinical trial at no cost to the awardee. Complete IDE or 510(k) documentation and license and a suitable supply of clinical materials would constitute the final deliverable. The offeror will provide a complete report of prior investigation along with all other elements of the IDE application and accompanying regulatory correspondence.

The offeror should provide clear project milestones that trigger review and payment. Representative project milestones include (not necessarily in sequential order):

- a device build and short-term survival study to identify additional failure modes
- elements of a quality system including product specification, design and failure mode analysis, design verification and test plan, biocompatibility and sterility assessment and plan, design review, design freeze
- manufacturing plan
- iterative ex vivo testing such as animal explants
- iteration for unexpected design or device failure
- FDA pre-IDE meeting #1 and #2
- modeling and fatigue study for chronic implant
- chronic GLP animal studies
- design of clinical protocol including informed consent, risk analysis for early feasibility, and case report form, whether or not conducted in collaboration with NHLBI Division of Intramural Research laboratory
- preparation of IDE
- submission and resubmission of IDE
- manufacturing of test articles

The offeror is expected to conduct animal experiments and provide care as required to obtain the IDE. The offeror is advised to propose how to proceed in case of hold from FDA.

091 Therapeutic Delivery of ADP-ribosylarginine Hydrolase

(Fast-Track proposals will not be accepted)

(Direct-to-Phase II proposals will **not** be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$250,000 for 18 months; Phase II: up to \$1,500,000 for 3 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

ADP-ribosyl-acceptor hydrolases (ARH) comprise a family of enzymes, which cleave the ADP-ribose-acceptor bond and reverse the effects of host and exogenous ADP-ribosyltransferases. ARH1 controls the amount of ADP-ribose-arginine in proteins, by reversing the ADP-ribosylation of arginine within host proteins. Previous studies showed that ARH1 counteracted in mice the pathology of cholera toxin, an NAD:arginine ADP-ribosyltransferase. ARH1 had a similar effect on Pseudomonas type III cytotoxins. Thus, the ability to deliver ARH1 into mammalian cells could have a positive therapeutic outcome in lung disease of cystic fibrosis patients. Since ARH1 is a member of the ARH/macro domain family of proteins that cleave the ADP-ribose-acceptor linkage with different substrate specificities, the findings in this study may have broad applicability, including the treatment of diseases characterized by oxidative stress and aging.

Project Goals

A phase I award would develop and test the potency of an ARH1-delivery platform prototype. The awardee would produce a deliverable that would be tested in cultured cells for the efficiency of ARH1 delivery and for the potency of ARH1 for the reversal of the pathology associated with Pseudomonas ExoS and ExoT.

A phase II award would allow production of an ARH1-delivery platform to test for the ability of ARH1 to reverse the pathology of 1) Pseudomonas type III-delivered ExoS and/or ExoT in ARH1-deficient mice and 2) cholera toxin in an intestinal model as proofs of principle. Safety testing and regulatory development of the chimeras would be conducted for use in human investigation. The awardee would conduct the studies with ARH1-deficient cells and mouse trials in collaboration with the investigator.

Phase I Activities and Expected Deliverables

- Construction of the ARH1-delivery platform as a gene fusion
- Production and purification > 50 mg amounts ARH1-delivery platform
- Removal of contaminating LPS from ARH1-delivery platform
- Determination that ARH1 translocation efficiency was equivalent to a positive control cargo in epithelial and lung cells and ARH-1 deficient lung cells
- Positive correlation for the ability of ARH1 to reverse the pathology of Pseudomonas type III-delivered ExoS and/or ExoT in epithelial and lung cells and ARH1-deficient cells

Phase II Activities and Expected Deliverables

- Production and purification >0.2 g amounts ARH1-delivery platform
- Removal of contaminating LPS from ARH1-delivery platform
- Positive correlation for the ability of ARH1 to reverse the pathology of 1) Pseudomonas type III-delivered ExoS and/or ExoT in the lungs of ARH1-deficient mice and 2) cholera toxin in an intestinal model conducted in collaboration with the investigator.

092 Selective Silencing of Stat3 Signaling to Treat Relapsed Disease After Transplantation

(Fast-Track proposals will be accepted)

(Direct-to-Phase II proposals will be accepted.)

Number of anticipated awards: 2

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

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is predominantly used to treat and cure hematologic malignancies, controlling disease through an immune-mediated graft versus malignancy effect. Relapse after allo-SCT remains a major cause of treatment failure, occurring in up to 40-80% of patients in high risk groups. Despite multiple therapeutic approaches, the outcomes after relapse are poor with less than 10% of patients surviving 2 years, especially when disease relapse occurs within 6 months of transplant. Evasion from immune attack and modification of the immune system by the disease (immune-editing effects) are proposed as a mechanism of post-transplant relapse.

Signal Transducer and Activator of Transcription 3 (STAT3) signaling is constitutively activated in most acute leukemia and other hematologic malignancies, allowing disease progression. Recent murine and human studies report that the STAT3 transcription factor plays a key role in the immunosuppressive tumor microenvironment which hampers an effective immune response against the tumor. Work in the laboratory of Dr. John Barrett in the NHLBI Division of Intramural Research reveals that blockade of STAT3 in myeloid cells overcomes the negative immune-editing effects of leukemia. Other research has also recently demonstrated that selective blockage of STAT3 in myeloid cells induces potent tumor antigen-specific immune responses, resulting in leukemia eradication in mouse models.

It is proposed that disease control could be achieved using selective STAT3 inhibitors to target hematologic malignancies, promote graft versus malignancy effects, and reactivate the immune response against relapse after allo-SCT. If the therapeutic efficacy of STAT3 blockade were established in the context of post-transplant relapse, treatment could logically be extended as post-remission therapy for all patients with myeloid malignancies in order to prevent recurrence of diseases. Selective STAT3 blockers may also find a therapeutic role in the control of solid tumors where immune suppression by the tumor is mediated by STAT3 activity.

Project Goals

The purpose of this project is to support the commercial development of selective STAT3 inhibitors as a treatment for relapsed disease after stem cell transplantation. STAT3 inhibitors should be designed to selectively target myeloid cells or hematologic malignancies, with no or minimal effects on STAT3 signaling in T cells or other immune-effector cell populations. The expected properties of selective STAT3 inhibitors in post-transplant relapse are not limited to direct toxicities against leukemia but include immune-modulation to promote graft versus malignancy effects. The goal of Phase I and II activities in this project is to develop a good manufacturing process (GMP) technique to generate selective STAT3 inhibitors for post-transplant relapse. After completion of the Phase I and II activities of this contract, a clinical trial of the selective STAT3 inhibitor could be conducted with the NIH Stem Cell Allogeneic Transplant Section, Hematology Branch at NHLBI for treatment of leukemia relapse after stem cell transplantation.

Offerors should include in their proposal:

- Clear description of the nature of the product (small molecule, engineered gene product, etc)
- Evidence of ownership or licensing of the product
- Evidence of experience and resources in GMP techniques for the commercialization of products

Phase I Activities and Expected Deliverables

- Demonstrate selectivity of STAT3 inhibition using human cells (leukemia cells, normal hematopoietic cells and lymphocytes)
- Demonstrate efficacy using potency assays, including in vitro reversal of leukemia-induced blockade of lymphocyte immune response
- Characterize mechanism of selectivity of STAT3 inhibition in myeloid cells or other malignant cells
- Initiation of the development of GMP grade STAT3 inhibitor

Specific Deliverables

- A complete standard operating procedure for generating GMP grade selective STAT3 inhibitors

Phase II Activities and Expected Deliverables

- IND-enabling toxicology studies in rodent and non-rodent models.

Specific Deliverables

- Validated potency and specificity of selective STAT3 inhibitors in leukemic cells. Toxicology studies demonstrating safety of reagents used

093 Cellular Immunotherapy After Stem Cell Transplantation

(Fast-Track proposals will be accepted.)

(Direct-to-Phase II proposals will be accepted.)

Number of anticipated awards: 2

Budget (total costs): Phase I: up to \$225,000 for 1 year Phase II: up to \$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 contract topic is intended to support the production of clinical-grade lentiviral vectors for the development of antigen-specific T cell therapy to improve the outcome of high-risk patients undergoing stem cell transplantation (SCT). Preclinical research in the laboratory of Dr. John Barrett in the NHLBI Division of Intramural Research (DIR) has identified a technique to generate powerful viral antigen and tumor antigen-specific T cells. Manufacture of these cells would initially be developed within the NIH Clinical Center and tested in Phase I/II clinical trials conducted within NIH (NHLBI, Stem Cell Allogeneic Transplant Section, Hematology Branch). The manufacture of such T cells for the clinical trials will require the large scale production of several lentiviral vectors that meet regulatory requirements prior to using them in the production of GMP-grade T cell products for clinical use. These antigen-specific T cells would be used for the prevention and treatment of life-threatening complications due to viral infections and relapse of hematological diseases in stem cell transplant recipients suffering from a variety of hematological disorders, including myelodysplastic syndrome (MDS), aplastic anemia, and leukemia and other lymphoproliferative and myeloproliferative diseases.

Project Goals

The long-term goal of this project is the development and early commercialization of a range of lymphocyte products to control virus infection and prevent or treat relapse of the underlying hematologic diseases post SCT. Phase I/II clinical trials would be conducted within NIH (NHLBI, Stem Cell Allogeneic Transplant Section,

Hematology Branch) to test safety and subsequently efficacy of antigen-specific T cells in (1) preventing or treating relapse of hematological diseases after transplant and (2) prevention and treatment of viral related complications after transplant.

Phase I Activities and Expected Deliverables

Phase I activities should support the development and validation of lentiviral vectors for gene delivery. The contracting NHLBI DIR laboratory is willing to provide feedback about design at all stages of development. The contracting DIR lab will test the final deliverable products for potency using several potency assays in vitro and in vivo in humanized mice.

Specific Deliverables

- Evaluate and optimize lentiviral vector constructs intended for clinical use.
- Develop and optimize methods to generate high titer lentiviral vectors possessing transduction efficiency of at least 70% in the human peripheral blood monocyte-derived dendritic cells.
- Develop methods to generate and transduce human dendritic cells in closed cell culture system.
- Manufacture GMP process-comparable lentiviral vectors for preclinical validation study in the NHLBI investigator's laboratory using cell culture and purification and concentration processes essentially identical to the GMP process but without the extensive qualification assays required for full GMP material.

Phase II Activities and Expected Deliverables

Phase II activities should support large scale manufacture of well-characterized lentiviral vectors under current Good Manufacturing Practices for use in Phase I/II clinical trials.

Specific Deliverables

- Validate the final lentiviral vector products for Replication Competent Lentivirus (RCL) and other safety issues and provide release testing to certify vectors for clinical use.
- Manufacture lentiviral vectors under current Good Manufacturing Practices for use in Phase I/II clinical trials. Provide Chemistry, Manufacturing, and Controls (CMC) documentation, Certificate of Analysis (CoA) to meet the regulatory requirements of FDA (Food and Drug Administration), IBCs (Institutional Biosafety Committees), IRB (Institutional Review Board), NIH RAC (Recombinant DNA Advisory Committee) and DSMB (Data Safety Monitoring Board) and support an Investigational New Drug (IND) and/or an Investigational Device Exemption (IDE).
- Assist investigators in pre-IND/IDE and IND/IDE meetings with FDA and other regulatory agencies.

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>.

029 Development of Novel Influenza Antivirals

(Fast-Track proposals will not be accepted)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1-2

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

Background

The annual morbidity and mortality associated with seasonal influenza, the continuing threat of highly pathogenic avian influenza with pandemic potential, and the emergence of influenza viruses with resistance to the two classes of currently licensed antivirals has created an urgent need to develop new therapeutics candidates that have the potential to prevent severe life-threatening complications of human influenza, improve patient outcomes, and provide more and better options for monotherapy and combination therapy with existing antivirals. There is a need for small molecule drug candidates that selectively inhibit influenza viral replication through a novel viral or host target and have activity against multiple subtypes of influenza A and drug-resistant viruses. New pharmacological strategies directed at modulating host factor and immune-mediated processes to reduce the lung injury and immunopathology in serious influenza are also needed.

Project Goal

The goal of this project is to support preclinical development of a novel small molecule therapeutic intervention with broad antiviral activity against multiple influenza A subtypes, including drug-resistant strains. Projects must focus on an antiviral lead candidate directed at an influenza viral target different from those exploited by licensed antivirals (M2 channel and neuraminidase inhibitors). Projects should focus on a novel viral target, such as HA, the polymerase complex, or NS1; a host target required for flu viral replication; or host factors involved in reducing lung injury and immunopathology.

Phase 1 activities

- Evaluations of an antiviral lead candidate compound for pharmacokinetic profile, efficacy and safety
- Proof of concept studies in a suitable animal model of influenza
- Development of analytical assays to characterize drug efficacy, toxicity and pharmacokinetics

Phase 2 activities

- Preclinical studies, including IND-enabling toxicity studies
- PK/ADMET studies
- Pilot lot or cGMP manufacture of Drug Substance
- Formulation and stability studies

030 Methods of Clinical Sample Preparation for Rapid Detection of Bacterial Pathogens

(Fast-Track proposals will be accepted)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1-2

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

Background

There is an urgent need for rapid, highly sensitive, easy to use, cost-effective clinical diagnostics that can identify Gram negative hospital-associated bacterial pathogens and determine antibiotic susceptibilities. During the last few years a great deal of progress has been made in the development of microfluidic and other diagnostic methods that reduce the time it takes to detect and identify bacterial pathogens from different clinical matrices such as blood, urine, bronchoalveolar lavage, sputum and CSF. However, these new diagnostic platforms require either sample processing and/or culture enrichment in order to work optimally, particularly when dealing with complex samples

such as blood. Therefore, the preparation and processing of clinical sample specimens to extract the analyte still remain barriers to rapid pathogen identification that must be overcome in order to realize the full potential of novel diagnostic platforms without the need for culture.

Project Goal

The goal of this solicitation is to develop rapid, modular clinical sample processing technologies that can be integrated into closed sample-to-answer infectious disease diagnostic platforms. Ideally, such sample processing technologies may employ selective binding/enrichment of pathogens, or their biochemical components, to concentrate samples and to reduce the amounts of interfering substances. The final product should require minimal operator effort and expertise. The proposed sample processing technology must be designed to rapidly extract the analyte from normally sterile sample types, such as blood, cerebral spinal fluid (CSF), and bronchoalveolar lavage.

Areas of research will include:

- Development of improved methodologies and technologies for rapid clinical sample processing, and if appropriate, concentration and recovery in a form suitable for integration with diagnostic platforms, and
- Development, incorporation, and validation of process controls.

Phase I activities

- Development of initial clinical sample processing prototype
- Development and validation of appropriate pathogen-capture/enrichment reagents, if appropriate
- Development, incorporation, and validation of process controls
- Demonstration that prototype is capable of capturing the pathogen and/or purifying the analyte(s) of interest

Phase II activities

- Continued development and validation of prototype
- Demonstration that final product recovers sufficient amounts of the pathogen and/or analyte(s) of interest to enable rapid diagnostics
- Integration of the modular clinical sample collection and processing into an integrated sample-to-infectious disease diagnostic platform

031 Inhaled Delivery of Clofazimine (CFZ) – An Important Anti-tuberculosis Drug

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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

Development of improved drug regimens to shorten treatment for MDR and DS TB and improve tolerance and safety is an extremely high research priority. Clofazimine is a drug approved decades ago for treatment of leprosy. Animal studies of the drug for TB treatment indicate that it may significantly reduce treatment duration, particularly in combinations including PZA. The effectiveness of the “Bangladesh” regimen provides support that inclusion of CFZ in MDR regimens may shorten treatment from 18 to 9-10 months, at least in populations with a low rate of resistance to other MDR drugs.

However, tolerance to orally administered clofazimine is often limited by skin discoloration and GI adverse events. In addition, CFZ substantially increased the QT interval. Inhaled delivery offers the potential to bypass these barriers while still maintaining effectiveness in the lungs by achieving high drug concentrations in the infected pulmonary tissue with lower systemic exposure, thus allowing increased immediate potency. A published study of inhaled delivery of a microparticle formulation of CFZ in a mouse TB model demonstrated that inhaled CFZ reduced lung CFUs much more substantially at 4 weeks than similar doses given by gavage. Given these potential benefits, an easy-to-use inhalation delivery system for CFZ would represent a significant advance in the treatment of tuberculosis. Though anti-tubercular drugs have been formulated into aerosolized particles by multiple research groups and numerous papers are available in the literature on formulating inhaled therapies for TB, no formulation has yet to be commercialized.

Project Goal

The goal of this solicitation is to develop an inexpensive, easy-to-use, inhaled delivery system for clofazimine to be used with combinations of systemic anti-tubercular drugs to improve the treatment of MDR and DS TB.

Phase I activities

- Development of an inhaled formulation of clofazimine.
- Development of an inexpensive, hand-held, self-contained platform for delivery of this formulation.
- Initial testing to quantitatively assess for drug efficacy, toxicity, and pharmacokinetics including required in-vitro studies.

Phase II activities

- Preclinical studies including required in-vivo testing in a standardized, reproducible, validated small animal model.
- Development of a well-defined formulation and delivery platform under good manufacturing practices (GMP).
- Quality control for ensuring and certifying uniformity from lot to lot.
- Scale-up and production for future Phase I clinical study.

032 Simple, Inexpensive Unit for Removing Cells from Small Amounts of Blood in Resource-Limited Settings

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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 rollout of antiretroviral therapy (ART) in resource-limited countries has resulted in substantial reductions in mortality and morbidity due to HIV. While ART regimens are very potent and reduce viral load (measured as HIV RNA copies/ml of plasma) to undetectable levels, virological failure still occurs in some patients. In most resource-limited settings, viral load measurement is not used to routinely monitor patients for virological failure due to cost and complexity of the test. Therefore, many patients are not switched to a second line therapy regimen in a timely manner, which can contribute to drug resistance, and many others are being switched unnecessarily to more costly treatment regimens. For this reason, current WHO recommendations include the use of viral load testing where feasible to monitor patients on ART for virological failure. Over the next several years, the use of viral load testing is expected to increase dramatically, with much of the increase due to new, simple viral load tests that can be performed at the point of care (POC). Many companies are developing such tests, which make use of finger stick

blood samples for testing. Whole blood contains both HIV RNA in plasma, as well as HIV RNA and DNA in peripheral blood mononuclear cells (PBMCs). This can cause inaccuracies in the test results, especially at the lower end of the linear range of the test, where the HIV RNA and DNA in cells can constitute a high proportion of the total HIV signal in the blood sample. A simple, inexpensive method for removing cells from very small amounts of blood is needed for use with POC HIV viral load assays. The blood will be obtained by finger stick (approximately 200 to 500 ul of blood). Removal of the cells must be performed very quickly in one step at the POC, without the need for electricity, and the resulting plasma must provide accurate and reproducible results in POC viral load assays.

Project goal

The goal of this solicitation is to develop an inexpensive, easy to use process that will remove cells from finger stick blood samples (approximately 500 ul) prior to use in POC viral load assays.

Phase I activities

- Development of a method for removing cells or processing to plasma
- Integration of the process into a single unit
- Initial testing of the product with at least one POC viral load technology using spiked blood samples, including several HIV subtypes

Phase II activities

- Validation testing with at least one POC viral load test, to include precision, accuracy, sensitivity, and specificity against standard viral load tests
- Production of the product 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

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:

157 Mobile Technologies Extending Reach of Primary Care for Substance-Use-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: 2-3

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 exceeding the above amounts and project periods may not be funded.

Objectives

Develop and test a prototype mobile/tablet technology-based application suitable for U.S. primary care settings, to serve as a low-cost user-friendly tool that primary care providers (PCPs) may use to deliver timely tailored feedback to patients following up on interventions for risky substance use. The feedback delivered should make sure patients engage in appropriate self-monitoring and self-management skills in adherence to treatment plans delivered during interventions for problematic substance use. Patients' answers should inform delivery of tailored feedback (matching level of problematic substance-use risk as determined by validated screening and assessment tools) supporting health-promotion behaviors, such as helping patients adhere to evidence-based motivational interviewing or other behavioral therapy principles. The application also should track health action items completed, such as linkage to indicated follow-up treatment. It should be designed with a specific aim of improving coordination and delivery of indicated services to primary care patients at risk of developing substance use disorders (SUD).

Background Information

NIDA seeks development and testing of a prototype mobile/tablet technology-based application to extend the reach of primary care services to patients at risk for developing SUD, with deliverables specified below. Recent healthcare reform laws provide unprecedented opportunities for expanded health insurance coverage and increased funding for SUD treatment services in primary care settings. However, for those patients who need such treatment services, there is limited availability and reach of primary care providers to follow-up on action plans established during initial primary-care interventions. Also, there are insufficient applications to aid PCPs in ensuring patients engage in necessary self-management skills for linkage to and engagement in needed follow-up treatment. Furthermore, PCPs typically have limited success in leveraging mobile applications to sustain temporary patient health-promotion behavioral changes initiated in primary care interventions. Moreover, mobile applications have rarely been employed to improve care coordination and integration of primary care with SUD treatment in medical settings.

There is large market opportunity and commercialization potential for developing such a mobile application. For instance, Section 2703 of the 2010 Patient Protection and Affordable Care Act (ACA) provides states with a "health home" insurance payment option for behavioral health providers treating chronic conditions, including SUD prevention and treatment providers. This ACA provision includes: "*the use of health information technology in providing health home services...and improving service delivery and coordination across the care continuum (including the use of wireless patient technology to improve coordination and management of care and patient adherence to recommendations made by their provider)*". Furthermore, according to the Pew Research Center, over 90% of adults in the U.S. currently own a cell phone. The tool developed in response to this solicitation should be able to be run on a feature phone as well as a smart phone. Thus, there is a large market opportunity in terms of intended customers for this mobile technology: Health insurance payers and health professionals in primary care settings.

Beginning in 2014, an ACA provision would require payers of health plans to cover early intervention and treatment for the full spectrum of SUD, as needed, similar to other medical procedures. However, the capacity to offer such services in primary care is limited due to a severe workforce shortage in well-trained SUD treatment professionals. The proposed mobile-health application would help address this problem by serving to enhance the coordination and reach of preventive SUD interventions in primary care.

Phase I Activities and Expected Deliverables

Develop and test the feasibility and acceptability of a mobile/tablet technology application prototype for use in primary care settings which aims to improve the coordination and reach of SUD primary care, with the following deliverables:

- The mobile application should include necessary functionality to serve as an aid to PCPs to improve the coordination/management of primary care services for patients screened for SUD in general medical settings, by:

- Enabling providers to continually monitor and deliver user-friendly, tailored (matching the level of problematic substance-use risk as determined by validated screening and assessment tools), timely multimedia feedback as a follow-up to primary care interventions, with an aim of reinforcing patient adherence to providers' recommendations in treatment plans;
- Delivering such feedback based on evidence-based SUD behavioral therapy principles suitable for primary care settings (such as motivational interviewing, motivational enhancement therapy, or other evidence-based interventions associated with an empathic, respectful, collaborative approach to promoting behavior change);
- Delivering timely tailored feedback designed to prompt and reinforce high-risk patients in engaging in necessary self-management and health-promotion skills to comply with primary care action plans and support effective linkage to- and patient engagement in needed follow-up specialty care;
- Employing evidence-based principles of shared-decision making and follow-up patient-centered care, appropriate for the target age group and population;
- Exhibiting the capability of being linked with health information technologies (HITs) such as electronic medical records (EMRs), electronic health records (EHRs), other health care systems (e.g., provider locations, appointment scheduling systems, etc.), web-based applications (social media sites), etc. Linking to such HITs should facilitate this tool's ability to support key features of SUD care management in primary care settings. These features include continuity of patient-centered care, coordinated or integrated care guidance from clinical guidelines, and shared-decision making among patients, their families, and primary care provider teams;
- Permitting mobile user input and interaction among provider, patient, and authorized caregiver, parent, significant other person support/monitoring;
- Building in incentives for meeting treatment-plan-adherence goals;
- Engaging patients in self-management behaviors through electronic (message, text) or voice (phone) reminders and follow-up contacts, in a manner shown to produce better treatment-engagement outcomes among patients with SUDs;
- Linking patients with relevant community resources such as wellness programs, mutual and peer support groups, low-cost medication programs, assisted living arrangements, health fairs, etc. to help patients manage their illness.

In addition, the mobile application should:

- With regards to patient privacy, be HIPAA, HITECH Act, and CFR 42 Part 2 (confidentiality of alcohol and drug abuse patient records) compliant;
- Use computational modeling, branching logic and/or query functions to develop sophisticated adherence-to-treatment-plan solution algorithms for the software;
- Offer a menu of tailored adherence-to-treatment-plan strategies, based upon each individual's baseline rate of treatment-plan adherence (and provide some rating mechanism for the strategies offered);
- Provide a baseline ecological momentary assessment (EMA) of the patient's status (such as physical and/or psychiatric symptoms, drug cravings/drug use, anxiety, mood states, etc.) and its impact on adherence to treatment plans, such that tailored interventions can be delivered to the patient, based upon that status;
- Exploit the device capabilities for GIS, GPS, SMS, phone, Bluetooth, online, video and other platforms of real-time communication, in a manner enhancing the functionalities of the phase I expected deliverables;
- Demonstrate acceptability, feasibility, and preliminary efficacy in improving patient linkage to and engagement in indicated follow-up SUD specialty care. Test the application on 8 patients screened and determined to be at a

high-risk for SUD, using a validated screening and assessment tool suitable for primary care settings, to gather preliminary data regarding the reliability of the application and its ease of use by patients and providers.

Phase II Activities and Expected Deliverables

Demonstrate a production model prototype's efficacy to increase significantly the proportion of primary care patients who are successfully linked to and receive indicated follow-up specialty SUD care. Provide evidence of a track record indicative of commercialization potential and that the proposed research will likely result in a marketable product (for example, from prior SBIR/STTR or other research initiatives, commitment of additional investment from private sector or other non-SBIR funding sources, other evidence of commercialization potential for the proposed research, etc.)

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:

007 Diagnostic Tools to Support the Elimination and Control of Neglected Tropical Diseases

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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

Neglected tropical diseases (NTDs) are bacterial and parasitic infections that disproportionately affect poor and marginalized populations around the world. A subset of NTDs, including lymphatic filariasis (1 billion people at risk in 73 countries), onchocerciasis (120 million people at risk in 37 countries), schistosomiasis (700 million at risk in 74 countries), trachoma (540 million at risk in 55 countries) and intestinal helminth infections (4 billion at risk, 1 billion infected, worldwide), can be effectively controlled through mass drug administration targeting affected populations. NTDs are primarily associated with high levels of morbidity due to the chronic nature of the infections. The prevalence of NTDs increases with age, thus, reduces the economic productivity of adults. In addition, school aged children are also affected, resulting in decreased physical and scholastic performance. In recent years, there have been significant increases in the number of countries implementing intervention programs to combat NTDs by implementing mass drug administration strategy (MDA) leading to a significant increase in treatment coverage in many endemic areas. Reducing the morbidity caused by NTDs is an objective of the Global Health Initiative (GHI) and the global elimination of lymphatic filariasis and trachoma are specific GHI targets. Unfortunately, currently

available diagnostic tools for geographical mapping of disease burdens and impact evaluation of intervention programs do not meet the needs of the global elimination goals. Additionally, the effort to eliminate onchocerciasis and lymphatic filariasis by MDA strategy using ivermectin, has been negatively affected by a high level co-endemicity with loiasis (also known as Eye Worm) due to a significant risk of severe adverse drug reactions in co-infected individuals. Therefore, geographical mapping of loiasis endemicity by using more effective diagnostic tools would be useful to accelerate the MDA work for onchocerciasis.

Project Goal

Better diagnostic tests are needed to guide programmatic decisions addressed by MDA. Despite the significant advances in bioinformatics and DNA genome sequencing, very limited knowledge from parasite genes/gene products are being translated into tools to assess and guide program decisions. Novel accurate tools for mapping, micro-mapping, and monitoring and evaluation of program impact are still needed. These tests should be field compatible, sensitive and specific, to support the NTD programs with elimination endpoints. New antibody tests could provide more sensitive tools to monitor transmission, facilitate decision-making, and conduct surveillance.

The specific project goal is to have prototype antibody-based assays that can address diagnostic gaps currently faced by NTD programs. Some of these gaps are: the need of rapid diagnosis for determination of prevalence and micro mapping; the detection of co-infections that hamper MDA activities (e.g., Loa loa infections in areas endemic for onchocerciasis, etc.); epidemiological surveillance, and evaluation of program impact through serological monitoring.

The potential advantages of antibody-based tests for post-MDA surveillance support the efforts to develop a standard platform for integrated surveillance for NTDs.

Phase I Activities and Expected Deliverables

Deliverables

- Prototype device or methodology for point of care application (field compatible) for simultaneous detection of one or more NTDs. A rapid diagnostic, field compatible antibody based assay will be highly desirable. Such device will help identify cases in specific areas, therefore allowing fast mapping for programmatic work, support surveillance activities, and could be the basis of program monitoring and evaluation activities. A desirable prototype should include either two or more of the NTDs listed above (like schistosomiasis and lymphatic filariasis), or (Loa loa and onchocerciasis and/or lymphatic filariasis).

Activities

- Determination of basic assay performance characteristics: preliminary sensitivity, specificity
- Field compatibility characteristics: stability/shelf life, storage requirements

Impact

Development of improved diagnostic tools will address CDC's efforts to address lymphatic filariasis in the Americas and the global health targets on NTDs. New and improved diagnostic tools will also enhance the commitment of donors and policy makers to the control and elimination programs for NTDs worldwide by providing higher quality information and increased confidence that public health goals are being met. Significant savings in human and financial resources could be obtained through the development of improved mapping and surveillance tools.

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:

037 Optical Character Recognition Software for Scanning Nutrition Facts Panel

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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

Poor nutrition contributes to chronic diseases. Heart disease and stroke are leading causes of death in the United States. Consumers are in need of tools and resources to aid them in making healthier food choices and public health is in need of brand level nutrition information to assess consumer intake and nutritional composition of the food supply. Several public health efforts are ongoing to improve nutrition, and reduce risk for associated diseases. Mobile technology is one tool consumers are using to manage health and nutrition. More than a quarter, about 29%, of adults who download apps utilize the apps to manage and keep track of their health. <http://www.pewinternet.org/2011/11/02/part-iv-what-types-of-apps-are-adults-downloading/>. Mobile technology can also aid in creation of brand level nutritional databases.

Current mobile applications (Apps) that provide nutrition information for packaged foods scan bar codes to give further information about a product. The barcodes themselves don't provide nutrition information; the barcode identifies a universal product code (UPC) and the UPC is then linked to the same UPC and associated nutrition values that are compiled in a database behind the App. These Apps are a great advantage to the App user who is looking to learn more about their potential purchase or explore healthier options. For the Apps to continue to be useful, their source database needs to be updated as new products go on the market or as product reformulation, including sodium reduction or other nutritional changes, occurs. Several nutrition Apps offer a feature when a

scanned product yields no results. Users can take pictures of the Nutrition Facts Panel (NFP) and the front of the package and upload them to the nutrition Apps. NFPs are standard and require FDA regulated nutrition information about the content of food products. Over time, the App owners will add the products submitted by users to their databases (crowd sourcing).

From an App owner/database perspective, receipt of the photos requires personnel to review the pictures and insert corresponding information into the database. Software, such as Optical Character Recognition (OCR) that can scan the photo or the NFP as opposed to bar codes can assist in two areas, 1) will only require database management to ensure validity and 2) allow for greater and timely inclusion of reformulated products. This ability could help public health collect up-to-date nutrient information of packaged foods. This technology can be useful to the marketplace of nutrition and health related App developers and owners. For example it can be paired with existing apps such as “Lose It! Fooducate,” and “Grocery IQ,” as well as with Australia’s George Institute’s mobile application “Foodswitch” to collect data on consumer preferences and sodium reduction.

Project Goal

The goal of this project is to create a mobile application that uses OCR to read NFPs directly from photos of labels taken with a smart phone. This SBIR proposal intends to help a small business build a technology that will create revolutionary OCR software that will be able to scan NFPs from any box, bag, can, or other packaged food items in grocery stores, convenience stores, and other places of business where packaged foods are sold. This technology will allow NFPs to be translated into user friendly information that can be scaled and integrated into a variety of mobile device applications that focus on nutrition and health/wellness.

Phase I Activities and Expected Deliverables

Deliverables

- OCR technology that has the ability to read and interpret NFPs and can be integrated into other mobile applications to add value to nutrition and health/wellness applications and increase ease of use for consumers leading to greater market acceptability.

Activities

- Collaborate with innovative tech-industry small business to create OCR technology to read and interpret nutrition facts panels.
- Test accuracy and validity of mobile application: OCR technology must be able to demonstrate the ability to successfully read and interpret NFPs into information that will add value to other mobile applications, and ultimately consumers.

Impact

By combining OCR technology with the nutrition and healthy lifestyle mobile applications, CDC and its partners can provide consumers, including those at risk, information to assist in making healthy choices when shopping for food, with the goal of reducing incidence of heart disease and stroke. Utilization of this technology and App will result in enhanced publically available nutrition information at the brand level. Having this information in hand will assist public health in tracking and better understanding sodium reformulation and reduction, and other nutritional changes. With this information, CDC can evaluate progress being made in the realm of sodium reduction and improve collaboration with the food industry to reduce sodium in the food supply and reduce incidence of heart disease and stroke.

Commercialization Potential

The resulting technology will be most useful to new and existing App developers, will be useful to consumers looking for more comprehensive and up to date nutrition information and may also be useful to businesses that compile and sell brand level nutrition information.

OCR technology is a technology that will revolutionize the way nutrition and health/wellness mobile applications can provide information to their customers. Data will be rich and interactive and will allow for greater automation of databases. The ease of use of the application will increase overall market share of nutrition mobile applications, encourage healthy eating for consumers, and ultimately may reduce incidence of heart disease and stroke. Health and Fitness App designers may be interested in utilizing (purchasing) this technology to increase the value and accuracy of the nutrition information delivered in their App and as a cost savings approach.

This type of nutrition labeling information is already being pulled together manually by several businesses and organizations. This information is proprietary and sold to interested parties. The data obtained from this technology is expected to be of interest to these same stakeholders as well as others. Downloading and utilizing a resulting dataset will be of interest to various businesses, organizations and governments.

NATIONAL CENTER FOR EMERGING ZOO NOTIC 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:

011 Development of Nanoparticle Dengue Diagnostic Tests

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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

Dengue is a major public health problem in tropical/subtropical areas, with an estimated 100 million dengue cases and 390 million dengue virus infections per year. Primary prevention of this mosquito transmitted disease is limited because of a lack of tools although vaccines and new vector control approaches are in late-stage development. Dengue presents as an acute febrile illness often without signs or symptoms that differentiate it from other diseases such as influenza, malaria and leptospirosis. Good clinical management early in the course of dengue prevents excess morbidity and mortality, but requires accurate laboratory diagnosis. Dengue diagnostic testing on a single serum specimen obtained early in the illness is now doable. Most patients present during the first days after fever onset when dengue virus (DENV) is present in blood. Molecular testing for DENV identifies almost all dengue cases; however, this method is not widely available in most dengue endemic countries. In addition, a soluble non-

structural DENV antigen (NS1) can be detected by immunoassay during this period but has somewhat lower sensitivity than molecular tests. Nanoparticle-based technology significantly increases the sensitivity of antigen and antibody detection tests, is used for molecular diagnostics, and has been used in multiplex formats. Microresonator constructs and nanowire-based field effect transistors allow this technology to detect biolytes at low femtomolar concentrations. Surface enhanced Raman scattering (SERS) and extrinsic Raman labels (ERLs) have been used with metal nanoparticles (gold, silver) organic reporter molecules to magnify the Raman response by $\sim 10^6$, which surpasses fluorescence.

Project Goal

The goal of the project is to develop prototype dengue diagnostic tests that identify DENV by either molecular or immuno-detector systems (e.g., DENV specific nucleic acid, NS1 antigen) using nanoparticle-based technology that includes, but is not limited to SERS and ERLs. Prototype tests should be developed with a product profile that includes a short-turn-around diagnostic result and use in resource constrained settings. Prototype tests that would be judged 'acceptable' are those that detect at least 80% of dengue cases during the early phase of the febrile illness across all DENV serotypes, in primary and secondary DENV infections and do not misdiagnose as dengue other flavivirus infections or infections due to other causes of febrile illness in dengue endemic areas.

Phase I Activities and Expected Deliverables:

- Develop a prototype, nanoparticle-based NS1 antigen detection test with whose preliminary data shows sensitivity comparable to commercially available NS1 antigen detection ELISAs.

Impact

The availability of DENV-specific, dengue diagnostic tests with high sensitivity and specificity would greatly change the impact of clinical case management, and would provide the tool needed to evaluate the effectiveness of dengue vaccines or improved vector control tools following their introduction.

Commercialization Potential

The market for dengue diagnostic tests has not been determined; however, it is estimated that 40-60% of the world's population resides in dengue endemic areas and approximately 100 million cases of dengue occur annually. One would expect that the annual market for dengue diagnostic tests would be many-fold greater than the number of dengue cases, since most people with acute febrile illnesses in dengue endemic areas would require testing. Dengue occurs in both low income as well as middle income developing countries, such as Brazil, Mexico and Thailand. Presently commercially available dengue diagnostic tests are widely used in these countries. In addition, the WHO has recommended dengue diagnostic testing as an adjunct to better target medical case management. Presently, a number of large companies produce dengue diagnostics, however, a point of care test with even a two-fold increase in sensitivity would have a measurable advantage over currently available tests.

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:

043 Yeast-derived Candidate of Hepatitis E Virus Vaccine

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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 E virus (HEV) causes epidemic and sporadic cases of hepatitis in humans. HEV infections are especially prevalent in developing countries but are found worldwide. It is a major cause of acute hepatitis globally, with an estimated one-third of the world's population having been infected with this virus. Most cases of HEV infection cause an acute liver disease. In endemic countries, the overall mortality rate of acute HEV infection is 1%-3% and reaches up to 30% in pregnant women. HEV genome was classified into four genotypes. HEV genotypes 1 and 2 infect humans along the fecal/oral transmission route and were found to cause large-scale outbreaks of hepatitis E in developing countries; while genotypes 3 and 4 are zoonotic and were found predominantly in sporadic cases or small food-borne outbreaks in developed countries. An estimated 80% of domestic pigs are HEV seropositive, with 40% of apparently healthy animals having detectable HEV at slaughterhouses. The HEV genome is a positive-sense, single-stranded RNA of about 7.2 kb and contains three overlapping open reading frames (ORFs). ORF2 encodes the viral capsid protein that contains the neutralizing antigenic epitope. This epitope is conformationally dependent and located at position 452-617 aa of the HEV ORF2 protein. HEV proteins comprising this ORF2 region were shown to form pseudoviral particles after expression either in *Escherichia coli* or in insect cells. Both *E.coli*- and baculovirus-derived products were shown to protect monkeys against virus challenge and to be effective in the prevention of HEV infection in humans. No commercial HEV vaccine is currently available. The yeast expression system was long adapted to the production of commercially available vaccines and, thus, is most suitable for production of the HEV vaccine. Proposals are being thought for the expression of HEV antigens in yeast and purification and evaluation of the expressed proteins as vaccine candidates.

Project Goal

The purpose of this project is to express the HEV ORF2 protein of genotype 1 and 3 in yeast and purify the expressed proteins. Considering that the antigens are planned to be evaluated as vaccine candidates, it is important to show that the purified proteins model the fully functional HEV neutralizing epitope.

Phase I Activities and Deliverables

Deliverables

- Genetic constructs expressing HEV proteins of genotype 1, 2 and 3 in yeast, *Hansenula polymorpha* or *Pichia pastoris*, and yeast strains expressing and secreting the antigens in the immunologically active form.

Activities

- Conduct genetic engineering experiments to construct plasmids for expression and secretion of HEV antigens using PCR products provided by CDC.
- Conduct experiments for obtaining yeast clones producing HEV antigens.
- Conduct experiments to show the HEV-specific immunological activity of the expressed proteins.

Impact

Yeast-derived HEV proteins may serve as vaccine candidates after evaluation in nonhuman primates. Use of different sequence variants of HEV genotypes 1, 2, 3 and 4 provides an opportunity to identify most immunogenic vaccine candidates that are suitable for vaccination programs in different countries. Genotype 3 and 4 vaccine candidates are suitable for immunization of farmed swine in order to prevent food-borne transmissions to humans. HEV infection is a serious threat to global public health. It causes large outbreaks and sporadic cases of acute hepatitis, and an estimated one-third of the world's population has been infected with HEV. It is the most or second most common cause of acute viral hepatitis among adults throughout Asia, the Middle East, and Africa. The burden of HEV genotypes 1 and 2 in 9 of 21 world health regions, which represent 71% of the world's population, was estimated to be 20 million cases per year, with 70,000 deaths and 3,000 stillbirths. In industrialized countries, the HEV seroprevalence can be as high as 20%. In patients with chronic liver disease, HEV infection has a mortality rate of up to 70%. A significant infection rate (up to 80%) among domestic pigs, with ~40% of animals in slaughterhouses being infected with zoonotic genotypes 3 and 4, contributes to human infections through food consumption. HEV vaccine is the most efficient way of preventing human HEV infections. In combination with swine immunization, HEV vaccination will lead to dramatic reduction of morbidity and mortality rate, and, potentially, to eradication of human HEV infections globally. Implementation of vaccination should benefit populations, especially pregnant women, in endemic countries of Africa and Asia, elderly men and immunocompromised persons in developed countries, and patients with chronic liver disease. Veterinary vaccination should benefit all countries with significant consumption of pork and pork-derived products.

Commercialization Potential

Yeast-derived HEV vaccine candidates have a commercial potential for veterinary immunization of farmed swine and for human vaccination especially in developing countries. Veterinary candidates will be based on HEV genotype 3 and 4 proteins. In view of numerous reports of the high HEV prevalence in domestic pigs and the cross-species transmission of swine strains to humans associated with ingestion of uncooked meat from pigs, immunization of domestic pigs should be considered as a potential strategy for reduction of the number of human infections. Considering that millions of pigs are raised annually in industrialized countries; e.g., 7.5x10⁶ pigs in the Netherlands alone; domestic swine population presents a significant commercial potential for veterinary vaccine. Application of human HEV vaccine in developing countries, especially among pregnant women, and industrialized countries, especially among elderly and patients with chronic hepatitis, and countries with high-level consumption of pork and pork-derived products, especially when uncooked; e.g., in sausages, presents a very substantial opportunity for commercialization.

044 Multiplex Assay for Simultaneous Detection of Hepatitis and Other Viruses

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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

Viral hepatitis is the leading cause of liver cancer and the most common reason for liver transplantation. More than 4.4 million Americans live with chronic hepatitis. To date, five viruses, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus (HDV) and hepatitis E virus (HEV) have been etiologically associated with viral hepatitis. The hepatitis viruses vary widely in their natural history, genome composition, and mode of transmission. Since viral hepatitis infections caused by the five viruses are clinically indistinguishable, disparate testing algorithms are being employed to determine the etiology of infection. Nucleic acid testing (NAT) remains the gold standard for detecting the viruses in blood and other body fluids. For multiplex detection of the

hepatitis viruses, CDC has adapted TaqMan® Gene Expression Array Cards for simultaneously detecting HAV RNA, HBV DNA, HCV RNA, HDV RNA and HEV RNA in blood samples (Journal of Clinical Virology, 2014, in press). For greater utility in resource-poor settings, multiplex technologies not dependent on thermal cycling are highly desirable.

Project Goal

Proposals are being sought for the development of a multiplex assay for simultaneous detection of genomes of blood-borne human pathogens including HAV, HBV, HCV, HDV and HEV in a format that is independent of thermal cycling. Such an assay will be useful for pathogen screening of blood and organ/tissue donors, antenatal clients, immigrants, sexually-transmitted diseases (STD) clinics and other target populations. The improvements to the current assay developed by CDC should be to its scalability, field-friendliness, and sample-processing simplicity. In the field, this new technology should be portable, with few manipulative steps, no need for electricity, and easy to interpret results. Additionally, it is desirable that the format should have the potential to add targets for other pathogens. The technology should not be electrically driven during the sample processing, detection and test-outcome display stages.

Phase I Activities and Deliverables

Deliverables

- Optimize assays for specific and sensitive detection of genomes of all five hepatitis viruses in a scalable, field-friendly system that does not require thermal cycling.

Activities

- Perform proof-of-principle experiments on the standard material.
- Determine limit of detection and analytical specificity of each assay.
- Improve the assays as necessary to obtain acceptable limit of detection and analytical specificity of each assay.

Impact

Simplification of CDC assays through scalability, field-friendly technology and simplified sample processing effort will allow laboratories at remote sites of the world to test their clinical specimens for all five hepatitis viruses simultaneously. This effort has a potential to impact large populations through more accessible and field-friendly molecular testing.

Commercialization Potential

This assay has great commercialization potential because it can be used to screen a large number of people for hepatitis viremia. Potential uses of such assay include, but are not limited to, global public health, disease surveillance, solid organ donor screening, STD clinics blood donor screening, border infections screening, and antenatal testing. Potentially, the greatest commercialization potential would be in detection of subsets of these assays, such as HBV and HCV or HAV and HEV.

045 Improved Antibody Preparation for Post-Exposure Prophylaxis Against Hepatitis A

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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 A virus (HAV) causes acute inflammatory disease of the liver. It is transmitted via the fecal-oral route from person-to-person contact and from consumption of contaminated water and food. In the United States, the incidence of hepatitis A has decreased substantially with sanitation improvements and introduction of childhood vaccination. Despite of HAV control measures, approximately 28,000 acute cases are reported annually in the United States, making it one of the most frequently reported notifiable diseases. Nevertheless, unvaccinated persons remain susceptible to infection acquired from food or during international travel. Further, older persons who are infected tend to develop severe disease. Immune globulin (IG), administered intra-muscularly, is recommended for post-exposure prophylaxis (PEP) against hepatitis A. Importantly, during the occurrence of the large HAV outbreak thousands of IG doses are required for disease control. However, low titers of anti-HAV-specific antibodies in commercial IG, resulting from declining immunity through herd protection, attenuate the capability of IG to neutralize HAV.

Project Goal

The goal of this project is to develop a neutralizing mAb for eventual use in humans as an alternative to the current IG preparations for PEP against HAV infection and Hepatitis A. Proposals are being sought for the development of alternative antibody preparations capable of effecting anti-HAV neutralization. Such preparations may be, but need not be limited to be constituted of human-murine chimeric monoclonal antibodies (mAbs). Humanized antibodies are already commercially available for prophylactic measures in other viral diseases. Palivizumab is a humanized monoclonal antibody against respiratory syncytial virus which has been to reduced hospitalization in infected children. Thus, the use of humanized antibodies is an attractive alternative for HAV-related disease control not only in the United States but globally. Considering that HAV neutralizing epitopes are well known, and that Fab human antibody regions have been mapped for these epitopes, the synthesis of humanized antibodies is attainable. The development of the post exposure prophylaxis alternative will most likely help prevent infection during the occurrence of HAV outbreaks and also among international traveler visiting endemic regions; thus, diminishing importation of cases and viral lineages into the country.

Phase I Activities and Deliverables

Activities

- Cloning of HAV antigens containing neutralizing epitopes
- Clonal expression of HAV candidate antigens

Impact

The availability of an anti-HAV human chimeric mAb will significantly improve the quality of PEP against HAV infection and disease. The possibility of generating highly homogeneous and efficacious preparations of neutralizing anti-HAV mAb is of significant public health importance for the United States and elsewhere in developed countries where herd immunity to HAV is waning and where hepatitis A as a disease has become more common.

Commercialization Potential

The use of human chimeric mAb as an alternative to IG for PEP should increase in demand considering the declining capability of current IG preparations used for PEP. Although hepatitis A vaccine can be used for PEP, it may take up to a week before antibody levels in peripheral blood reach sufficient titers to effect neutralization. Importantly, older vaccines are known to achieve suboptimal post-vaccination responses, so subjects will benefit from passive use of human chimeric mAb, in addition to active immunization given soon after HAV exposure.

HAV PEP is still required for the management of outbreaks in different regions of the world and during an occurrence of a large HAV outbreak in the United States.

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:

029 Thermostable Dry Vaccine Formulation for Microneedle Administration

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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. Development of a thermostable microneedle format for one of the topic targeted diseases could result in a platform technology with high utility for other vaccine. Multiple companies are working on microneedles vaccine delivery systems and other companies are working on vaccine thermostability. The objective of this topic is to focus on both goals in a single project. The target cost of the final product should be comparable to current vaccine costs, however, a thermostable microneedle could result in significant cost savings in cold chain, shipping and administration cost..

Project Goal

Develop and test a prototype thermostable microneedle vaccine formulation for one of the following diseases: polio, rotavirus, measles, or influenza.

Phase I Activities and Expected Deliverables

Deliverables

- Development of a thermostable vaccine formulation.

Activities

- Process thermostable vaccine into microneedle format which has no residual sharps.
- Assess thermostability of vaccine microneedle at 37 Celsius over four months.

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. A 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). A dry microneedle vaccine for any of the target diseases could have significant impact in increasing the availability and accessibility of the vaccine, reducing the costs of immunization and providing a new platform technology for delivery of all vaccines. Measles elimination is targeted by every WHO region and the global eradication of polio is a high priority. Both objectives require achieving high coverage in hundreds of millions of people and technologies like thermostable microneedles to facilitate high coverage could have a significant impact. Rotavirus and influenza are ubiquitous diseases and vaccines are underutilized in many developing countries. Thermostable microneedle delivery could significantly accelerate vaccine use in developing countries and reduce morbidity and mortality from these diseases.

Commercialization Potential

Hundreds of millions of vaccines are delivered annually. 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). The reduction of these costs for such a large market drives substantial commercialization potential although significant public and private investment will be needed to achieve licensure of the new vaccines.

030 Thermostable Oral Vaccines to Combat Enteric Diseases

(Fast-Track proposals will not be accepted.)

(Direct to Phase II 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. Every child born in the world should receive (at least 3 doses of) polio vaccine. However, the logistic difficulties inherent in maintaining the vaccines in the cold chain and vaccination by injection create barriers to high vaccine coverage. Maintenance of the cold-chain is expensive and current rotavirus vaccines have high storage volumes and complex cold chain requirements. Vaccination by injection requires highly skilled vaccinators, vaccine reconstitution with risks of contamination and bio-waste disposal of millions of syringes and needles to prevent reuse or injuries. Currently the live oral polio vaccine is being phased out for safety reasons and the world is transitioning to injected inactivated polio vaccine. An oral delivery format for a thermostable non-live polio vaccine would facilitate the transition from the current live oral polio vaccine. Other enteric diseases could also benefit from thermostable oral delivery formats. Oral rotavirus, hepatitis A and cholera vaccines are available but the thermostability requirement coupled with the packing volume of the vaccines are logistic limitations to high coverage. Oral vaccines for hepatitis B are in development. The global number of deaths due to rotavirus infection in children aged less than 5 was estimated to have been 527,000 (475,000 – 580,000) in 2004, with about 90% percent of them in Africa or Asia. Each year, approximately 600,000 HBV-related deaths occur worldwide and WHO has set a target for all infants to receive

Hepatitis B vaccine. Globally, 783 million people do not use improved sources of drinking water and are at risk of cholera and other enteric diseases. In the United States, hepatitis A vaccine is routinely recommended for children. In developing countries with very poor sanitary and hygienic conditions (parts of Africa, Asia and Central and South America), infection is usually acquired during early childhood.

Multiple organizations are researching different methods of thermostabilization of vaccines including spray drying, sugar glass coating, silk protein preservation and preservation with biodegradable polymers. This topic is intended to focus thermostabilization methods on oral delivery formats.

Project Goal

Develop and test a prototype thermostable oral vaccine for one of the following diseases: polio, rotavirus, cholera, hepatitis A or hepatitis B.

Phase I Activities and Expected Deliverables

Deliverables

- Development of a thermostable vaccine formulation.

Activities

- Process thermostable vaccine into oral delivery format
- Assess thermostability of vaccine at 37 Celsius over three months.

Impact

A thermostable oral 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.

Commercialization Potential

Hundreds of millions of doses of vaccines for enteric diseases such as rotavirus and polio are produced and sold on annual basis. Increasing the thermostability of these vaccines and creating novel oral delivery formats would enhance their value. Significant private or public investment in development and testing of the new vaccines may be required to assist vaccine manufacturers in covering the start costs of adopting the new vaccine technologies.

13 APPENDICES

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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